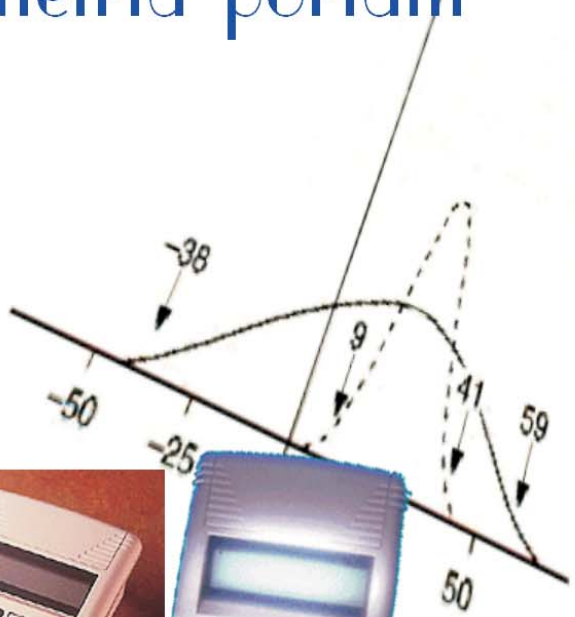
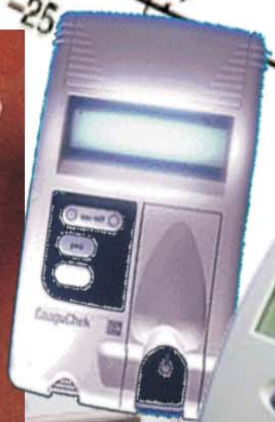
SET

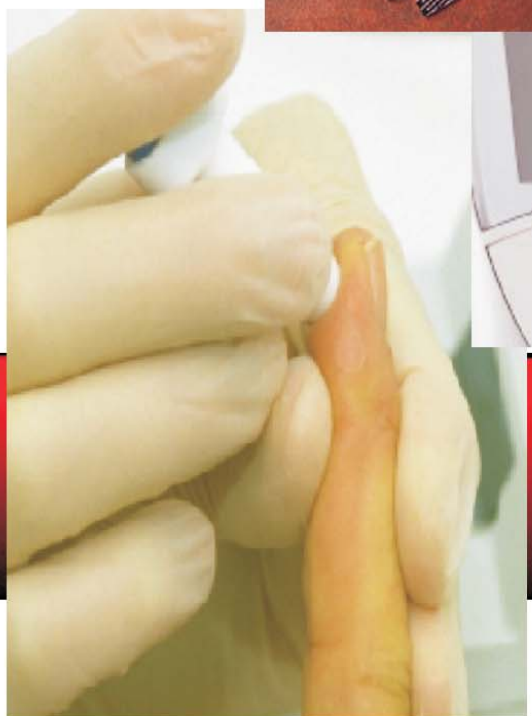
Valencia, octubre 2001

INFORME VALORATIVO URGENTE

Evaluación del INR mediante coagulometría portátil







Índice del informe

páginas

INFORME VALORATIVO A DEMANDA

I.- ANTECEDENTES

En fecha 19-IX-2001 se recibió en este servicio escrito de la Dirección General para la Prestación Farmaceútica, solicitando informe sobre las características de la determinación del INR (*) mediante coagulómetros portátiles. Se indicaba en el mencionado escrito la necesidad de aportar información sobre aspectos tales como seguridad, eficacia, eficiencia y utilidad clínica de dichos sistemas y particularmente referida al que reseñaba como más utilizado: COAGUCHECK (sic).

En fecha 24-IX-2001 el Servicio de Evaluación de Tecnologías solicita a la citada Dirección General, la transmisión de la información disponible relativa al tema que pudiera completar la recabada por otras vías.

Con fecha 5-X-2001 se recibe escrito de la citada dirección general, en el que se anexa informe de la Agencia de Evaluación de Tecnologías Sanitarias del Instituto de Salud Carlos III relativo a los coagulómetros portátiles, del que ya se disponía en este Servicio. El citado informe del Instituto de Salud Carlos III -de fecha 27-III-2001 - refiere diversas evidencias contrastadas tras el análisis de la información pertinente, siendo la referencia bibliográfica más reciente utilizada del año 1999. En dicho informe se manifiesta asímismo, que la realización de una revisión sistemática conforme a criterios de seguridad, eficiencia y utilidad clínica, precisaría de la habilitación de un proyecto a largo plazo tal como el diseño y actividades para dicho tipo de análisis requiere.

* INR= Razón normalizada internacionalmente del tiempo de protrombina. **$INR=(TP/MNTP)^{ISI}$**

TP= tiempo de protrombina en paciente

MNTP= media geométrica de tiempo de protrombina en sanos

ISI= índice de sensibilidad internacional (del reactivo utilizado –tromboplastina-)

II.- PLANTEAMIENTO PREVIO

La solicitud del informe valorativo recibida de la Dirección General de Prestaciones Farmaceúticas, abarca un amplio campo prospectivo (seguridad, eficacia, eficiencia y utilidad clínica).

La confección del presente informe valorativo se ha ajustado en lo posible al plazo de contestación urgente solicitado por el demandante. Un planteamiento futuro con plazos de recopilación, análisis y prospección más largos, permitirían obtener un mejor análisis del impacto futuro y de mayor profundidad, así como un más adecuado ajuste a las preguntas a contestar. Un planteamiento de este tipo (recomendable para este tema), se situaría en línea con las especificaciones y plazos fijados para los Informes a Demanda, referidos en la Guía de Evaluación de Tecnologías de este Servicio (abril 2000).

A la vista de lo anterior, el informe ya elaborado por la Agencia de Evaluación de Tecnologías Sanitarias del Instituto Carlos III, parece adecuado a la finalidad y plazos de respuesta perseguidos. No obstante para incrementar el aporte de información preciso para la toma de decisiones, en el presente informe se ha pretendido recopilar además de la información previamente disponible, aquella de nueva aparición no referenciada en el trabajo del Carlos III. Para ello se ha recurrido a diversos servicios, organismos, bases de datos y repertorios bibliográficos que pudieran aportarnos datos, informaciones relevantes y evidencias para el tema y los campos a evaluar.

II.- ESTRATEGIA DE BÚSQUEDA

Siendo el campo de indagación tan general y extenso como la nota de petición de la Dirección General de Prestación Farmaceútica reseñaba, hemos procedido en dos fases.

En una primera se ha indagado sobre aspectos generales relativos a monitores de TP (tiempo de protrombina) portátiles, indagando especialmente sobre aspectos relativos a seguridad, eficacia, exactitud y validez.

En una segunda fase se ha analizado con toda la profundidad posible, los aspectos relativos a la efectividad y coste-efectividad (eficiencia) del uso de monitores de TP (tiempo de protrombina) portátiles para la autoadaministración de pruebas (autotest) del INR y autodosificación de anticoagulantes orales por los propios pacientes.

En este apartado y posteriores, se reseñarán diversos datos considerados como elocuentes y representativos de toda la información contrastada. De la lectura de este cuerpo del informe y sus anexos, se puedan obtener claros elementos de juicio para acometer decisiones basadas en la evidencia científica.

II.I.- DATOS MANEJADOS

1.- Tras la recepción y lectura del informe referido del Carlos III, se procede a realizar búsquedas dirigidas en diversas bases de datos de evaluación de tecnologías y científicas a las que desde este servicio se tiene acceso pleno o parcial: INAHTA, ISTAH, AEETSA, CDR-NHS, COCHRANE LIBRARY, FDA (U.S. Food and Drug Administration) y EMEA (European Agency for the Evaluation of Medicinal Products). En dichos procesos indagatorios, se han empleado métodos de sondeo aproximativos recursivo-selectivos al tema buscado. Así mismo en información anexada se presentan los artículos o resúmenes de las referencias más relevantes y que dan apoyo a las recomendaciones que se plantean en el informe.

2.- Mediante las búsquedas dirigidas empleadas se han localizado una serie de análisis evaluativos efectuados por diversos proveedores de evaluación na-

cionales y extranjeros. La existencia y posibilidad de acceso a revisiones sistemáticas, metaanálisis y diversos ensayos clínicos controlados ha permitido aumentar la base científica en la que se apoyan los elementos de juicio, así como las recomendaciones y sugerencias que se plantean al final del informe.

3.- Tras los procesos de búsqueda dirigida, las referencias halladas de forma inmediata han sufrido un cotejo selectivo previo a su análisis y consideración definitiva. En dicho sentido los criterios ponderados de selección empleados han sido:

1.- Relevancia de la información aportada para la indagación
2.- Robustez del diseño y método científico empleado
3.- Entornos socioeconómicos comparables o análogos al nuestro
4.- Información completa accesible

Las referencias han sido analizadas en su versión íntegra siempre que ha sido posible acceder a ellas, no desdeñándose aquella otra de relevancia pero a la que sólo se ha podido ser acceder en su formato no completo.

4.- En una segunda etapa se han sondeado como registros específicos, (aparte de las bases antes descritas), los repertorios bibliográficos Medline, Synergy y Ovid (con acceso limitado para este último), y la National Guideline Clearinghouse. De ellas se han extraído trabajos científicos de indudable interés para el trabajo. Dichos trabajos han sido analizados según los criterios antes expresados.

Tras la lectura, extracto y análisis de la profusa información final seleccionada –una selección relevante de la cual se presenta en anexo-, se pueden avanzar determinadas conclusiones:

II.- RESUMEN DE LA INFORMACIÓN ANALIZADA

1.- Los tratamientos orales anticoagulantes se están introduciendo cada día más como remedio y coadyuvante en diversas patologías. Algunos autores de nuestro entorno (Europa y USA), cifran que en el 2001 entre el 1 y el 1'5 % de la población sería susceptible de tratamiento o profilaxis oral con anticoagulantes. Este tratamiento iría dirigido a reducir los daños derivados de alteraciones o circunstancias tromboembólicas de carácter crónico (la mayor parte) o temporal de diverso tipo.

2.- Los efectos adversos en este tipo de tratamientos, son más frecuentes en pacientes con tiempos de protrombina (TP) situados durante más tiempo fuera del intervalo terapeútico.

ESTUDIO	GRUPOS	NÚMERO PACIENTES	TIEMPO EN RANGO TP (% DÍAS)	GRANDES HEMORRAGIAS (%/año)	TROMBO-EMBOLISMOS (%/año)
1	A	23	93	0	0
	C	23	75	0	0
2	A	40	-	0	0
3	A	162	56	5'7	9
	D	162	33	12	13
4	B	20	89	0	0
	C	20	68	0	0
5	B	20	77	-	-
	D	20	53	-	-
6	B	90	57 / 53**	2'2	2'2
	D	89	34 / 43**	2'2	4'5
7	B	581	78	1'8	2'4
	D	567	60	2'7	4'6
8	B	75	92	4'5*	0'9
	D	75	59	10'9*	3'6

Abreviaciones:
A: Autotesteo por paciente;
B: autodosificación por paciente;
C: Anticoagulación unidad de coagulación;
D: atención habitual
** Grandes y no grandfes hemorragias
* Tiempo en rango a los 3 y a los 6 meses

1 White RH, McCurdy A, Marensdorff H, et al. Home prothrombin time monitoring after the initiation of warfarin therapy: a randomized, prospective study. Ann Intern Med. 1989;111:730-737.
2 Anderson D, Harrison L, Hirsh L. Evaluation of a portable prothrombin time monitor for home use by patients who require long-term oral anticoagulant therapy. Arch Intern Med. 1993;153:1441-1447.
3 Beyth RJ, Landefeld CS. Prevention of major bleeding in older patients treated with warfarin: results of a randomized trial [abstract]. J Gen Intern Med. 1997;12:66.
4 Ansell J, Patel N, Ostrovsky D, et al. Long-term patient self-management of oral anticoagulation. Arch Intern Med. 1995;155:2185-2189.
5 Hasenkam JM, Kimose HH, Knudsen L, et al. Self-management of oral anticoagulant therapy after heart valve replacement. Eur J Cardiothorac Surg. 1997;11:935-942.
6 Sawicki PT, Working Group for the Study of Patient Self-Management of Oral Anticoagulation. A structured teaching and self-management program for patient receiving oral anticoagulation. A randomized controlled trial JAMA. 1999;281:145-150.
7 Koertke H, Minami K, Breymann T, et al. INR self-management following mechanical heart valve replacement.
8 Horstkotte D, Piper C, Wiemer M, et al. Improvement of prognosis by home prothrombin estimation in patients with life-long anticoagulant therapy [abstract]. Eur Heart J. 1996; 17(suppl):230.

Table I. Indications for oral anticoagulation, target INR and grade of recommendation.

Indication	Target INR	Grade of recommendation
Pulmonary embolus	2·5	A
Proximal deep vein thrombosis	2·5	A
Calf vein thrombus	2·5	A
Recurrence of venous thromboembolism when no longer on warfarin therapy	2·5	A
Recurrence of venous thromboembolism whilst on warfarin therapy	3·5	C
Symptomatic inherited thrombophilia	2·5	C
Antiphospholipid syndrome	3·5	B
Non-rheumatic atrial fibrillation	2·5	A
Atrial fibrillation due to rheumatic heart disease, congenital heart disease, thyrotoxicosis	2·5	C
Cardioversion	2·5	B
Mural thrombus	2·5	B
Cardiomyopathy	2·5	C
Mechanical prosthetic heart valve	3·5	B
Bioprosthetic valve	Not indicated	A (see text)
Ischaemic stroke without atrial fibrillation	Not indicated	A (see text)
Retinal vessel occlusion	Not indicated	C (see text)
Peripheral arterial thrombosis and grafts	Not indicated	A (see text)
Coronary artery thrombosis	Not indicated	A (see text)
Coronary artery graft thrombosis	Not indicated	A (see text)
Coronary angioplasty and stents	Not indicated	A (see text)

 British Journal of Haematology **101**: 374-

3.- Para que la anticoagulación sea efectiva y se minimice el riesgo de efectos adversos (trombo-embolización o fenómenos hemorrágicos), los TP de los pacientes deben estar ajustados al intervalo terapeútico. Para ello se deben ajustar las dosis de anticoagulante en cada paciente de forma que se optimicen las ventajas del tratamiento.

Circunstancias nutricionales, medicamentosas, comórbidas y otras personales y coyunturales (peor cuantificadas en la literatura), precisan ser consideradas para ajustar las dosis. Este ajuste y su reflejo en el INR, debe ser monitorizado de forma periódica, buscando siempre asegurar el mejor intervalo terapeútico en cada situación y la continuidad del TP en el valor o intervalo aconsejado.

4.- Del mismo modo, para intervalos terapeúticos de INR más altos, se observa una mayor incidencia de efectos hemorrágicos adversos.

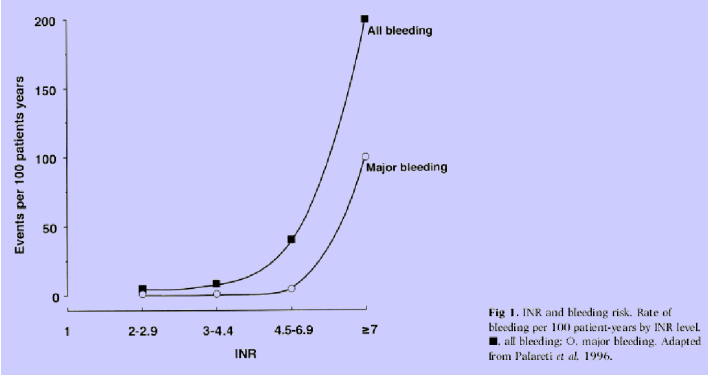


Fig 1. INR and bleeding risk. Rate of bleeding per 100 patient-years by INR level. ■, all bleeding; ○, major bleeding. Adapted from Palareti *et al.* 1996.

5.- La estandarización del TP mediante su indicador corregido (INR), ofrece una forma más eficaz de ajustar efectivamente el TP para cada paciente anticoagulado oralmente. Este indicador, auspiciado por la OMS, ha venido a paliar en gran medida los efectos indeseables de la variabilidad interlaboratorios que se producía anteriormente. El INR es un indicador del propio tiempo de protrombina, pero normalizado internacionalmente. El INR ajusta el PT "bruto del paciente" refiriéndolo a un PT en personas sanas y ajustándolo según la sensibilidad de los reactivos biológicos que se utilizan para cada prueba (ISI).

Table 6. Capillary whole blood (point-of-care) PT instruments.

Instrument	Clot Detection Methodology	Home Use Approval
Protime Monitor 1000 Coumatrak* Ciba Corning 512 Coagulation Monitor* CoaguChek Plus* CoaguChek Pro* CoaguChek Pro/DM*	Clot initiation: Thromboplastin Clot detection: Cessation of blood flow through capillary channel	
CoaguChek Thrombolytic Assessment System	Clot initiation: Thromboplastin Clot detection: Cessation of movement of iron particles	Yes**
ProTIME Monitor Hemochron Jr# GEM PCL#	Clot initiation: Thromboplastin Clot detection: Cessation of blood flow through capillary channel	Yes
Avocet$_{PT}$	Clot initiation: Thromboplastin Clot detection: Thrombin generation detected by fluorescent thrombin probe.	Yes

* All instruments in this category are based on the original Biotrack model (Protime Monitor 1000) and licensed under different names. The latest versions available are the CoaguChek Pro and Pro/DM (as models evolved they acquired added capabilities). Earlier models are no longer available.
** CoaguCheck only
# Hemochron Jr and GEM PCL are simplified versions of the ProTIME Monitor.

Hematology 2000 Jack E. Ansell

Los multiples instrumentos y equipos portátiles existentes en el mercado que pueden realizar estas mediciones del INR, deben ser comparados en cuanto a su exactitud, fiabilidad y estabilidad con el patrón o "gold standard". Éste patrón es siempre una técnica clásica en laboratorio fijo, realizada en condiciones idóneas tanto en cuanto a recogida de muestra, transporte, procesamiento de muestra, normalización de reactivos y controles de calidad internos y externos.

Es necesario indicar ahora, que entre la numerosa variedad de dispositivos medidores de TP o INR, existen varios cuya tipificación comercial incluye el literal "COAGUCHEK". A este respecto reseñaremos tanto el **BÖEHRINGER MANHEIM** COAGUCHEK **PST ®**, como el **ROCHE Diagnostics** COAGUCHEK **S System ®**.

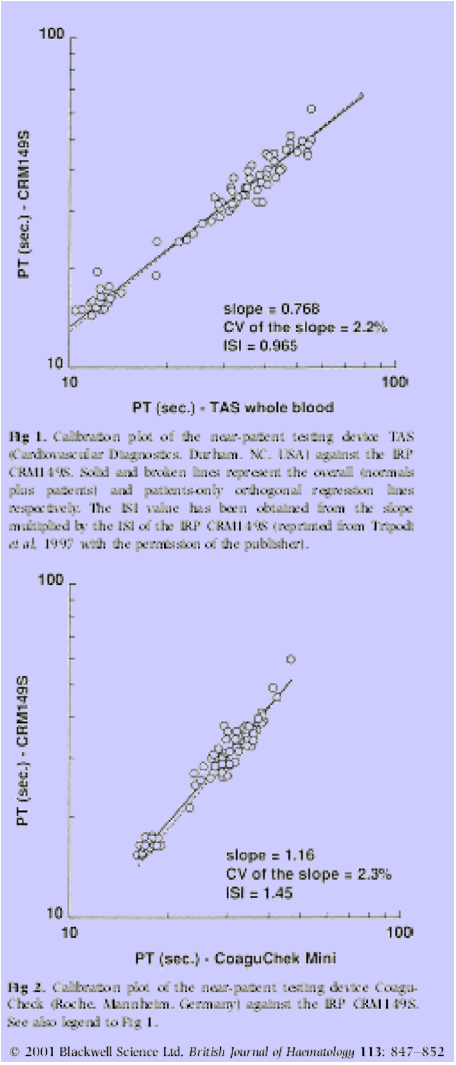


Fig 1. Calibration plot of the near-patient testing device TAS (Cardiovascular Diagnostics, Durham, NC, USA) against the IRP CRM149S. Solid and broken lines represent the overall (normals plus patients) and patients-only orthogonal regression lines respectively. The ISI value has been obtained from the slope multiplied by the ISI of the IRP CRM149S (reprinted from Tripodi et al. 1997 with the permission of the publisher).

Fig 2. Calibration plot of the near-patient testing device CoaguChek (Roche, Mannheim, Germany) against the IRP CRM149S. See also legend to Fig 1.

 British Journal of Haematology 113: 847–852

6.- Diversos estudios realizados con los coagulómetros portátiles existentes, parecen demostrar una relativa exactitud y precisión de dichos dispositivos en la determinación del INR en los valores terapeúticos más habituales. Los estudios realizados en cuanto a su seguridad y eficacia son parejos para todos los existentes en el mercado. No obstante su intervalo de mayor exactitud se sitúa en una escala de INR en torno al 2'5.

Conforme los valores reales (según el "patrón-oro") se alejan del intervalo de INR comentado (2'5), la variabilidad de las medidas en los portátiles aumenta, disminuyendo la precisión.

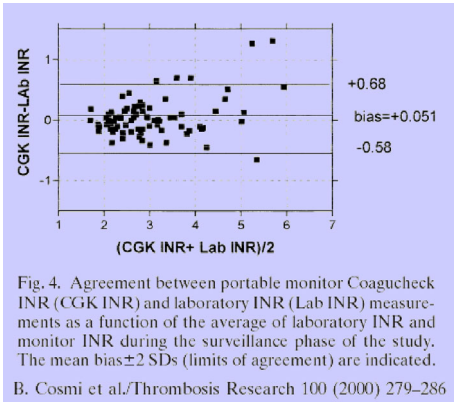


Fig. 4. Agreement between portable monitor Coagucheck INR (CGK INR) and laboratory INR (Lab INR) measurements as a function of the average of laboratory INR and monitor INR during the surveillance phase of the study. The mean bias±2 SDs (limits of agreement) are indicated.

B. Cosmi et al./Thrombosis Research 100 (2000) 279–286

En valores alejados, la exactitud y fiabilidad obtenida no aconsejan su uso.

No obstante dentro del rango habitual en el que suele plantearse el intervalo terapeútico para un importante número de los pacientes con anticoagulación oral, puede considerarse que dichos dispositivos aportan medidas adecuadas. Sin embargo y para ello debe asegurarse que la técnica analítica se realice correctamente y los materiales que para ello se utilizan hayan sido adecuadamente almacenados, transportados y empleados, así como sujetos a las condiciones ambientales prefijadas. En dicho sentido cabe recalcar la im-

portancia de la formación e instrucción del personal (sanitario o no) que realice las extracciones o punciones y el procesamiento de la muestra.

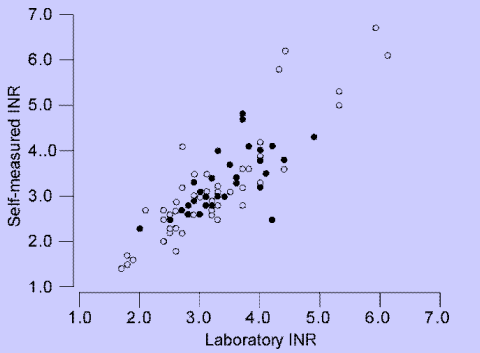


Figure 1: **Correlation between the self-measured INR from whole capillary blood at home and the virtually simultaneously measured laboratory INR from a venous blood sample**
The filled symbols and the open symbols represent measurements from patients taking phenoprocoumon or acenocoumarol, respectively.

In The Lancet. Vol 356.July 8, 2000. Manon E Cromheecke

7.- Existen estudios que demuestran la bondad de las mediciones con los COAGUCHEC® respecto al patrón-oro, para el intervalo de INR antes especificado. Estos estudios (tanto lo financiados por las empresas comercializadoras, como aquellos otros donde no se reseña este factor), avalan la posibilidad de determinar el INR mediante estos instrumentos sobre pacientes bien controlados y calibrando periódicamente procedimientos y equipos. En este sentido existen trabajos que aportan evidencias de la fiabilidad de las mediciones realizadas con estos dispositivos tanto si es realizado por personal sanitario del nivel especializado, por personal sanitario del nivel primario, por personal no sanitario de instituciones sanitarias, por unidades farmaceúticas de vigilancia e incluso por el propio paciente si éste ha sido adecuadamente entrenado, formado y educado.

No obstante para valores alejados del intervalo óptimo, serían aconsejables sistemas de medición más precisos que permitieran adoptar decisiones terapeúticas más ajustadas. Teniendo en cuenta los problemas de sobre o subestimación de INR que con los portátiles pudieran darse, el uso únicamente de los portátiles sólo pudiera reconmendarse para ciertos intervalos terapeúticos (aconsejados terapeúticamente para

From a clinical point of view, decisions about OAT dosing will be affected by small differences in the INR range between 1.5 and 3. In patients in the high therapeutic range (e.g., INR 3–4.5) subsequent OAT dosing based on the portable monitor might result in under-coagulation and an increased risk of thromboembolic events. In the surveillance phase of our study, however, only one patient suffered a thrombotic event (non-fatal acute myocardial infarction). Further studies are required to evaluate the feasibility and safety of home PT testing and OAT self-adjustment. Our results indicate that the portable monitor is accurate for INR values lower than 3.0, especially for values between 2.0 and 3.0. Accuracy of monitor performance is dependent on the expertise of different centers.

The support of Roche Diagnostics is acknowledged. The help of Simone Fariselli in analyzing the data is gratefully acknowledged.

B. Cosmi et al./Thrombosis Research 100 (2000) 279–286

ciertos enfermos y patologías).

Por otro lado es necesario estar atentos a las próximas recomendaciones del grupo europeo, que auspiciado por la UE, está analizando y estudiando este tema y del que se esperan actualizaciones y pautas decisionales sobre la automonitorización domiciliaria.

8.- Los últimos estudios aparecidos, declaran la bondad de la autoregulación de las dosis de anticoaugulantes orales por los propios pacientes, tras la determinación del INR con coagulómetros portátiles. El diseño, la forma de realización de estos estudios, sus resultados y la potencia de éstos, así como aspectos relacionados con la validez externa, **exigirían para una posible extrapolación** lo siguiente:

- **.- Las decisiones de dosificación siempre deben tener la tutoría de los facultativos**
- **.- El seguimiento de los pacientes debe ser extremadamente minucioso y continuado**
- **.- Los pacientes inmersos en dichos procesos, deben ser selectivamente elegidos y previamente entrenados y formados en dichos procedimientos**
- **,- Periódicamente debe ser asegurada la plena calidad y adecuación de los dispositivos de testeo y sus reactivos**

9.- Existen trabajos – generalmente financiados por las empresas comercializadoras - que declaran como elegibles las estrategias de automonitorización y autoregulación de la dosis por parte del paciente, ya que se esgrime que los

Table 2. Annual Anticoagulation Management Costs Per Patient

Management Strategy	Number of Tests per Year: Baseline	Number of Tests per Year: (Range)	Costs to Managed Care Organization	Costs to Patients and Their Caregivers	Total Management Costs
Usual care	14	(9–23)	$157*	$239§	$396
Anticoagulation clinic testing	23	(11–28)	$233†	$520‖	$753
Patient self-testing	52	(29–73)	$660‡	$200¶	$860

*Baseline estimates assume 2 minutes physician (MD) time for 90% of tests valued at $72/h, 13 minutes of nursing (RN) time per test valued at $23.40/h, equipment and supply cost of $4 per test.
†Baseline estimates assume 2 minutes MD time for 10% of tests valued at $72/h, 15 minutes of RN time per test valued at $23.40/h, $4 reagent cartridge per test and $1,385 per capillary monitor per 200 patients served, allocated over 5 years of use.
‡Baseline estimates assume 2 minutes of MD time for 10% of tests valued at $72/h, 8 minutes of RN time per test valued at $23.40/h, $4 reagent cartridge per test, and $1,385 per capillary monitor allocated over 5 y of use.
§Baseline estimates assume 17 minutes of patient (PT) and caregiver (CG) time per test valued at $14.10/h with CG accompanying 30% of PTs, 26 mi per test valued at $0.30/mi (CG assumed to travel with PT) and 52 travel minutes per test valued at $14.10/h (no mileage or travel time for 7 tests assumed to coincide with routine office visits).
‖Baseline estimates assume 20 minutes of PT and CG time per test valued at $14.10/h with CG accompanying 30% of PTs, 26 mi per test valued at $0.30/mi (CG assumed to travel with PT) and 52 travel minutes per test valued at $14.10/h (no mileage or travel time for 7 tests assumed to coincide with routine office visits).
¶Baseline estimates assume 15 minutes of PT and CG time per test valued at $14.10/h with CG assisting 9% of PTs with self-testing.

Elston Lafata et al., Cost-effectiveness of Warfarin Management Strategies JGIM Volume 15, January 2000

resultados obtenidos avalan una mejor relación coste-efectividad y coste-utilidad para dicha alternativa. No obstante en **estos estudios**, a parte de los factores expresados anteriormente en los apartados 7 y 8 y concurrentes también en estos trabajos, se **han empleado imputaciones de costes posiblemente alejados de la realidad española** y AVACs de construcción no contrastada, **así como prevalencias de patologías** causantes de anticoagulación oral **e incidencias de efectos adversos no ajustadas a la información disponible sobre nuestro entorno**.

10.- En cuanto a la repercusión social, una variable de obligada consideración en una evaluación tecnológica de esta especie, algunos de los siguientes factores pueden estar presionando la introducción de estos dispositivos de forma franca en el sistema:

1.- La existencia de procedimientos y dispositivos implantados en el sistema sanitario de aparente similitud para la detección de otros parámetros en sangre en otro tipo de enfermedades (diabetes).

2.- El alto grado de satisfacción del que informan algunos trabajos que recurren a estrategias de automonitorización y autodosificación, en comparación con la práctica de la monitorización ejercida directamente por el médico. Sin embargo no hemos detectado ningún estudio cuyo objetivo principal sea esta medición.

3.- El relativo "bajo coste unitario" de adquisición de cada dispositivo y cada tira (±130.000 pts; tira reactiva ±480 pts).

4.- La reducción aparente de esfuerzo y ahorro de tiempo que los servicios asistenciales pueden percibir que se produciría en caso de delegar en el propio paciente los procedimientos de extracción, analítica, lectura y ajuste de dosis.

En contra de esto existen una serie de elementos contrarios a los anteriores que cabe considerar:

1.- La anticoagulación oral es de más más frecuente instauración en personas mayores. **Las dificultades sensoriales, psicológicas y anímicas** en este grupo no suelen ser equiparables con otros grupos etários (por ejemplo jóvenes y personas activas). Así mismo los períodos de convivencia con la automonitorización y autodosificación suelen ser de por vida en los procesos de comparación, como la diabetes, pudiendo llegar a ser plenamente integrada en los hábitos de vida.

Por otro lado las incorrectas mediciones del INR y de la autodosificación en la autocoagulación oral, sí **pueden desembocar en efectos adversos que debuten sin período ventana o prodrómico previo, directamente en complicaciones de alta gravedad médico-quirúrgica**.

Table 1. Event Rate per 100 Patient Years by Time Spent Below, In, and Above Therapeutic Range

	Below		In		Above	
Events	Baseline	(Range)	Baseline	(Range)	Baseline	(Range)
Thromboembolic first events						
Fatal	0.05	(0–0.30)	0.01	(0–0.05)	0.00	(0–0.05)
Life-threatening	1.58	(1.0–6.0)	0.47	(0–1.0)	0.11	(0–1.0)
Serious	14.68	(8.0–16.0)	2.52	(1.0–6.0)	2.29	(1.0–6.0)
Thromboembolic subsequent events						
Fatal	0.01	(0–0.3)	0.00	(0–0.05)	0.01	(0–0.05)
Life-threatening	0.32	(0–5.0)	0.04	(0–1.0)	0.44	(0–1.0)
Serious	2.45	(0–6.0)	0.88	(0–6.0)	1.60	(1.0–6.0)
Hemorrhagic first events						
Fatal	0.05	(0–0.3)	0.04	(0–0.3)	0.20	(0–0.6)
Life-threatening	0.61	(0–1.0)	0.49	(0–1.0)	2.66	(0.5–4.0)
Serious	5.87	(3.0–8.0)	5.12	(3.0–8.0)	12.83	(10.0–20.0)
Hemorrhagic subsequent events						
Fatal	0.02	(0–0.3)	0.02	(0–0.3)	0.07	(0–0.6)
Life-threatening	0.30	(0–1.0)	0.25	(0–1.0)	0.96	(0.5–4.0)
Serious	1.30	(0–8.0)	1.85	(0–8.0)	5.73	(3.0–20.0)

Presented at the Society of General Internal Medicine 21st annual meeting, Chicago, Il, April 23–25, 1998; Building Bridges IV: Improving the Public's Health Through Research Partnerships, Oakland, Calif, May 7–9, 1998; Association for Health Services Research, Washington, DC, June 21–23, 1998; European Cardiology Conference, Vienna, Austria, August 24–28, 1998; and Anticoagulation Forum's 5th annual conference, Vancouver, BC, May 13–15, 1999.

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2.- Diversos trabajos mencionan la ansiedad e inseguridad que ciertos pacientes perciben ante la automonitorización y la autodosificación.

3.- La experiencia acumulada permite observar en los estudios existentes que **para las pautas de automonitorización se duplica o triplica el uso del dispositivo y del número de tiras reactivas**. Esto se refleja en estudios muy controlados y con protocolos ajustados de vigilancia. No resulta aventurado por tanto prever que la efectiva implantación real de esta alternativa pudiera **desencadenar un uso de mate-**

riales reactivos todavía mucho más elevado que el planteado en los estudios; máxime si esta tendencia es alentada.

4.- Los diversos estudios de costes analizados avalan que los costes imputables a la organización de la red asistencial son mucho más elevados en el caso de estrategias de automonitorización. Así mismo los costes organizacionales y de personal para vigilar adecuadamente dichas estrategias pueden absorver los ahorros que a priori pudieran plantearse y que se emplena como argumento a favor de su implantación.

IV.- RECOMENDACIONES Y SUGERENCIAS

A la luz de los datos analizados, se plantean una serie de ejes para la actuación de diversos servicios competentes para cada una de las materias a abordar:

1.- De la información analizada, parece desprenderse que los dispositivos portátiles (entre ellos los denominados COAGUCHEK®) para la monitorización del INR en pacientes sometidos a anticoagulación oral, **cumplen su finalidad especialmente para los intervalos terapeúticos al uso**.

2.- La determinación del INR mediante las técnicas de laboratorio fijo tradicionales sigue considerándose como el patrón de referencia idóneo.

3.- Se precisan más estudios - y de mayor precisión y validez externa - para poder dotarse de evidencias definitivas en cuanto a la efectividad real de la automonitorización del INR mediante este tipo de dispositivos y la autodosificación por parte de los propios pacientes. Se requiere también mejor información sobre la seguridad de estas prácticas en diferentes tipos de pacientes y adecuada a nuestro medio.

4.- Para la actuación rutinaria y domiciliaria de los servicios asistenciales, **pudiera estar aconsejada la utilización de este tipo de dispositivos para cierto tipo de pacientes** sometidos a anticoagulación oral con intervalos terapeúticos de adecuada medida con estos dispositivos.

5.- **En caso de implantarse** estrategias de utilización de estos dispositivos, las labores de atención, los niveles asistenciales de decisión, modulación y monitorización, así como las pautas de actuación y responsabilidades a ejercer por cada uno, debiera ser integrado en **una guía de actuación a ejercer con los pacientes sometidos a anticoagulación oral**.

En dicho sentido parece de utilidad la tercera edición de la guía de anticoagulación oral de la Haemostasis and Thrombosis Task Force, así como la guía de 16 de noviembre del año 2000, editada por la Agence Française de Sécurité Sanitaire.

Table III. Responsibilities of lead clinician for anticoagulant service.

1. Receive referrals and approve need for anticoagulation
2. Give advice on duration and intensity of anticoagulation
3. Ensure system is in place for patients to receive urgent medical advice relating to anticoagulation
4. Ensure participation in national laboratory quality assurance scheme and monitor performance
5. Ensure regular clinical audit
6. Ensure anticoagulant guidelines are available, including the management of over-anticoagulation
7. Provide general practitioners involved in anticoagulant care with advice and guidelines
8. Approve computer assisted management programmes prior to implementation
9. Ensure adequate training is available for all personnel
10. Provide written approval for personnel, detailing levels of responsibility

Table IV. Recommendations for non-medical personnel involved in anticoagulant service.

1. Personnel should be responsible to the lead clinician organizing the anticoagulant service
2. Personnel should have received adequate training and should be approved prior to commencement of duties
3. Dose recommendations and recall should be made according to written protocols or computer assisted guidelines
4. Recommendations should be available for review by the clinician
5. The clinician should be alerted to patients with an INR > 8 and those with bleeding problems
6. Personnel should provide patient education regarding anticoagulant therapy

British Journal of Haematology 1998, 101, 374–387

Guideline

GUIDELINES ON ORAL ANTICOAGULATION: THIRD EDITION

*Prepared by the Haemostasis and Thrombosis Task Force for the British Committee for Standards in Haematology. Members of the working party: T. P. Baglin and P. E. Rose. Members of the Haemostasis and Thrombosis Task Force: I. D. Walker (Chair), S. Maehin (Secretary), T. P. Baglin, T. W. Barrowcliffe, B. T. Colvin, M. Greaves, C. A. Ludlam, I. J. Mackie, F. E. Preston and P. E. Rose.

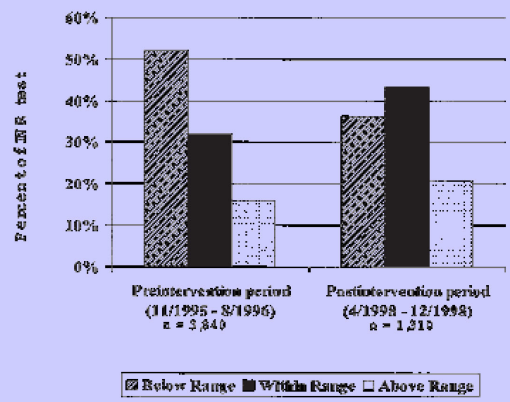

Figure 4 Distribution of the INR values before and after implementation of an improvement programme for anticoagulation therapy in the community.

intervention All steps of INR testing from blood sampling through dosing instructions to patients were modified as follows:

(i) Information forms for patients and physicians were distributed.
(ii) Guidelines for blood sampling and treatment were issued to physicians, nurses and patients.
(iii) A patient education programme was developed: physicians gave their patients a detailed description regarding the purpose and importance of the anticoagulation therapy, the correct method of taking the drugs, potential side effects, how to prevent and identify them and the effects of drugs and other foods on anticoagulation control.
(iv) The technique of collecting samples and their transport from the collection station to the central laboratory was improved. These changes included implementation of proper procedures including collection of samples with a correct blood/citrate ratio, use of tubes not past expiry date and transport of samples at the proper temperature.

International Journal for Quality in Health Care 2001; Volume 13, Number 3: pp. 209–213
TIWA YERMIAHU[1], JONATHAN E. ARBELLE[2], DARIA SHMARTZ[1], YARON LEVY[1], NOAM TRACTINSKY[3] AND AM PORATH[1]

[1]Hematology Laboratory and Institute and [2]Department of Internal Medicine, Soroka Medical Center, and [3]Department of Industrial Engineering and Management, Ben Gurion University of the Negev, Beer Sheva, Israel

6.- Los mejores resultados en términos de efectividad no cabe esperarlos por tanto de la aparición aislada de un nuevo dispositivo de medición.

Es más bien de la articulación de programas que aúnen estrategias dirigidas a la comunidad, personal sanitario y educación e información de los pacientes de donde se desprenden los mejores logros.

En dicho sentido cabe recalcar que mediante el seguimiento estricto de guías adecuadas de manejo, terapia y monitorización, el uso de protocolos computerizados de manejo individual del paciente, la puesta en marcha de mecanismos de comprobación de seguimiento terapeútico, así como calibraciones y testeos de los instrumentos analíticos utilizados para el seguimiento de este tipo de pacientes, es de donde se obtienen los mejores y más efectivos resultados.

7.- De cara a obtener mejoras, la puesta en marcha de estrategias basadas meramente en la automonitorización por parte del paciente, puden suponer un **enorme impacto económico, organizativo y estructural**. Por tanto, sólo deberían ser adoptadas tras efectuar un adecuado estudio pormenorizado en prospección de sus efectos. Aun así, la propia utilidad clínica del procedimiento es previsble que favorezca su extensión hacia pacientes y condiciones en los que su valoración marginal sea muy inferior a sus costes. En tal

sentido **convendría valorar reforzar las guías de práctica con mecanismos de autorización y monitorización de su empleo**.

Valencia 23 de octubre del año 2001

Servicio de Evaluación de Tecnologías

ANEXOS

RECOPILACIÓN DE ARTÍCULOS PRIMARIOS RECOPILADOS DE BASES DE DATOS MANEJADAS (indizados resumidamente según fecha de publicación)

UI - 21080236
PMID- 11211618
DA - 20010209
DCOM- 20010222
IS - 0002-9173
VI - 115
IP - 2
DP - 2001 Feb
TI - Prothrombin measurement using a patient self-testing system. Oral Anticoagulation Monitoring Study Group.
PG - 280-7
AB - We enrolled 82 patients receiving oral anticoagulation in a pilot trial of a point-of-care (POC) prothrombin time (PT) device in a patient self-testing (PST) application in 7 US and Canadian hospital-based anticoagulation centers. The properly selected and suitably trained patients were given the PT device to test at home for 6 weeks. Patients returned within 3 hours of the self-test to the hospital clinic where a repeated test was performed by a health care professional using the patient's POC device (clinic). Blood specimens were obtained for routine laboratory PT determinations by the local hospital laboratory (hospital) and a reference laboratory. International Normalized Ratio agreement between the home test and the clinic test was excellent. Home results correlated well with reference laboratory results. Using the reference laboratory as a standard, 68% of hospital and 66% of home results matched
the patient's therapeutic range classification of the reference laboratory result. Participants overwhelmingly reported satisfaction and willingness to perform the self-test. Our results confirm the equivalence of the PST PT and a reference laboratory result and suggest that PST PT technology is an appropriate and useful adjunct to routine oral anticoagulation monitoring methods.
CN - Oral Anticoagulation Monitoring Study Group.
LA - eng
PT - Clinical Trial
PT - Journal Article
CY - United States
TA - Am J Clin Pathol
JC - 3FK
JID - 0370470
RN - 0 (Anticoagulants)
RN - 0 (Reagent Kits, Diagnostic)
SB - AIM
SB - IM
MH - Adolescence
MH - Adult
MH - Aged
MH - Aged, 80 and over
MH - Anticoagulants/therapeutic use
MH - Female
MH - Human
MH - Male
MH - Middle Age
MH - Outpatient Clinics, Hospital
MH - Pilot Projects
MH - *Point-of-Care Systems
MH - *Prothrombin Time
MH - Questionnaires
MH - *Reagent Kits, Diagnostic
MH - Reproducibility of Results
MH - Self Care/*instrumentation
MH - Support, Non-U.S. Gov't
EDAT- 2001/02/24 12:00
MHDA- 2001/03/03 10:01
PST - ppublish
SO - Am J Clin Pathol 2001 Feb;115(2):280-7.

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UI - 21080237
PMID- 11211619
DA - 20010209
DCOM- 20010222
IS - 0002-9173
VI - 115
IP - 2
DP - 2001 Feb
TI - Point-of-care prothrombin time measurement for professional and patient self-testing use. A multicenter clinical experience. Oral Anticoagulation Monitoring Study Group.
PG - 288-96
AB - We enrolled 386 subjects in a multicenter study of a point-of-care (POC) prothrombin time (PT) testing device. POC tests were performed by health care professionals using venous and finger-stick specimens and by patients using finger-stick specimens. Venous blood also was analyzed in the local hospital laboratory and a national reference laboratory. Accurate POC results were obtained by professionals using both types of specimens. Patients' results were equivalent to those of professionals. The identification of the patient's therapeutic status based on the International Normalized Ratio (INR) was equivalent for POC and local hospital laboratory PT results; 75% of local laboratory results and 77% of POC results were within 0.4 INR of reference laboratory results, while 93% of either system (POC or local laboratory) were within 0.7 INR. Patients overwhelmingly reported satisfaction with the self-test, including the finger stick and device operation. The INR from the POC device is clinically equivalent to the laboratory INR for assessment of anticoagulation status and management decisions in professional and self-testing environments. Patients can learn to perform accurate PT testing, and POC PT testing is feasible in patients' homes.
CN - Oral Anticoagulation Monitoring Study Group.
LA - eng
PT - Clinical Trial
PT - Journal Article
PT - Multicenter Study

CY - United States
TA - Am J Clin Pathol
JC - 3FK
JID - 0370470
RN - 0 (Anticoagulants)
RN - 0 (Reagent Kits, Diagnostic)
SB - AIM
SB - IM
MH - Adolescence
MH - Adult
MH - Aged
MH - Aged, 80 and over
MH - Anticoagulants/therapeutic use
MH - Child
MH - Child, Preschool
MH - Comparative Study
MH - Female
MH - *Health Personnel
MH - Human
MH - Infant
MH - Laboratories, Hospital
MH - Male
MH - Middle Age
MH - *Point-of-Care Systems
MH - *Prothrombin Time
MH - *Reagent Kits, Diagnostic
MH - Reference Values
MH - Reproducibility of Results
MH - Self Care/*instrumentation
MH - Support, Non-U.S. Gov't
EDAT- 2001/02/24 12:00
MHDA- 2001/03/03 10:01
PST - ppublish
SO - Am J Clin Pathol 2001 Feb;115(2):288-96.

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UI - 21301466
PMID- 11408745
DA - 20010615
DCOM- 20010906
IS - 0301-0147
VI - 31
IP - 1
DP - 2001 Jan-Feb
TI - Comparative study of a portable prothrombin time monitor employing three different systems in oral anticoagulant units.
PG - 18-25
AB - The aim of this study was to evaluate the accuracy of the portable coagulometer CoaguChek (Roche Diagnostics) as a prothrombin time (PT) monitor, and to correlate capillary blood results with those of three different routine methods used for monitoring oral anticoagulant therapy (OAT): capillary, plasma and whole blood samples. Three hospitals participated in the study with a total of 235 patients on OAT. The international normalized ratio (INR) results obtained with CoaguChek were compared with those obtained using each of the routine methods. The study presents a good correlation between the PT monitor and the three methods studied: r = 0.9745 (hospital A), r = 0.9283 (hospital B), r = 0.9136 (hospital C). A simplified concordance test of the methods results in a nine-field comparison table showing concordances of 87.2, 85.7 and 68.4%, respectively. The absolute difference (mean +/- SD) between laboratory A and CoaguChek INRs was 0.0571 +/- 0.2042, with values of 0.04286 +/- 0.3906 for laboratory B and 0.6986 +/- 0.6170 for laboratory C. These results confirm that CoaguChek could be used as a new method for oral anticoagulant monitoring, and is in best agreement with the capillary blood PT system. Copyright 2001 S. Karger AG, Basel
AD - FIDEC Fundacion para la Investigacion y Docencia de las Enfermedades Cardiovasculares, Facultad de Medicina y Odontologia, Universidad del Pais Vasco/Euskal Herriko Unibertsitatea, Hospital de Basurto, Bilbao, Spain. bdbvarim@lg.ehu.es
AU - Vacas M
AU - Fernandez MA
AU - Martinez-Brotons F
AU - Lafuente PJ
AU - Ripoll F
AU - Alvarez C
AU - Iriarte JA
LA - eng
PT - Evaluation Studies
PT - Journal Article
PT - Multicenter Study
CY - Switzerland
TA - Haemostasis
JC - FYG
JID - 0371574
SB - IM
MH - Comparative Study
MH - Human
MH - International Normalized Ratio
MH - Monitoring, Ambulatory/*instrumentation/*standards
MH - *Prothrombin Time
MH - Regression Analysis
MH - Reproducibility of Results
EDAT- 2001/06/16 10:00
MHDA- 2001/09/08 10:01
AID - hae31018 [pii]
URLF- http://www.online.karger.com/library/karger/renderer/dataset.exe?jcode=HAE&action=render&rendertype=fulltext&uid=HAE.hae31018
URLS- http://www.karger.com/journals/hae/hae_jh.htm
PST - ppublish
SO - Haemostasis 2001 Jan-Feb;31(1):18-25.

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UI - 21033721
PMID- 11189796
DA - 20010117
DCOM- 20010201
IS - 0148-9917
VI - 24
IP - 1
DP - 2001 Jan
TI - Predicting patient intent to return from satisfaction scores.

PG - 44-50
AB - This study describes the development of a patient satisfaction assessment instrument used at the Medical University of South Carolina Outpatient Services clinics. Three years of responses were analyzed and a logistic regression model is presented to identify components of care that predict patient intent to return for additional care. Waiting time and understanding doctor's explanation were the only items that were significant predictors of intent to return. Additionally, the calculated probability of a return visit was used to calculate the potential impact of changes in mean satisfaction scores on the number of patient visits to the hospital ambulatory clinics.
AD - Center for Health Care Research, Medical University of South Carolina, Charleston, South Carolina, USA.
AU - Zoller JS
AU - Lackland DT
AU - Silverstein MD
LA - eng
PT - Journal Article
CY - United States
TA - J Ambulatory Care Manage
JC - H49
JID - 7802876
SB - H
MH - Health Care Surveys
MH - Hospitals, University/utilization
MH - Human
MH - Logistic Models
MH - Motivation
MH - Outpatient Clinics, Hospital/*standards/utilization
MH - Patient Acceptance of Health Care/*psychology
MH - Patient Satisfaction/*statistics & numerical data
MH - Quality Indicators, Health Care
MH - Questionnaires
MH - South Carolina
MH - Support, Non-U.S. Gov't
EDAT- 2001/02/24 12:00
MHDA- 2001/02/28 10:01
PST - ppublish
SO - J Ambulatory Care Manage 2001 Jan;24(1):44-50.

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UI - 20567113
PMID- 11115236
DA - 20001218
DCOM- 20010104
IS - 0003-9942
VI - 57
IP - 12
DP - 2000 Dec
TI - Safety of discontinuation of anticoagulation in patients with intracranial hemorrhage at high thromboembolic risk.
PG - 1710-3
AB - BACKGROUND: Limited data are available to guide the management of anticoagulation in patients with intracranial hemorrhage (ICH) at high thromboembolic risk. OBJECTIVE: To review the management of anticoagulation in patients with ICH at high thromboembolic risk. PATIENTS AND METHODS: We reviewed the management of anticoagulation in 141 patients
who have a high risk of ischemic stroke and have ICH while taking warfarin. The 30-day risk of ischemic stroke while not taking anticoagulation treatment was determined using Kaplan-Meier survival estimates. RESULTS: The indications for anticoagulation were a prosthetic heart valve (52 patients [group 1]), atrial fibrillation and cardioembolic stroke (53 patients [group 2]), and a recurrent transient ischemic attack or an ischemic stroke (36 patients [group 3]). A prior ischemic stroke occurred in 14 (27%) of group 1 patients and in 23 (43%) of group 2 patients. Death occurred in 43% of the 141 patients. The median time not taking warfarin in this cohort was 10 days. Three patients had an ischemic stroke within 30 days of warfarin therapy discontinuation. Using Kaplan-Meier survival estimates, the probability of having an ischemic stroke at 30 days following warfarin therapy cessation in groups 1, 2, and 3 was 2.9% (95% confidence interval, 0%-8.0%), 2.6% (95% confidence interval, 0%-7.6%), and 4.8% (95% confidence interval, 0%-13.6%), respectively. In the 35 patients who had warfarin therapy restarted, none had recurrence of ICH during the same hospitalization. CONCLUSIONS: Discontinuation of warfarin therapy for 1 to 2 weeks has a comparatively low probability of embolic events in patients at high embolic risk. This should be taken into consideration when deciding whether to continue or discontinue anticoagulation in these patients at high embolic risk. Early recurrence of ICH is exceedingly uncommon.
AD - Department of Neurology, Mayo Clinic, W8B, 200 SW First St, Rochester, MN
55905, USA.
AU - Phan TG
AU - Koh M
AU - Wijdicks EF
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - Arch Neurol
JC - 80K
JID - 0372436
RN - 0 (Anticoagulants)
SB - AIM
SB - IM
CIN - Arch Neurol. 2000 Dec;57(12):1682-4
MH - Adult
MH - Aged
MH - Aged, 80 and over
MH - Anticoagulants/*administration & dosage/adverse effects/therapeutic use
MH - Female
MH - Human
MH - Intracranial Hemorrhages/*drug therapy
MH - Male
MH - Middle Age
MH - Recurrence
MH - Retrospective Studies
MH - Risk Factors
MH - Support, Non-U.S. Gov't
MH - Thromboembolism/complications/*prevention & control
MH - Treatment Outcome
EDAT- 2000/12/15 11:00
MHDA- 2001/02/28 10:01
AID - noc00071 [pii]
PST - ppublish

SO - Arch Neurol 2000 Dec;57(12):1710-3.

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UI - 20567326
PMID- 11114792
DA - 20001214
DCOM- 20010104
IS - 1051-5313
VI - 11
IP - 4
DP - 2000 Dec
TI - Home anticoagulation monitoring is safe and effective.
PG - 4-5
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - Harv Heart Lett
JC - C2Z
JID - 9425723
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - K
MH - Anticoagulants/*therapeutic use
MH - Human
MH - *International Normalized Ratio
MH - *Self Care
MH - Warfarin/*therapeutic use
EDAT- 2000/12/15 11:00
MHDA- 2001/02/28 10:01
AID - H1200b [pii]
URLF- http://www.health.harvard.edu/medline/Heart/H1200b.html
PST - ppublish
SO - Harv Heart Lett 2000 Dec;11(4):4-5.

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UI - 20569296
PMID- 11119184
DA - 20010207
DCOM- 20010208
IS - 0884-8734
VI - 15
IP - 12
DP - 2000 Dec
TI - Use of an orientation clinic to reduce failed new patient appointments in primary care.
PG - 878-80
AB - Patients who fail to attend initial appointments reduce clinic efficiency. To maximize attendance by newly referred outpatients, we introduced a mandatory group orientation clinic for all new patients and determined its effects on no-show rates. Orientation clinic also provided health care screening and opportunities for patient feedback. The new patient no-show rate for initial provider visits decreased significantly from 45% before institution of orientation clinic to 18% afterwards (P<.0001). The total no-show (patients who failed to attend orientation clinic or an initial provider visit) rate of the postintervention group was 51% (P = .28, compared with before the intervention). This intervention improved the efficiency and minimized the wasted time of our clinicians.
AD - General Internal Medicine Section, San Francisco Veterans Affairs Medical Center, Department of Medicine, University of California, San Francisco, 94121, USA.
AU - Jain S
AU - Chou CL
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - J Gen Intern Med
JC - JGI
JID - 8605834
SB - IM
MH - *Appointments and Schedules
MH - Comparative Study
MH - Female
MH - Hospitals, Veterans
MH - Human
MH - Intervention Studies
MH - Male
MH - Middle Age
MH - Outcome Assessment (Health Care)/methods
MH - Outpatient Clinics, Hospital/*organization & administration
MH - Patient Compliance/psychology/*statistics & numerical data
MH - Patient Dropouts/statistics & numerical data
MH - Patient Education/*methods
MH - Primary Health Care/methods/*organization & administration
MH - San Francisco
EDAT- 2000/12/19 11:00
MHDA- 2001/03/03 10:01
AID - jgi00201 [pii]
PST - ppublish
SO - J Gen Intern Med 2000 Dec;15(12):878-80.

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UI - 21003999
PMID- 11117921
DA - 20001214
DCOM- 20001222
IS - 0140-6736
VI - 356
IP - 9244
DP - 2000 Nov 25
TI - Health-seeking behaviour of individuals with a cough of more than 3 weeks.
PG - 1823-4
AB - Sex inequalities can lead to poorer access to health care and delays to diagnosis of tuberculosis in women. In a population-based survey we assessed health-seeking behaviour in adults with long-term cough. The prevalence of cough was 1% (213) and 2% (279) in men and women, respectively. Women took more health-care actions than men, but chose less qualified providers and reported lower health expenditure per visit. Delay before seeking hospital treatment was longer for women (41 days) than men (19 days; p=0.04), and more men (27; 36%) than women (14; 14%; p=0.0006) reported giving a sputum sample at hospital. Sex-sensitive strategies for tuberculosis control are needed and should take into account sex

differences in health-care seeking behaviour as well as a possible sex bias among health-care providers.
AU - Thorson A
AU - Hoa NP
AU - Long NH
LA - eng
PT - Letter
CY - England
TA - Lancet
JC - LOS
JID - 2985213R
SB - AIM
SB - IM
MH - Adolescence
MH - Adult
MH - Aged
MH - Aged, 80 and over
MH - Cough/*therapy
MH - Female
MH - Human
MH - Male
MH - Middle Age
MH - *Patient Acceptance of Health Care
MH - Support, Non-U.S. Gov't
MH - Time Factors
MH - Vietnam
EDAT- 2000/12/16 11:00
MHDA- 2001/02/28 10:01
PST - ppublish
SO - Lancet 2000 Nov 25;356(9244):1823-4.

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UI - 21032752
PMID- 11194746
DA - 20010117
DCOM- 20010201
IS - 0025-729X
VI - 173
IP - 10
DP - 2000 Nov 20
TI - Managed care.
PG - 557-8
AU - Majoor JW
AU - Loff B
AU - Sundararajan V
AU - Ibrahim JE
LA - eng
PT - Letter
CY - Australia
TA - Med J Aust
JC - M26
JID - 0400714
SB - IM
MH - Australia
MH - *Health Care Reform
MH - Human
MH - *Managed Care Programs
MH - *Outcome Assessment (Health Care)
EDAT- 2001/02/24 12:00
MHDA- 2001/02/28 10:01
PST - ppublish
SO - Med J Aust 2000 Nov 20;173(10):557-8.

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UI - 20534727
PMID- 11082095
DA - 20001211
DCOM- 20010104
IS - 0959-8138
VI - 321
IP - 7271
DP - 2000 Nov 18
TI - The courts' role in decisions about medical treatment.
PG - 1282-4
AD - Official Solicitor's Office, London WC2A 1DD, UK. oatesl@offsol.fsnet.co.uk
AU - Oates L
LA - eng
PT - Journal Article
CY - ENGLAND
TA - BMJ
JC - BMJ
JID - 8900488
SB - AIM
SB - IM
MH - Adolescence
MH - Adult
MH - Child
MH - *Decision Making
MH - Human
MH - Informed Consent/legislation & jurisprudence
MH - Mental Competency/*legislation & jurisprudence
MH - Patient Acceptance of Health Care
MH - Treatment Refusal
EDAT- 2000/11/18 11:00
MHDA- 2001/02/28 10:01
URLF- http://bmj.com/cgi/content/full/321/7271/1282
PST - ppublish
SO - BMJ 2000 Nov 18;321(7271):1282-4.

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UI - 20566290
PMID- 11113271
DA - 20001218
DCOM- 20010301
IS - 0049-3848
VI - 100
IP - 4
DP - 2000 Nov 15
TI - Accuracy of a portable prothrombin time monitor (Coagucheck) in patients on chronic oral anticoagulant therapy: a prospective multicenter study.
PG - 279-86

AB - A portable prothrombin time (PT) monitor allows patients on oral anticoagulant therapy (OAT) to measure their PT at home. The purpose of the study was to evaluate the accuracy and precision of a portable PT monitor (Coagucheck, Roche Diagnostics, Mannheim, Germany) as compared with laboratory methods. The prospective study was conducted in four centers of the Italian Federation of Anticoagulation Clinics. A one-month instruction phase was followed by a six-month surveillance phase. Seventy-eight subjects on stable OAT (48 men, 30 women, age range: 18-75)
were selected on a volunteer basis. Dual measurements of INR values were performed in each subject both from finger capillary blood by the monitor and from venous blood by the Anticoagulation Clinic laboratory in three instruction sessions. The mean difference (bias) of the monitor INR results when compared with the average of laboratory INR and monitor INR results was -0.025 (limits of agreement-LA: -0.84/+0.81 INR units). The mean bias was -0.0675 (LA: -0.37/+0.23), +0.018 (LA: -0.39/+0.35), and
+0.039 (LA: -0.49/+0.55), respectively, for INR values lower than 2.0, between 2.0 and 3.0, and greater than 3.0. The overall precision coefficient of monitor INR was 0.370, while it was 0.23, 0.46, 0.29, and 0.21, respectively, in Centers 1, 2, 3, and 4. The overall variation coefficient was 6.5% while it was 3.7%, 8.5%, 4.7%, and 4.9%, respectively, in Centers 1, 2, 3, and 4. Coagucheck has an acceptable level of accuracy for INR values in the range between 2.0 and 3.0. A wide variation in monitor performance was found among centers.
AD - Divisione di Angiologia, Ospedale S.Orsola Malpighi, Bologna, Italy. bcosmi@med.unibo.it
AU - Cosmi B
AU - Palareti G
AU - Moia M
AU - Carpenedo M
AU - Pengo V
AU - Biasiolo A
AU - Rampazzo P
AU - Morstabilini G
AU - Testa S
LA - eng
PT - Evaluation Studies
PT - Journal Article
PT - Multicenter Study
CY - UNITED STATES
TA - Thromb Res
JC - VRN
JID - 0326377
RN - 0 (Anticoagulants)
SB - IM
MH - Administration, Oral
MH - Adolescence
MH - Adult
MH - Aged
MH - Anticoagulants/*administration & dosage
MH - Chi-Square Distribution
MH - Chronic Disease
MH - Comparative Study
MH - Female
MH - Human
MH - International Normalized Ratio
MH - Male
MH - Middle Age
MH - Monitoring, Ambulatory/*instrumentation/standards
MH - Prospective Studies
MH - *Prothrombin Time
MH - Reproducibility of Results
MH - Support, Non-U.S. Gov't
EDAT- 2000/12/13 11:00
MHDA- 2001/03/07 10:01
AID - S0049384800003236 [pii]
PST - ppublish
SO - Thromb Res 2000 Nov 15;100(4):279-86.

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UI - 20521621
PMID- 11067825
DA - 20001115
DCOM- 20001121
IS - 0009-9147
VI - 46
IP - 11
DP - 2000 Nov
TI - Measurement of prothrombin time in EDTA plasma with combined thromboplastin reagent.
PG - 1844-6
AD - Valkeakoski District Hospital Laboratory, 37600 Valkeakoski, Finland. juha.horsti@tays.fi
AU - Horsti J
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - Clin Chem
JC - DBZ
JID - 9421549
RN - 0 (Anticoagulants)
RN - 0 (Citrates)
RN - 0 (Indicators and Reagents)
RN - 60-00-4 (Edetic Acid)
RN - 9035-58-9 (Thromboplastin)
SB - IM
MH - *Anticoagulants
MH - Citrates
MH - Comparative Study
MH - *Edetic Acid
MH - Human
MH - Indicators and Reagents
MH - International Normalized Ratio
MH - *Prothrombin Time
MH - *Thromboplastin
EDAT- 2000/11/09 11:00
MHDA- 2001/02/28 10:01
URLF- http://www.clinchem.org/cgi/content/full/46/11/1844
PST - ppublish
SO - Clin Chem 2000 Nov;46(11):1844-6.

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UI - 21033408

PMID- 11186249
DA - 20010117
DCOM- 20010208
IS - 0022-3573
VI - 52
IP - 11
DP - 2000 Nov
TI - Therapeutic monitoring of warfarin: the appropriate response marker.
PG - 1405-10
AB - Warfarin is a 4-hydroxycoumarin anticoagulant drug used for the prevention
and management of thromboembolic and vascular diseases. It acts through the inhibition of the vitamin K-dependent transcarboxylation reactions that convert precursors of clotting factors into their active form. Appropriate use of warfarin requires patient monitoring and dosage adjustments, to ensure its safety and efficacy. The aim of this work was to clarify the relationship between traditional (prothrombin time, usually expressed as the international normalized ratio; INR) and alternative (clotting factors II and X) warfarin response markers to establish their usefulness for therapeutic drug monitoring. Seventy adult outpatients, aged between 31 and 86 years old, were involved in the study. All subjects received warfarin in a monotherapy regimen and had been on a stable dosing
schedule for at least two weeks to assure a steady-state condition. A total of 81 prothrombin times (expressed as INR), and factor II and factor X activity were simultaneously determined. Eleven patients presented repeated measurements at different time periods under the same dosing regimen. The results obtained from regression and cluster analysis showed a close relationship between factors II and X ($r = 0.73$), a weak correlation between INR and both factor II ($r = -0.35$) and factor X ($r = -0.36$), and a very slight dependency between warfarin and the response markers used. In addition, it seems that independent of the selected response marker, in long-term warfarin therapy, reproducible responses can be obtained over time if a steady-state condition is achieved. The coefficients of variation for factors II and X were greater (35.44 and 37.93%, respectively) than INR (14.50%), indicating that INR is a more precise measure than either factor II or factor X. In conclusion, INR appears to be the most appropriate warfarin response marker for therapeutic drug monitoring due to its universality, objectivity as a direct physiological effect measurement, and the available information regarding appropriate endpoints. However, when INR values are not in accordance with patient response therapy, factor II and factor X should be considered as an alternative to optimize warfarin therapy.
AD - Faculty of Pharmacy, University of Coimbra, Portugal.
AU - Costa IM
AU - Soares PJ
AU - Afonso M
AU - Ratado P
AU - Lanaot JM
AU - Falcao AC
LA - eng
PT - Evaluation Studies
PT - Journal Article
CY - England
TA - J Pharm Pharmacol
JC - JNR
JID - 0376363
RN - 0 (Anticoagulants)
RN - 0 (Biological Markers)
RN - 81-81-2 (Warfarin)
RN - 9001-26-7 (Prothrombin)
RN - 9001-29-0 (Factor X)
SB - IM
MH - Adult
MH - Aged
MH - Aged, 80 and over
MH - Anticoagulants/*pharmacology/therapeutic use
MH - Biological Markers/analysis
MH - Dose-Response Relationship, Drug
MH - Drug Monitoring
MH - Factor X/analysis
MH - Female
MH - Human
MH - Male
MH - Middle Age
MH - Prothrombin/analysis
MH - Prothrombin Time
MH - Sensitivity and Specificity
MH - Support, Non-U.S. Gov't
MH - Thromboembolism/drug therapy
MH - Treatment Outcome
MH - Vascular Diseases/drug therapy
MH - Warfarin/*pharmacology/therapeutic use
EDAT- 2001/02/24 12:00
MHDA- 2001/03/03 10:01
PST - ppublish
SO - J Pharm Pharmacol 2000 Nov;52(11):1405-10.

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UI - 21025101
PMID- 11149264
DA - 20010108
DCOM- 20010125
VI - 99
IP - 8
DP - 2000 Nov
TI - How to measure the success of public health.
PG - 9
AU - Chapin J
LA - eng
PT - Editorial
CY - United States
TA - WMJ
JC - CYB
JID - 9716054
SB - IM
MH - Human
MH - Outcome Assessment (Health Care)
MH - *Public Health
MH - Wisconsin
EDAT- 2001/01/10 11:00
MHDA- 2001/02/28 10:01
PST - ppublish
SO - WMJ 2000 Nov;99(8):9.

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UI - 20498701
PMID- 11042238
DA - 20001114
DCOM- 20001130
IS - 0002-9343
VI - 109
IP - 6
DP - 2000 Oct 15
TI - Management and dosing of warfarin therapy.
PG - 481-8
AB - When initiating warfarin therapy, clinicians should avoid loading doses that can raise the International Normalized Ratio (INR) excessively; instead, warfarin should be initiated with a 5-mg dose (or 2 to 4 mg in the very elderly). With a 5-mg initial dose, the INR will not rise appreciably in the first 24 hours, except in rare patients who will ultimately require a very small daily dose (0.5 to 2.0 mg). Adjusting a steady-state warfarin dose depends on the measured INR values and clinical factors: the dose does not need to be adjusted for a single INR that is slightly out of range, and most changes should alter the total weekly dose by 5% to 20%. The INR should be monitored frequently (eg, 2 to 4 times per
week) immediately after initiation of warfarin; subsequently, the interval between INR tests can be lengthened gradually (up to a maximum of 4 to 6 weeks) in patients with stable INR values. Patients who have an elevated INR will need more frequent testing and may also require vitamin K1. For example, a nonbleeding patient with an INR of 9 can be given low-dose vitamin K1 (eg, 2.5 mg phytonadione, by mouth). Patients who have an excessive INR with clinically important bleeding require clotting factors (eg, fresh-frozen plasma) as well as vitamin K1.
AD - Division of General Medical Science (BFG), Washington University School of Medicine, St. Louis, Missouri, USA.
AU - Gage BF
AU - Fihn SD
AU - White RH
LA - eng
ID - HS10133/HS/AHCPR
PT - Journal Article
PT - Review
PT - Review, Tutorial
CY - UNITED STATES
TA - Am J Med
JC - 3JU
JID - 0267200
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - AIM
SB - IM
MH - Administration, Oral
MH - Anticoagulants/*administration & dosage/adverse effects/blood/*pharmacology
MH - Drug Administration Schedule
MH - Drug Monitoring
MH - Hemorrhage/chemically induced/*prevention & control
MH - Human
MH - International Normalized Ratio
MH - Monitoring, Ambulatory
MH - Support, Non-U.S. Gov't
MH - Support, U.S. Gov't, P.H.S.
MH - Warfarin/*administration & dosage/adverse effects/blood/*pharmacology
RF - 105
EDAT- 2000/10/24 11:00
MHDA- 2001/02/28 10:01
AID - S0002934300005453 [pii]
PST - ppublish
SO - Am J Med 2000 Oct 15;109(6):481-8.

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UI - 20485390
PMID- 11030681
DA - 20001120
DCOM- 20001120
IS - 0959-8138
VI - 321
IP - 7266
DP - 2000 Oct 14
TI - Walk-in primary medical care centres: lessons from Canada.
PG - 928-31
AD - Department of Primary Care and Population Sciences, Royal Free and University College Medical Schools, University College London, Royal Free Campus, London NW3 2PF, UK. melvyn.jones@ucl.ac.uk
AU - Jones M
LA - eng
PT - Journal Article
PT - Review
PT - Review, Tutorial
CY - ENGLAND
TA - BMJ
JC - BMJ
JID - 8900488
SB - AIM
SB - IM
CIN - BMJ. 2000 Oct 14;321(7266):909-10
MH - Adult
MH - Aged
MH - Canada
MH - Child

MH - *Community Health Centers
MH - Delivery of Health Care/*organization & administration
MH - Health Services Accessibility
MH - Human
MH - *Patient Acceptance of Health Care
MH - Primary Health Care/*organization & administration
MH - Support, Non-U.S. Gov't
RF - 23
EDAT- 2000/10/13 11:00
MHDA- 2001/02/28 10:01
URLF- http://bmj.com/cgi/content/full/321/7266/928
PST - ppublish
SO - BMJ 2000 Oct 14;321(7266):928-31.

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UI - 20508765
PMID- 11054979
DA - 20010221
DCOM- 20010222
IS - 1060-0280
VI - 34
IP - 10
DP - 2000 Oct
TI - Accidental over-anticoagulation: substitution error by a foreign pharmacy.
PG - 1132-5
AB - OBJECTIVE: To describe an episode of inadvertent and excessive anticoagulation caused by mistaken substitution of medication by a pharmacy outside the US. CASE SUMMARY: A 57-year-old white woman was found to have profound prolongation of her prothrombin time (56.9 sec) and international normalized ratio (22.18), with other coagulation parameters relatively normal. She had no prior history of bleeding diatheses and was not taking any prescribed anticoagulants. Her coagulopathy rapidly corrected with the administration of fresh frozen plasma and vitamin K. After her medications were visually inspected, it was discovered that she had purchased her prescription medications from a pharmacy in Mexico and that she inadvertently had been taking a preparation of warfarin (proprietary name in Mexico, "Romesa") instead of the prescribed ramipril for her hypertension (proprietary name in Mexico, "Ramace"). After removal of the incorrect medication, she experienced no further prolongation of her coagulation parameters. DISCUSSION: Medication errors contribute significantly to adverse events for patients. The frequency of different types of medication errors is reviewed, and problems specific to the use of warfarin are detailed. Circumstances that might lead to a patient seeking prescription medication outside of the US are also discussed. CONCLUSIONS: The acquisition of prescription medications from pharmacies outside of the US can have adverse consequences, especially if the foreign name of the medication is different from its American name, while sounding similar to other medications that also might be dispensed in foreign pharmacies.
AD - Department of Internal Medicine, Texas Tech University School of Medicine, Lubbock, USA.
AU - Suwanvecho S
AU - Baker JR
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - Ann Pharmacother
JC - BBX
JID - 9203131
RN - 0 (Angiotensin-Converting Enzyme Inhibitors)
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
RN - 87333-19-5 (Ramipril)
SB - IM
MH - Angiotensin-Converting Enzyme Inhibitors/adverse effects
MH - Anticoagulants/administration & dosage/*adverse effects
MH - Blood Pressure/drug effects
MH - Case Report
MH - Female
MH - Heart Rate/drug effects
MH - Human
MH - *Medication Errors
MH - Mexico
MH - Middle Age
MH - Overdose
MH - *Pharmacies
MH - Ramipril/adverse effects
MH - United States
MH - Warfarin/adverse effects
EDAT- 2000/10/31 11:00
MHDA- 2001/03/03 10:01
PST - ppublish
SO - Ann Pharmacother 2000 Oct;34(10):1132-5.

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UI - 21041464
PMID- 11198768
DA - 20010125
DCOM- 20010215
IS - 0268-8697
VI - 14
IP - 5
DP - 2000 Oct
TI - Prothrombin complex concentrate for oral anticoagulant reversal in neurosurgical emergencies.
PG - 458-61
AB - The incidence of spontaneous intracranial haemorrhage has increased markedly in line with the increased use of oral anticoagulant agents. Recent guidelines for reversal of this acquired coagulation defect in an emergency have been established, but they are not adhered to in all centres. Our unit is referred between 20 and 60 patients per year (1994-1999) who are anticoagulated and require urgent neurosurgical intervention. In order to investigate this, we performed a prospective study using prothrombin complex concentrate (PCC). PCC was given to the first six patients with intracranial haemorrhage admitted to the neurosurgical unit requiring urgent correction of anticoagulation (Group 1) and compared with patients receiving standard treatment with fresh frozen plasma and vitamin K (Group 2). Mean International Normalised Ratios of Group 1 were 4.86 pretreatment and 1.32 posttreatment, and of Group 2 were 5.32 and 2.30, respectively. Results for complete reversal and reversal time were significant for PCC with $p < 0.001$. We recommend PCC for rapid and effective reversal of warfarin in life-threatening neurosurgical emergencies.
AD - Department of Neurosurgery, Queen's Medical Centre, University Hospital, Nottingham, NG2 7UH, UK.
AU - Cartmill M
AU - Dolan G
AU - Byrne JL
AU - Byrne PO
LA - eng
PT - Journal Article
CY - England
TA - Br J Neurosurg
JC - AHZ
JID - 8800054
RN - 0 (Anticoagulants)
RN - 0 (Blood Coagulation Factors)
RN - 12001-79-5 (Vitamin K)

RN - 37224-63-8 (prothrombin complex concentrates)
RN - 81-81-2 (Warfarin)
SB - IM
MH - Adult
MH - Aged
MH - Anticoagulants/*antagonists & inhibitors
MH - Blood Coagulation Factors/*therapeutic use
MH - Cerebral Hemorrhage/blood/*surgery
MH - Comparative Study
MH - Emergencies
MH - Female
MH - Hematoma, Subdural/blood/surgery
MH - Human
MH - International Normalized Ratio
MH - Male
MH - Middle Age
MH - Pilot Projects
MH - Preoperative Care/*methods
MH - Prospective Studies
MH - Subarachnoid Hemorrhage/blood/surgery
MH - Vitamin K/therapeutic use
MH - Warfarin/*antagonists & inhibitors
EDAT- 2001/02/24 12:00
MHDA- 2001/03/03 10:01
PST - ppublish
SO - Br J Neurosurg 2000 Oct;14(5):458-61.

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UI - 20571646
PMID- 11122271
DA - 20010117
DCOM- 20010125
IS - 0141-9854
VI - 22
IP - 5
DP - 2000 Oct
TI - INR: Intervals of measurement can safely extend to 14 weeks.
PG - 291-3
AB - The number of patients taking warfarin is increasing. Each of these patients requires regular blood tests to ensure that the level of anticoagulation reaches and remains within a defined target range. INR monitoring is expensive and time-consuming and the frequency of the tests has repercussions for NHS resources and patient convenience. Guidelines regarding this are available, but the research on which these are based is extremely limited. Many centres in the UK are using extended intervals between tests that exceed the current guidelines. This study shows that for selected patients the interval between INR tests can safely be extended to 14 weeks with the potential for longer intervals.
AD - Haematology Department, St. Richards' Hospital Chichester, West Sussex, UK. Victoria@Lidstone.net
AU - Lidstone V
AU - Janes S
AU - Stross P
LA - eng
PT - Journal Article
CY - ENGLAND
TA - Clin Lab Haematol
JC - DKF
JID - 7907061
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - IM
MH - Anticoagulants/therapeutic use
MH - Blood Coagulation/drug effects
MH - Blood Coagulation Tests/*standards
MH - Human
MH - *International Normalized Ratio
MH - Monitoring, Physiologic/standards
MH - Prothrombin Time
MH - Retrospective Studies
MH - Time Factors
MH - Warfarin/therapeutic use
EDAT- 2000/12/21 11:00
MHDA- 2001/02/28 10:01
AID - clh315 [pii]
PST - ppublish
SO - Clin Lab Haematol 2000 Oct;22(5):291-3.

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UI - 21000404
PMID- 11183894
DA - 20001101
DCOM- 20001102
IS - 0197-2456
VI - 21
IP - 5 Suppl
DP - 2000 Oct
TI - Adherence to behavioral and pharmacological interventions in clinical research on older adults. Proceedings of a conference. May 1998, Winston-Salem, North Carolina, USA.
PG - 155S-247S
LA - eng
PT - Congresses
PT - Overall
CY - United States
TA - Control Clin Trials
JC - DSL
JID - 8006242
SB - IM
MH - Aged
MH - *Clinical Trials/standards
MH - Human
MH - Outcome Assessment (Health Care)
MH - *Patient Compliance
MH - Support, Non-U.S. Gov't
MH - Support, U.S. Gov't, P.H.S.
EDAT- 2001/02/24 12:00
MHDA- 2001/02/28 10:01

PST - ppublish
SO - Control Clin Trials 2000 Oct;21(5 Suppl):155S-247S.

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UI - 20472505
PMID- 11018570
DA - 20001027
DCOM- 20001102
IS - 0197-2456
VI - 21
IP - 5 Suppl
DP - 2000 Oct
TI - Studying adherence to therapeutic regimens: overview, theories, recommendations.
PG - 156S-63S
AB - Prediction of adherence and planning of behavior change can be systematically accomplished by using or modifying well-investigated theories. An overview of these models and recommendations for their use is offered. Control Clin Trials 2000;21:156S-163S
AD - Department of Kinesiology, University of Waterloo, Ontario, Canada.
AU - Brawley LR
AU - Culos-Reed SN
LA - eng
ID - 1R13AG16229-01/AG/NIA
PT - Journal Article

CY - UNITED STATES
TA - Control Clin Trials
JC - DSL
JID - 8006242
SB - IM
MH - Aged
MH - *Clinical Trials
MH - Human
MH - *Models, Psychological
MH - Outcome Assessment (Health Care)
MH - *Patient Compliance
MH - Support, Non-U.S. Gov't
MH - Support, U.S. Gov't, P.H.S.
EDAT- 2000/10/06 11:00
MHDA- 2001/02/28 10:01
AID - S0197245600000738 [pii]
PST - ppublish
SO - Control Clin Trials 2000 Oct;21(5 Suppl):156S-63S.

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UI - 20488364
PMID- 11036893
DA - 20001018
DCOM- 20001101
IS - 0140-6736
VI - 356
IP - 9233
DP - 2000 Sep 9
TI - A palliative-care intervention and death at home: a cluster randomised trial.
PG - 888-93
AB - BACKGROUND: The Palliative Medicine Unit at University Hospital of Trondheim, Norway, started an intervention programme that aims to enable patients to spend more time at home and die there if they prefer. Close cooperation was needed with the community health-care professionals, who acted as the principal formal caregivers, and a multidisciplinary consultant team coordinated the care. We did a cluster randomised trial to assess the intervention's effectiveness compared with conventional care METHODS: Community health-care districts in and around Trondheim, Norway, were defined as the clusters to be randomised. We enrolled 434 patients (235 assigned intervention and 199 conventional care [controls]) in these districts who had incurable malignant disease and an expected survival of 2-9 months. Main outcomes were place of death and time spent in institutions in the last month of life. FINDINGS: 395 patients died. Of these, more intervention patients than controls died at home (54 [25%] vs 26 [15%], p<0.05). The time spent at home was not significantly increased, although intervention patients spent a smaller proportion of time in nursing homes in the last month of life than did controls (7.2 vs 14.6%, p<0.05). Hospital use was similar in the two groups. INTERPRETATION: The palliative-care intervention enabled more patients to die at home. More resources for care in the home (palliative care training and staff) and an increased focus on use of nursing homes would be necessary, however, to increase time at home and reduce hospital admissions.
AD - Unit of Applied Clinical Research, Norwegian University of Science and Technology, Kreftbygget, University Hospital of Trondheim. mjordhoy@online.no
AU - Jordhoy MS
AU - Fayers P
AU - Saltnes T
AU - Ahlner-Elmqvist M
AU - Jannert M
AU - Kaasa S
LA - eng
PT - Clinical Trial
PT - Journal Article
PT - Randomized Controlled Trial
CY - ENGLAND
TA - Lancet
JC - LOS
JID - 2985213R
SB - AIM
SB - IM
MH - Adult
MH - Aged
MH - Aged, 80 and over
MH - Community Health Services/manpower
MH - Comparative Study
MH - Confidence Intervals
MH - Death
MH - Female
MH - *Home Care Services
MH - Hospitalization
MH - Human
MH - Intervention Studies
MH - Male
MH - Middle Age
MH - Neoplasms/therapy
MH - Norway
MH - Nursing Homes
MH - Outcome Assessment (Health Care)
MH - *Palliative Care

MH - Patient Care Team
MH - Regression Analysis
MH - Support, Non-U.S. Gov't
MH - Survival Rate
EDAT- 2000/10/19 11:00
MHDA- 2001/02/28 10:01
PST - ppublish
SO - Lancet 2000 Sep 9;356(9233):888-93.

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UI - 20533406
PMID- 11080939
DA - 20001120
DCOM- 20001130
IS - 0016-3813
VI - 136
IP - 5
DP - 2000 Sep-Oct
TI - [Role of the patient in the treatment of disease]
PG - 529-32
AU - Lifshitz A
LA - spa
PT - Journal Article
TT - El papel del paciente en la atencion de enfermedades.
CY - MEXICO
TA - Gac Med Mex
JC - FFF
JID - 0010333
SB - IM
MH - Alternative Medicine
MH - Databases
MH - Human
MH - Patient Acceptance of Health Care
MH - Patient Advocacy
MH - Patient Compliance
MH - Patient Education
MH - *Patient Participation
MH - *Physician-Patient Relations
MH - Self Care
EDAT- 2000/11/18 11:00
MHDA- 2001/02/28 10:01
PST - ppublish
SO - Gac Med Mex 2000 Sep-Oct;136(5):529-32.

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UI - 20452127
PMID- 10999498
DA - 20010118
DCOM- 20010118
IS - 0277-0008
VI - 20
IP - 9
DP - 2000 Sep
TI - Adequacy of anticoagulation in patients with atrial fibrillation coming to a hospital.
PG - 1060-5
AB - STUDY OBJECTIVE: To evaluate the adequacy of anticoagulation in patients with atrial fibrillation (AF) coming to a hospital. DESIGN: Retrospective medical record review. SETTING: Tertiary care hospital. PATIENTS: Consecutive patients with a history of AF who had been prescribed warfarin and who had the international normalized ratio (INR) measured when they arrived at the hospital. Those who developed AF as a complication during hospitalization were excluded. MEASUREMENTS AND MAIN RESULTS: Of 1085
patients, 375 (mean age 73 yrs, 56.3% men) were eligible for further evaluation. Most had nonvalvular AF; in 44.5% the INR was subtherapeutic, in 36.5% it was therapeutic, and in 18.9% it was supratherapeutic. Patients admitted for any thromboembolic event and for ischemic stroke were significantly more likely to have subtherapeutic INRs. CONCLUSION: It is well documented in the literature that warfarin is underprescribed, but our results suggest that even in treated patients, about half are inadequately protected from thromboembolism.
AD - Division of Cardiology, University of Alberta, Edmonton, Canada.
AU - Bungard TJ
AU - Ackman ML
AU - Ho G
AU - Tsuyuki RT
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - Pharmacotherapy
JC - PAR
JID - 8111305
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - IM
MH - Aged
MH - Analysis of Variance
MH - Anticoagulants/*administration & dosage
MH - Atrial Fibrillation/*drug therapy
MH - Cerebrovascular Accident/*prevention & control
MH - Chi-Square Distribution
MH - Female
MH - Human
MH - International Normalized Ratio/*statistics & numerical data
MH - Male
MH - Middle Age
MH - Patients/statistics & numerical data
MH - Retrospective Studies
MH - Support, Non-U.S. Gov't
MH - Thromboembolism/*prevention & control
MH - Warfarin/*administration & dosage
EDAT- 2000/09/22 11:00
MHDA- 2001/02/28 10:01
PST - ppublish
SO - Pharmacotherapy 2000 Sep;20(9):1060-5.

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UI - 20386820
PMID- 10927732
DA - 20000828
DCOM- 20000828

LR - 20001218
IS - 0003-9926
VI - 160
IP - 15
DP - 2000 Aug 14-28
TI - Oral anticoagulation management in primary care with the use of computerized decision support and near-patient testing: a randomized, controlled trial.
PG - 2343-8
AB - BACKGROUND: There is increased pressure on primary care physicians to monitor oral anticoagulation. OBJECTIVE: To test the null hypothesis that oral anticoagulation care can be provided at least as well in primary care through a nurse-led clinic, involving near-patient testing and computerized decision support software, compared with routine hospital management based on a variety of clinical outcome measures. METHODS: A randomized, controlled trial in 12 primary care practices in Birmingham, England (9 intervention and 3 control). Two control populations were used: patients individually randomly allocated as controls in the intervention practices (intrapractice controls) and all patients in control practices (interpractice controls). Intervention practices' patients were randomized to the intervention (practice-based anticoagulation clinic) or control (hospital clinic) group. The main outcome measure was therapeutic control of the international normalized ratio. RESULTS: Three hundred sixty-seven patients were recruited (122 intervention patients, 102 intrapractice control patients, and 143 interpractice control patients). Standard measures of control of the international normalized ratio (point prevalence) showed no significant difference between the intervention and control groups. Data on proportion of time spent in the international normalized ratio range showed significant improvement for patients in the intervention group (paired t test, P =.008). CONCLUSIONS: Nurse-led anticoagulation clinics can be implemented in novice primary care settings by means of computerized decision support software and near-patient testing. Care given by this model is at least as good as routine hospital follow-up. The model is generalizable to primary health care centers operating in developed health care systems.
AD - Department of General Practice, Medical School, The University of Birmingham, England. D.A.Fitzmaurice@bham.ac.uk
AU - Fitzmaurice DA
AU - Hobbs FD
AU - Murray ET
AU - Holder RL
AU - Allan TF
AU - Rose PE
LA - eng
PT - Clinical Trial
PT - Journal Article
PT - Randomized Controlled Trial
CY - UNITED STATES
TA - Arch Intern Med
JC - 7FS
JID - 0372440
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - AIM
SB - IM
MH - Administration, Oral
MH - Adult
MH - Aged
MH - Anticoagulants/*administration & dosage/adverse effects
MH - Comparative Study
MH - *Decision Making, Computer-Assisted
MH - *Decision Support Techniques
MH - Female
MH - Human
MH - International Normalized Ratio
MH - Long-Term Care
MH - Male
MH - Middle Age
MH - Nurse Practitioners
MH - Outpatient Clinics, Hospital
MH - *Primary Health Care
MH - Software
MH - Support, Non-U.S. Gov't
MH - Thromboembolism/etiology/*prevention & control
MH - Treatment Outcome
MH - Warfarin/*administration & dosage/adverse effects
EDAT- 2000/08/06 11:00
MHDA- 2000/09/02 11:01
AID - ioi90592 [pii]
PST - ppublish
SO - Arch Intern Med 2000 Aug 14-28;160(15):2343-8.

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UI - 20386840
PMID- 10927752
DA - 20000828
DCOM- 20000828
LR - 20001218
IS - 0003-9926
VI - 160
IP - 15
DP - 2000 Aug 14-28
TI - Geriatric assessment and anticoagulation in elderly patients with chronic atrial fibrillation.
PG - 2402-3
AU - Bellelli G
AU - Rozzini R
AU - Barbisoni P
AU - Sabatini T
AU - Trabucchi M
LA - eng
PT - Comment
PT - Letter
CY - UNITED STATES
TA - Arch Intern Med
JC - 7FS
JID - 0372440
RN - 0 (Anticoagulants)
RN - 50-78-2 (Aspirin)
RN - 81-81-2 (Warfarin)
SB - AIM
SB - IM
CON - Arch Intern Med. 2000 Jan 10;160(1):41-6
MH - Aged
MH - Anticoagulants/*administration & dosage
MH - Aspirin/administration & dosage

MH - Atrial Fibrillation/*drug therapy
MH - *Geriatric Assessment
MH - Human
MH - Intracranial Embolism/prevention & control
MH - Patient Compliance
MH - Warfarin/*administration & dosage
EDAT- 2000/08/06 11:00
MHDA- 2000/09/02 11:01
AID - ilt0814-10 [pii]
PST - ppublish
SO - Arch Intern Med 2000 Aug 14-28;160(15):2402-3.

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UI - 20402385
PMID- 10942929
DA - 20001205
DCOM- 20001205
IS - 0390-6078
VI - 85
IP - 8
DP - 2000 Aug
TI - Assessment of patient capability to self-adjust oral anticoagulant dose: a multicenter study on home use of portable prothrombin time monitor (COAGUCHECK).
PG - 826-31
AB - BACKGROUND AND OBJECTIVES: Self-testing and self-monitoring with portable prothrombin time (PT) monitors has been shown to be feasible and safe. However the ability of patients on chronic oral anticoagulant therapy (OAT) to self-adjust their dose without specific training has never been properly evaluated. The aims of this study were to evaluate: 1) the ability of patients on chronic OAT to self-adjust their dose without specific training; 2) the integration of a portable PT monitor (Coagucheck, Roche Diagnostics, Germany) for home use into routine patient care in anticoagulation clinics. DESIGN AND METHODS: A nested case-control study was conducted in four centers of the Italian Federation of Anticoagulation Clinics (FCSA). Patients (n=78) on stable OAT for at least 6 months (cases: 47 men, 31 women, age range: 18-75 years) were enrolled on a volunteer basis after passing an Abbreviated Mental Test and providing informed consent. After three instruction sessions on the use of Coaguchek, subjects performed the PT test at home, communicated the INR results to the Center and suggested the dose adjustment and date for next control as they thought appropriate. However, they were requested to follow the prescription made by the Center. Controls (78 subjects) matched by age (+/- 5 years), sex and therapeutic range with the cases, were selected from among those who attended the anticoagulation clinics and managed by usual care. RESULTS: When compared with the dose prescribed by the Clinic, the dose suggested by warfarin and acenocoumarol users was equal to or within +/- 6% of the mean weekly dose in 80% and 82% of suggestions, respectively. Time spent in the therapeutic range during the study was the same (80%) for cases and controls. INTERPRETATION AND CONCLUSIONS: Selected patients on chronic anticoagulant therapy can acquire a satisfactory ability for self-adjustment of OAT dose without specific training.
AD - Divisione di Angiologia, Ospedale S.Orsola Malpighi, Bologna, Italy.
AU - Cosmi B
AU - Palareti G
AU - Carpanedo M
AU - Pengo V
AU - Biasiolo A
AU - Rampazzo P
AU - Morstabilini G
AU - Testa S
LA - eng
PT - Journal Article
PT - Multicenter Study
CY - ITALY
TA - Haematologica
JC - FYB
JID - 0417435
RN - 0 (Anticoagulants)
RN - 152-72-7 (Acenocoumarol)
RN - 81-81-2 (Warfarin)
SB - IM
MH - Acenocoumarol/*administration & dosage/adverse effects/pharmacology
MH - Administration, Oral
MH - Adolescence
MH - Adult
MH - Aged
MH - Anticoagulants/*administration & dosage/adverse effects/pharmacology
MH - Case-Control Studies
MH - Female
MH - Hemorrhage/chemically induced/epidemiology
MH - Human
MH - International Normalized Ratio/*instrumentation
MH - Italy
MH - Male
MH - Middle Age
MH - Outcome Assessment (Health Care)
MH - Patient Acceptance of Health Care
MH - *Patient Compliance/statistics & numerical data
MH - *Prothrombin Time
MH - Questionnaires
MH - Random Allocation
MH - Self Administration
MH - *Self Care
MH - Support, Non-U.S. Gov't
MH - Thromboembolism/epidemiology/prevention & control
MH - Warfarin/*administration & dosage/adverse effects/pharmacology
EDAT- 2000/08/16 11:00
MHDA- 2001/02/28 10:01
URLS- http://www.haematologica.it/abstr/cosmi8508.htm
PST - ppublish
SO - Haematologica 2000 Aug;85(8):826-31.

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UI - 20431490
PMID- 10976978
DA - 20001206
DCOM- 20010222
IS - 1075-5535
VI - 6

IP - 4
DP - 2000 Aug
TI - Alternative/complementary medicine: wider usage than generally appreciated.
PG - 321-6
AB - OBJECTIVE: To test the hypothesis that there is substantial use of a practitioner of alternative/complementary medicine by patients traditionally considered to be underserved. DESIGN: Cross-sectional, self-administered survey study. SETTINGS: Three university hospital-affiliated general ambulatory clinics serving patients of different socioeconomic status and racial origin. SUBJECTS: Five hundred and thirty-six (93% of those attending) consecutive clinic attendees. OUTCOME MEASURES: Past use and desired future use of one or more practitioners of five modalities of alternative/complementary medicine and willingness to pay for these modalities out-of-pocket. RESULTS: Past usage and desired future usage of one or more practitioners of alternative/complementary medicine was comparable at the three clinic sites despite wide differences in socioeconomic status and willingness/ability to pay out-of-pocket for these services. Multivariable analyses revealed lower self-rated health status and female gender (both $p < 0.006$) but not income, race, age or education as independent, significant predictors of use of a practitioner of alternative/complementary medicine. CONCLUSION: Usage of alternative/complementary medicine is not confined to any well-circumscribed socioeconomic group and is common in patients often considered to be underserved. Self-assessed lower health status is significantly and independently associated with use of a practitioner of alternative/complementary care.
AD - Department of Medicine, University of Colorado School of Medicine, Denver 80262, USA.
AU - Wolsko P
AU - Ware L
AU - Kutner J
AU - Lin CT
AU - Albertson G
AU - Cyran L
AU - Schilling L
AU - Anderson RJ
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - J Altern Complement Med
JC - CY7
JID - 9508124
SB - IM
MH - Adolescence
MH - Adult
MH - Aged
MH - Alternative Medicine/*utilization
MH - Colorado
MH - Cross-Sectional Studies
MH - Female
MH - Human
MH - Male
MH - *Medically Underserved Area
MH - Middle Age
MH - Patient Acceptance of Health Care/ethnology/*statistics & numerical data
MH - Questionnaires
MH - Socioeconomic Factors
MH - Support, Non-U.S. Gov't
EDAT- 2000/09/08 11:00
MHDA- 2001/03/03 10:01
PST - ppublish
SO - J Altern Complement Med 2000 Aug;6(4):321-6.

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UI - 20405884
PMID- 10947914
DA - 20001201
DCOM- 20001201
IS - 0929-5305
VI - 10
IP - 1
DP - 2000 Aug
TI - Home monitoring and management of warfarin therapy: an anticoagulation clinic perspective.
PG - 55-7
AD - Anticoagulation Service, University of Massachusetts Memorial Medical Center, Worcester, Massachusetts 01655, USA.
AU - Stuart TL
LA - eng
PT - Journal Article
PT - Review
PT - Review, Tutorial
CY - NETHERLANDS
TA - J Thromb Thrombolysis
JC - DDY
JID - 9502018
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - IM
MH - Anticoagulants/administration & dosage
MH - Disease Management
MH - Drug Monitoring/*methods/psychology
MH - Human
MH - Patient Education
MH - *Point-of-Care Systems/economics/standards
MH - Warfarin/*administration & dosage
RF - 7
EDAT- 2000/08/18 11:00
MHDA- 2001/02/28 10:01
PST - ppublish
SO - J Thromb Thrombolysis 2000 Aug;10(1):55-7.

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UI - 20384408
PMID- 10924937
DA - 20000907
DCOM- 20000907
LR - 20001218
IS - 0025-5564
VI - 166
IP - 2
DP - 2000 Aug

TI - A stochastic-covariate failure model with an application to case-control analysis.
PG - 149-72
AB - A stochastic process X(t) is periodically stationary (and ergodic) if, for every k> or =1 and every (t(1),ellipsis,t(k)) in R(k), the sequence of random vectors (X(t(1)+n),ellipsis,X(t(k)+n))n=0,+1, ellipsis, is stationary (and ergodic). For such an ergodic process, let T be a positive random variable defined on the sample space of the process, representing a time of failure. The local failure-rate function is assumed to be of the form up(x),-infinity<x<infinity, where p(x) is a non-negative continuous function, and u>0 is a small number, tending to 0; and, for each u,T=T(u) is the corresponding failure-time. It is shown that X(T(u)) and uT(u) have, for u-->0, a limiting joint distribution and are, in fact, asymptotically independent. The marginal distributions are explicitly given. Let Y be a random variable whose distribution is the limit of that of X(T(u)). Under the hypothesis that p(x) is unknown or of known functional form but with unknown parameters, it is shown how p(x) can be estimated on the basis of independent copies of the random variable Y. The results are applied to the analysis of a case-control study featuring a 'marker' process X(t) and an 'event-time' T. The event in the study is considered to be particularly rare, and this is reflected in the assumption u-->0. The control-distribution is identified with the average marginal distribution of the (periodically stationary) marker process X(t), and the case-distribution is identified with that of Y. The particular application is a biomedical trial to determine the risk of stroke in terms of the level of an anticoagulant in the blood of the patient.
AD - Department of Mathematics, Courant Institute of Mathematical Sciences, New York University, 251 Mercer Street, NY, New York 10012, USA. sberman@cims.nyu.edu
AU - Berman SM
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - Math Biosci
JC - BET
JID - 0103146
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - IM
MH - Anticoagulants/blood/therapeutic use
MH - *Case-Control Studies
MH - Cerebrovascular Accident/prevention & control
MH - Human
MH - *Models, Statistical
MH - Normal Distribution
MH - Numerical Analysis, Computer-Assisted
MH - Prothrombin Time
MH - Stochastic Processes
MH - Warfarin/blood/therapeutic use
EDAT- 2000/08/05 11:00
MHDA- 2000/09/09 11:01
AID - S0025556400000298 [pii]
PST - ppublish
SO - Math Biosci 2000 Aug;166(2):149-72.

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UI - 20417235
PMID- 10963245
DA - 20000908
DCOM- 20000908
LR - 20010918

IS - 0140-6736
VI - 356
IP - 9224
DP - 2000 Jul 8
TI - Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison.
PG - 97-102
AB - BACKGROUND: Vitamin K antagonist treatment is effective for prevention and treatment of thromboembolic events but frequent laboratory control and dose-adjustment are essential. Small portable devices have enabled patient self-monitoring of anticoagulation and self-adjustment of the dose. We compared this self-management of oral anticoagulant therapy with conventional management by a specialist anticoagulation clinic in a randomised cross-over study. METHODS: 50 patients on long-term oral anticoagulant treatment were included in a randomised controlled crossover study. Patients were self-managed or were managed by the anticoagulation clinic for a period of 3 months. After this period the alternative strategy was followed for each patient. Prothrombin time (expressed as international normalised ratio [INR]) were measured at intervals of 1-2 weeks in both periods without knowledge of type of management. The primary endpoint was the number of measurements within the therapeutic range (therapeutic target value +/-50.5 INR units). FINDINGS: There was no significant difference in the overall quality of control of anticoagulation between the two study periods. Patients were for 55% and for 49% of the treatment period within a range of +/-0.5 from the therapeutic target INR during self-management and anticoagulation clinic management, respectively (p=0.06). The proportion of patients who spent most time in the therapeutic target range was larger during self-management than during anticoagulation clinic-guided management. The odds ratio for a better control of anticoagulation (defined as the period of time in the therapeutic target range) during self-management compared with anticoagulation clinic-guided management was 4.6 (95% CI 2.1-10.2). A patient-satisfaction assessment showed superiority of self-management over conventional care. INTERPRETATION: Self-management of INR in the population in this study is feasible and appears to result in control of anticoagulation that is at least equivalent to management by a specialist anticoagulation clinic. It is also better appreciated by patients. Larger studies are required to assess the effect of this novel management strategy on the incidence of thromboembolic or bleeding complications.
AD - Department of Cardiopulmonary Surgery, Academic Medical Centre, University of Amsterdam, Netherlands.
AU - Cromheecke ME
AU - Levi M
AU - Colly LP
AU - de Mol BJ
AU - Prins MH
AU - Hutten BA

AU - Mak R
AU - Keyzers KC
AU - Buller HR
LA - eng
PT - Clinical Trial
PT - Journal Article
PT - Randomized Controlled Trial
CY - ENGLAND
TA - Lancet
JC - LOS
JID - 2985213R
RN - 0 (Anticoagulants)
SB - AIM
SB - IM
CIN - ACP Journal Club 2001 Mar-Apr;134(2):62
CIN - Lancet. 2000 Oct 21;356(9239):1437
MH - Administration, Oral
MH - Adult
MH - Aged
MH - Ambulatory Care/*methods/psychology
MH - Anticoagulants/*therapeutic use
MH - Comparative Study
MH - Cross-Over Studies
MH - Drug Monitoring/*methods/psychology
MH - Feasibility Studies
MH - Female
MH - Human
MH - International Normalized Ratio
MH - Long-Term Care/methods/psychology
MH - Male
MH - Middle Age
MH - Patient Education/methods
MH - Patient Satisfaction
MH - Questionnaires
MH - Reproducibility of Results
MH - Self Administration/*methods/psychology
MH - Treatment Outcome
EDAT- 2000/08/30 11:00
MHDA- 2000/09/19 11:01
PST - ppublish
SO - Lancet 2000 Jul 8;356(9224):97-102.

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UI - 20325444
PMID- 10865011
DA - 20000823
DCOM- 20000823
LR - 20001218
IS - 0172-0643
VI - 21
IP - 4
DP - 2000 Jul-Aug
TI - Capillary whole blood monitoring of oral anticoagulants in children in outpatient clinics and the home setting.
PG - 347-52
AB - A whole blood prothrombin time/international normalized ratio (PT/INR) monitor (CoaguChek, Roche Diagnostics Corp., Indianapolis, IN) was assessed in children for its accuracy, reliability, safety, and acceptance by health care personnel and patient's families. The PT/INR values measured by the CoaguChek monitor showed an excellent correlation with PT/INR values measured by the Hospital for Sick Children (HSC) laboratory (r = 0.96) and Hamilton Civic Hospitals Research Centre (HCHRC) laboratory
(r = 0.92) in clinic patients and a close correlation with PT/INR values measured by the HSC laboratory (r = 0.76) and HCHRC laboratory (r = 0.74)
in patients at home. Reduced correlation in the home setting did not adversely affect clinical management. The whole blood PT/INR monitor is safe and accurate for children requiring oral anticoagulation therapy in either the outpatient clinic or home setting.
AD - Hospital for Sick Children, Toronto, Ontario, Canada.
AU - Marzinotto V
AU - Monagle P
AU - Chan A
AU - Adams M
AU - Massicotte P
AU - Leaker M
AU - Andrew M
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - Pediatr Cardiol
JC - PA3
JID - 8003849
RN - 0 (Anticoagulants)
SB - IM
MH - Administration, Oral
MH - Adolescence
MH - Anticoagulants/*blood
MH - Blood Coagulation Tests/*instrumentation
MH - Child
MH - Child, Preschool
MH - Evaluation Studies
MH - Home Care Services, Hospital-Based
MH - Human
MH - Infant
MH - Infant, Newborn
MH - International Normalized Ratio
MH - Monitoring, Ambulatory/*instrumentation
MH - Ontario
MH - Outpatient Clinics, Hospital
MH - Prospective Studies
MH - Prothrombin Time
MH - Support, Non-U.S. Gov't
MH - Whole Blood Coagulation Time
EDAT- 2000/06/24 11:00
MHDA- 2000/08/29 11:01
AID - 10.1007/s002460010078 [pii]
URLS-
http://link.springer.de/link/service/journals/00246/bibs/0021004/00210347.htm
PST - ppublish
SO - Pediatr Cardiol 2000 Jul-Aug;21(4):347-52.

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UI - 20397695
PMID- 10943779
DA - 20001121
DCOM- 20001222
IS - 0737-1209
VI - 17
IP - 4
DP - 2000 Jul-Aug
TI - Evaluation of telenursing outcomes: satisfaction, self-care practices, and cost savings.
PG - 305-13
AB - Info-Sante CLSC, the Quebec telenursing service, is a telephone health line nursing service that was implemented in 1995 in every local community service center (CLSC; n = 141) of 15 regional health authorities in the Province of Quebec, Canada. It is, at present, one of the most important first-line health services and it operates in continuity with the other resources in the health and social service system. Info-Sante CLSC operates 24 hours a day, 7 days a week, and received more than 2,260,000 calls in 1997. This article will report the findings from the first province-wide survey of the service, based on a stratified random sample of 4,696 callers. The findings revealed that most respondents were highly satisfied with the service; they followed the nurses' advice and carried out self-care measures as recommended. Nursing interventions helped respondents feel self-reliant, like they could solve the same or similar problems should they occur in the future. The vast majority of respondents considered that the call they made to Info-Sante CLSC was useful in finding a solution to their problems. The vast majority also claimed that they would certainly call Info-Sante CLSC again should another problem occur. The majority reported they would have turned to another type of resource if Info-Sante CLSC had not existed; half of the respondents stated that they would have used emergency departments and a third would have consulted a doctor in private practice.
AD - Faculty of Nursing Sciences, Universite Laval, Quebec, Canada.
AU - Hagan L
AU - Morin D
AU - Lepine R
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - Public Health Nurs
JC - PHN
JID - 8501498
SB - IM
SB - N
MH - Adolescence
MH - Adult
MH - Aged
MH - *Attitude to Health
MH - Community Health Nursing/*methods
MH - Cost Savings
MH - Female
MH - *Hotlines
MH - Human
MH - Male
MH - Middle Age
MH - *Outcome Assessment (Health Care)
MH - Patient Satisfaction
MH - Quebec
MH - *Remote Consultation/economics
MH - Self Care
MH - Support, Non-U.S. Gov't
EDAT- 2000/08/16 11:00
MHDA- 2001/02/28 10:01
PST - ppublish
SO - Public Health Nurs 2000 Jul-Aug;17(4):305-13.

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UI - 20441148
PMID- 10985133
DA - 20000926
DCOM- 20000926
LR - 20001218
IS - 0038-2469
VI - 90
IP - 7
DP - 2000 Jul
TI - Audit of a walk-in oral anticoagulation clinic that uses near-patient testing.
PG - 706-7
AU - Djordjevic Z
AU - Coetzee MJ
AU - Badenhorst PN
AU - Nel M
AU - Joubert G
LA - eng
PT - Letter
CY - SOUTH AFRICA
TA - S Afr Med J
JC - U4R
JID - 0404520
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - IM
MH - Adult
MH - Aged
MH - Aged, 80 and over
MH - *Ambulatory Care Facilities
MH - Anticoagulants/*administration & dosage/adverse effects
MH - Female
MH - Human
MH - Male
MH - Medical Audit/*organization & administration
MH - Middle Age
MH - Patient Satisfaction
MH - Prothrombin Time
MH - Questionnaires
MH - Warfarin/*administration & dosage/adverse effects
EDAT- 2000/09/14 11:00
MHDA- 2000/09/30 11:01
PST - ppublish
SO - S Afr Med J 2000 Jul;90(7):706-7.

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UI - 20376060
PMID- 10920672
DA - 20001002
DCOM- 20001002
LR - 20001218
IS - 1438-3276
VI - 142
IP - 25
DP - 2000 Jun 22
TI - [Self control of blood coagulation values. The overwhelming majority of patients can be educated]
PG - 54-5
LA - ger
PT - Journal Article
TT - Selbstkontrolle der Gerinnungswerte. Die uberwiegende Mehrzahl der Patienten kann geschult werden.
CY - GERMANY
TA - MMW Fortschr Med
JC - DHP
JID - 100893959
RN - 0 (Anticoagulants)
SB - IM
MH - Anticoagulants/*administration & dosage/adverse effects
MH - *Blood Coagulation Tests
MH - Equipment Design
MH - Human
MH - *Patient Education
MH - *Self Care/instrumentation
EDAT- 2000/08/02 11:00
MHDA- 2000/10/07 11:01
PST - ppublish
SO - MMW Fortschr Med 2000 Jun 22;142(25):54-5.

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UI - 20367446
PMID- 10909717
DA - 20000919
DCOM- 20000919
LR - 20001218
IS - 0036-7672
VI - 130
IP - 24
DP - 2000 Jun 17
TI - [Patient self-monitoring of oral anticoagulation with CoaguChek]
PG - 916-23
AB - We investigated the feasibility, quality and safety of patient self-control of oral anticoagulation. The patients were selected by their physicians on the basis of criteria such as compliance, skills and motivation. After theoretical and practical training they self-monitored and self-adjusted their anticoagulant dosage for 6 months by weekly self-measurement of their INR values using a capillary whole blood prothrombin time monitor (CoaguChek). Venous INR measurements once a month served as quality control. There were 51 study participants, who performed a median 5 INR measurements per month. 75.8% of all registered INR values were within the recommended individual INR target ranges. The coefficient of correlation between capillary (y) and venous (x) INR values was r = 0.87 (regression analysis y = 1.0 x -0.2). The concordance of capillary and venous INR values was 80% with respect to the individual INR target ranges. There were 5 minor bleeding episodes and no overt thromboembolic recurrences during the study period. In conclusion, the study demonstrated that patient self-control of oral anticoagulation is feasible and achieves a high percentage of INR values within the recommended target ranges. Therefore, self-control of oral anticoagulation can be offered to skilled and motivated patients as an alternative to physician-guided antiocogulation. However, specific training of these selected patients is necessary.
AD - Hamatologisches Zentrallabor, Inselspital, Universitatsspital Bern.
AU - Caliezi C
AU - Waber M
AU - Pfiffner D
AU - Saner H
AU - Lammle B
AU - Wuillemin WA
LA - ger
PT - Journal Article
TT - Patienten-Selbstkontrolle der oralen Antikoagulation mit CoaguChek.
CY - SWITZERLAND
TA - Schweiz Med Wochenschr
JC - UEI
JID - 0404401
RN - 0 (Anticoagulants)
SB - IM
MH - Adult
MH - Aged
MH - Aged, 80 and over
MH - Anticoagulants/*administration & dosage/adverse effects
MH - Dose-Response Relationship, Drug
MH - Female
MH - Human
MH - *International Normalized Ratio
MH - Long-Term Care
MH - Male
MH - Middle Age
MH - Monitoring, Ambulatory/*instrumentation
MH - Patient Compliance
MH - Predictive Value of Tests
MH - *Prothrombin Time
MH - Self Care/*instrumentation
MH - Support, Non-U.S. Gov't
MH - Thrombophilia/blood/*drug therapy/etiology
EDAT- 2000/07/26 11:00
MHDA- 2000/09/23 11:01
PST - ppublish
SO - Schweiz Med Wochenschr 2000 Jun 17;130(24):916-23.

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UI - 20363230
PMID- 10899356
DA - 20001115
DCOM- 20001115
IS - 0049-3848
VI - 98

IP - 6
DP - 2000 Jun 15
TI - Home-made anticoagulation monitor vs. CoaguCheck-Plus monitoring of oral
anticoagulation.
PG - 571-5
AD - Ludwig Boltzmann Institute for Research in Epilepsy and Neuromuscular Disorders, Vienna, Austria. fij@2nr.nkr.magwien.gv.at
AU - Finsterer J
AU - Stollberger C
AU - Hopmeier P
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - Thromb Res
JC - VRN
JID - 0326377
RN - 0 (Anticoagulants)
RN - 435-97-2 (Phenprocoumon)
SB - IM
MH - Administration, Oral

MH - Adult
MH - Aged
MH - Aged, 80 and over
MH - Anticoagulants/administration & dosage/*blood
MH - Blood Coagulation Tests/instrumentation/*methods
MH - Comparative Study
MH - Drug Monitoring/*instrumentation/standards
MH - Female
MH - Human
MH - International Normalized Ratio
MH - Male
MH - Middle Age
MH - Phenprocoumon/pharmacology/therapeutic use
MH - Reproducibility of Results
MH - Self Care
MH - Thromboembolism/drug therapy
EDAT- 2000/07/19 11:00
MHDA- 2001/02/28 10:01
AID - S0049384800002073 [pii]
PST - ppublish
SO - Thromb Res 2000 Jun 15;98(6):571-5.

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UI - 20416746
PMID- 11067280
DA - 20001019
DCOM- 20001019
LR - 20001218
IS - 1063-8490
VI - 9
IP - 3
DP - 2000 Jun
TI - Our quality-assurance methods aren't so sure.
PG - 41-2, 48
AD - Center for Mental Health Policy, Vanderbilt University, USA.
bickman@attglobal.net
AU - Bickman L
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - Behav Healthc Tomorrow
JC - B7R
JID - 9308264
SB - H
MH - Education, Continuing
MH - Evaluation Studies
MH - Inservice Training
MH - Mental Health Services/*standards
MH - Outcome Assessment (Health Care)
MH - *Quality Assurance, Health Care
MH - Support, Non-U.S. Gov't
MH - United States
EDAT- 2000/11/07 11:00
MHDA- 2000/11/07 11:01
PST - ppublish
SO - Behav Healthc Tomorrow 2000 Jun;9(3):41-2, 48.

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UI - 20319208
PMID- 10859580
DA - 20000928
DCOM- 20000928
LR - 20001218
IS - 0929-5305
VI - 9 Suppl 1
DP - 2000 Jun
TI - Anticoagulation clinics and patient self-testing for patients on chronic warfarin therapy: A cost-effectiveness analysis.
PG - S13-9
AB - This study was intended to evaluate the cost-effectiveness of anticoagulation clinic care and self-testing for the management of patients on chronic warfarin therapy. Using a 5-year Markov model, we evaluated the health and economic outcomes associated with each of three different anticoagulation management approaches: (1) usual care, (2) anticoagulation clinic testing with a capillary monitor, and (3) patient self-testing with a capillary monitor. Data available in the published literature and data from a large health system were used to develop model assumptions. Model results indicate that over a 5-year period, compared with usual care, anticoagulation clinic testing results in a total of 1.7 fewer thromboembolic events and 2.0 less hemorrhagic events per 100 patients. Another 4.0 thromboembolic events and 0.8 hemorrhagic events are
avoided with patient self-testing compared with anticoagulation clinic testing. In addition to the health advantages of these strategies, both also have cost advantages. When the costs incurred by provider organizations and patients are considered, patient self-testing is the most cost-effective alternative, resulting in an overall cost saving.
AD - Henry Ford Health System, Detroit, Michigan 48202, USA.
AU - Lafata JE
AU - Martin SA
AU - Kaatz S
AU - Ward RE

LA - eng
PT - Journal Article
CY - NETHERLANDS
TA - J Thromb Thrombolysis
JC - DDY
JID - 9502018
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - IM
MH - Anticoagulants/*economics/therapeutic use
MH - Comparative Study
MH - Drug Costs/*statistics & numerical data
MH - Drug Monitoring/economics
MH - Hemorrhage/economics/prevention & control
MH - Human
MH - Markov Chains
MH - Outpatient Clinics, Hospital/economics
MH - Self-Examination/economics
MH - Thromboembolism/economics/prevention & control
MH - Warfarin/*economics/therapeutic use
EDAT- 2000/06/22 10:00
MHDA- 2000/09/30 11:01
PST - ppublish
SO - J Thromb Thrombolysis 2000 Jun;9 Suppl 1:S13-9.

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UI - 20375912
PMID- 10920524
DA - 20000822
DCOM- 20000822
LR - 20001218
IS - 0212-6567
VI - 25
IP - 9
DP - 2000 May 31
TI - [Evaluation of results in primary are: the MPAR-5 project]
PG - 653-60, 662
AD - Servei Catala de la Salut, Institut Catala de la Salut.
AU - Jimenez Villa J
AU - Cutillas Castell S
AU - Martin Zurro A
LA - spa
PT - Journal Article
TT - Evaluacion de resultados en atencion primaria: el proyecto MPAR-5.
CY - SPAIN
TA - Aten Primaria
JC - A5F
JID - 9111075
SB - IM
MH - Data Collection
MH - Feasibility Studies
MH - Human
MH - *Outcome Assessment (Health Care)/methods
MH - Primary Health Care/*standards
MH - *Program Evaluation
MH - Spain
MH - Support, Non-U.S. Gov't
EDAT- 2000/08/02 11:00
MHDA- 2000/08/29 11:01
PST - ppublish
SO - Aten Primaria 2000 May 31;25(9):653-60, 662.

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UI - 20280764
PMID- 10823258
DA - 20000905
DCOM- 20000905
LR - 20011003
IS - 0340-6245
VI - 83
IP - 5
DP - 2000 May
TI - A prospective controlled trial comparing weekly self-testing and self-dosing with the standard management of patients on stable oral anticoagulation.
PG - 661-5
AB - Oral anticoagulant therapy requires frequent laboratory controls of its intensity to assure therapeutic efficacy and to prevent potentially life threatening adverse events. It is generally assumed, that increasing the frequency of testing would lead to a better control of anticoagulation. We tested this hypothesis in a prospective controlled trial comparing weekly self-testing and self-dosing (self management) with the standard-management of these patients in an anticoagulation clinic. Only patients with stable anticoagulation were included into the study. We recorded 2733 weekly determinations of the intensity of anticoagulation (INR) in 49 patients on self-testing and self-dosing and 539 determinations of the INR in 53 patients on standard-management. Two intensities of anticoagulation were used in each group: a target INR of 3.5 for patients with artificial heart valves (target range: 2.5-4.5) and a target INR 2.5 (target range: 2.0-3.0) for patients with atrial fibrillation or venous thromboembolism. The deviation from the target INR, the fraction of INR determinations within the preset therapeutic range and the difference between the target INR and the actually achieved mean INR were the three major endpoints of the study. The mean deviation from the target INR was smaller in the groups of patients on self-management compared to the patients on standard-management. Individual deviations were significantly ($p < 0.0001$) dependent on the type of management in interaction with the treatment intensity in a general linear model. Patients on weekly self-testing and self-dosing had more INR values within the therapeutic range than patients on standard-management (86.2% vs. 80.1% at INR range 2.5-4.5; 82.2 vs. 68.9 at INR range 2.0-3.0). The achieved mean INR was almost identical with the target INR in the patients on self-management but was significantly ($p < 0.005$) below the target INR in the high intensity anticoagulation group on standard-management (target INR:3.5; achieved mean INR: 3.19; CI 0.95: 3.05-3.34). Our data show, that weekly self-testing and self-dosing leads to a better control of anticoagulation than standard treatment in an anticoagulation clinic.
AD - Division of Hematology and Hemostaseology, University of Vienna, Austria. herbert.watzke@akh-wien.ac.at
AU - Watzke HH
AU - Forberg E
AU - Svolba G
AU - Jimenez-Boj E

AU - Krinninger B
LA - eng
PT - Clinical Trial
PT - Controlled Clinical Trial
PT - Journal Article
CY - GERMANY
TA - Thromb Haemost
JC - VQ7
JID - 7608063
RN - 0 (Anticoagulants)
RN - 0 (Coumarins)
RN - 91-64-5 (coumarin)
SB - IM
CIN - Thromb Haemost. 2000 Nov;84(5):931-2
MH - Administration, Oral
MH - Adult
MH - Aged
MH - Algorithms
MH - Anticoagulants/*administration & dosage/adverse effects/pharmacology/therapeutic use
MH - Blood Coagulation/drug effects
MH - Case Management
MH - Comparative Study
MH - Coumarins/*administration & dosage/adverse effects/pharmacology/therapeutic use
MH - Drug Administration Schedule
MH - Female
MH - Heart Valve Prosthesis
MH - Hemorrhage/chemically induced
MH - Human
MH - *International Normalized Ratio/instrumentation
MH - Male
MH - Middle Age
MH - Patient Acceptance of Health Care
MH - Patient Compliance
MH - Patient Education
MH - Prospective Studies
MH - Self Administration
MH - Self Care
MH - Thromboembolism/drug therapy/prevention & control
EDAT- 2000/05/24 09:00
MHDA- 2000/09/09 11:01
PST - ppublish
SO - Thromb Haemost 2000 May;83(5):661-5.

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UI - 20280771
PMID- 10823265
DA - 20000905
DCOM- 20000905
LR - 20001218
IS - 0340-6245
VI - 83
IP - 5
DP - 2000 May
TI - A comparison of point-of-care instruments designed for monitoring oral anticoagulation with standard laboratory methods.
PG - 698-703
AB - Our study compared point-of-care (POC) device monitoring with traditional clinical laboratory methods device of patients on oral anticoagulant therapy. The POC devices used in the study were Coumatrak, CoaguChek, CoaguChek Plus, Thrombolytic Assessment System (TAS) PT-One, TAS PTNC, TAS
PT, Hemachron Jr. Signature, ProTime Microcoagulation System, and Medtronics ACT II. The clinical laboratory method used thromboplastins with different ISI values: Innovin and Thromboplastin C Plus (TPC). All POC INRs showed strong correlation with both laboratory methods, with correlation coefficients of >0.900. All POC methods demonstrated a significant ($p<0.05$) difference in INR values, except the TAS PTNC and ACT II INRs (p: 0.12 and 0.71 respectively) when compared with Innovin INRs. All POC INRs were significantly different from TPC generated INRs ($p<0.05$). Comparisons of the POC INRs to the group mean of the POC methods,
show higher correlation ($R>0.93$), but there were still significant ($p<0.05$) differences noted between the POC group INR mean and CoaguChek
Plus, ACT II, TAS PT-One, TAS PTNC, and Hemachron Jr Signature INRs. These data indicate that POC INR biases exist between laboratory methods and POC devices. Until a suitable whole blood INR standardization method is available, we conclude that clinicians using point-of-care anticoagulation monitoring should be aware of differences between POC and parent laboratory values.
AD - University of California, Davis Medical Center, Sacramento, USA.
AU - Gosselin R
AU - Owings JT
AU - White RH
AU - Hutchinson R
AU - Branch J
AU - Mahackian K
AU - Johnston M
AU - Larkin EC
LA - eng
PT - Journal Article
CY - GERMANY
TA - Thromb Haemost
JC - VQ7
JID - 7608063
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
RN - 9035-58-9 (Thromboplastin)
SB - IM
MH - Administration, Oral
MH - Animal
MH - Anticoagulants/*pharmacology/therapeutic use
MH - Calibration
MH - Comparative Study
MH - Human
MH - International Normalized Ratio/*instrumentation/standards
MH - *Point-of-Care Systems/standards
MH - Rabbits
MH - Reference Standards
MH - Reproducibility of Results
MH - Sensitivity and Specificity
MH - Thromboplastin/chemical synthesis/standards

MH - Warfarin/*pharmacology/therapeutic use

EDAT- 2000/05/24 09:00
MHDA- 2000/09/09 11:01
PST - ppublish
SO - Thromb Haemost 2000 May;83(5):698-703.

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UI - 20247813
PMID- 10786089
DA - 20000601
DCOM- 20000601
LR - 20001218
IS - 1438-3276
VI - 142
IP - 11
DP - 2000 Mar 16
TI - [Good therapy control requires a standardized test. Thrombosis ABC, 13: INR instead of Quick]
PG - 41
AD - Inneren Abteilung, DRK-Krankenhaus Westerwald, Hachenburg.
AU - Stiefelhagen P
LA - ger

PT - Journal Article
TT - Gute Therapiekontrolle braucht einen standardisierten Test. Thrombose-ABC, Folge 13: INR statt Quick.
CY - GERMANY
TA - MMW Fortschr Med
JC - DHP
JID - 100893959
RN - 0 (Anticoagulants)
RN - 0 (Coumarins)
RN - 91-64-5 (coumarin)
SB - IM
MH - Anticoagulants/adverse effects/*therapeutic use
MH - Comparative Study
MH - Coumarins/adverse effects/*therapeutic use
MH - Human
MH - *International Normalized Ratio
MH - Long-Term Care
MH - Predictive Value of Tests
MH - *Prothrombin Time
MH - Thromboembolism/blood/*drug therapy
EDAT- 2000/04/29 09:00
MHDA- 2000/06/03 09:00
PST - ppublish
SO - MMW Fortschr Med 2000 Mar 16;142(11):41.

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UI - 20171817
PMID- 10704660
DA - 20000411
DCOM- 20000411
LR - 20001218
IS - 0049-3848
VI - 97
IP - 6
DP - 2000 Mar 15
TI - Comparison between routine laboratory prothrombin time measurements and
fingerstick determinations using a near-patient testing device (Pro-Time).
PG - 495-8
AD - Department of Clinical and Experimental Medicine, Thrombosis Center, University of Padova School of Medicine, Padova, Italy.
AU - Biasiolo A
AU - Rampazzo P
AU - Furnari O
AU - Filippi B
AU - Pengo V
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - Thromb Res
JC - VRN
JID - 0326377
RN - 0 (Anticoagulants)
SB - IM
MH - Anticoagulants/administration & dosage/therapeutic use
MH - Blood Coagulation Tests/instrumentation/*methods
MH - Comparative Study
MH - Diagnostic Tests, Routine/*methods
MH - Human
MH - International Normalized Ratio
MH - *Prothrombin Time
MH - Reproducibility of Results
MH - Treatment Outcome
EDAT- 2000/03/08 09:00
MHDA- 2000/04/15 09:00
AID - S0049384899001917 [pii]
PST - ppublish
SO - Thromb Res 2000 Mar 15;97(6):495-8.

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UI - 20225638
PMID- 10762302
DA - 20000518
DCOM- 20000518
LR - 20001218
IS - 0141-9854
VI - 22
IP - 1
DP - 2000 Feb
TI - Anti-coagulant monitoring service delivery: a comparison of costs of hospital and community outreach clinics.
PG - 33-40
AB - Anti-coagulated patients are monitored at regular intervals to ensure that their warfarin dosage is appropriate for their target International Normalized Ratio. The traditional setting for this monitoring has been the hospital clinic. Technological advances allow-- and with growing numbers of anti-coagulated patients, are leading to-- greater provision of monitoring clinics outside the hospital, at a more convenient location nearer patients' homes. This paper discusses the differences in organization between a hospital clinic and one set in the community

(although provided by the hospital), and compares their costs. The comparison demonstrates the greater average cost per appointment in outreach of pound sterling 13.12 under current arrangements. Estimates are presented of incremental cost per appointment of pound sterling 3.93 and pound sterling 15.88 for a 10% increase in weekly patient numbers put through hospital and outreach clinics, respectively. Cost estimates are also presented for suggested alterations to hospital clinics that may reduce patient inconvenience, and the conditions under which outreach provision might be expanded at comparable cost to hospital provision are also examined.
AD - Health Economics Research Group, Brunel University, Uxbridge, Middlesex, UK. andrew.davies@brunel.ac.uk
AU - Davies A
AU - Buxton MJ
AU - Patterson DL
AU - Webster-King J
LA - eng
PT - Journal Article
CY - ENGLAND
TA - Clin Lab Haematol
JC - DKF
JID - 7907061
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - IM
MH - Aged
MH - Anticoagulants/administration & dosage/blood/economics
MH - Community Health Services/economics
MH - Community-Institutional Relations/economics
MH - Comparative Study
MH - Costs and Cost Analysis
MH - Drug Monitoring/*economics/methods
MH - England
MH - Female
MH - Hospitalization/economics
MH - Human
MH - International Normalized Ratio/economics/standards
MH - Male
MH - Middle Age
MH - National Health Programs/economics
MH - Questionnaires
MH - Support, Non-U.S. Gov't
MH - Time Factors
MH - Travel/economics
MH - Warfarin/administration & dosage/*blood/*economics
EDAT- 2000/04/13 09:00
MHDA- 2000/05/20 09:00
AID - clh282 [pii]
PST - ppublish
SO - Clin Lab Haematol 2000 Feb;22(1):33-40.

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UI - 20132286
PMID- 10668852
DA - 20000222
DCOM- 20000222
LR - 20001218
IS - 0009-9236
VI - 67
IP - 1
DP - 2000 Jan
TI - Overconsumption detected by electronic drug monitoring requires subtle interpretation.
PG - 44-7
AB - BACKGROUND: Electronic compliance monitoring has provided new variables to
describe drug intake behavior and new strategies to improve compliance. However, as evaluated in this study, the recording of opening events of pill bottles does not necessarily mean drug intake. METHODS: In an open 3-week trial with an oral vitamin combination, drug intake was recorded with use of an electronic pill box that contained 25 capsules and that registered each opening of the bottle. Thirty-seven patients were asked to take one capsule every morning for 21 days. Opening and closing events were related to the results of pill counts and patient interviews at the end of the trial. RESULTS: Drug consumption was 101.8% (663 recorded opening and closing events) in the 31 patients who completed the trial. Pill boxes were opened more than once by 10 patients on at least one monitored day. For seven patients the total number of openings was >25 (range, 26 to 29) and thus exceeded the number of capsules provided. A third interview of these patients revealed real overconsumption in only two patients. Six patients remembered that they had shown the device to relatives or friends or that they had checked to see whether they had closed the pill box well, thus turning a "curiosity event" into a drug intake event. CONCLUSION: In short-term studies particularly, such curiosity events may substantially modify the electronic assessment of compliance surrogates. In these trials the combined evaluation of electronic openings, pill counts, and interviews may be a suitable way to reveal such openings without pill intake.
AD - Department of Internal Medicine, University Hospital, Basel, Switzerland.

AU - Arnet I
AU - Haefeli WE
LA - eng
PT - Clinical Trial
PT - Journal Article
CY - UNITED STATES
TA - Clin Pharmacol Ther
JC - DHR
JID - 0372741
RN - 0 (Vitamins)
SB - AIM
SB - IM
MH - Administration, Oral
MH - Adult
MH - Aged
MH - Female
MH - Human
MH - Male
MH - Middle Age
MH - Patient Compliance/*statistics & numerical data
MH - Patient Discharge
MH - Self Administration/*statistics & numerical data
MH - Support, Non-U.S. Gov't
MH - Vitamins/administration & dosage
EDAT- 2000/02/11 09:00
MHDA- 2000/02/26 09:00

PST - ppublish
SO - Clin Pharmacol Ther 2000 Jan;67(1):44-7.

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UI - 20132638
PMID- 10669154
DA - 20000225
DCOM- 20000225
LR - 20001218
IS - 0340-6245
VI - 83
IP - 1
DP - 2000 Jan
TI - The management of oral anticoagulant therapy: the patient's point of view.
PG - 49-53
AB - The aims of this study were to investigate on the general adhesion of the patients to oral anticoagulant therapy, and particularly on the quality of life of our patients, the doctor-patient relationship and the Centre-patient relationship. For this purpose we administered a questionnaire containing 17 main questions each with a maximum of 4 secondary questions. The questionnaire was administered to two groups of 127 and 137 oral anticoagulated patients (127 males and 137 females, mean age 55 +/- 19 years), followed at two Anticoagulation Clinics, in two Italian cities, Cagliari (Sardinia) and Padua (North East Italy). The cities differed in the number of patients monitored and the management modalities of anticoagulation. The results show that oral anticoagulant therapy does not limit the life-style of the patients. Only 11% of the patients complain of limitations to their daily life. Fifty-two percent believe their health has improved, and 87% are not afraid of negative consequences. The doctor-patient relationship is considered very important by 96% of patients. Seventy-eight percent refer to the Anticoagulation Clinic also for other health problems, 93% consider it important to be assessed by the doctor at the Anticoagulation Clinic, while 83% believe the doctor should always hand out the results personally. We conclude that in general oral anticoagulant therapy is accepted by the majority of patients, in spite of the need for periodic monitoring. The doctor-patient relationship should be taken into account, even in the case of a monitored, computer-assisted method of dose-adjustment.
AD - Dipartimento di Scienze Mediche, University of Cagliari, Italy.
AU - Barcellona D
AU - Contu P
AU - Sorano GG
AU - Pengo V
AU - Marongiu F
LA - eng
PT - Journal Article
CY - GERMANY
TA - Thromb Haemost
JC - VQ7
JID - 7608063
RN - 0 (Anticoagulants)
SB - IM
MH - Administration, Oral
MH - Adult
MH - Aged
MH - Anticoagulants/*administration & dosage
MH - Female
MH - Human
MH - Male
MH - Middle Age
MH - *Physician-Patient Relations
MH - *Quality of Life
MH - Questionnaires
MH - Thromboembolism/*prevention & control/*psychology
EDAT- 2000/02/11 09:00
MHDA- 2000/03/04 09:00
PST - ppublish
SO - Thromb Haemost 2000 Jan;83(1):49-53.

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UI - 99426395
PMID- 10498107
DA - 19991005
DCOM- 19991005
LR - 20001218
IS - 0002-838X
VI - 60
IP - 3
DP - 1999 Sep 1
TI - Monitoring warfarin therapy.
PG - 764, 766
AU - Beanland DR
AU - Dorsey DA
LA - eng
PT - Comment
PT - Letter
CY - UNITED STATES
TA - Am Fam Physician
JC - 3BT
JID - 1272646
RN - 0 (Anticoagulants)
RN - 12001-79-5 (Vitamin K)
RN - 81-81-2 (Warfarin)
SB - AIM
SB - IM
CON - Am Fam Physician. 1999 Feb 1;59(3):635-46
MH - Anticoagulants/*adverse effects
MH - Case Report
MH - Epistaxis/*chemically induced
MH - Human
MH - International Normalized Ratio
MH - Male
MH - Middle Age
MH - Prothrombin Time
MH - Vitamin K/therapeutic use
MH - Warfarin/*adverse effects
EDAT- 1999/09/25 09:00
MHDA- 1999/09/25 09:00
PST - ppublish
SO - Am Fam Physician 1999 Sep 1;60(3):764, 766.

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UI - 99318310
PMID- 10391426
DA - 19990910
DCOM- 19990910
LR - 20001218
IS - 0277-0008
VI - 19
IP - 6
DP - 1999 Jun
TI - Outpatient self-management of warfarin therapy: a pilot study.
PG - 787-93
AB - Self-testing and adjusting of warfarin dosages by patients is an evolving strategy for management of oral anticoagulation. We performed this open, prospective, 3-month pilot study to assess the feasibility of conducting a large, randomized trial comparing self-managed with physician-managed anticoagulation. Ten competent patients with planned anticoagulation for at least 3 months were provided education on warfarin therapy and trained to use an individualized warfarin nomogram. International normalized ratios (INRs) were determined weekly for 12 weeks and reported with warfarin dosages to the investigator for the first 8 weeks only. Eight patients elected to use a home monitor (ProTime) to measure INRs. Patients maintained 76.5% (range 50-91.7%) of INRs within the target range. In 119
dosage adjustment decisions, there were only 3 errors (2.5%). No bleeding or thrombotic complications occurred. To confirm concordance, initial and final INRs were measured concurrently by the ProTime monitor and laboratory. The mean absolute difference for 16 paired INR determinations was 0.33 (range 0.02-0.9). All patients expressed satisfaction and a desire to continue with self-management. This pilot study provides support for conducting a prospective, large-scale, randomized trial.
AD - Pharmaceutical Sciences CSU, Vancouver General Hospital, Faculty of Pharmaceutical Sciences, University of British Columbia, Canada.
AU - Sunderji R
AU - Campbell L
AU - Shalansky K
AU - Fung A
AU - Carter C
AU - Gin K
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - Pharmacotherapy
JC - PAR
JID - 8111305
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - IM
MH - Administration, Oral
MH - Adult
MH - Aged
MH - *Ambulatory Care
MH - Anticoagulants/*administration & dosage
MH - Comparative Study
MH - *Drug Monitoring/methods
MH - Female
MH - Human
MH - International Normalized Ratio
MH - Male
MH - Middle Age
MH - Pilot Projects
MH - Prospective Studies
MH - Self Administration
MH - Warfarin/*administration & dosage
EDAT- 1999/07/03 10:00
MHDA- 1999/07/03 10:00
PST - ppublish
SO - Pharmacotherapy 1999 Jun;19(6):787-93.

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UI - 99309592
PMID- 10380494
DA - 19990709
DCOM- 19990709
LR - 20001218
IS - 0023-7205
VI - 96
IP - 20
DP - 1999 May 19
TI - [Better AVK treatment with self monitoring. Dosage can be regulated in time]
PG - 2482, 2485-7
AB - As long-term anticoagulant treatment, with warfarin for instance, is associated with a risk of both thrombotic and thrombolytic complications, blood testing for dose regulation is necessary at 3-8-week intervals, which is expensive and inconvenient for patients who must take time off work and travel to and fro. A new technique, using small portable monitors designed for home use by patients, makes self-management of anticoagulant treatment possible. In Germany, over 25,000 patients had their own monitor by the end of 1998. After appropriate instruction, the German patients are able to monitor their prothrombin time and adjust their anticoagulant treatment accordingly. In case of problems they contact their GP. In a two-year pilot study conducted at the Anticoagulation Clinic of Sahlgrenska University Hospital, Gothenburg, in 1996-98, where 51 patients on long-term anticoagulant treatment were trained in self-management, the results of over 1,000 patient-hours of treatment showed self-management to be at least as safe as management by the clinic. The level of patient satisfaction is high, in terms of safety and freedom from regular hospital attendance during working hours, and the convenience of self-monitoring on holiday or business trips. As the patients do their testing once a week, the risk of complications is also reduced.
AD - Koagulationscentrum, Sahlgrenska Universitetssjukhuset, Goteborg.
AU - Stigendal L
AU - Andre U
AU - Christenson B
LA - swe
PT - Journal Article
TT - Battre AVK-terapi med egenkontroll. Dosen kan justeras i tid.
CY - SWEDEN
TA - Lakartidningen
JC - LON
JID - 0027707
RN - 0 (Anticoagulants)
RN - 12001-79-5 (Vitamin K)
RN - 81-81-2 (Warfarin)
SB - IM

MH - Anticoagulants/*administration & dosage/adverse effects
MH - *Blood Coagulation Tests/economics/instrumentation/standards
MH - Germany
MH - Human
MH - Patient Education
MH - Patient Satisfaction
MH - Pilot Projects
MH - Prothrombin Time
MH - Quality Assurance, Health Care
MH - Quality of Life
MH - *Self Care
MH - Sweden
MH - Vitamin K/*blood
MH - Warfarin/therapeutic use
EDAT- 1999/06/25 10:00
MHDA- 1999/06/25 10:00
PST - ppublish
SO - Lakartidningen 1999 May 19;96(20):2482, 2485-7.

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UI - 99309593
PMID- 10380495
DA - 19990709
DCOM- 19990709
LR - 20001218
IS - 0023-7205
VI - 96
IP - 20
DP - 1999 May 19
TI - [Coordinated Swedish transfer is recommended during 1999. Prothrombin complex measurement should be indicated as a quota, not percent]
PG - 2489-91
AD - Avdelningen for klinisk kemi, Karolinska sjukhuset, Stockholm.
AU - Egberg N
AU - Hillarp A
AU - Johnsson H
AU - Lindahl T
AU - Stigendal L
LA - swe
PT - Journal Article
TT - Samordnad svensk overgang rekommenderas under 1999. Protrombinkomplexmatning bor anges som en kvot, inte i procent.
CY - SWEDEN
TA - Lakartidningen
JC - LON
JID - 0027707
RN - 0 (Anticoagulants)
RN - 12001-79-5 (Vitamin K)
SB - IM
MH - Anticoagulants/administration & dosage/adverse effects
MH - Calibration
MH - Human
MH - *International Normalized Ratio
MH - *Prothrombin Time
MH - Quality Assurance, Health Care
MH - Sweden
MH - Vitamin K/blood
EDAT- 1999/06/25 10:00
MHDA- 1999/06/25 10:00
PST - ppublish
SO - Lakartidningen 1999 May 19;96(20):2489-91.

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UI - 20176470
PMID- 10711130
DA - 20000713
DCOM- 20000713
LR - 20001218
IS - 1088-5471
VI - 3
IP - 3
DP - 1999 May-Jun
TI - Outpatient management of patients on warfarin.
PG - 280-9
AB - The recent publication of the American College of Chest Physicians (ACCP) Fifth Consensus Conference on Antithrombotic Therapy provides the primary care clinician with a thorough guideline for the treatment and prevention of thromboembolic diseases. These recommendations are reviewed in this article as they relate to the outpatient management of patients receiving warfarin. Common drug-drug, drug-food, and drug-disease interactions also are reviewed along with practical dosing recommendations.
AD - Veterans Affairs Medical Center, West Palm Beach, FL 33410, USA.
AU - Beckey NP
LA - eng
PT - Journal Article
PT - Review
PT - Review, Tutorial
CY - UNITED STATES
TA - Lippincotts Prim Care Pract
JC - CU6
JID - 9706704
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - N
MH - Ambulatory Care/*methods
MH - Anticoagulants/*administration & dosage
MH - Drug Interactions
MH - Drug Monitoring/*methods/nursing
MH - Human
MH - International Normalized Ratio
MH - Patient Selection
MH - Practice Guidelines
MH - Primary Health Care/*methods
MH - Warfarin/*administration & dosage
RF - 8
EDAT- 2000/03/11 09:00
MHDA- 2000/07/15 11:00
PST - ppublish
SO - Lippincotts Prim Care Pract 1999 May-Jun;3(3):280-9.

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UI - 99181273

PMID- 10081432

DA - 19990401
DCOM- 19990401
LR - 20001218
IS - 1081-5880
VI - 5
IP - 3
DP - 1999 Feb 25
TI - Home monitoring for warfarin users.
PG - 5
LA - eng
PT - News
CY - UNITED STATES
TA - Health News
JC - C23
JID - 9800495
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - K
MH - Anticoagulants/*administration & dosage
MH - Drug Monitoring/*methods
MH - *Home Nursing
MH - Human
MH - Self Care/instrumentation
MH - Warfarin/*administration & dosage
EDAT- 1999/03/19 03:02
MHDA- 1999/03/19 03:02
PST - ppublish
SO - Health News 1999 Feb 25;5(3):5.

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UI - 99114588
PMID- 9916557
DA - 19990128
DCOM- 19990128
LR - 20001218
IS - 1051-5313
VI - 9
IP - 5
DP - 1999 Jan
TI - A new approach to monitoring anticoagulation therapy: testing prothrombin time at home.
PG - 2-4
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - Harv Heart Lett
JC - C2Z
JID - 9425723
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - K
MH - Anticoagulants/*therapeutic use
MH - Drug Monitoring/methods
MH - Human
MH - International Normalized Ratio
MH - *Prothrombin Time
MH - *Self Care
MH - Warfarin/*therapeutic use
EDAT- 1999/01/23 19:28
MHDA- 1999/01/23 19:28
PST - ppublish
SO - Harv Heart Lett 1999 Jan;9(5):2-4.

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UI - 99257149
PMID- 10327217
DA - 19990713
DCOM- 19990713
LR - 20001218
IS - 0094-6176
VI - 25
IP - 1
DP - 1999
TI - Management of oral anticoagulant therapy in Italy.
PG - 27-31
AB - The clinical outcome of oral anticoagulant therapy (OAT) depends on how successful physicians and patients are in achieving and maintaining levels of anticoagulation capable of preventing thromboembolic events without increasing the risk of hemorrhagic complications. Concerning the patient, education and compliance are the major problems. Concerning the physicians, the management of patients receiving OAT is a complex task that requires frequent laboratory testing, dosage regulation, prompt diagnosis, and treatment of thromboembolic and hemorrhagic events. Anticoagulation clinics, which provide patient education, close monitoring of prothrombin times and continuous clinical surveillance, have been claimed to help in improving the overall quality of OAT. In 1989, following the experience of other countries, a national Federation of Centers for the Surveillance of Anticoagulant (FCSA) therapies was founded in Italy. In the last 10 years the main objectives of FCSA have been: (1) favoring the development of new centers in areas of the country lacking proper services; (2) standardazing the management of OAT by recommending organizational and technical procedures; (3) stimulating participation in laboratory quality-control programs; (4) implementing continuous education programs for medical and paramedical personnel and for the patients themselves; (5) making health administrators aware of the social impact of OAT and of the need for the formal recognition of the centers; and (6) planning and organizing multicenter studies. Some of these goals have been successfully achieved, but problems remain to be solved to guarantee an optimal control of OAT in the entire national territory.
AD - Institute of Internal and Vascular Medicine, University of Perugia, Italy.
AU - Berrettini M
AU - Agnelli G
LA - eng
PT - Journal Article
PT - Review
PT - Review, Tutorial
CY - UNITED STATES
TA - Semin Thromb Hemost
JC - UKS
JID - 0431155
RN - 0 (Anticoagulants)
SB - IM

MH - Administration, Oral
MH - Anticoagulants/administration & dosage/*therapeutic use
MH - Human
MH - Italy
MH - Thrombosis/*drug therapy
RF - 8
EDAT- 1999/05/18 05:23
MHDA- 1999/05/18 05:23
PST - ppublish
SO - Semin Thromb Hemost 1999;25(1):27-31.

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UI - 99257164
PMID- 10327232
DA - 19990713
DCOM- 19990713
LR - 20001218
IS - 0094-6176
VI - 25
IP - 1
DP - 1999
TI - The effect of self-monitoring the INR on quality of anticoagulation and quality of life.
PG - 123-6
AB - In a prospective cohort study the influence of self-monitoring of the International Normalized Ratio (INR) was examined on 100 consecutive patients for a period of 6 months. Quality of life changed in a positive way. Independence and better organization of vacation and spare time were the most frequently mentioned advantages of the new method. Quality of anticoagulation by using a self-monitoring device was improved compared to the values before using the self-monitoring device. For measuring the INR, the usage of a portable monitor as the primary method can be recommended in selected patients receiving oral long-term anticoagulation.
AD - 1st Department of Medicine, Faculty of Clinical Medicine Mannheim, University of Heidelberg, Germany.
AU - Kulinna W
AU - Ney D
AU - Wenzel T
AU - Heene DL
AU - Harenberg J
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - Semin Thromb Hemost
JC - UKS
JID - 0431155
RN - 0 (Anticoagulants)
SB - IM
MH - *Anticoagulants/administration & dosage/adverse effects
MH - Cohort Studies
MH - Female
MH - Human
MH - International Normalized Ratio
MH - Male
MH - Middle Age
MH - Prospective Studies
MH - Quality of Life
MH - Self Administration/psychology
MH - *Thrombosis/drug therapy/psychology
EDAT- 1999/05/18 05:23
MHDA- 1999/05/18 05:23
PST - ppublish
SO - Semin Thromb Hemost 1999;25(1):123-6.

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UI - 99257161
PMID- 10327229
DA - 19990713
DCOM- 19990713
LR - 20001218
IS - 0094-6176
VI - 25
IP - 1
DP - 1999
TI - Cost-effectiveness of self-managed anticoagulant therapy in Germany.
PG - 103-7
AB - In this study, the cost-effectiveness of anticoagulation self-management--which is now established in Germany--was compared with the conventional method of monitoring oral anticoagulant therapy by the patient's family physician or by a specialist. Costs were determined based on the usual conditions in Germany such as frequency of testing and control testing, scope of the tests, and diagnostic and therapeutic standards for thromboembolic or bleeding complications. In addition to direct monitoring costs, we determined the costs for treating minor and serious complications and used them to calculate overall therapy costs. The incidence of complications was estimated based on the results of more recent studies. The only costs considered in this study were those covered by the primary cost carrier--the government-controlled health insurance funds--and included outpatient visits and, in cases of serious complications, acute inpatient treatment and rehabilitation. It was shown that the costs to treat minor complications only slightly affected annual, overall treatment costs. The potential reduction in incidences of serious bleeding and thromboembolic complications due to anticoagulation self-management--which is independent of the indication for oral anticoagulation--reduced overall therapy costs from DM 2,061.48/patient-year for conventional therapeutic methods to DM 1,342.46/patient-year for patients under self-management of anticoagulation.
AD - Department of Hemostaseology and Transfusion Medicine, Kerckhoff-Klinik, Bad Nauheim, Germany.
AU - Taborski U
AU - Wittstamm FJ
AU - Bernardo A
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - Semin Thromb Hemost
JC - UKS
JID - 0431155
RN - 0 (Anticoagulants)
SB - IM
MH - *Anticoagulants/administration & dosage/economics/therapeutic use
MH - Cost-Benefit Analysis

MH - Germany
MH - Human
MH - Self Administration/economics
MH - *Thrombosis/drug therapy/economics
EDAT- 1999/05/18 05:23
MHDA- 1999/05/18 05:23
PST - ppublish
SO - Semin Thromb Hemost 1999;25(1):103-7.

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UI - 98281368
PMID- 10178826
DA - 19980608
DCOM- 19980608
LR - 20001218
IS - 1089-5841
VI - 3
IP - 5
DP - 1998 May
TI - Coagulation rates check at home.
PG - 52
LA - eng
PT - News
CY - UNITED STATES
TA - Telemed Virtual Real
JC - CTN
JID - 9617314
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - T
MH - Anticoagulants/*administration & dosage
MH - *Blood Coagulation Tests/instrumentation
MH - Hip Prosthesis
MH - Human
MH - *Self Care
MH - Warfarin/*administration & dosage
EDAT- 1998/04/07
MHDA- 1998/04/07
PST - ppublish
SO - Telemed Virtual Real 1998 May;3(5):52.

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UI - 97379681
PMID- 9236480
DA - 19970807
DCOM- 19970807
LR - 20001218
IS - 0002-9343
VI - 103
IP - 1
DP - 1997 Jul
TI - Determinants of compliance with anticoagulation: A case-control study.
PG - 11-7
AB - BACKGROUND: The number of patients for whom long-term anticoagulation is indicated has increased dramatically over the past decade. Good patient compliance is necessary to safely realize the benefits of anticoagulation,

yet barriers to compliance with anticoagulation therapy have not been studied. METHODS: We conducted a case-control study in the Anticoagulation Therapy Unit (ATU) at Massachusetts General Hospital. Forty-three patients who had been discharged from the ATU for noncompliance (cases) and 89 randomly selected compliant ATU controls were interviewed. Noncompliant cases had self-discontinued warfarin or were taking warfarin with inadequate monitoring of international normalized ratio (INR) levels. Telephone interviews assessed sociodemographic features, indication for anticoagulation, patient satisfaction, and health beliefs. RESULTS: Noncompliant cases were more likely to be younger (mean 53.7 years versus 68.7 years, $P < 0.0001$), male (odds ratio [OR] 3.5, 95% confidence interval [CI] 1.5, 8.2) and nonwhite (OR 6.4, 95% CI 1.9, 21.9), and less likely to have had a stroke or transient ischemic attack (OR 0.2, 95% CI 0.1, 0.7). In open-ended questioning, cases were more likely to report that they did not know why warfarin had been prescribed (OR 4.4, 95% CI 1.4, 14.2). Noncompliant cases were more likely not to have a regular physician (OR 11.1, 95% CI 3.6, 50.0); among patients with a regular physician, noncompliant cases were more likely to feel dissatisfied. Examination of health beliefs revealed that noncompliant cases felt more burdened by taking warfarin, and perceived fewer health benefits. CONCLUSIONS: Patients who are noncompliant with warfarin share distinctive clinical characteristics. Notably, younger, male patients who have not experienced a thromboembolic event are more likely to forego INR testing or to stop anticoagulation therapy completely. Improved patient education, physician involvement, and ease of monitoring may improve compliance, particularly among younger male patients.
AD - General Internal Medicine Unit, Massachusetts General Hospital, Boston USA.
AU - Arnsten JH
AU - Gelfand JM
AU - Singer DE
LA - eng
ID - 5T32PE11001-07/PE/BHP
PT - Journal Article
CY - UNITED STATES
TA - Am J Med
JC - 3JU
JID - 0267200
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - AIM
SB - IM
MH - Adult
MH - Age Factors
MH - Aged
MH - Anticoagulants/*therapeutic use
MH - Blood Coagulation Tests
MH - Case-Control Studies
MH - Female
MH - Human
MH - Male
MH - Middle Age
MH - Odds Ratio
MH - *Patient Compliance
MH - Questionnaires
MH - Sex Factors

MH - Support, Non-U.S. Gov't
MH - Support, U.S. Gov't, P.H.S.
MH - Warfarin/therapeutic use
EDAT- 1997/07/01
MHDA- 1997/07/01
PST - ppublish
SO - Am J Med 1997 Jul;103(1):11-7.

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UI - 97339713
PMID- 9196312
DA - 19970805
DCOM- 19970805
LR - 20001218
IS - 1010-7940
VI - 11
IP - 5
DP - 1997 May
TI - Self management of oral anticoagulant therapy after heart valve replacement.
PG - 935-42
AB - OBJECTIVE: Patients with mechanical heart valves require lifelong oral anticoagulant treatment which entails frequent blood sampling and dosage adjustment. The purpose of this study was to investigate the feasibility of letting heart valve operated patients manage blood specimen analysis and dosage adjustment themselves. METHODS: A total of 21 patients were enrolled in the study and followed for at least 9 months postoperatively. Immediately after the heart valve operation they were trained in operating a CoaguChek international normal ratio (INR) monitor to analyze capillary whole blood samples. Subsequently training in dosage adjustment was accomplished and all patients were considered fully capable of self management after 30 weeks. In the training period, parallel laboratory INR measurements were made at 3-4 week intervals for reference. A control group of 20 patients was matched, respectively, to the study group. The INR target range was 2.0-3.0. RESULTS: Out of the 21 study patients 19 continued self management beyond 9 months. The median INR value obtained with the monitor was within therapeutic target range for all study patients and only 15 out of 20 control patients were within this range. The mean systematic deviation between laboratory and CoaguChek INR was 7.8% but each patient had a constant characteristic deviation from -11 to +21%. The study patients were within therapeutic target range 77% of the time compared with 53% for the control patients. CONCLUSIONS: Self management of oral anticoagulation is feasible for selected patients and constitutes a significant service improvement compared with conventional management. The CoaguChek monitor seems sufficiently accurate and reliable for self testing and the treatment quality is comparable or even better than conventional management. Assessment of the rate of bleeding and thrombo-embolic events shall be settled in studies comprising larger number of patients.
AD - Department of Cardiothoracic and Vascular Surgery, Skejby Sygehus, Aarhus University Hospital, Aarhus N, Denmark. skejmh@aau.dk
AU - Hasenkam JM
AU - Kimose HH
AU - Knudsen L
AU - Gronnesby H
AU - Halborg J
AU - Christensen TD
AU - Attermann J
AU - Pilegaard HK
LA - eng
PT - Journal Article
CY - NETHERLANDS
TA - Eur J Cardiothorac Surg
JC - AOJ
JID - 8804069
RN - 0 (Anticoagulants)
SB - IM
MH - Administration, Oral
MH - Adult
MH - Aged
MH - Anticoagulants/*administration & dosage/therapeutic use
MH - Blood Coagulation Tests/methods
MH - *Blood Specimen Collection
MH - Case-Control Studies
MH - Feasibility Studies
MH - Female
MH - Follow-Up Studies
MH - *Heart Valve Prosthesis
MH - Human
MH - Male
MH - Middle Age
MH - Postoperative Care
MH - Self Administration
MH - *Self Care
MH - Support, Non-U.S. Gov't
MH - Time Factors
EDAT- 1997/05/01
MHDA- 1997/05/01
PST - ppublish
SO - Eur J Cardiothorac Surg 1997 May;11(5):935-42.

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UI - 97267345
PMID- 10166414
DA - 19970514
DCOM- 19970514
LR - 20001218
IS - 0891-1525
VI - 10
IP - 10
DP - 1996 Oct
TI - Self-test for pro-times: some day, for some patients.
PG - 5-7
AU - Titus K
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - CAP Today
JC - CAP
JID - 8704824
RN - 0 (Anticoagulants)

SB - T
MH - Anticoagulants/*therapeutic use
MH - Drug Monitoring
MH - Hematologic Tests/*instrumentation
MH - Human
MH - *Prothrombin Time
MH - Self Care/*instrumentation
EDAT- 1996/09/04
MHDA- 1996/09/04
PST - ppublish
SO - CAP Today 1996 Oct;10(10):5-7.

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UI - 96048968
PMID- 7487240
DA - 19951130
DCOM- 19951130
LR - 20001218
IS - 0003-9926
VI - 155
IP - 20
DP - 1995 Nov 13
TI - Long-term patient self-management of oral anticoagulation.
PG - 2185-9
AB - BACKGROUND: The management of oral anticoagulation is fraught with difficulties. This study assessed a new model of anticoagulation management regarding the ability, safety, and efficacy of patients to self-monitor and self-adjust the dose of their oral anticoagulants guided by a capillary whole-blood prothrombin time (PT) monitor. METHODS: This investigation is a retrospective cohort study of 20 patients compared with 20 matched control patients receiving oral anticoagulation at a tertiary medical institution. RESULTS: Study patients monitored their PTs 2153 times during a mean interval of 44.7 months compared with 1608 PTs in matched control patients during a mean interval of 42.5 months. Study patients made an average of 11.5 dosage changes per patient, contrasted with 22.7 changes per control patient ($P < .001$). The PTs in study patients were within the recommended therapeutic range in 88.6% (95% confidence interval, 87.2 to 89.9) of the determinations compared with 68.0% (95% confidence interval, 65.7 to 70.3; $P < .001$) of the determinations made by the matched control patients. In response to the 2153 PTs, study patients made 67 (3.1%) dosage decisions that were considered incorrect based on physician guidelines. None of these changes led to adverse outcomes. There was no significant difference in complication rates between the two groups. CONCLUSIONS: Results from what
is the first long-term study of patient self-monitoring of PTs and self-adjustment of the warfarin sodium dosage for oral anticoagulation suggest that patients can successfully measure their own PTs, adjust their own warfarin dosage, and achieve a degree of therapeutic effectiveness at least as good, if not better than patients managed in an anti-coagulation clinic. Larger, prospective, randomized trials are needed to confirm the efficacy and safety of this new approach to therapy and to assess its cost-effectiveness.
AD - Department of Medicine, University of Massachusetts Medical School, Worcester, USA.
AU - Ansell JE
AU - Patel N
AU - Ostrovsky D
AU - Nozzolillo E
AU - Peterson AM
AU - Fish L
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - Arch Intern Med
JC - 7FS
JID - 0372440
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
SB - AIM
SB - IM
MH - Administration, Oral
MH - Adolescence
MH - Adult
MH - Aged
MH - Anticoagulants/*administration & dosage
MH - Capillaries
MH - Child
MH - Child, Preschool
MH - Female
MH - Human
MH - Infant
MH - Male
MH - Matched-Pair Analysis
MH - Middle Age
MH - Prothrombin Time
MH - Retrospective Studies
MH - Self Administration
MH - Warfarin/administration & dosage
EDAT- 1995/11/13
MHDA- 1995/11/13
PST - ppublish
SO - Arch Intern Med 1995 Nov 13;155(20):2185-9.

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UI - 95387184
PMID- 7658268
DA - 19951005
DCOM- 19951005
LR - 20001218
IS - 0022-3476
VI - 127
IP - 3
DP - 1995 Sep
TI - Home monitoring of warfarin therapy in children with a whole blood prothrombin time monitor.
PG - 389-94
AB - We prospectively evaluated a capillary whole blood prothrombin time (PT) monitor (Biotrack, Ciba Corning) in an outpatient pediatric anticoagulation clinic (40 clinic patients) and in age-matched healthy subjects (30 control subjects). Subsequently, 23 children requiring warfarin therapy were placed on a home program (home patients) using the PT monitor; their parents were trained and the results followed by clinic staff. The PT results were reported as internationalized normalized ratios

(INRs). The laboratory and PT-monitor INR values were similar for the clinic patients and the control subjects (y = 0.76x + 0.38; r = 0.93; p < 0.001). The accuracy of the PT monitor (the difference between INR values and the laboratory INR) was best at an INR of 2.5 to 3.5; 90% of paired INR values were within 0.8 INR units. The average duration of monitoring for home patients was 13 months (range, 2 to 60 months). They had an average of 3 dose measurements (range, 1 to 11 measurements) and 1.8 dose changes (range, 0.6 to 4.5 changes) per month. Of the 599 measurements, 63% were within the therapeutic range, similar to those for clinic patients; the dose requirements were also similar. There was 1 significant bleeding event, a subdural hematoma in a patient with an INR of 4.1, and 1 catheter-related thrombotic event with an INR of 1.2; both children recovered. Of the 23 families, one discontinued home monitoring because of parental discomfort, 2 children died of their primary disease, 6 completed warfarin therapy, and 14 remain on the home program. We conclude that the whole blood PT/INR monitor is safe and offers practical advantages to children requiring anticoagulation.
AD - Children's Hospital at Chedoke-McMaster, Hamilton, Ontario, Canada.
AU - Massicotte P
AU - Marzinotto V
AU - Vegh P
AU - Adams M
AU - Andrew M
LA - eng
PT - Journal Article
CY - UNITED STATES
TA - J Pediatr
JC - JLZ
JID - 0375410
RN - 81-81-2 (Warfarin)
SB - AIM
SB - IM
MH - Adolescence
MH - Child, Preschool
MH - Comparative Study
MH - Drug Monitoring/instrumentation/*methods/statistics & numerical data
MH - Evaluation Studies
MH - Female
MH - Home Nursing/*methods/statistics & numerical data
MH - Human
MH - Infant
MH - Linear Models
MH - Male
MH - Patient Education
MH - Prospective Studies
MH - *Prothrombin Time
MH - Support, Non-U.S. Gov't
MH - Warfarin/*administration & dosage
EDAT- 1995/09/01
MHDA- 1995/09/01
AID - a65557 [pii]
PST - ppublish
SO - J Pediatr 1995 Sep;127(3):389-94.

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UI - 96059992
PMID- 7501312
DA - 19960117
DCOM- 19960117
LR - 20001218
IS - 0361-1817
VI - 20
IP - 9
DP - 1995 Sep
TI - International Normalized Ratio (INR): an improved way to monitor oral anticoagulant therapy.
PG - 15-6, 21-2
AB - Oral anticoagulant therapy may be inappropriately managed and thus potentially place the warfarin-treated patient at an increased and unnecessary risk of bleeding or thromboembolic complications. This management issue is largely due to variations in measuring the pro-thrombin time. These variations may lead to an inaccurate and inconsistent assessment of the patient's true level of anticoagulation. The adoption of the International Normalized Ratio (INR) is recommended because it provides a mathematical correction for one of these variations--specifically, the thromboplastin reagents currently used. This article focuses on the appropriate use of the INR to monitor patients' responses to warfarin sodium therapy. It is vitally important for health care providers to be aware of the INR, to use it in clinical practice, and to interpret it correctly.
AD - Department of Medicine, Massachusetts General Hospital, Boston, USA.
AU - Oertel LB
LA - eng
PT - Journal Article
PT - Review
PT - Review, Tutorial
CY - UNITED STATES
TA - Nurse Pract
JC - OA1
JID - 7603663
RN - 0 (Anticoagulants)
RN - 81-81-2 (Warfarin)
RN - 9035-58-9 (Thromboplastin)
SB - IM
SB - N
MH - Administration, Oral
MH - Aged
MH - Anticoagulants/*administration & dosage/*blood
MH - Bias (Epidemiology)
MH - Case Report
MH - Drug Monitoring/*methods
MH - Human
MH - Male
MH - *Prothrombin Time
MH - Reference Standards
MH - Reproducibility of Results
MH - Thromboplastin/standards
MH - Warfarin/*administration & dosage/*blood
RF - 12
EDAT- 1995/09/01
MHDA- 1995/09/01
PST - ppublish
SO - Nurse Pract 1995 Sep;20(9):15-6, 21-2.

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UI - 95337271
PMID- 7612787
DA - 19950822
DCOM- 19950822
LR - 20001218
IS - 0212-6567
VI - 15
IP - 9
DP - 1995 May 31
TI - [Therapeutic quality control of follow-up of oral anticoagulation in primary care: 4-year experience]
PG - 555-60
AB - OBJECTIVE. To find the rate of therapeutic control and the frequency of complications among patients receiving oral anticoagulant therapy, attending in a primary care center. DESIGN. Descriptive study over the last four years. SETTING. An urban primary care center. PATIENTS AND METHODS. We included all patients in oral anticoagulant treatment controlled in our center among 1989 and 1993, excluding that patients with less than three months in control, or discontinued control. The prothrombin time was measured by international normalized ratio (INR). To measure the therapeutic quality control, we used the method proposed by the International Society of Thrombosis and Haemostasis. The frequency of complications was measured in number of events/100 patients/year.
RESULTS.
In the 136 patients studied the average time in control was 23.57 months. The 68.37 percent of determinations were within satisfactory ranges. The frequency of minor hemorrhages was 13.36 by 100 patients/year, 1.08 of major hemorrhages, and 2.53 of thromboembolism events. CONCLUSIONS. The
results obtained in this audit are similar to the communicated by other centers. The therapeutic control of oral anticoagulants can carry out in primary care with enough quality and some advantages: more facility to health education, better accessibility, and more integration of anticoagulation therapy in global care of patients.
AD - Centro de Salud Isabel II de Parla, Madrid.
AU - Alonso Roca R
AU - Puche Lopez N
AU - de la Fuente Arriaran MD
AU - Serrano Santos P
AU - Garcia Monterrubio L
LA - spa
PT - Journal Article
PT - Review
PT - Review Literature
TT - Control de calidad terapeutico del seguimiento de la anticoagulacion oral en atencion primaria: cuatro anos de experiencia.
CY - SPAIN
TA - Aten Primaria
JC - A5F
JID - 9111075
RN - 0 (Anticoagulants)
SB - IM
CIN - Aten Primaria. 1995 Nov 30;16(9):574
CIN - Aten Primaria. 1995 Nov 30;16(9):574-5
CIN - Aten Primaria. 1995 Oct 31;22(7):469
MH - Administration, Oral
MH - Adolescence
MH - Adult
MH - Aged
MH - Aged, 80 and over
MH - Anticoagulants/*therapeutic use
MH - Female
MH - Follow-Up Studies
MH - Human
MH - Male
MH - Middle Age
MH - *Primary Health Care
MH - Quality Control
MH - Time Factors
RF - 39
EDAT- 1995/05/31
MHDA- 1995/05/31
PST - ppublish
SO - Aten Primaria 1995 May 31;15(9):555-60.

CIERTOS ARTÍCULOS DE INTERÉS POR EL TEMA TRATADO INCLUIDOS EN EL MATERIAL ANEXADO

1 Advances in therapy and the management of antithrombotic drugs for venous thromboembolism.
Jack E. Ansell,
American Society of hematology.
hemtology 2000.
EVIDENCIA RELATIVA: 3'5

Analiza las vías fisiológicas y bioquímicas de la coagulación
Analiza los mecanismos de acción de los diversos anticoagulantes
A partir pág 275: Manging oral anticoagulant therapy: optimizing patient outcomes.
Tabla de tipos de estudios con modelos de gestión anticoagulnate
Autotesteo y autodosificación: validez de los métodos de monitorización (tabla 8), (tabla 7): efectos adversos de diversos tipos de estrategias. (tabla 9): estrategias con autotesteo.

2 Home-made anticoagulation monitor vs. CoaguCheck-Plus monitoring of oral anticoagulation
J.Finsterer, Austria
Thrombosis Research, 2000
EVIDENCIA RELATIVA: 2

Monitorizan con CoaguCheck (Böhringer) y HACOM los mismos pacientes. Sólo 19 pacientes e indican que es posible si se pone bien la rampita.

3 The cost-effectiveness of different management strategies for patients on chronic warfarin therapy.
Jennifer Elston Lafata
Journal General Internal Medcine, 2000
EVIDENCIA RELATIVA: 1

Financiado por Böhringer. Imputa prevalencias y probabilidades según datos de diversos estudios. Analiza mediante Markov a 5 años Compara cuidados usuales, seguimiento clínico y autotesteo.
Indica los riesgos adversos de donde los saca y los qualys no precisa muy bien su construcción. Los costes del aparato y entrenamiento de pacientes son los dados por Roche. Costes indican como los han obtenido, aplicando hora de trabajo de USA.
El tiempo en INR lo saca de estudios previos que indican (según Éstos) mejores seguimientos en autotesteo. Dicen que en conjunto es más efectivo el autotesteo en domicilio.

4 Assessment of patient capability to self-adjust oral anticoagulant dose: a multicenter study on home use of portable prothrombin time monitor (COAGUCHECK)
Benil de Cosmi
Haematologica, 2000
EVIDENCIA RELATIVA: 2

Financiado por Roche
Pacientes 47 casos y hasta los 78 controles con autotesteo monitorizado.
A pesar de decir que no hay entrenamiento, en realidad llevan tiempo en ello y han sido adiestrados
Importantes limitaciones y sesgos
Es mejor la autogestión pero debe ser más estudiada

5 Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison
Manon E Cromheecke, Amsterdam
The Lancet, 2000
EVIDENCIA RELATIVA: 3

Primera fase estudia concordancia autotesteo y autodosis con gestión clínica. (15 pacientes)
Segunda fase : primer tiempo autogestión, segundo tiempo clínica (50 pacientes)
Son adecuadamente formados
La autogestión controlada por los clínicos es adecuada y causa satisfacción

6 Anticoagulation management in primary care: a trial-basic economic evaluation
David Pare
British Journal of Haematology, 2000
EVIDENCIA RELATIVA: 3

126 pacientes en estrategia en primaria y en hospital para control anticoagulación
Mejores resultados en primaria pero mayor coste. Faltaría un análisis de coste efectividad.

7 A capillary whole blood method for mesuring the INR
EJ Bamford
Clin.Lab.Haem., 2000
EVIDENCIA RELATIVA: 4

Comparan autoanalizadores de laboratorio con método tradicional
Observan buen comportamiento salvo excepciones para algunos parámetros que comentan
Indican que hace falta más estudios con otros instrumentos

8 Guidelines on oral anticoagulation: third edition
Haemostasis and Thrombosis Task Force for the British Committee for Standars in Haematology Members
British Journal of Haematology, 1998
EVIDENCIA RELATIVA: 4

Guia de todo lo relativo a anticoagulación
tabla I recomendaciones de objetivos INR y grado de recomendación
Tabla III y IV responsabilidades de médicos y no médicos

DOCUMENTO Nº 1

Advances in Therapy and the Management of Antithrombotic Drugs for Venous Thromboembolism

Jack E. Ansell (Chair), Jeffrey I. Weitz., and Anthony J. Comerota

This review focuses on antithrombotic therapy for venous thromboembolism and covers a diverse range of topics including a discussion of emerging anticoagulant drugs, a renewed focus on thrombolytic agents for selected patients, and an analysis of the factors leading to adverse events in patients on warfarin, and how to optimize therapy. In Section I Dr. Weitz discusses new anticoagulant drugs focusing on those that are in the advanced stages of development. These will include drugs that (a) target factor VIIa/tissue factor, including tissue factor pathway inhibitor and NAPc2; (b) block factor Xa, including the synthetic pentasaccharide and DX9065a; (c) inhibit factors Va and VIIIa, i.e., activated protein C; and (d) block thrombin, including hirudin, argatroban, bivalirudin and H376/95. Oral formulations of heparin will also be reviewed.

In Section II, Dr. Comerota will discuss the use of thrombolysis for selected patients with venous thromboembolism. Fibrinolytic therapy, which has suffered from a high risk/benefit ratio for routine deep venous thrombosis, may have an important role to play in patients with iliofemoral venous thrombosis. Dr. Comerota presents his own results with catheter-directed thrombolytic therapy and the results from a large national registry showing long-term outcomes and the impact on quality of life.

In Section III, Dr. Ansell presents a critical analysis of the factors responsible for adverse events with oral anticoagulants and the optimum means of improving outcomes. The poor status of present day anticoagulant management is reviewed and the importance of achieving a high rate of "time in therapeutic range," is emphasized. Models of care to optimize outcomes are described, with an emphasis on models that utilize patient self-testing and patient self-management of oral anticoagulation which are considered to be the ultimate in anticoagulation care. The treatment of venous and arterial thromboembolism is undergoing rapid change with respect to the development of new antithrombotic agents, an expanding list of new indications, and new methods of drug delivery and management. In spite of these changes, many of the traditional therapeutics are still with us and continue to play a vital role in the treatment of thromboembolic disease. The following discussion touches on a wide range of therapeutic interventions, from old to new, exploring the status of anticoagulant drug development, describing a new intervention for iliofemoral venous thrombosis, and analyzing the critical factors for safe and effective therapy with oral anticoagulants.

I. New Anticoagulant Drugs

*Jeffrey I. Weitz, M.D.**

Thrombogenesis

Arterial thrombosis is the most common cause of myocardial infarction, stroke and limb gangrene. Because arterial thrombi, which form under conditions of high flow, consist of platelet aggregates held together by small amounts of fibrin, strategies to inhibit arterial thrombogenesis focus mainly on drugs that block platelet function, but often include anticoagulants to prevent fibrin deposition.[1] In contrast, venous thrombi, which can cause post-phlebitic syndrome or lead to pulmonary embolism and death, consist mainly of fibrin and red blood cells, and develop under low flow conditions in the deep calf veins. Coagulation at these sites is initiated by vascular trauma and is augmented by venous stasis. Anticoagulants are the drugs of choice for the prevention or treatment of venous thrombosis, or of cardioembolic events.

Injury to the arterial or venous wall exposes nonvascular tissue factor-expressing cells to blood.[2] Ex-

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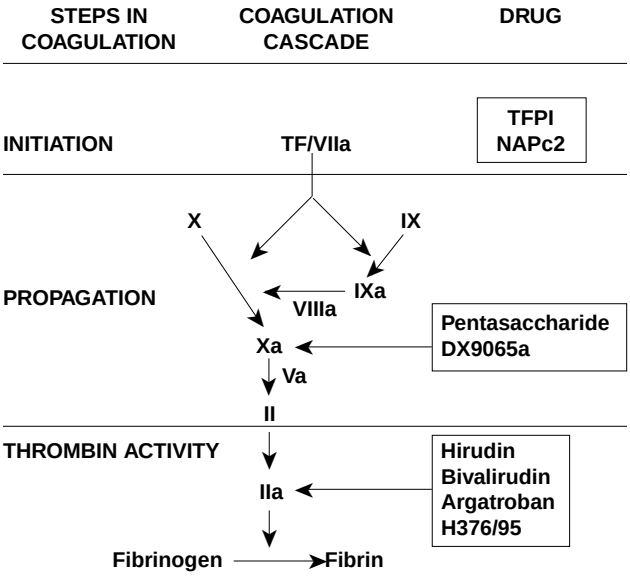

Figure 1. Steps in blood coagulation and sites of action of new anticoagulants.

Initiation of coagulation is triggered by the factor VIIa/tissue factor complex (VIIa/TF), which activates factor IX (IX) and factor X (X). Activated factor IX (IXa) propagates coagulation by activating factor X in a reaction that utilizes activated factor VIII (VIIIa) as a cofactor. Activated factor X (Xa), with activated factor V (Va) as a cofactor, converts prothrombin (II) to thrombin (IIa). Thrombin then converts fibrinogen to fibrin. Tissue factor pathway inhibitor (TFPI) and nematode anticoagulant peptide (NAPc2) target VIIa/TF, whereas synthetic pentasaccharide and DX-9065a inactivate Xa. Hirudin, bivalirudin, argatroban, and H376/95 inactivate thrombin.

posed tissue factor triggers coagulation (**Figure 1**) by binding factor VII or activated factor VII (factor VIIa). Tissue factor-bound factor VIIa undergoes autoactivation,[3] and the resultant factor VIIa/tissue factor complex then activates factor IX and factor X, leading to the generation of factor IXa and factor Xa, respectively. Factor IXa binds to factor VIIIa on membrane surfaces to form intrinsic tenase, the complex that activates factor X. By feedback activation of factor VII, factor Xa amplifies the initiation of clotting.[2]

Factor Xa propagates coagulation by binding to factor Va on membrane surfaces to form the prothrombinase complex. Factor Xa within this complex activates prothrombin to thrombin which then dissociates from the membrane surface and converts fibrinogen to fibrin monomer. Fibrin monomers polymerize to form the fibrin mesh, which is stabilized and crosslinked by factor XIIIa, a thrombin-activated transglutaminase. Thrombin amplifies its own generation by feedback activation of factor V and factor VIII. Thrombin also can activate factor XI, thereby leading to further factor Xa generation.[4]

New Anticoagulant Strategies

Anticoagulant strategies to inhibit thrombogenesis have focused on inhibiting thrombin, preventing thrombin generation, or blocking initiation of coagulation (Figure 1). Coagulation factors that have been targeted for inactivation include thrombin, factor Xa, factor IXa, and the factor VIIa/tissue factor complex. Other approaches to attenuating thrombogenesis include enhancing endogenous anticoagulant pathways or promoting fibrinolysis. Only a small number of potential candidate drugs are under development, and even fewer have progressed to clinical testing. Only compounds in more advanced stages of clinical development, which are listed in **Table 1**, will be discussed here; new fibrinolytic drugs and antiplatelet agents will not be described.

Thrombin Inhibitors

Thrombin can be inhibited indirectly by agents that activate naturally occurring thrombin inhibitors (namely, antithrombin or heparin cofactor II) or directly by drugs that bind to thrombin and prevent its interaction with substrates.

Indirect Thrombin Inhibitors

Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are cornerstones for prevention and treatment of venous thrombosis and also are widely used in combination with antiplatelet drugs or thrombolytic agents for treatment of acute coronary ischemic syndromes. Because LMWH can be given without laboratory monitoring, it is a useful drug for out-of-hospital treatment.[5] Consequently, LMWH is gradually replacing heparin for treatment of venous thrombosis. LMWH also is useful for treatment of unstable angina.[5]

Delivery systems have recently been developed making it possible to give UFH or LMWH orally. These delivery systems utilize synthetic amino acids such as sodium N-(8[2-hydroxybenzoyl]amino) caprylate (SNAC) to facilitate heparin absorption by the gut.[6] Although absorption is limited and somewhat variable, sufficient amounts of heparin can be delivered orally to prolong the activated partial thromboplastin time.[6] With phase I[7] and phase II[8] trials completed, phase III studies comparing SNAC/heparin with LMWH for thromboprophylaxis in patients undergoing elective hip or knee arthroplasty are now underway.

Dermatan sulfate, which acts as an anticoagulant by activating heparin cofactor II,[9] has been shown to be more effective than low-dose UFH for thromboprophylaxis in cancer patients.[10] Because its low specific activity and poor solubility limit the amount of drug that can be given by subcutaneous injection, dermatan sulfate has yet to be evaluated in the treatment setting.

Table 1. Status of new anticoagulant drugs.

Target	Drug	Route	Status	Indication
VIIa/TF	TFPI*	Intravenous	Phase III	Sepsis
	NAPc2*	Subcutaneous	Phase II	Thromboprophylaxis in patients undergoing elective knee arthroplasty
Va/VIIIa	APC*	Intravenous	Phase III	Sepsis
Xa	Pentasaccharide	Subcutaneous	Phase III	Thromboprophylaxis in patients undergoing elective hip or knee arthroplasty; treatment of venous thrombosis
	DX-9065a	Intravenous	Phase II	Unstable angina
Xa/IIa	SNAC/heparin*	Oral	Phase II	Thromboprophylaxis in patients undergoing elective hip or knee arthroplasty
IIa	Hirudin	Intravenous	Approved	Heparin-induced thrombocytopenia
			Under review	Unstable angina and non-ST-elevation myocardial infarction
	Bivalirudin	Intravenous	Approved	Alternative to heparin in patients undergoing percutaneous coronary interventions
	Argatroban	Intravenous	Approved	Heparin-induced thrombocytopenia
	H376/95	Oral	Phase III	Thromboprophylaxis in patients undergoing elective hip or knee arthroplasty; treatment of venous thrombosis
			Phase II	Alternative to warfarin in patients with atrial fibrillation

Abbreviations: APC, activated protein C; NAPc2, nematode anticoagulant peptide c2; SNAC, sodium N-(8[2-hydroxybenzoyl]amino) caprylate; TFPI, tissue factor pathway inhibitor

Direct Thrombin Inhibitors

Direct thrombin inhibitors have potential advantages over UFH because they can inhibit fibrin-bound thrombin,[11-13] an important mediator of thrombus growth. In addition, direct thrombin inhibitors produce a more predictable anticoagulant response than UFH because they do not bind to plasma proteins and are not neutralized by platelet factor 4, a heparin-binding protein released from activated platelets.[14] Hirudin, bivalirudin and argatroban are parenteral direct thrombin inhibitors that are approved for certain indications, whereas H376/95 is an orally active agent currently under investigation.

Hirudin

Hirudin, a 65-amino acid polypeptide originally isolated from the salivary glands of the medicinal leech *Hirudo medicinalis*, is now available through recombinant DNA technology.[15] It is a potent and specific inhibitor of thrombin that forms a stoichiometric, slowly reversible complex with the enzyme.[16] Its globular amino-terminal domain interacts with the active site of thrombin, while its carboxy-terminal domain binds to exosite 1 on the enzyme.[17]

Hirudin is cleared predominantly by the kidneys, undergoes little hepatic metabolism[18] and has a plasma half-life of 40 minutes after intravenous administration and approximately 120 minutes after subcutaneous injection. Its almost irreversible binding to thrombin may be considered a potential weakness, as no antidote is available should bleeding occur.

Hirudin has been used successfully to treat patients with thrombotic complications of heparin-induced thrombocytopenia (HIT)[19-20] and has been licensed for this indication in North America .[21] It also has been used effectively as an alternative to heparin during cardiopulmonary bypass in a small number of patients with HIT.[22,23] Hirudin has been shown to be superior to low-dose subcutaneous UFH or LMWH for thromboprophylaxis in patients undergoing elective hip arthroplasty and does not increase the risk of bleeding in this high-risk setting.[24,25] In patients with unstable angina and non-ST-elevation myocardial infarction, hirudin appears to be more effective than UFH.[26,27] Although hirudin increases the risk of major bleeding in these patients, there is no increase in life-threatening bleeds.[27] Hirudin is now under consideration for licensing in patients with unstable angina and non-ST segment elevation myocardial infarction.

Bivalirudin

A semi-synthetic bivalent thrombin inhibitor, bivalirudin is comprised of a dodecapeptide analogue of the carboxy-terminal of hirudin that binds to exosite 1 on thrombin linked to an active-site-directed moiety, D-Phe-Pro-Arg-Pro, by four glycine residues.[28] Unlike hirudin, bivalirudin produces only transient inhibition of the active site of thrombin because once bound to thrombin, the Arg-Pro bond on the amino-terminal extension of bivalirudin is cleaved, converting bivalirudin into a lower affinity inhibitor.[29] The shorter half-life of bivalirudin may ren-

der bivalirudin safer than hirudin. Based on phase III trials showing enhanced safety of bivalirudin relative to UFH in patients undergoing coronary angioplasty,[30,31] bivalirudin is now licensed in North America for this indication. In contrast to hirudin, only a fraction of bivalirudin is renally excreted, suggesting that hepatic metabolism and proteolysis at other sites contribute to its clearance.[32]

Argatroban

A carboxylic acid derivative, argatroban binds noncovalently to the active site of thrombin.[33] Argatroban is an effective alternative to heparin in patients with HIT and is approved for this indication. Studies are now underway to evaluate argatroban for treatment of arterial thrombosis.

H376/95

A prodrug oral formulation of melagatran, H376/95 is an uncharged lipophilic drug with little intrinsic activity against thrombin. H376/95 is well absorbed from the gastrointestinal tract and undergoes rapid biotransformation to melagatran, an active site-directed thrombin inhibitor.[34,35] The drug produces a predictable anticoagulant response after oral administration, and little or no laboratory monitoring appears to be necessary. Phase II studies with H376/95 for prevention and treatment of venous thrombosis have been completed, and phase III trials for these indications are now underway.

Factor IXa Inhibitors

Strategies to block factor IXa, a factor essential for amplification of coagulation, include active-site-blocked factor IXa and monoclonal antibodies against factor IX/IXa.

Active-site-blocked factor IXa

By competing with factor IXa for incorporation into the intrinsic tenase complex that assembles on the surface of the activated platelets, active site-blocked factor IXa inhibits clot formation in vitro and blocks coronary artery thrombosis in a canine model.[36] These observations support the concept that agents that inhibit factor IXa will modulate thrombosis.

Antibodies against factor IX/IXa

Monoclonal antibodies against factor IX/IXa either block factor X activation by factor IXa[37] or bind to the Gla-domains of factor IX and inhibit factor IX activation in addition to blocking factor IXa activity.[38,39] A chimeric humanized derivative of the latter antibody has antithrombotic activity in a rat arterial thrombosis model.[38,39] Phase I studies with this agent have been completed.

Factor Xa Inhibitors

Factor Xa inhibitors include a synthetic pentasaccharide, an analogue of the pentasaccharide sequence of heparin[40] that acts indirectly by activating antithrombin, as well as direct inhibitors that include recombinant analogues of natural inhibitors and synthetic drugs that target the active site of factor Xa. In contrast to UFH and LMWH, which have limited ability to inhibit platelet-bound factor Xa,[5,42] direct inhibitors of factor Xa inactivate both factor Xa bound to phospholipid surfaces and free factor Xa.[41]

Synthetic Pentasaccharide

Synthetic pentasaccharide, which has higher specific activity than UFH or LMWH,[40] enhances the rate of factor Xa inactivation by antithrombin but has no effect on the rate of thrombin inhibition. The drug is given subcutaneously on a once-daily basis. Phase III trials comparing synthetic pentasaccharide with LMWH for venous thrombosis prevention and treatment are well underway.

Natural inhibitors

Natural inhibitors of factor Xa include tick anticoagulant peptide (TAP), antistasin and lefaxin, none of which has been tested in humans. TAP, a 60-amino acid polypeptide isolated from the soft tick, *Ornithodoros moubata*, forms a stoichiometric complex with factor Xa.[41] TAP appears to bind to factor Xa in a two-step fashion.[41] An initial low affinity interaction involves a site distinct from the catalytic site of the enzymes, which may be analogous to exosite 1 of thrombin. This is followed by a high affinity interaction with the active site, which results in formation of a stable enzyme-inhibitor complex.

Antistasin is a 119 amino acid polypeptide isolated from the salivary glands of the Mexican leech, *Haementeria officinalis*.[43] Both native and recombinant forms of antistasin are tight-binding, slowly reversible inhibitors of factor Xa.[44] Like TAP, antistasin is highly selective for factor Xa. Lefaxin is a 30 kDa polypeptide isolated from the saliva of the *Haemanteria depressa* leech.[45] Although the gene encoding this protein has yet to be cloned, limited sequence analysis shows no homology between lefaxin and other natural inhibitors of factor Xa.

Synthetic factor Xa inhibitors

Nonpeptidic, low-molecular-weight, reversible inhibitors of factor Xa, such as DX-9065a,[46] YM-60828,[47] SF 303 and SK 549,[48,49] are effective in animal thrombosis models. Intravenous DX9065a is currently undergoing phase II testing in patients with unstable angina. YM-60828, a more potent analog of DX-9065a, has been reported to have oral bioavailability in squirrel monkeys,[47] whereas SK 549 exhibits oral bioavailability in rabbits.[48,49]

Factor VIIa/Tissue Factor Pathway Inhibitors

Strategies aimed at blocking the factor VIIa/tissue factor pathway have received much recent attention given that coagulation is initiated via this pathway.[2] Recombinant tissue factor pathway inhibitor (TFPI) and recombinant nematode anticoagulant peptide (NAPc2) are the agents in the most advanced stages of development.

TFPI

Only small amounts of this factor Xa-dependent inhibitor of factor VIIa circulate in blood in the free state or are stored in platelets. Most of the TFPI is bound to lipoproteins or to the endothelium.[50] Full-length TFPI is released from the endothelium when UFH or LMWH is given, presumably because these agents displace TFPI bound to endothelial glycosaminoglycans. When administered intravenously, TFPI has a short half-life because it is rapidly cleaved into non-functional truncated forms by an unknown protease. In pigs, TFPI attenuates injury-induced neointimal hyperplasia, and it inhibits smooth muscle cell migration in vitro. TFPI attenuates the coagulopathy and improves survival in sepsis models in baboons or rabbits.[50] Based on these results, TFPI is now undergoing phase III evaluation in patients with sepsis.

NAPc2

Small proteins have been isolated from *Ancylostoma caninum* that contain *Ascaris*-type protease motifs.[51] Some of these proteins directly inhibit factor Xa, whereas others, like NAPc2, bind to a noncatalytic site on factor X or factor Xa and inhibit factor VIIa within the factor VIIa/tissue factor complex.[52] Because it binds to factor X, as well as factor Xa, NAPc2 has a half-life of almost 50 hours after subcutaneous injection. Functionally, however, NAPc2 behaves like TFPI and attenuates sepsis-induced coagulopathy in laboratory animals. NAPc2 is currently undergoing phase II testing for prevention of venous thrombosis in patients undergoing elective knee arthroplasty.

Enhancement of Endogenous Anticoagulant Activity

Strategies aimed at enhancing endogenous anticoagulant activity have focused on the protein C anticoagulant pathway and include administration of (a) protein C or activated protein C concentrates, (b) soluble thrombomodulin, (c) thrombin derivatives that preferentially activate protein C, or (d) small molecules that bind to thrombin and induce allosteric changes similar to those evoked by thrombin's interaction with thrombomodulin.

Protein C derivatives

Both plasma-derived and recombinant forms of protein C are available. Intravenous activated protein C shows promise in the treatment of patients with sepsis-induced coagulopathy,[53] and is currently undergoing phase III testing for this indication.

Soluble thrombomodulin

Soluble thrombomodulin complexes with thrombin and induces a conformational change in the active site of the enzyme that abolishes its procoagulant activity and converts it into a potent activator of protein C.[54] Now available by recombinant DNA technology,[55] soluble thrombomodulin is an effective antithrombotic agent in a variety of animal models.[56,57]

Thrombin variants

Thrombin can be mutated to dissociate its procoagulant and anticoagulant substrate specificity, and when infused into animals it can activate protein C and have minimal procoagulant activity. Most promising of the thrombin variants are those that have the Glu residue at position 229 replaced by an Ala or Lys residue.[58,59]

Allosteric modulators of thrombin

A promising strategy is the development of small molecules that bind to thrombin and induce conformational changes in its active site similar to those evoked by thrombin's interaction with thrombomodulin. Small ligands of limited potency have recently been identified.[60]

Modulation of Endogenous Fibrinolytic Activity

Although traditional antithrombotic strategies have been aimed at inhibiting platelet function or blocking coagulation, a better understanding of physiologic fibrinolysis has identified potential methods to enhance endogenous fibrinolytic activity. These include (a) blocking type 1 plasminogen activator inhibitor (PAI-1), (b) inhibition of carboxypeptidase B-like enzymes, or (c) inhibition of activated factor XIII (factor XIIIa).

PAI-1 inhibitors

PAI-1 is the major physiologic inhibitor of tissue-type plasminogen activator (t-PA) and urinary-type plasminogen activator (u-PA). Consequently, inhibition of PAI-1 results in increased endogenous fibrinolytic activity. PAI-1 activity can be reduced by decreasing PAI-1 gene expression or by reducing the activity of PAI-1. Lipid-lowering drugs, such as niacin and fibrates, decrease PAI-1 synthesis in vitro.[61,62] These agents are not specific for PAI-1, however, and also affect the synthesis of other proteins.

Peptides have been identified that block PAI-1 activity either by preventing insertion of the reactive center loop upon cleavage by the target protease[63] or by converting PAI-1 into a latent conformation.[64] However, the effectiveness of these agents has yet to be tested in vivo. A more promising strategy is the development of small

molecule PAI-1 inhibitors, some of which exhibit antithrombotic activity in vivo.[65]

Procarboxypeptidase B inhibitors

Procarboxypeptidase B or thrombin-activatable fibrinolysis inhibitor (TAFI) is a latent carboxypeptidase B-like enzyme that is activated by the thrombin/thrombomodulin complex.[66] Upon activation, the carboxypeptidase attenuates fibrinolysis, presumably by cleaving carboxy-terminal lysine residues from fibrin.[67] Removal of these lysine residues decreases plasminogen or plasmin binding to fibrin, thereby retarding the lytic process. Given this mechanism of action, inhibitors of procarboxypeptidase B should enhance fibrinolytic activity, a concept supported by studies in dogs and rabbits demonstrating that a potato-derived carboxypeptidase B inhibitor increases t-PA-induced thrombolysis.[68,69]

Recently, thrombin variants have been identified that have decreased ability to activate procarboxypeptidase B yet retain their ability to activate protein C.[70] These findings raise the possibility that the antifibrinolytic activity of thrombin can be blocked without affecting its ability to activate the protein C pathway.

Factor XIIIa inhibitors

A thrombin-activated transglutaminase, factor XIIIa crosslinks the α- and γ-chains of fibrinogen to form α-polymers and γ-dimers, respectively. Crosslinking stabilizes the fibrin polymer and renders it more refractory to degradation by plasmin.[71] Inhibition of factor XIIIa, therefore, has the potential to increase the susceptibility of the thrombus to lysis. Tridegin, a peptide isolated from the giant Amazon leech, *Haementeria ghilianti*, is a specific inhibitor of factor XIIIa and enhances fibrinolysis in vitro when added prior to clotting of fibrinogen.[72,73] Destabilase, a leech enzyme that hydrolyzes γ-γ crosslinks,[74,75] also provides a promising approach to reversing the consequences of factor XIIIa-mediated fibrin crosslinking.

Challenges and Opportunities for New Anticoagulant Drugs

Further clinical testing is needed to define the role of new anticoagulants and to establish their benefit-to-risk profiles and their cost-effectiveness, especially when evaluating drugs with marginal advantages over existing agents. Although hirudin has been shown to be superior to low-dose UFH or LMWH for thromboprophylaxis in patients undergoing major orthopedic surgery of the lower limbs,[24,25] hirudin is unlikely to gain wide acceptance for this indication unless its cost is comparable to that of LMWH. Only limited information is available on the use of hirudin for the treatment of venous thrombosis. Cost considerations may also limit the utility of synthetic pentasaccharide[40] or NAPc2[52] in this setting, should these drugs prove superior to those in current use.

The success of hirudin for thromboprophylaxis in high-risk patients bodes well for orally available agents in this class. With progressive reductions in hospital stay, and evidence that the risk of thrombosis remains high for several weeks after major orthopedic surgery to the lower limbs,[76-78] orally available drugs that have a rapid onset of action and need little or no laboratory monitoring may prove to be more convenient than LMWH or coumarin derivatives. Although oral delivery systems for UFH or LMWH are promising,[7,8] variable absorption may limit the utility of this approach. In contrast, a prodrug form of melagatran exhibits good bioavailability after oral administration[34,35] and has undergone promising phase II testing for thromboprophylaxis in orthopedic patients.

The effectiveness of orally available drugs that target factor Xa, or clotting enzymes higher in the coagulation cascade, remains to be established. However, the success of synthetic pentasaccharide in phase II thromboprophylaxis trials suggests that factor Xa inhibitors will be effective in this setting.

There remains a need for orally active anticoagulants that are safer than coumarin derivatives given the mounting evidence that patients who develop venous thromboembolism in the absence of identifiable risk factors require long-term anticoagulation.[79-82] Orally active drugs that target thrombin or factor Xa have the potential to be superior to coumarins for this indication, if they can be administered safely with little or no laboratory monitoring.

II. Thrombolytic Therapy for Iliofemoral Deep Venous Thrombosis: An Opportunity Missed?

*Anthony J. Comerota, M.D., FACS**

Patients with the post-thrombotic syndrome are frequently encountered in clinical practice, but therapeutic interventions are often of little help. Venous hypertension and valvular incompetence are important pathophysiologic precursors of the post-thrombotic syndrome and occur frequently following iliofemoral venous thrombosis. Åkesson et al[83] followed 20 patients with iliofemoral venous thrombosis who were treated with conventional anticoagulation. After 5 years, 95% of the patients had ambulatory venous hypertension and 90% demonstrated objective signs and symptoms of venous insufficiency. Fifty percent of patients had calf muscle pump dysfunction, 15% suffered the debilitating symptoms of venous claudication and another 15% developed venous ulcers during the short follow-up. O'Donnell and Browse re-

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ported a 10-year follow-up of patients with iliofemoral venous thrombosis.[84] They objectively documented the extreme post-thrombotic morbidity of this condition, with many patients finding it difficult to maintain their employment due to incapacitating swelling and leg ulceration. Although restoring patency to the deep venous system is an ideal goal of therapy for acute deep venous thrombosis (DVT), pharmacologic and mechanical methods designed to clear the deep venous system remain controversial. Accumulated data[85] (**Table 2**) and randomized trials[86,87] (**Table 3**) demonstrate that more patients have patency of their venous system or reduced post-thrombotic symptoms after treatment with thrombolytic therapy compared to standard anticoagulation, yet thrombolytic agents are used infrequently by most physicians in the United States.

Since standard anticoagulant therapy has failed to reduce the post-thrombotic syndrome and systemic lytic therapy has been disappointing, we employed catheter-directed thrombolysis for patients with no contraindications to lytic therapy, and iliofemoral venous thrombectomy for those with major contraindications or who fail catheter-directed thrombolysis[88] (**Figures 2** and **3**). The following reviews our results of catheter-directed thrombolysis for iliofemoral DVT and places these results into perspective with those of other centers that have adopted a similar approach.

Catheter-Directed Thrombolysis

Between 1988 and 2000, 54 patients were treated with catheter-directed thrombolysis for occlusive iliofemoral DVT at Temple University Hospital. Mean age was 45 years (range 17–68 years), and average duration of leg symptoms was 5.2 days (range 2–30 days). All patients had the diagnosis established with venous duplex imaging and iliofemoral phlebography. Five patients were known to have recent pulmonary emboli (PE), and the remainder had no symptoms of PE. Seven of our patients had vena caval filters placed at the time of treatment. Three patients had vena caval thrombosis extending above a previously placed vena caval filter, and four patients had a vena caval filter inserted as part of their current therapy.

In patients in whom the catheter-directed approach failed and those with an absolute contraindication to thrombolytic therapy or multiple relative contraindica-

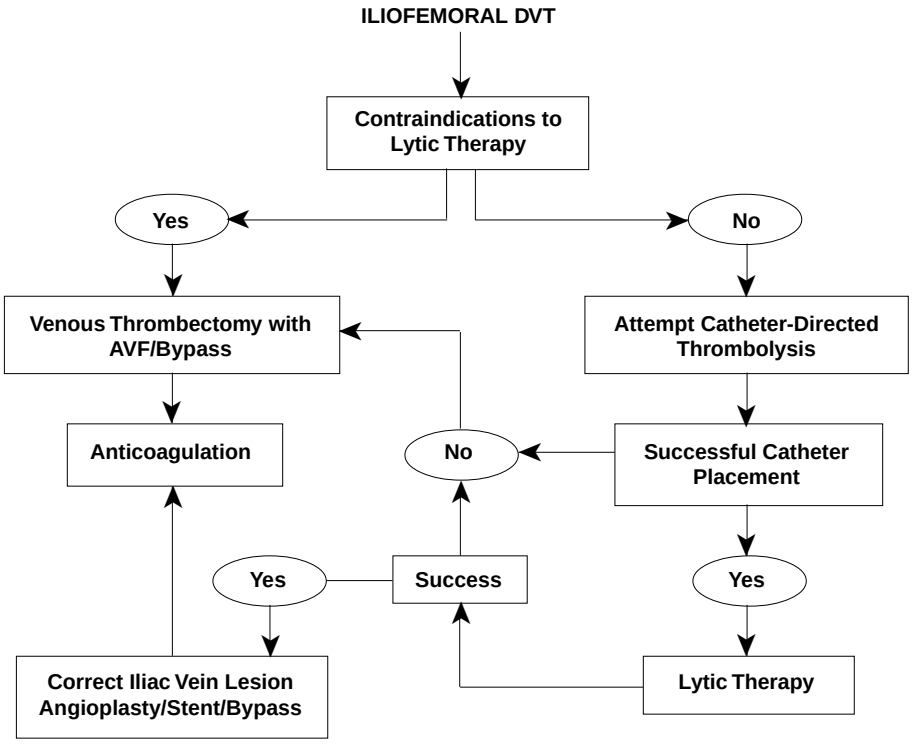

Figure 2. Algorithm for the treatment of acute iliofemoral DVT.

Table 2. Venographic outcome of anticoagulation versus thrombolytic therapy for acute deep venous thrombosis: Results of 13 studies (from Comerota et al[85]).

Outcome	Heparin	Thrombolysis
	n = 254	n = 337
Significant or complete lysis	4%	45%
Partial lysis	14%	18%
No change or worse	82%	37%

Table 3. Heparin versus thrombolytic therapy for proximal DVT: Long-term symptomatic results (follow-up 1.6 to 5.0 years) (from Comerota et al[85]).

Post-Thrombotic Syndrome	Heparin	Streptokinase
	n = 39	n = 39
Severe	21%	5%
Moderate	59%	31%
None	21%	64%

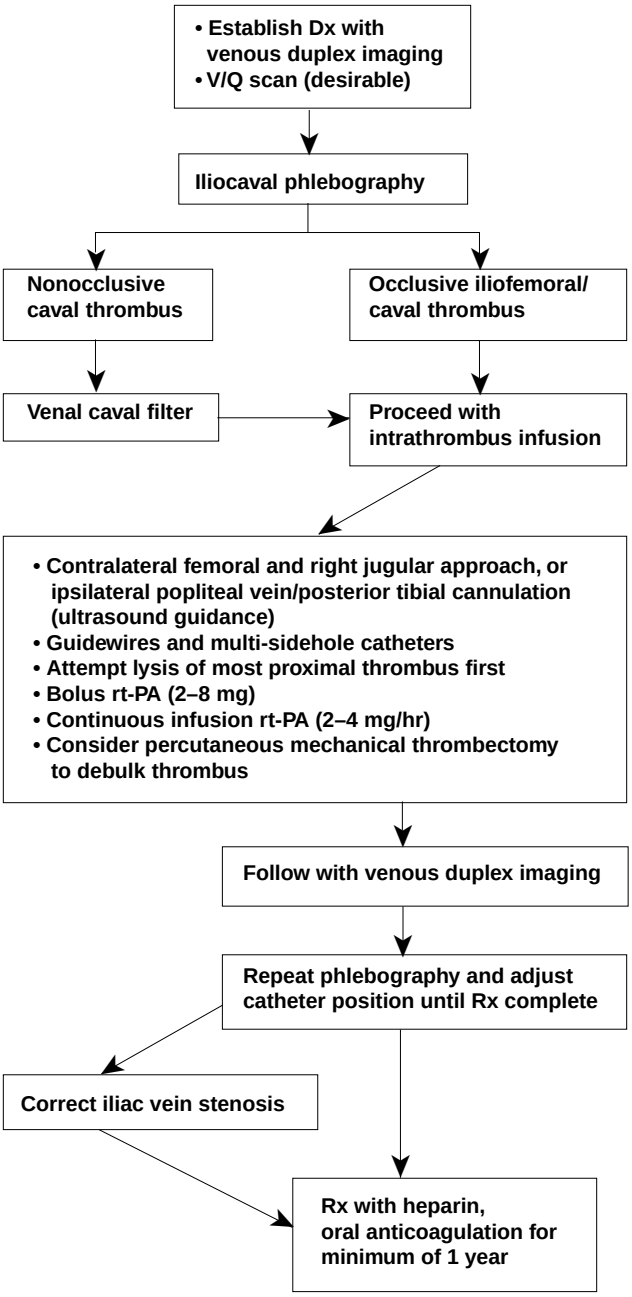

Figure 3. Algorithm for catheter-directed thrombolysis for iliofemoral DVT.

tions, a venous thrombectomy and adjunctive arteriovenous fistula was performed under general anesthesia. Patient follow-up was 2–98 months, with a mean of 46 months.

Initially, direct intra clot infusion was achieved by advancing a catheter from the contralateral femoral vein, the right internal jugular vein or both to the site of the clot. More recently, an ipsilateral popliteal vein puncture was the preferred approach; ultrasound guided posterior tibial vein puncture was used in selected patients.
Urokinase was used initially, delivering a 250,000-500,000 U bolus followed by a continuous infusion of 250,000–300,000 U/hr. With the recent removal of urokinase from the market because of concerns of potential viral contamination, seven recent patients were treated with recombinant tissue plasminogen activator (rt-PA). A bolus of 4–8 mg of rt-PA was given followed by 2–4 mg/hr. All patients received heparin at 500–1,000 u/hr. Venous duplex imaging was used to follow lysis of the infrainguinal clot and as much of the iliac venous system as could be visualized. Therapy continued until maximal lysis was achieved. Following completion of lytic therapy, heparin was continued and the patient converted to oral anticoagulation. If the infusion catheter could not be appropriately positioned within the iliac vein thrombus, a venous thrombectomy was recommended.

Table 4. Success of catheter-directed thrombolysis for iliofemoral DVT in 54 patients.

Outcomes	Number (%)
Successful catheter position	51 (94%)
Poor initial position	2
Common femoral vein perforation	1
Successful lysis	45 (88%)
Failed lysis	6 (12%)
Chronic occlusion	2
Reason unknown	2
Early reocclusion (persistent iliac lesion)	2
Complication	
Puncture site hematoma	8 (15%)
Blood transfusion	4 (7%)
Operative evacuation of hematoma and repair of common femoral vein	1 (2%)
Perforation of common femoral vein	1 (2%)
Long-term Outcome*	
Asymptomatic	14 (26%)
Moderate improvement	28 (52%)
Mild improvement	6 (11%)
Unchanged	6 (11%)

*Clinical outcome classification from Porter et al[89]

Table 4 summarizes the outcome of catheter-directed thrombolysis. Ninety-four percent of patients had successful positioning of the catheter and 88% had a successful lytic outcome. Of those who failed, two had known chronic occlusions and in two patients the reason for failure was unknown. Two patients suffered early rethrombosis due to persistent iliac vein stenosis.

Urokinase was the lytic agent used in 47 of the 54 patients. The duration of urokinase infusion ranged from 12–72 hours with the mean of 30 hours and an average total dose of 7.8 million units. Of the seven patients who received rt-PA, the duration of therapy was 12–40 hours with a mean of 22 hours and an average total dose of 48 mg.

The most common complication, puncture site hematoma, occurred in 15% of our patients. Blood transfusion was required in four patients (7%). One patient required operative evacuation of a puncture site hematoma and repair of the common femoral vein. One patient suffered perforation of the common femoral vein at the origin of the profunda during initial catheter positioning and was not infused with a lytic agent. Five patients who had unsuccessful thrombolysis were subsequently treated with operative venous thrombectomy.

The long-term results of treatment are categorized according to their clinical outcome and the SVS/ISCVS clinical classification[89] of chronic venous disease.

The results of catheter-directed thrombolysis for acute iliofemoral DVT have been gratifying when contrasted to the natural history of patients treated with standard anticoagulation. Plate and colleagues demonstrated that patients who had patency restored to their thrombosed iliofemoral venous segments had the lowest ambulatory venous pressure and the fewest post-thrombotic symptoms long term,[90-92] indicating that the long-term benefit of treatment is directly related to eliminating thrombus from the deep venous system and maintaining its patency.

Proper catheter positioning within the thrombus is important for a successful lytic outcome. However, once lysis is complete, patency depends upon correction of an underlying iliac stenosis, if one exists. A persistent lesion leads to an unacceptable high rate of re-thrombosis.

Urokinase was the preferred plasminogen activator until 1999, when it was removed from the market by the FDA because of concerns about viral contamination during the manufacturing process. With rt-PA, results are at least equivalent if not better than those obtained with urokinase. The duration of lysis appears shorter without any increase in bleeding complications.

Bjarnason et al[93] reported their 5-year experience treating iliofemoral DVT in 87 lower extremities. They reported a technical success rate of 79%. Patients with acute DVT (< 21 days) enjoyed an 85% success compared to only 42% of those who had chronic DVT (> 21 days). Iliofemoral DVT was more successful than femoral popliteal DVT (83% vs 63%), and patients with an underlying malignancy had a significantly worse primary patency (41% 2-year patency rate compared to 75% in patients without malignant disease). They experienced six major complications.

Mewissen et al[94] summarized the results of a prospective national venous registry. Two hundred and twenty-one patients with iliofemoral DVT and 79 with femoral popliteal DVT were treated with urokinase infusions. Complete clot lysis was observed in 31% of the infusions, 50–99% lysis in 52% and ≤ 50% lysis in 17%. Thirty-four percent of patients with acute DVT had complete clot lysis, whereas only 19% of patients with chronic DVT had patency restored. Seventy-nine percent of limbs with complete lysis remained patent at one year compared to 58% of limbs with 50–99% lysis and 32% of limbs with ≤ 50% lysis. Patency at one year was significantly better in patients treated for iliofemoral DVT compared to those treated with femoral-popliteal DVT (64% versus 47%, respectively). No patient with femoral-popliteal DVT for more than 10 days prior to treatment achieved complete clot lysis. Following lysis, 99 iliac and 5 femoral vein stenoses underwent angioplasty and stenting. It was apparent that correction of any residual iliac vein lesion improved patency. At one year 74% of the limbs treated with balloon dilation and stenting remained patent as compared with 53% of the limbs without angioplasty and stenting. Stenting was not helpful in the femoral–popliteal segment and four of the five stents placed in that location rethrombosed early (mean of 42 days), with the remaining patient lost to follow-up. Major bleeding complications occurred in 11%. Thirty-nine percent of the bleeding complications occurred at the venous puncture site and 13% were the result of a retroperitoneal bleed. Twenty-eight percent of the patients bled from other sites including musculoskeletal, gastrointestinal or genitourinary systems. There was one fatal intracranial hemorrhage and one patient suffered a subdural hematoma, for a frequency of major neurologic complications of 0.4%. Pulmonary emboli during infusion occurred in six patients (1%), a frequency comparable to patients treated with anticoagulation. One patient suffered a fatal pulmonary embolism; therefore, two patients died as a direct result of catheter-directed thrombolysis for a mortality rate of 0.4% in this series.

The venous registry offered an opportunity to evaluate whether catheter-directed thrombolysis had a beneficial long-term effect on patients compared to standard anticoagulation. An 80-item health related quality-of-life questionnaire was developed that contained items assessing demographics, clinical history, clinical functioning and well-being as well as specific DVT-related items.[95] The questionnaire was administered to 98 patients with iliofemoral DVT treated at least 6 months earlier.[96] Sixty-eight patients were identified through the national DVT registry and were treated with catheter-directed thrombolysis, and 30 patients were treated with standard anticoagulation for their iliofemoral DVT. Patients randomized to thrombolysis were younger (53 years) than the heparin treatment group (61 years); however, all heparin treated patients were candidates for thrombolytic therapy (no contraindication). Patients who received catheter-directed thrombolysis reported better overall physical functioning (P = .046), less stigma (P = .033), less health distress (P = .022) and fewer post-thrombotic symptoms (P = .006) compared to patients treated with anticoagu-

lation alone. Within the lytic group, phlebographically successful lysis correlated with an improved health related quality of life (P = .038). Patients who failed thrombolysis had a similar quality-of-life outcome to heparin-treated patients.

In summary, catheter-directed thrombolysis can be recommended for patients with symptomatic iliofemoral DVT. rt-PA is currently used as a 4–5 mg bolus followed by an infusion of 2–4 mg/hr. Once lysis is complete, any residual iliac vein lesion must be promptly corrected with balloon angioplasty and stenting if necessary. Successful lysis is associated with a reduction of post-thrombotic morbidity and improves health-related quality of life. It appears that patients with iliofemoral deep venous thrombosis who are not treated with catheter-directed thrombolysis (or iliofemoral venous thrombectomy) have missed an opportunity to preserve deep venous function and avoid serious post-thrombotic consequences.

III. Managing Oral Anticoagulant Therapy: Optimizing Patient Outcomes

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The coumarin-type oral anticoagulants have been in use for over 50 years and have remained critically important drugs in the primary and secondary prevention of thromboembolism. In the last 20 years, their use has expanded commensurate with an increased understanding of the important role of thromboembolism in cardiovascular disorders. Considerable efforts have also been applied to improving patient outcomes by identifying the appropriate indications for treatment and the appropriate therapeutic range through large randomized controlled trials, and by improving prothrombin time (PT) results reporting through the use of the International Normalized Ratio (INR). Unfortunately, the benefits of these improvements have not always been realized because of poor patient and dose management leading to a high incidence of serious adverse events. This review emphasizes the important risk factors associated with adverse events and describes the critical factors and models of management that achieve the best outcomes.

Risk Factors for Adverse Events

Clinicians must be aware of how major adverse events are defined when interpreting and comparing the results from clinical trials since precise estimates can only be made if there is consistency between classification schemes in clinical reports.[97] Most investigators divide adverse events into minor and major categories with major events including fatal or life threatening bleeds (e.g., intracranial or retroperitoneal) or bleeding with a defined drop in hemoglobin, leading to transfusion of a specified number of units of blood, or leading to hospitalization.

Intensity of treatment

The most important factor influencing the risk of bleeding is the intensity of anticoagulant therapy.[98-107] Four randomized studies (**Table 5**) have specifically demonstrated that the risk of clinically important bleeding is reduced by targeting a lower therapeutic range.[98-101] Additional studies have shown what amounts to an exponential increase in hemorrhagic events as the INR increases above 5.0.[102,104,105,108]

Patient characteristics

Several patient characteristics have also been associated with a higher risk of bleeding during anticoagulation.[97,102,106-117] The patient factor most consistently demonstrated to be predictive of major bleeding is a history of bleeding (especially gastrointestinal bleeding).[97,106,112] Other factors include a history of stroke and the presence of a serious comorbid condition such as renal insufficiency, anemia or hypertension.

The relationship between older age and anticoagulant associated bleeding is controversial. Reports suggest that older individuals are not at increased risk for bleeding,[97,109,118-128] while others describe such an association.[102,106,108,113,115,129-132] Whether age is simply associated with co-morbid conditions, which themselves are risk factors for bleeding (e.g., colonic polyps, concomitant medications, or poor anticoagulant control due to lack of compliance) or is directly causal is difficult to determine. Studies indicate that older patients who have high quality anticoagulation management, such as that provided by an anticoagulation clinic, have the same risk of bleeding as their younger counterparts.[133] Some studies that attempted to separate the effect of age from co-morbid conditions associated with age concluded that age in and of itself is not a major independent risk factor,[97,120,134,135] while others have found it to be an independent risk factor[102,107] even after controlling for the intensity of the anticoagulant effect. Individuals who are otherwise good candidates for anticoagulation should not have anticoagulation withheld because of their age. However, elderly patients should be monitored more carefully in order to maximize their time in therapeutic range.

Time in therapeutic range

A strong relationship between time in therapeutic range (TTR) and bleeding or thromboembolic rates has been observed across a large number of studies with different patient populations, different target ranges, different scales for measuring intensity of anticoagulation (i.e., PT,

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Table 5. Intensity of anticoagulation versus outcome.

Study	No. of Patients	INR Range	Total Bleeds
Hull 1982[98]	96	3.0-4.5	22.4%
DVT		2.0-2.5	4.3%
Turpie 1988[99]	210	2.5-4.0	13.9%
Tissue valves		2.0-2.5	5.9%
Saour 1990[100]	247	7.4-10.8	42.4%
Mechanical valves		1.9-3.6	21.3%
Altman 1991[101]	99	3.0-4.5	24.0%
Mechanical valves		2.0-2.9	6.0%

PT ratio, and INR), and different models of dose management. [104,105, 108,118,121,136-140] Time in therapeutic range must be interpreted with caution across studies because different methods are used to measure TTR. These include expressing TTR as a rate (% of INRs that are therapeutic or % that are therapeutic at one point in time), or as actual days spent in or out of range (linear interpolation method of Rosendaal et al[141]). The results of all of these methods are influenced by the choice of target INR range and therefore, the TTR can be enhanced considerably if the target range is expanded, even in the absence of any actual improvements in the quality of anticoagulation management. Another deficiency is that the various methods of assessment treat small departures from target range as identical to large departures, even though the former would have much less impact on clinical outcomes than the latter. These differences must be taken into account when comparing results across multiple studies. **Table 6** summarizes data from studies where the quality of anticoagulation as reflected by TTR was assessed.

Frequency of testing

The optimal frequency of monitoring the INR is dependent on many factors, including patient compliance, transient fluctuations in comorbid conditions, the addition or discontinuation of other medications, changes in diet, the quality of dose adjustment decisions, and whether treatment is early or late in the course of therapy. Recent clinical trials suggest that time in therapeutic range, and presumably fewer adverse events, can be maximized by more frequent testing.[142,143] This is particularly true in studies utilizing patient self-testing with point-of-care (POC) devices where access to testing is virtually unlimited. Horstkotte et al[142] specifically addressed this issue in 200 patients with mechanical cardiac valves where he found that the percent of INRs within target range varied from 48% when monitoring occurred at an average interval of 24 days, to 89% when monitoring was at an average of every 4 days. It is difficult to find studies where investigators report both TTR as well as achieved frequency of testing. The studies highlighted in Table 6 indicate the few reports where this information was provided and shows a direct correlation between increased frequency of testing and TTR.

Managing the Risks of Oral Anticoagulant Therapy

Although several developments have improved the safety and efficacy of oral anticoagulation, less has occurred to substantially improve the management of oral anticoagulation. There is now growing evidence that coordinated programs focused on anticoagulant management achieve a high rate of maintaining patients in therapeutic range leading to improved outcomes.[144]

Anticoagulation Management Services

A systematic approach to the management of therapy by specialized programs (anticoagulation clinics) significantly improves clinical outcomes by improving time in therapeutic range, lessening the frequency of hemorrhage or thrombosis, and decreasing the use of medical resources leading to more cost-effective therapy. These programs are characterized by a knowledgeable provider who manages therapy, an organized system of follow up, reliable prothrombin time monitoring, and good patient communication and education.

Most patients today are managed by their personal physician along with all other patients in their physician's practice without an organized program of management, education or follow-up (designated "usual care").[106,112,116] **Table 7** summarizes the few studies assessing clinical outcomes in this "usual care" model of management. These studies indicate a combined rate of major hemorrhage and of recurrent or de novo thromboembolism of 15% per patient year of therapy. These adverse events are generally a consequence of poor therapeutic control with hemorrhage or thrombosis occurring as a consequence of excessive or subtherapeutic anticoagulation. These outcomes can be contrasted to the rates identified in a large number of retrospective and some prospective studies of care delivered by an anticoagulation service (Table 7).[97,104,108,115,118-122,145-147] These studies indicate a more than 40% reduction in both major hemorrhage and thrombosis compared to usual care. Lastly, Table 7 summarizes studies examining both models of management where coordinated care is measured against a control group of usual care within each study.[114,148-150] These nonrandomized, retrospective analyses provide further evidence for the benefit of coordinated care.

A few studies also suggest a significant cost benefit to coordinated vs. usual care by a reduction in adverse events and reduced utilization of hospital services. Gray et al[151] estimated a savings of $860 per patient year of therapy due to reduced hospital days per patient year.

Table 6. Time in therapeutic range achieved under different models of anticoagulation management and with different testing frequencies.

Study	Predominant Model of Management	% Time in Therapeutic Range*	% Above Range	% Below Range	Frequency of Monitoring§
Garabedian, 1985[148]	UC	64	—	—	—
Gottlieb, 1994[170]	**UC**	**50**	**30**	**20**	**q 25 days§**
Holm, 1999[171]	UC	63	8	29	—
Beyth, 1997[162]	UC	33	16	51	—
Horstkotte, 1998[143]	**UC**	**59**	**—**	**—**	**q 19 days §**
Sawicki, 1999[165]	UC	34	16	50	—
Palaretti, 1996[115]	ACC	68	6	26	q 15 days§
Cannegeiter, 1995[104]	**ACC**	**61**	**8**	**31**	**q 18.9 days §**
Lundstrom, 1989[172]	ACC	92	—	—	—
Garabedian, 1985[148]	ACC	86	—	—	—
White, 1989[160]	ACC	75	—	—	
Ansell, 1995[163]	**ACC**	**68**	**10**	**22**	**q 16 days §**
Conte, 1986[145]	ACC	59	12	29	—
Seabrook, 1990[146]	ACC	86	7	7	once a month
White, 1989[160]	PST	93	—	—	—
Beyth, 1997[162]	PST	56	14	30	—
Ansell, 1995[163]	PSM	89	5	6	q 13.8 days §
Horstkotte, 1998[143]	**PSM**	**92**	**—**	**—**	**q 4 days §**
Sawicki, 1999[165]	PSM	57	10	33	—
AFASAK, 1989[140]	RCT	73	0.6	26	—
BAATF, 1990[138]	RCT	83	9	8	q 3 weeks
SPAF I, 1991[173]	RCT	71	5	23	at least once a month
SPAF II, 1994[174]	RCT	74	5	21	at least once a month
SPAF III, 1996	RCT	61	14	25	at least once a month
SPINAF, 1992[132]	RCT	56	15	29	monthly
CAFA, 1991[139]	RCT	44	16	40	q 3 weeks
AFASAK II, 1999[175]	RCT	73	9	18	not > q 4 weeks
EAFT, 1993[105]	RCT	59	9	32	q 5 weeks
Hellemans, 1999[176]	RCT	48	24	28	q 2-6 weeks
Hutten, 1999[177]	RCT	61	—	—	—

Abbreviations: UC, usual care; ACC, anticoagulation clinic; PST, patient self-testing; PSM, patient self-management; RCT, randomized controlled trial

* Time in range represents mean or median percent of PTs or days in range.

§ Those studies that documented the *achieved* frequency of monitoring as opposed to the stated goal for monitoring interval are in bold.

Chiquette et al[150] reported cost savings through a coordinated approach compared to usual care of approximately $1,320 per patient year of therapy.

Patient Self-Testing and Patient Self-Management

As a result of technological advances in prothrombin time measurement, there is potential for further simplifying and improving anticoagulation management by POC testing. POC testing allows for the determination of a prothrombin time from a fingerstick sample of whole blood and consequently opens the possibility for patient self-testing. Portability of instrumentation means that prothrombin time measurements are no longer confined to the physician's office, a private laboratory or a nearby hospital, but can be moved into the patient's home or even taken with the patient when traveling. Standardization of reagents and instruments, as well as reliance on the INR, further reduces the inaccuracies of multiple reagents and laboratories.

Since the late 1980s, a number of instruments have been introduced or are in development (**Table 8**). These instruments are based on clot detection methodology using thromboplastin to initiate clot formation, while the endpoint of clot detection varies from instrument to instrument. The validity of this methodology was initially established in 1987 by Lucas et al[152] who used the Biotrack instrument (Coumatrak; Biotrack Inc; Freemont, CA) and showed a correlation coefficient of 0.96 between reference plasma PTs and capillary whole blood PTs. Within-day precision using two different levels of controls revealed coefficient of variations of 4.9% and 2.9%. Similar results have been obtained by others,[153,154] but some investigators have identified limits of comparability due to the high International Sensitivity Index (i.e.

Table 7. Clinical outcomes with usual care versus anticoagulation clinic care.

Studies	Patient Years (%/pt yr)	Major Hemorrhage (%/pt yr)	Thrombo-embolism (%/pt yr)	Combined
Usual care studies*	1,537	6.8%	8.1%	~ 15%
Anticoagulation clinic studies**	19,361	4.3%	4.8%	~ 9%
Comparison studies:				
Usual care	944	5.7%	8.4%	~14%
vs				
Anticoagulation clinic#	986	1.6%	1.5%	~ 3 %

* Landefeld 1989,[106] Gitter 1995,[116] Beyth 1998.[112]
** Davis 1977,[128] Fofar 1982,[118] Errichetti 1984,[119] Conte 1986,[145] Petty 1988,[120] Charney 1988,[121] Bussey 1989,[122] Seabrook 1990,[146] Fihn 1993,[97] van der Meer 1993,[108] Cannegieter 1995,[104] Palareti 1996[115]
# Garabedian 1985,[148] Cortelazzo 1993,[114] Wilt 1995,[149] Chiquette 1998;[150] these represent individual studies that assessed outcomes in both usual care and an anticoagulation clinic. They also represent a greater proportion of more recent studies utilizing the INR and low and high intensity of therapy compared to the anticoagulation clinic studies only.

low sensitivity) of one company's thromboplastin, as well as the inability to determine a true geometric mean normal prothrombin time for the instrument.[155,156] Studies by McCurdy and White[157] indicated that the INR correlation was adequate within an INR range of 2.0–3.0 (the therapeutic range for most indications), but began to lose its comparability as the INR increased above the 4.5 range. A recent comparative study of nine different POC devices showed that all devices correlated well with different laboratory methods and thromboplastins, but most instruments showed significant differences from the laboratory results.[158] This study illustrated the limitations of using local reference material and the need to know each instrument's bias compared to a local laboratory if that is the reference being used.

Although the appropriate studies have not been done, it is possible that this new system is significantly more reliable and consistent than the variable and haphazard PT monitoring often employed in the usual care of most patients on oral anticoagulants.[159]

A number of studies have demonstrated the ability of patients to perform self-testing and obtain an accurate result.[160-162] Patients can then call their physician and obtain instructions for warfarin dose adjustment. **Table 9** summarizes those studies where clinical outcomes, either time in therapeutic range or adverse events, have been reported. Patient self-testing can also incorporate patient self-management of warfarin dosing, and a number of studies have shown this model of care to be safe and effective as well.[143,163-166]

Based on the foregoing, POC PT monitors offer the potential to improve the safety profile of anticoagulant therapy; to improve patient satisfaction and possibly patient compliance; and by reducing the labor intensity of physician management, to encourage the more wide-

Table 8. Capillary whole blood (point-of-care) PT instruments.

Instrument	Clot Detection Methodology	Home Use Approval
Protime Monitor 1000 Coumatrak* Ciba Corning 512 Coagulation Monitor* CoaguChek Plus* CoaguChek Pro* CoaguChek Pro/DM*	Clot initiation: Thromboplastin Clot detection: Cessation of blood flow through capillary channel	
CoaguChek Thrombolytic Assessment System	Clot initiation: Thromboplastin Clot detection: Cessation of movement of iron particles	Yes**
ProTIME Monitor Hemochron Jr# GEM PCL#	Clot initiation: Thromboplastin Clot detection: Cessation of blood flow through capillary channel	Yes
$Avocet_{PT}$	Clot initiation: Thromboplastin Clot detection: Thrombin generation detected by fluorescent thrombin probe.	Yes

* All instruments in this category are based on the original Biotrack model (Protime Monitor 1000) and licensed under different names. The latest versions available are the CoaguChek Pro and Pro/DM (as models evolved they acquired added capabilities). Earlier models are no longer available.
** CoaguCheck only
# Hemochron Jr and GEM PCL are simplified versions of the ProTIME Monitor.

Table 9. Patient self-testing and self-management studies.

Study	Study Groups	No. of Patients	Time in Range (% or days)	Major Hemorrhage (%/pt-yr)	Thrombo-embolism (%/pt-yr)
White[160] 1989	PST	23	93	0	0
	ACC	23	75	0	0
Anderson[161] 1993	PST	40	—	0	0
Beyth[162] 1997	PST	162	56	5.7	9
	UC	163	33	12	13
Ansell[163] 1995	PSM	20	89	0	0
	ACC	20	68	0	0
Horstkotte[143] 1996	PSM	75	92	4.5*	0.9
	UC	75	59	10.9*	3.6
Hasenkam[164] 1997	PSM	20	77	NA	NA
	UC	20	53	NA	NA
Sawicki[165] 1999	PSM	90	57 / 53**	2.2	2.2
	UC	89	34 / 43**	2.2	4.5
Koertke[166] 2000	PSM	581	78	1.8	2.4
	UC	567	60	2.7	4.5

Abbreviations: PST, patient self-testing; PSM, patient self-management; ACC, anticoagulation clinic; UC, usual care
*Major and minor bleeding;
**time in range at 3 months and 6 months.

spread use of warfarin. The cost-effectiveness of such therapy needs to be studied.

Data Management and Computerized Dosing

An obstacle to the safety and effectiveness of warfarin therapy is the poor quality of dose management as currently practiced.[144] As indicated in Table 6, there is a wide range of success in achieving TTR. A usual care model appears to yield the worst results with a TTR between 33–64%. Even in randomized controlled trials where patient care is often highly structured, TTR varies between 48–83%. Achieved TTR appears to be best in either an anticoagulation management service model or with patient self-management (approximately 60–90%). Computer assistance by the use of dedicated programs may, however, improve dose management and time in range.

The first randomized study of computerized dosing in 1993[167] showed that three contemporary computer programs all performed as well as an experienced medical staff of an anticoagulation management service in achieving a target INR of 2.0 to 3.0, but the computer achieved significantly better control when more intensive therapy was required (INR 3.0 to 4.5). In another randomized study[168] of 101 long-term anticoagulated patients with prosthetic cardiac valves, computerized warfarin adjustments proved comparable to manual regulation in the percentage of INR values maintained within the therapeutic range, but required 50% fewer dose adjustments. The first multicenter randomized trial of one computerized dosage program in 1998[169] showed a 22% overall improvement of control with the program (Dawn AC®) compared to performance by the medical staff. The computer program gave significantly better INR control than experienced medical staff for all 285 patients for all target INR ranges. The study also showed that the natural increased caution of medical staff in dosing patients at a higher INR range is not shared by the computer. It cannot be assumed, however, that all computer programs will be equally successful, and new programs will require independent validation by randomized controlled studies to determine the extent of their ability to accurately predict dosage control.

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DOCUMENTO Nº 2

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THROMBOSIS RESEARCH

ORIGINAL ARTICLE

Home-Made Anticoagulation Monitor vs. CoaguCheck-Plus® Monitoring of Oral Anticoagulation

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Key Words: International normalized ratio; Thrombotest; Blood trail; Self-monitoring; Phenprocovman

Monitoring of oral anticoagulation is usually carried out by general practitioners, internists, specialized laboratories, and, increasingly, by the patients themselves. Usually, self-monitoring is performed by means of sophisticated, commercially available coagulometers, like the CoaguCheck-Plus® (Böhringer Mannheim Co., Indianapolis, IN, USA) [1–4]. Recently, it has been shown that self-monitoring of oral anticoagulation can also be performed by simply measuring the length of a blood trail after having run down an oblique plane [home-made anticoagulation monitor (HACOM)] [5,6]. Little is known about the relationship between the HACOM and established International Normalized Ratio (INR) determination methods. The present study aimed to find whether the accuracy of the HACOM is comparable with that of the INR determination by means of the CoaguCheck-Plus®, in a single patient and in a group of patients and healthy volunteers.

1. Materials and Methods

The single patient was a 46-year-old pastor who was anticoagulated with phenprocoumon because of recurrent venous thromboembolism in the right lower limb and in the left iliac vein. Recurrent thromboembolism was due to a homozygous G1691A mutation in the factor V gene, leading to an APC-resistance of 1.13 (normal, >2.0). The group of patients comprised 19 subjects (11 women, 8 men) aged 28–83 years. Sixteen of the subjects were anticoagulated with phenprocoumon and three of them were healthy volunteers. None of the patients took acetylsalicylic acid or any other medication known to affect blood coagulation. The single patient performed the HACOM and the CoaguCheck-Plus® by himself. In the group of patients and the healthy volunteers, the HACOM and CoaguCheck-Plus® measurements were carried out by the authors. In this group of patients, additionally the thrombotest was performed from cubital blood to assess the accuracy of the CoaguCheck-Plus®.

The single patient performed the HACOM according to the following procedure: Before starting the test, the plane of the table on which the HACOM was performed was horizontally positioned by means of a water level. Then a blood drop of 30 μl from the fingertip was pipetted near the upper width of an even glassplate (length 40 cm, width 5 cm, thickness 8 mm) that was fixed to a wooden frame [5]. The glassplate was then tilted by 65.5° by bringing the wooden frame into the adequate position (Figure 1). When the running blood drop had come to a complete standstill, the trail length was measured with a ruler. The glassplate was then cleaned with aryl-substituted oxibenzol. For application of the HACOM in the

Abbreviations: HACOM, home-made anticoagulation monitor.

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Fig. 1. Home-made anticoagulation monitor (HACOM) after tilting the wooden frame by 65.5°. In this position, the blood drop was running down longer or shorter, depending on the degree of anticoagulation.

group of patients, the following modifications were made: 1) To avoid spreading of the blood trail, a glassplate with a groove was used. 2) To reduce free calcium ions, sterilized water (Aqua bidest®, Braun, Ma. Enzersolorf, Austria) was used as a cleaning solution. 3) To avoid trails longer than the glassplate, 20 μl, instead of 30 μl, were pipetted. 4) To reduce the ionization of the glassplate during cleaning and drying, a deerskin towel was used (modified HACOM).

To perform the CoaguCheck-Plus® (Böhringer Mannheim Co.), blood was drawn from the same source on the fingertip as for the HACOM. The interval between the performance of the HACOM and the CoaguCheck-Plus® was less than 1 minute. The thrombotest was determined from cubital blood with Thrombotest Reagent® (Nycomed Pharma AG, Oslo, Norway) in the hospital's laboratory, and results were expressed as INR values according to the manufacturer's batch specific instructions. Correlations were expressed as Pearson's correlation coefficients.

2. Results

Altogether, the single patient performed 19 measurements by means of the HACOM and the CoaguCheck-Plus® INR within 14 weeks. Mean±SD trail length of these 19 determinations was 21.0±1.9 cm. The shortest trail length was 19.4 cm (INR, 2.0), and the longest was 23 cm (INR, 1.7) (Figure 2). Mean±SD of the 19 INR determinations with the CoaguCheck-Plus® was 1.86±0.27. The lowest INR value was 1.3 (trail length, 20.8 cm), and the highest value was 2.4 (trail length, 22.1 cm). The correlation between the HACOM and the CoaguCheck-Plus® was not significant ($r=0.29$, $p>0.05$) (Figure 2).

In the group of 19 patients the shortest trail length was 5.7 cm (CoaguCheck-Plus® INR, 1.0), and the longest length was 35.9 cm (CoaguCheck-Plus® INR, 4.0) (Figure 3A). The lowest CoaguCheck-Plus® INR value was 0.9 (trail length, 11.2 cm), and the highest value was 4.0 (trail length, 35.9 cm). The correlation between the HACOM and the CoaguCheck-Plus® was nonlinear (Figure 3A). A nonlinear correlation was also found between the HACOM and the thrombotest from cubital blood (Figure 3B). The correlation between the CoaguCheck-Plus® and the thrombotest from cubital blood was positive, linear, and significant ($r=0.94$, $p<0.05$).

3. Discussion

Recently, measuring the trail length of a blood drop running down an oblique plane (HACOM) has been shown to be a promising, simple, and cheap method for self-monitoring of oral anticoagulation [5]. By standardizing inclination of the oblique plane, drop size, ambient temperature, and the air humidity, the correlation between the blood trail length and the thrombotest was additionally influenced only by the platelet count [6]. In a group of 10 [5] and 28 [6] patients, the correlation between the thrombotest (%) and the HACOM was

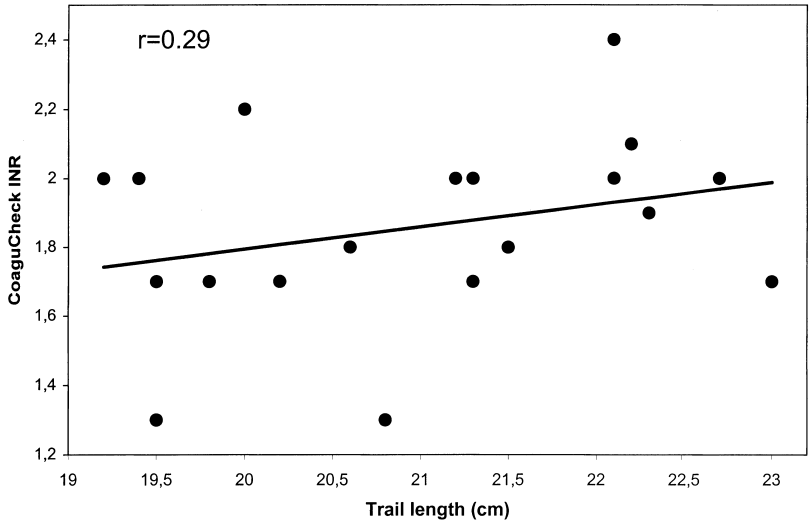

Fig. 2. Correlation between the HACOM and the CoaguCheck-Plus® in a single patient (19 measurements).

linear ($r=-0.88$ and $r=-0.52$, respectively). In the present study, the correlation between the HACOM and the CoaguCheck-Plus® was linear in the single patient, but nonlinear in the group of patients. The missing correlation in the single patient is questionable, since the INR range was small. A small INR range could make an originally bended regression line straight. Thus, it remains unclear whether the differences in the correlations between HACOM and CoaguCheck-Plus® in the single patient and the group of patients can be attributed only to the modifications of the HACOM. The nonlinear correlation in the group of patients is consistent with the previously established nonlinear correlation between the thrombotest (%) and the INR values [7].

The differences between the results of the present and the previous studies [5,6] might be due to the selection bias, the different group sizes, and the slightly different experimentation procedures. In the first study [5], drop size was not standardized, and blood for the thrombotest was taken from a cubital vein. In the second study [6], capillary blood was taken for the HACOM as well as for the thrombotest, and drop size was standardized to 30 μl. Furthermore, the CoaguCheck-Plus® can give unexpected and inconsistent results [8,9]. Accordingly, on two occasions our patient had CoaguCheck-Plus® values outside the optimal range (1.3 and 1.9), which were higher when tested 1–2 hours later in the laboratory, where he usually controls his anticoagulation (1.8 and 2.3, respectively). One reason for the inconsistent results of the CoaguCheck-Plus® might be that blood from the same pool was used for the HACOM and the CoaguCheck-Plus®. Possibly, coagulation was more activated in the second blood sample used for the CoaguCheck-Plus®. The nonlinear correlation between the HACOM and the CoaguCheck-Plus® in the group of patients of the present study is consistent with the nonlinear correlation between the INR and the thrombotest (%).

The HACOM was modified because we often observed blood trails that were not straight but that deviated considerably from the ideal line. These deviations were not taken into account when measuring the length of the trail. We also wanted to exclude any influence of alcohols in the cleaning solutions, of calcium ions, of the evenness of the groove, and the ionization of the glassplate. Irrespective of these modifications, care was taken that the blood had come to a complete standstill, particularly at the end of its run, when it is sometimes difficult to decide whether the blood has stopped or not. Furthermore, the drop size needs to be accurately standardized. We propose to use 20-μl blood drops to avoid them from running over the edge of the glassplate.

4. Summary

This study shows that the modified HACOM might become a favorable and cheap device for self-moni-

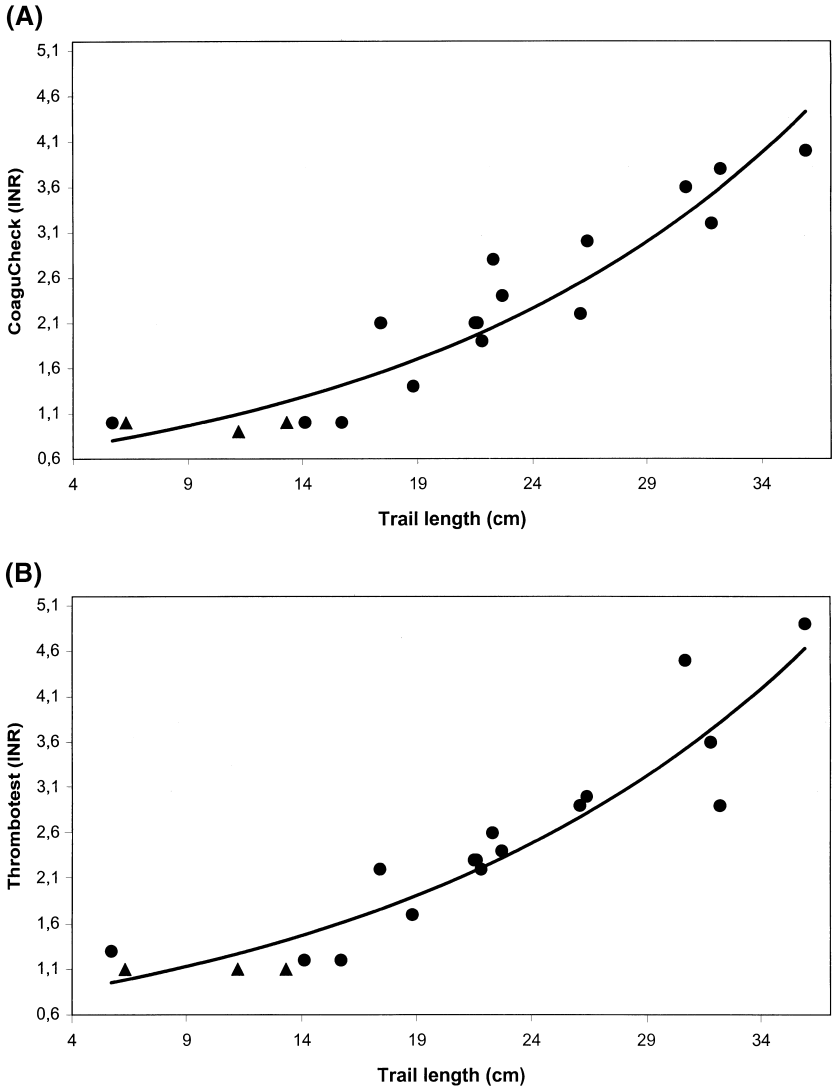

Fig. 3. Correlation between the HACOM and the CoaguCheck-Plus® in a group of 16 patients (circles) and 3 healthy volunteers (triangles) (A). Additionally, the correlation between the HACOM and the thrombotest, expressed as INR, from cubital blood is shown (B).

toring oral anticoagulation, provided that the drop size is kept constant, that the surface of the groove is maximally even, that neutral cleaning solutions are used, and that the ionization of the glassplate is maximally reduced.

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The Cost-Effectiveness of Different Management Strategies for Patients on Chronic Warfarin Therapy

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DOCUMENTO Nº 3

OBJECTIVE: **To examine the cost-effectiveness of moving from usual care to more organized management strategies for patients on chronic warfarin therapy.**

DESIGN: **Using information available in the scientific literature, supplemented with data from a large health system and, when necessary, expert opinion, we constructed a 5-year Markov model to evaluate the health and economic outcomes associated with each of three different anticoagulation management approaches: usual care, anticoagulation clinic testing with a capillary monitor, and patient self-testing with a capillary monitor.**

PATIENTS: **Three hypothetical cohorts of patients beginning long-term warfarin therapy were used to generate model results.**

MAIN RESULTS: **Model results indicated that moving from usual care to anticoagulation clinic testing would result in a total of 1.7 thromboembolic events and 2.0 hemorrhagic events avoided per 100 patients over 5 years. Another 4.0 thromboembolic events and 0.8 hemorrhagic events would be avoided by moving to patient self-testing. When direct medical care costs and those incurred by patients and their caregivers in receiving care were considered, patient self-testing was the most cost-effective alternative, resulting in an overall cost saving.**

CONCLUSIONS: **Results illustrate the potential health and economic benefits of organized care management approaches and capillary monitors in the management of patients receiving warfarin therapy.**

KEY WORDS: **anticoagulation management; cost-effectiveness analysis; decision analytic model; warfarin.**
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Warfarin is the mainstay of long-term anticoagulation therapy in the United States. Although warfarin therapy reduces disability and fatal thromboembolic events, it can also cause disabling and fatal hemorrhagic events.[1] Therefore, to maximize the efficacy of warfarin, frequent monitoring of the international normalized ratio (INR) of the prothrombin time is required.

The majority of patients receiving chronic warfarin therapy are managed in traditional office settings, but some are managed in formal anticoagulation clinics.[2] Such clinics have been shown to improve the time spent within therapeutic range, as well as to reduce thromboembolic events and hemorrhagic complications.[3,4] With the 1997 Food and Drug Administration approval of capillary monitors for patient use, it became possible not only to have INR values available immediately, but also for patients to determine their INR without traveling to a clinic or laboratory. The few studies that have evaluated the effectiveness of home testing have found that patients testing at home check their INRs more often and are within the therapeutic range more often than those tested in an anticoagulation clinic.[5-7] Others have found that patient self-testing decreases adverse events,[8] and is preferred by patients.[9]

Despite evidence that the tighter therapeutic control allowed by the introduction of organized anticoagulation clinics and capillary monitors may prevent complications, the introduction of such clinics and devices has been relatively slow, and the cost-effectiveness of the different testing and monitoring alternatives remains unknown. We therefore sought to evaluate the cost-effectiveness of three management alternatives: usual care, anticoagulation clinic testing, and patient self-testing.

METHODS

The Decision Model

An overview of the underlying decision tree is presented in Figure 1. For modeling purposes, we assumed "usual care" to consist of a venipuncture blood draw for an INR, delayed test results, and no organized anticoagulation clinic. "Anticoagulation clinic testing" consisted of in-clinic capillary monitors for INRs, immediate test results, and an organized anticoagulation clinic. (Organized anticoagulation clinics generally consist of dedicated nursing or pharmacy staff who use explicit protocols and processes to monitor and adjust dosage among patients on warfarin therapy and to seek physician consult). "Patient self-testing" consisted of at-home capillary monitors for INRs with immediate test results managed by patients telephoning these results to an organized anticoagulation clinic.

As illustrated in Figure 1, for each monitoring alternative, the time patients spend below, in, and above

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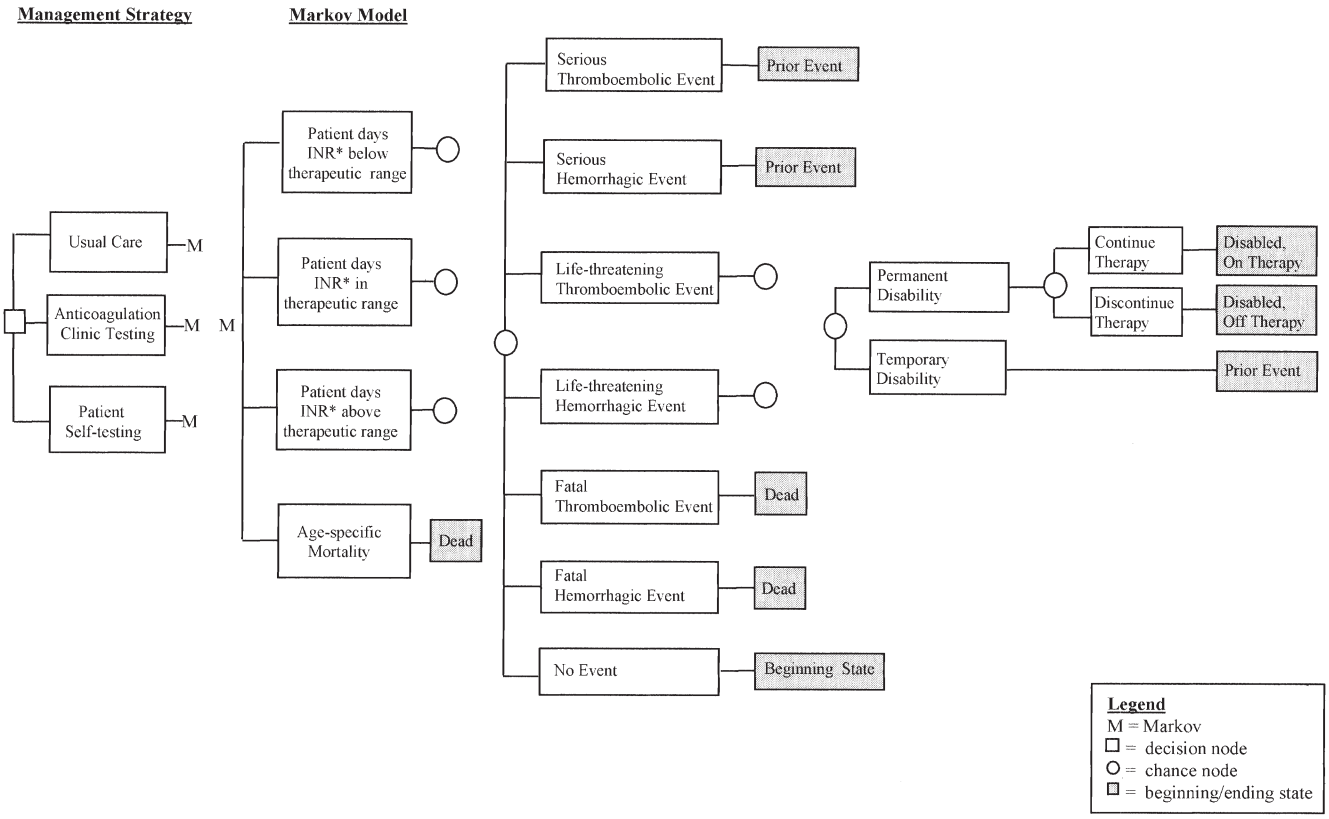

FIGURE 1. Model overview. *indicates international normalized ratio of the prothrombin time.

therapeutic range is estimated and used to derive the associated risk of first and subsequent thromboembolic and hemorrhagic events. Once an event occurs, individuals are at risk of temporary and permanent disabilities. Among individuals who become permanently disabled, there is a risk of discontinuing anticoagulation therapy and thus being at an increased risk of subsequent thromboembolic events.

The decision tree was operationalized as a Markov model in Excel. In the model, hypothetical cohorts of patients are followed for 5 years following warfarin therapy initiation. To parallel the clinical data on thromboembolic and hemorrhagic events available, the model was built to be reflective of patients initiating therapy at age 57 years.[10,11] With each 1-year cycle of the model, patients move among five defined health states (no prior event; prior event, nondisabled, continuing therapy; prior event, permanently disabled, continuing therapy; prior event, permanently disabled, discontinued therapy; and dead). Transitions among these states were defined using event probabilities drawn from the scientific literature, supplemented with information available within the authors' institution and, when voids remained, expert opinion.

Specifically, four key clinical assumptions were needed: (1) estimates of the time spent below, in, and above therapeutic range for each of the three management alternatives; (2) the risk of incurring an adverse event associated with these times; (3) the risk of disability following an adverse event; and (4) among those permanently disabled, the risk of discontinuing anticoagulation therapy. These clinical assumptions and the corresponding transition probabilities are described below.

For the baseline model, the estimated times spent below and above therapeutic range for usual care reflected those reported by Chiquette et al.,[3] Hasenkam et al.,[7] Gottlieb and Salem-Schatz,[12] and our own clinical experiences. Using the average of these values, we assumed patients receiving usual care spend 33% of their time (range, 15%–50%) below and 17% of their time (range, 10%–25%) above therapeutic range. For anticoagulation clinic testing, we assumed that patients spend 26% percent of their time (range, 8%–40%) below and 9% of their time (range, 1%–17%) above therapeutic range to reflect the averages of those reported by a number of large anticoagulation clinical trials,[13-21] as well as data from four observational studies.[3,6,22,23] For patient self-testing, patients were assumed to spend 6% of their time (range, 5%–15%) below and 5% of their time (range, 1%–7%) above therapeutic range, reflecting the average of those reported by White et al., [23] Anderson et al.,[9] Ansell et al.,[6] and Hasenkam et al.[7]

Associated with these estimates of time spent below, in, and above therapeutic range are first and subsequent thromboembolic and hemorrhagic event rates (Table 1).

Table 1. Event Rate per 100 Patient Years by Time Spent Below, In, and Above Therapeutic Range

	Below		In		Above	
Events	**Baseline**	**(Range)**	**Baseline**	**(Range)**	**Baseline**	**(Range)**
Thromboembolic first events						
Fatal	0.05	(0–0.30)	0.01	(0–0.05)	0.00	(0–0.05)
Life-threatening	1.58	(1.0–6.0)	0.47	(0–1.0)	0.11	(0–1.0)
Serious	14.68	(8.0–16.0)	2.52	(1.0–6.0)	2.29	(1.0–6.0)
Thromboembolic subsequent events						
Fatal	0.01	(0–0.3)	0.00	(0–0.05)	0.01	(0–0.05)
Life-threatening	0.32	(0–5.0)	0.04	(0–1.0)	0.44	(0–1.0)
Serious	2.45	(0–6.0)	0.88	(0–6.0)	1.60	(1.0–6.0)
Hemorrhagic first events						
Fatal	0.05	(0–0.3)	0.04	(0–0.3)	0.20	(0–0.6)
Life-threatening	0.61	(0–1.0)	0.49	(0–1.0)	2.66	(0.5–4.0)
Serious	5.87	(3.0–8.0)	5.12	(3.0–8.0)	12.83	(10.0–20.0)
Hemorrhagic subsequent events						
Fatal	0.02	(0–0.3)	0.02	(0–0.3)	0.07	(0–0.6)
Life-threatening	0.30	(0–1.0)	0.25	(0–1.0)	0.96	(0.5–4.0)
Serious	1.30	(0–8.0)	1.85	(0–8.0)	5.73	(3.0–20.0)

Transition probabilities for event rates were derived from a longitudinal study of patients seen in five anticoagulation clinics.[5,10,11] Published data from this study were supplemented with unpublished data provided by Dr. Stephan Fihn and colleagues. The average age of this population was 57 years and 81% were male. Thirty percent had a primary indication of deep vein thrombosis or pulmonary embolism, while 26% and 14% were on warfarin for valvular disease and atrial fibrillation, respectively. Finally, 21% had experienced a cerebral or systemic embolism, 7% had other circulatory conditions, and the remaining 3% were on warfarin for other conditions.[10]

Although the study by Fihn et al. was done before INR reporting was commonplace: however, the classification system for prothrombin time therapeutic range used in their study afforded the ability to translate into INR-defined therapeutic ranges.[10] To do so, we assumed an international sensitivity index (ISI) of 2.3.[10] As proposed by Fihn et al., events were classified into three categories requiring medical care: serious, life-threatening, or fatal.[10,11] Serious events include bleeding that requires endoscopy, recurrent deep vein thrombosis, and transient ischemic attack. Life-threatening events are those that require urgent treatment or cause irreversible sequelae; examples include myocardial infarction, stroke, and bleeding leading to surgery.

We assumed that 60% of all life-threatening thromboembolic events[24-28] and 10% of all life-threatening hemorrhagic events[5] resulted in permanent disability. Among some patients incurring a disabling event, the risk associated with continued warfarin use most likely outweighs the potential benefits. Our model therefore allowed for a proportion of those who were permanently disabled to discontinue warfarin therapy. To our knowledge, no published data are available on the percentage of individuals who discontinue therapy after becoming permanently disabled. As a baseline, we assumed that 50% would do so after a permanently disabling event. Among individuals who discontinued therapy, the risks of a subsequent thromboembolic event (17%) and hemorrhagic event (1%) were derived from those reported for members of the control group of a large randomized anticoagulation trial for secondary prevention.[15]

Using data from several studies that have assigned utilities to the adverse events associated with anticoagulation therapy,[29-33] we also estimated the quality-adjusted life years (QALYs) expected with each management alternative. For patients who suffered a temporarily disabling event, a utility of 0.75 was assigned for the 30 days following the event. For individuals who suffered a permanently disabling event, a utility of 0.50 was assigned from the time of the event until death or the end of the 5-year modeling period, whichever came first. Because the validity and reliability of these reported QALYs is untested, we elected to vary these estimates over a wide range in the sensitivity analyses.

For each of these assumptions, we conducted sensitivity analyses to determine the robustness of model results to underlying assumptions. One-way sensitivity analysis was conducted for assumptions of particular interest, and multiple-way sensitivity analysis was conducted using Crystal Ball,[34] a program that enables Monte Carlo analysis. The more uncertain the data on which we based an assumption, the wider the range we tested around the assumption in the sensitivity analyses.

All data were compiled and all analyses and interpretations were conducted by the authors, independent of Roche Diagnostic (formerly Boehringer Mannheim) staff, the funding source for the study. The two exceptions to this were data on the base model device cost and estimated

time required to train patients in its use, both of which were provided by Roche Diagnostic staff.

Cost Data

The direct medical care costs of anticoagulation monitoring and of thromboembolic and hemorrhagic events are used to estimate the model. These costs were drawn from the scientific literature, supplemented with information available within the authors' institution and, when needed, expert opinion. To approximate the reference case as recommended by the Panel on Cost-Effectiveness in Health and Medicine,[35] we included the costs associated with anticoagulation testing, monitoring, and adverse events (including nursing home costs), as well as the costs incurred by patients and their caregivers in receiving care. Model results are presented from two perspectives: a medical provider perspective, which includes all direct medical care costs, including nursing home costs; and a societal perspective, which includes the costs incurred by medical providers, and by patients and their caregivers in receipt of care. All costs and health outcomes were discounted at a base rate of 3%,[35] and all monetary amounts reflect 1997 dollars.

As shown in Table 2, annual anticoagulation management costs were derived using an estimated testing frequency of 14 times per year for usual care,[12] 23 times per year for anticoagulation clinic testing,[6] and 52 times per year for patient self-testing.[8] The frequencies for usual care and anticoagulation clinic testing are consistent with experiences within our own institution; all reflect the average testing frequency for patient populations that include those who spend time both within and outside the therapeutic range. Included in the direct medical care costs of anticoagulation management were the costs of equipment, supplies, and staff time (i.e., nurse and physician time). Although we assumed the average physician time per consult to be consistent across the three management alternatives (i.e., 2 minutes),[36] we assumed the frequency with which the physician is consulted to be reduced once an anticoagulation clinic had been established (i.e., 90% vs. 10%).[36] Nursing time per test was assumed to be 13 minutes for usual care, 15 minutes for anticoagulation clinic testing, and 8 minutes for patient self-testing. Valuation of these resources was achieved by using prevailing wage and price data from our institution and therefore reflects the acquisition cost to a provider organization. Also reflective of the acquisition cost to a provider organization was the price used in the base model for the capillary monitor—$1,385.

Included in the costs of anticoagulation management faced by patients and their caregivers were time and travel costs (Table 2). Time costs, which include travel, waiting, training, and testing times, were estimated to be 17 minutes for usual care, 20 minutes for anticoagulation clinic testing, and 15 minutes for self-testing.[36] They were valued using prevailing national wage rates for individuals aged 55 to 64 years ($14.10 per hour).[37] From experiences in our anticoagulation clinic, we assumed 30% of patients were accompanied by a family member for clinic-based testing. Nine percent were assumed to receive help with home testing.[38] So as to estimate only the marginal costs associated with INR testing, no travel costs were associated with any testing assumed to occur during routine visits. (In the base model, we assumed seven such visits per year.)

Table 3 presents the average cost for adverse events used in the model. Included in these were office visit, emergency department, and hospital admission costs. The underlying resource use (e.g., length of stay) from which these estimates were derived was from the stroke-related literature,[39,40] as well as a sample of 50 patients receiving

Table 2. Annual Anticoagulation Management Costs Per Patient

Management Strategy	Number of Tests per Year		Costs to Managed Care Organization	Costs to Patients and Their Caregivers	Total Management Costs
	Baseline	(Range)			
Usual care	14	(9–23)	$157*	$239§	$396
Anticoagulation clinic testing	23	(11–28)	$233†	$520‖	$753
Patient self-testing	52	(29–73)	$660‡	$200¶	$860

**Baseline estimates assume 2 minutes physician (MD) time for 90% of tests valued at $72/h, 13 minutes of nursing (RN) time per test valued at $23.40/h, equipment and supply cost of $4 per test.*

†Baseline estimates assume 2 minutes MD time for 10% of tests valued at $72/h, 15 minutes of RN time per test valued a t $23.40/h, $4 reagent cartridge per test and $1,385 per capillary monitor per 200 patients served, allocated over 5 years of use.

‡Baseline estimates assume 2 minutes of MD time for 10% of tests valued at $72/h, 8 minutes of RN time per test valued at $23.40/h, $4 reagent cartridge per test, and $1,385 per capillary monitor allocated over 5 y of use.

§Baseline estimates assume 17 minutes of patient (PT) and caregiver (CG) time per test valued at $14.10/h with CG accompanying 30% of PTs, 26 mi per test valued at $0.30/mi (CG assumed to travel with PT) and 52 travel minutes per test valued at $14.10/h (no mileage or travel time for 7 tests assumed to coincide with routine office visits).

‖Baseline estimates assume 20 minutes of PT and CG time per test valued at $14.10/h with CG accompanying 30% of PTs, 26 mi per test valued at $0.30/mi (CG assumed to travel with PT) and 52 travel minutes per test valued at $14.10/h (no mileage or travel time for 7 tests assumed to coincide with routine office visits).

¶Baseline estimates assume 15 minutes of PT and CG time per test valued at $14.10/h with CG assisting 9% of PTs with self-testing.

Table 3. Adverse Event Costs

Event Severity	Average Cost per Event: Thromboembolic Events	Average Cost per Event: Hemorrhagic Events
Fatal	$5,112	$11,232
Life-threatening	$19,280	$20,980
Serious	$10,684	$3,044

anticoagulation therapy from our institution. Valuation of these resources was achieved by using our institution's cost estimates and published data.[41] For individuals who were institutionalized, the cost of nursing home care was also included.

RESULTS

Baseline Analysis

Table 4 presents the number of adverse events by severity expected with each of the three management strategies. As illustrated in Table 4, 3.7 events per 100 patients could be avoided by moving from usual care to anticoagulation clinic testing, and another 4.9 events per 100 patients could be avoided by moving from anticoagulation clinic testing to patient self-testing over a 5-year period.

Because the majority of these events are not fatal, the expected differences in life years among the three alternatives are relatively small (i.e., <0.2). However, as many life-threatening and serious events result in disability, moving from usual care to anticoagulation clinic testing would result in an increase of 0.5 QALY per 100 patients, and moving from anticoagulation clinic testing to patient self-testing would result in an additional 0.8 QALY per 100 patients over the 5-year period.

Table 5 presents the discounted 5-year costs associated with each of the three management alternatives. Although the increased frequency of testing that occurs with anticoagulation clinic testing (23 vs 14) drives up the costs of testing compared with those incurred in usual care, these cost increases are more than offset with the savings due to avoided adverse events and their sequelae, making anticoagulation clinic testing a financially appealing alternative to usual care in terms of associated medical care costs. On the other hand, moving from anticoagulation clinic testing to patient self-testing is expected to result in an overall increase in medical care costs, as the savings due to reduced adverse events are not completely offset by the increased costs of testing.

Table 5. Five-Year Costs per 100 Patients by Management Strategy*

Management Strategy	Medical Care Costs	Patient and Caregiver Costs	All Costs
Usual care	$419,514	$110,223	$529,737
Anticoagulation clinic testing	$405,560	$240,110	$645,671
Patient self-testing	$526,014	$96,713	$622,727

**All costs are reported in 1997 dollars.*

In addition to the direct medical care costs, we considered the costs incurred by patients and their caregivers in receiving care. Because of the increased frequency of testing (and the associated time and travel costs), an increase of almost $130,000 per 100 patients is realized in the costs incurred by patients and their caregivers when moving from usual care to anticoagulation clinic testing. On the other hand, because of the reduction in time and travel costs associated with patient self-testing, even with a substantial increase in the frequency of testing, an overall cost saving of over $140,000 per 100 patients would be realized when moving from anticoagulation clinic testing to patient self-testing.

The net result is that the discounted incremental cost-effectiveness ratios differ substantially depending on whether or not the costs incurred by patients and their caregivers are included. As illustrated in Table 6, when these costs are considered ("All Costs"), moving from usual care to anticoagulation clinic testing results in a cost-effectiveness ratio of $31,327 per avoided event (or $232,226 per QALY), and moving from anticoagulation clinic testing to patient self-testing results in an expected cost saving. However, when patient and caregiver costs are ignored, moving from usual care to anticoagulation clinic testing results in a cost saving, while moving from anticoagulation clinic testing to patient self-testing results in a cost-effectiveness ratio of $24,818 per avoided event (or $153,504 per QALY).

Sensitivity Analyses

We conducted one-way sensitivity analyses for model assumptions including time spent outside therapeutic range, disability rates, the resource use associated with adverse events, the proportion of the disabled population

Table 4. Number of Adverse Events per 100 Patients Over 5 Years

Management Strategy	Total	Thromboembolic Events: Fatal	Thromboembolic Events: Life-threatening	Thromboembolic Events: Serious	Hemorrhagic Events: Fatal	Hemorrhagic Events: Life-threatening	Hemorrhagic Events: Serious
Usual care	30.65	0.05	1.50	11.91	0.17	2.24	14.78
Anticoagulation clinic testing	26.95	0.04	1.27	10.48	0.14	1.85	13.17
Patient self-testing	22.10	0.03	0.82	6.92	0.12	1.62	12.60

Table 6. Cost-Effectiveness Ratios

Ratio	Medical Care Costs	All Costs
Cost per Event		
Usual care to anticoagulation clinic testing	Cost saving	$31,327
Anticoagulation clinic testing to patient self-testing	$24,818	Cost saving
Cost per QALY		
Usual care to anticoagulation clinic testing	Cost saving	$232,226
Anticoagulation clinic testing to patient self-testing	$153,504	Cost saving

that discontinued therapy, the resources required for anticoagulation management, the wage rate used to value patient and caregiver time, and the discount rate. In general, model findings of overall cost increases or savings were most sensitive to assumptions regarding time spent below and above therapeutic range. For example, a relatively small change in the time spent below and above therapeutic range (i.e., 4%–6%) led to a cost increase instead of a savings in medical care costs when moving from usual care to anticoagulation clinic testing. In addition, the model findings of cost increases or savings are sensitive to annual testing frequency. For example, if frequency of testing for patient self-testing increases to 57 times a year (base 52), then moving from anticoagulation testing to patient self-testing would no longer be cost saving when all costs are included, although the cost would still be a modest $608 per event avoided or $3,758 per QALY. Converseley, overall model results were not sensitive to the discount rate used (range, 0%–10%), or assumptions regarding the percentage of patients discontinuing therapy after a permanent disability (range, 20%–80%), the wage rate used to value patient and caregiver time (range, $11–$17 per hour), and the annual number of tests that would occur during routine visits (range, 4–14).

A multi-way sensitivity analysis, in which all assumptions within the model were allowed to vary within their specified ranges, confirmed overall results. Moving from usual care to anticoagulation clinic testing is likely to result in a reduction in the number of events (88% certainty), an increase in life years (79% certainty), and a decrease in disabled life years (80% certainty). Similarly, moving from anticoagulation clinic testing to patient self-testing will also result in a reduction in the number of events (91% certainty), an increase in life years (85% certainty), and a decrease in disabled life years (95% certainty). In addition, when only medical care costs are considered, results indicate that moving from usual care to anticoagulation clinic testing is likely to be cost saving (80% certainty), and when patient and caregiver costs incurred are included, moving from anticoagulation clinic testing to patient self-testing may result in a cost saving (48% certainty).

DISCUSSION

Consistent evidence exists that the more time a patient spends within his or her therapeutic range, the fewer events he or she has. The practical issues of how to manage patients most appropriately to keep them within therapeutic range, however, remain unclear. The establishment of anticoagulation clinics seems to be the current best answer, and a randomized trial evaluating their effectiveness is currently underway.[2] Incorporating newer technologies, like capillary monitors, into the management process may further improve patient outcomes. This model addresses both the health and economic implications of more organized management of patients receiving chronic warfarin therapy: anticoagulation clinic testing and patient self-testing.

Model results illustrate the potential health benefits of such a move: over a 5-year period, moving from usual care to anticoagulation clinic testing would reduce the number of adverse events per 100 patients by 3.7, and moving from anticoagulation clinic testing to patient self-testing would result in a reduction of another 4.9 events.

The model also illustrates the importance of considering fully the economic impact to each of the different entities involved. From a medical care provider perspective, this model demonstrates that an anticoagulation clinic testing approach would provide a cost-effective, in fact a cost-saving, alternative to usual care. However, the burden that such an approach would place on patients and their caregivers cannot be ignored. The increased frequency of testing associated with anticoagulation clinic testing relative to usual care substantially increases the time- and travel-related costs to patients and their caregivers. Once these costs are included, patient self-testing becomes the most cost-effective alternative to usual care.

Two potential limitations of the model warrant reiteration. First, the adverse event rates used were based on a population that included relatively few patients with atrial fibrillation. Ideally, we would have based estimates of event rates on data derived from a population more reflective of those currently receiving warfarin therapy, that is, one with a larger percentage of patients with atrial fibrillation. However, we know of no database that includes thromboembolic and hemorrhagic event rates by either management alternative or time within therapeutic range for such a population. Second, although we are conducting a randomized clinical trial comparing time spent within and outside therapeutic range by different management alternatives, to date no such trial data exist. Therefore, we were forced to rely on observational data for modeling assumptions regarding time spent below, in, and above therapeutic range. Although model findings of cost savings are sensitive to these assumptions, the relative ranking of the alternatives generally is not. That is, almost without exception, anticoagulation clinic testing is the most cost-effective alternative to usual care when costs to patients and their caregivers are ignored, and once these costs are included, patient self-testing becomes the most clinically effective and cost-effective alternative.

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THROMBOSIS RESEARCH

ORIGINAL ARTICLE

Accuracy of a Portable Prothrombin Time Monitor (Coagucheck) in Patients on Chronic Oral Anticoagulant Therapy: A Prospective Multicenter Study

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Abstract

A portable prothrombin time (PT) monitor allows patients on oral anticoagulant therapy (OAT) to measure their PT at home. The purpose of the study was to evaluate the accuracy and precision of a portable PT monitor (Coagucheck, Roche Diagnostics, Mannheim, Germany) as compared with laboratory methods. The prospective study was conducted in four centers of the Italian Federation of Anticoagulation Clinics. A one-month instruction phase was followed by a six-month surveillance phase. Seventy-eight subjects on stable OAT (48 men, 30 women, age range: 18–75) were selected on a volunteer basis. Dual measurements of INR values were performed in each subject both from finger capillary blood by the monitor and from venous blood by the Anticoagulation Clinic laboratory in three instruction sessions. The mean difference (bias) of the monitor INR results when compared with the average of laboratory INR and monitor INR results was −0.025 (limits of agreement−LA: −0.84/+0.81 INR units). The mean bias was −0.0675 (LA: −0.37/+0.23), +0.018 (LA: −0.39/+0.35), and +0.039 (LA: −0.49/+0.55), respectively, for INR values lower than 2.0, between 2.0 and 3.0, and greater than 3.0. The overall precision coefficient of monitor INR was 0.370, while it was 0.23, 0.46, 0.29, and 0.21, respectively, in Centers 1, 2, 3, and 4. The overall variation coefficient was 6.5% while it was 3.7%, 8.5%, 4.7%, and 4.9%, respectively, in Centers 1, 2, 3, and 4. Coagucheck has an acceptable level of accuracy for INR values in the range between 2.0 and 3.0. A wide variation in monitor performance was found among centers.

Key Words: Oral anticoagulants; Prothrombin time; Point-of-care testing; Anticoagulation clinic; Accuracy; Precision

Portable monitors allow patients on chronic oral anticoagulant therapy (OAT) to measure their prothrombin time (PT) at home from capillary blood obtained from a finger-stick [1,2]. Recently, randomized clinical trials have shown that both home PT self-testing and dose self-adjustment are feasible and safe in patients on chronic OAT [3,4,5].

Several studies have evaluated the accuracy of

Abbreviations: AMT, Abbreviated Mental Test; CGK, Coagucheck; FCSA, Federazione Italiana Centri Sorveglianza Anticoagulati; INR, International Normalized Ratio; ISI, International Sensitivity Index; OAT, oral anticoagulant therapy; PT, prothrombin time.

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the PT monitor by comparing its results with laboratory methods [6,7,10]. Monitor PT values were compared within a single laboratory [6,7,10] or, rarely, with a laboratory reference thromboplastin standard using the tilt tube method [7,10] for the prothrombin time readings. Limited data are available on comparisons performed between portable monitor INR results and INR values determined in several different routine laboratories.

The aim of this study was to evaluate the accuracy and precision of a portable PT monitor (Coagucheck, Roche Diagnostics, Mannheim, Germany) as compared with routine laboratory methods. Thus, we conducted a prospective study in four centers of the Italian Federation of Anticoagulation Clinics (FCSA).

1. Patients and Methods

1.1. Study Subjects

Consecutive patients were selected on a volunteer basis among those who attended the four participating Anticoagulation Clinics and who were on stable OAT for at least six months. Each patient was administered the Hodkinson's Abbreviated Mental test (AMT) [8] to evaluate information-memory and concentration levels. Written informed consent to participate to the study was obtained from patients with a normal AMT. Exclusion criteria were the following: age less than 18 years, manual impairment, refusal to agree to informed consent.

1.2. Prothrombin Time Monitor

Briefly, the Coagucheck is a portable laser photometer that is battery powered. When a drop of blood (non-citrated) obtained from a finger-stick (minimum 25–10 μL) is applied to a disposable plastic cartridge, it is drawn by capillary action into a chamber containing rabbit brain thromboplastin, where it mixes with the reagent. A pulsating magnetic field is initiated, causing paramagnetic iron oxide particles contained in the cartridge to move. As the blood sample clots, the absence in particle movement is detected by a reduction in reflectance. The resulting clotting time is recorded and displayed in PT ratio and INR units.

The monitor is internally calibrated so that the mean normal PT is 12.6 seconds. Calibration information specific to the thromboplastin in each lot of strips is coded on a lot-specific chip that is inserted into the monitor. The ISI declared by the manufacturer for the thromboplastin reagent is 1.8.

1.3. Study Intervention

The study consisted of one-month instruction phase, followed by a six-month surveillance phase.

1.3.1. Instruction Phase

The patients were instructed in the use of Coagucheck in three training sessions. In each session, dual measurements of INR values (both by the monitor and the Anticoagulation Clinic laboratory) were performed in each subject. Both tests were performed in the same clinic within 2 hours of each other. PT laboratory measurements were performed by technicians unaware of the monitor INR results. In the first session, after a brief explanation of the functioning of the monitor and a demonstrative test, patients obtained the capillary blood and performed the test with the help of the instructors. In the second session, patients were required to perform the test from capillary blood by the monitor by themselves, but they could ask for assistance from the instructors. In the third session, the patients were required to perform the test from three different finger-sticks entirely by themselves with no assistance from the instructors. In the third training session, study subjects were required to perform the test successfully under supervision before being allowed to proceed with the study for six months. Patients were provided with the prothrombin time monitor Coagucheck, a finger-stick device (Softclix II, Boehringer Mannheim, Mannheim, Germany), disposable lancets, and a box of 12 prothrombin time cartridges. During the instruction phase of the study, the same lot of portable monitor cartridges was used in each center.

In all patients, venous blood was drawn to fill completely 5 mL siliconized vacutainer tubes (Becton Dickinson, Milan, Italy) containing 0.5 mL of 0.129 mL/L buffered sodium citrate. Platelet poor plasma was separated after centrifugation for 10 minutes at 3500 rpm.

PT laboratory measurements were performed

using the photo-optical MLA Electra 1600 instruments (Hemoliance, Instrumentation Laboratory, Milan, Italy) in Centers 1 and 3, MLA Electra 1400 (Hemoliance, Instrumentation Laboratory, Milan, Italy) in Center 4, and STA (Roche Diagnostics, Mannheim, Germany) in Center 3. The thromboplastin reagents used for PT laboratory measurements were the following: Neoplastin Plus reagent (Roche Diagnostics, Mannheim, Germany, ISI: 1.26) in Center 2, Recombiplastin (Hemoliance, Instrumentation Laboratory, Milan, Italy, ISI: 0.9-1) in the other three Centers. All centers affiliated with FCSA participate in an external quality-control program.

The ISI values were adjusted for the instrument–thromboplastin combination in all centers. The laboratory calibrated the local ISI value in Centers 1 and 3.

1.3.2. Anticoagulant Therapy Surveillance

On the day of each scheduled PT control, the patients were required to perform the PT test by Coagucheck at home and then communicate the resulting INR value to the center (preferably by fax, using a standard form to be filled in). The physician in charge at the Anticoagulation Clinic prescribed the dose and indicated the date for next control. The patients were also requested to communicate any difficulties encountered in performing the test and the number of the tests performed in case of difficulty. After approximately three months from the start of the surveillance phase, on a designated day, patients were also required to have their PT measured at the Anticoagulation Clinic laboratory within 3 hours of their home test. PT laboratory measurements were performed by technicians unaware of the monitor INR results.

The protocol was approved by the Ethics Committee of Research involving human subjects at each of the four centers involved in the study.

1.4. Study Outcome Measures

1.4.1. Instruction Phase

The primary outcome measures were the accuracy and precision or repeatability of the portable monitor results. Thus, the INR results measured by the portable monitor were compared with those obtained by the Anticoagulation Clinic laboratory.

The accuracy was determined by calculating the following: a) the bias and limits of agreement of the monitor INR in comparison with the average of laboratory INR and monitor INR, according to the method of Bland and Altman [9]; b) the clinically relevant agreement (which is also referred to as efficiency), defined as the proportion of monitor INRs that agreed with the laboratory INRs as being both within, above, or below the patient recommended therapeutic range [10]; c) the "interval agreement," evaluated as the proportion of monitor INRs that were within 0.4 INR units of the laboratory INR. The criteria for agreement were established a priori, without knowledge of the INR results [11].

Agreement was defined also in relation to the magnitude of INR. The bias and limits of agreement were determined for laboratory INR values <2.0; between 2.0 and 3.0; and >3.0.

The precision or repeatability coefficient of the monitor results was determined by considering the INR values obtained in the last session of the instruction phase by three different finger-sticks [9].

1.4.2. Anticoagulant Therapy Surveillance

The primary outcome measures were the following: the accuracy of PT monitor at three months; the clinically relevant agreement between monitor INR and laboratory INR measured after three months from the start of the study; and the interval agreement, as previously defined. The secondary outcome measure was the number of technical difficulties that the patients encountered in performing the portable monitor PT during the six-month study period.

1.5. Statistical Analysis

Data are expressed as mean$\pm$SD or 95% confidence limits as appropriate.

Data analyses included *t*-test and chi-square, when appropriate. To test agreement between the portable PT monitor system and standard laboratory-based PT, bias analyses were used according to Bland and Altman [9]. The bias (mean bias, average of the differences) represents the systemic error between the two monitoring techniques; SD of the bias is representative of the random error or variability between different monitoring techniques. Mean difference$\pm$2 SDs are known as the

Table 1. Baseline characteristics of study patients

Sex (M/F)	48/30
Age range (years)	18–75
Mean; 95% CL	53.7 (51.1–56.6)
Duration of OAT	
Mean; 95% CL (years)	5.6 (4.7–6.5)
Range (years)	0.8–17.5
Targeted therapeutic range	
INR: 2.0–3.5	47/78 (60%)
INR: 2.5–4.5	31/78 (40%)
Acenocoumarol users	29
Range 2.0–3.5	13/29 (45%)
Range 2.5–4.5	16/29 (55%)
Warfarin users	49
Range 2.0–3.5	34/49 (70%)
Range 2.5–4.5	15/49 (30%)
Diagnosis	
Prosthetic heart valve	31
Venous thromboembolism	18
Atrial fibrillation	7
Other	22

limits of agreement [9]. McNemar's test for paired proportions was used to compare the proportion of true positive and true negative agreement of monitor INR and laboratory INR with the therapeutic range during the instruction and surveillance phase.

A two-tailed p value <0.05 was considered significant. The statistical analyses were conducted with the statistical package SOLO (BMDP Statistical Software, Los Angeles, CA, USA).

2. Results

Ninety-six subjects who were regularly attending the four Anticoagulation Clinics volunteered to participate in the study. Eighteen patients were excluded during the instruction phase for the following reasons: failure at the AMT ($n=6$); refusal to participate ($n=4$); manual impairment ($n=2$); hospitalization ($n=2$); finger-stick impossible because of too thick skin ($n=1$); treatment suspension ($n=1$); diagnosis of cancer ($n=1$); and positive HIV testing ($n=1$).

Seventy-eight subjects were enrolled in the study. Baseline characteristics of study patients are illustrated in Table 1.

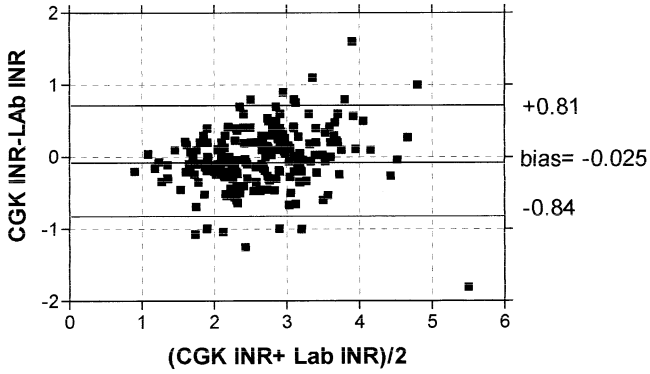

Fig. 1. Agreement between portable monitor Coagucheck INR (CGK INR) and laboratory INR (Lab INR) measurements as a function of the average of laboratory INR and monitor INR during the instruction phase of the study. The mean bias±2 SDs (limits of agreement) are indicated.

3. Instruction Phase

3.1. Agreement between Portable Monitor and Laboratory Results

During the instruction phase, 230 dual INR measurements were performed. The bias and limits of agreement of the monitor INR results when compared with the laboratory INR results are indicated in Figure 1.

The bias and limits of agreement of the monitor INR results when compared with the laboratory INR results for each of the four centers are indicated in Figure 2. The mean bias and limits of agreement were significantly lower in Center 4 when compared to the other three centers ($p<0.001$).

The overall clinically relevant agreement for the instruction phase is indicated in Table 2 (Panel A). The proportion of monitor INRs that agreed with the laboratory INRs as being within, above, and below the therapeutic range in all centers was 42%, 29%, and 8%, respectively. The overall agreement was 79%. The clinically relevant agreement was higher in Center 1 (92%) when compared to Center 2 ($p=0.0013$) and Center 4 ($p=0.0226$). No difference in clinically relevant agreement was observed between Centers 1 and 3.

INR values obtained with the monitor were within 0.4 INR units 76% of the times, when the data from all centers were analyzed. The agreement within 0.4 INR units was 85%, 66%, 81%, and 70% in Centers 1, 2, 3, and 4, respectively.

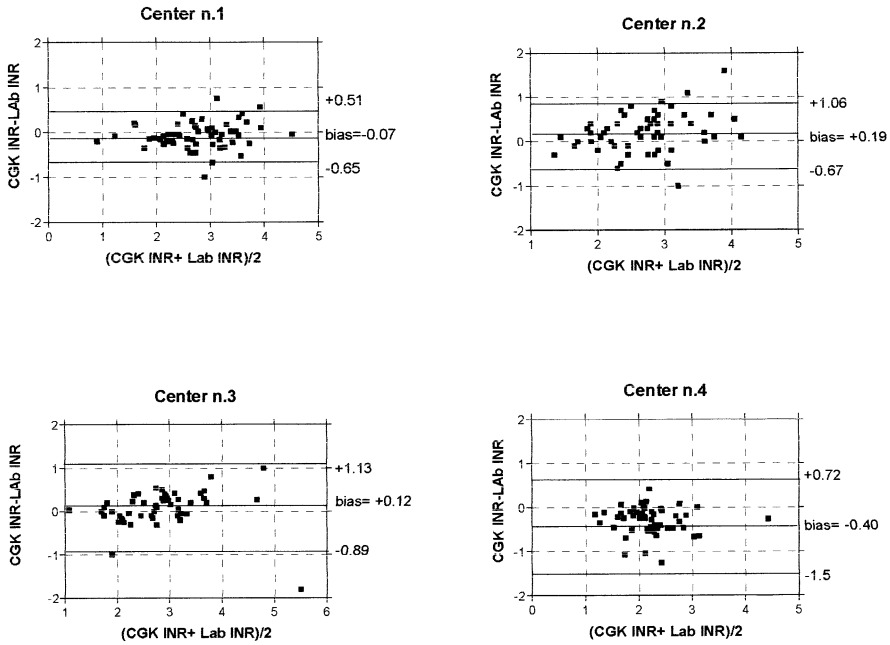

Fig. 2. Agreement between portable monitor Coagucheck INR (CGK INR) and laboratory INR (Lab INR) measurements as a function of the average of laboratory INR and monitor INR in the four participating centers during the instruction phase. The mean bias±2 SDs (limits of agreement) are indicated.

3.2. Agreement between Portable Monitor and Laboratory Results in Relation to Magnitude of INR

The mean bias of portable monitor INR for values below 2.0 was −0.0675 (LA:−0.37/+0.23). The mean bias for INR values between 2.0 and 3.0 was−0.018 (LA:−0.39/+0.35). The mean bias for values above 3.0 was +0.034 (LA:−0.49/+0.55).

The distribution of agreement according to the magnitude of INR in each center is indicated in Figure 3.

The overall repeatability coefficient of monitor INR results was 0.37. It was 0.233, 0.461, 0.289, and 0.212, respectively, in Centers 1, 2, 3 and 4.

The overall variation coefficient was 6.5% (95% confidence limits; CL: 5.4–7.6%). It was 3.7% (95% CL: 2.1–5.2%) in Center 1, 8.5% (95% CL: 6.8–10.2%) in Center 2, 4.7% (95% CL: 3–6.4%) in Center 3, and 4.9% (95% CL: 2.3–7.5%) in Center 4.

Table 2. Clinically relevant agreement between monitor INR results and laboratory INR results

Panel A Targeted range	**Instruction phase**				
Center	**1**	**2**	**3**	**4**	**All centers**
Both within %	57	35	48	27	42% (96/230)
Both above %	8	10	15	0	29% (66/230)
Both below %	27	22	19	48	8% (19/230)
Total agreement*	92	67	82	75	79% (181/230)

*Chi–square $p=0.0077$ among Centers 1, 2, 3, and 4.
Center 1 vs. 2: $p=0.0013$; Center 1 vs. 3: $p=0.16$; Center 1 vs. 4: $p=0.0226$.

Panel B Targeted range	**Surveillance phase**				
Center	**1**	**2**	**3**	**4**	**All centers**
Both within %	71	33	0	59	46% (32/70)
Both above %	12	20	0	6	13% (9/70)
Both below %	0	17	50	24	17% (12/70)
Total agreement*	83	70	50	89	76% (53/70)

*Chi–square: $p=0.2081$ among Centers 1, 2, 3, and 4.
Center 1 vs. 2: ns; Center 1 vs. 3: ns; Center 1 vs. 4: ns.

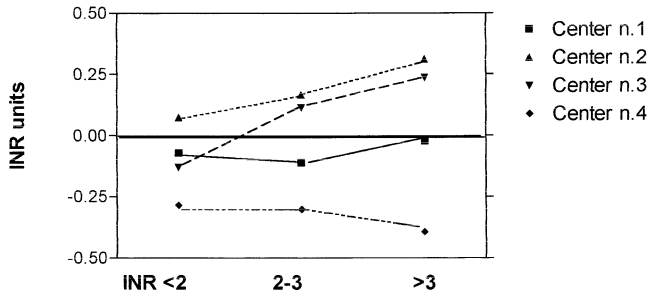

Fig. 3. Agreement between portable monitor Coagucheck INR and laboratory INR measurements (y-axis) is plotted as a function of increasing INR values (*x*-axis) in each of the participating centers.

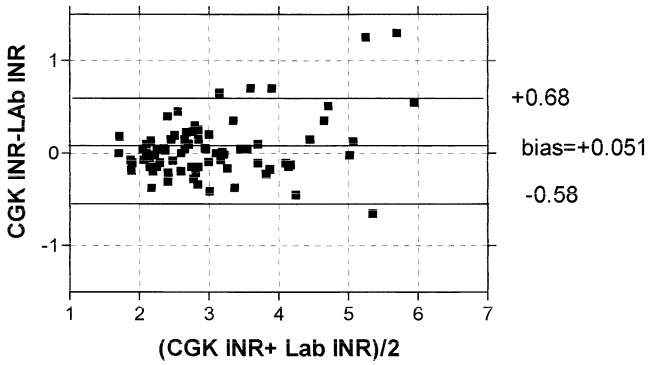

Fig. 4. Agreement between portable monitor Coagucheck INR (CGK INR) and laboratory INR (Lab INR) measurements as a function of the average of laboratory INR and monitor INR during the surveillance phase of the study. The mean bias±2 SDs (limits of agreement) are indicated.

4. Surveillance Phase

4.1. Agreement between Portable Monitor and Laboratory Results

Seventy INR dual measurements were performed after three months from the start of the surveillance phase. The mean bias and the limits of agreement for all centers are shown in Figure 4. The mean bias and limits of agreement were −0.127 (LA:−0.502/+0.248),+0.206 (LA:−0.587/+1.00),+0.221 (LA:−0.183/+0.627) and−0.077 (LA:−0.378/+0.223), respectively, in Centers 1, 2, 3, and 4.

The clinically relevant agreement is shown in Table 2 (Panel B). During the surveillance phase, the proportion of monitor INR that agreed with the laboratory INRs as being within, above, or below the therapeutic range was 46%, 13%, and 17%, respectively. The overall agreement was 76%. No significant difference in clinically relevant agreement was observed among the four centers.

INR values obtained with the monitor were within 0.4 INR units 67.5% of times, when the data from all centers were analyzed. The agreement within 0.4 INR units was 61%, 78%, 62.5%, and 64.5% in Centers 1, 2, 3, and 4, respectively.

4.2. Technical Difficulties

No problems in the performance of the test were reported in 79% (638/808) of determinations. In 12% (97/808) of determinations, the blood drop resulted insufficient. In 1.8% (15/808) of determinations, difficulty in placing the drop in the well of the cartridge was reported. Technical difficulties due to the monitor functioning were rare (0.6%). One cartridge was used in 79.7% (644/808) of determinations, two cartridges were used in 9.4% (76/808) of determinations; three or more cartridges were used in 11% (88/808) of determinations. The mean number of tests (cartridges) the patients performed (used) per INR determination was 1.34.

5. Discussion

In our study we evaluated the accuracy of Coagucheck as compared with the routine laboratory methods employed in four Centers of the Italian Federation of Anticoagulation Clinics (FCSA). FCSA is a network of Italian Anticoagulation Clinics, and each affiliated center is required to take part to an external laboratory quality-control program [12].

We evaluated both the statistical agreement and the clinically relevant agreement between Coagucheck INR values and laboratory INR values.

The analysis of the data from all centers indicate that Coagucheck underestimates INR values below 2.0, while it overestimates INR values above 3.0. The mean bias was the lowest for INR values between 2.0 and 3.0. A significant bias (either positive or negative) has been reported in several studies for most portable PT monitor INRs, especially within the INR ranges of 2.0–2.5, relative to the parent laboratory [6,7,8,10,11,13].

The accuracy of the monitor measurements undoubtedly varies from laboratory to laboratory. Several sources of variance are involved: the ISI value of both the CGK reagent and the thromboplastins used in the laboratory, the normal control values, and the instruments used in the different laboratories [14]. The overestimation of INR values above 3 may be due to the ISI value of the Coagucheck thromboplastin as declared by the manufacturer (1.8) when compared to the ISI values of the thromboplastins employed in the three centers (Neoplastin Plus in Center 3 and Recombiplastin in Centers 1 and 2). In Center 4, however, Coagucheck underestimated INR values in all ranges. This center was employing the same thromboplastin (Recombiplastin) as Centers 1 and 3, but

local calibration of the thromboplastin ISI was not performed in Center 4. An instrument effect might have been involved, as a different instrument model (MLA Electra 1400) was employed in Center 4. During the surveillance phase, the limits of agreement were narrower than in the instruction phase both when the data were analyzed for all centers and when the data were stratified by center. No significant difference in the mean bias was observed in Center 4 when compared to the other centers during the surveillance phase. This effect might be due to the better training of patients after three months of home PT testing; or the different lots of cartridges for the PT monitor provided by the manufacturer to the centers during the surveillance phase of the study.

The overall clinically relevant agreement between monitor INR and laboratory INR was similar during the instruction and surveillance phases. When the data from each center were considered, a significant greater agreement was observed during the instruction phase in Center 1 when compared to the other three centers. However, in the surveillance phase no significant difference was observed in the clinically relevant agreement among the four centers. These data must be interpreted with caution because of the limited number of comparisons in Center 3 ($N=6$).

The precision (repeatability) of monitor INR is modest (0.370). The low precision of monitor INR measurements is not unexpected because of the added variables of differences in finger-stick and in cartridges used in each test.

During the surveillance phase, difficulties in performing the test were reported in 21% of determinations, mostly due to insufficient blood drop. These data indicate that even in well-trained patients, home PT testing still requires particular care and ability.

Our results should be interpreted in the light of possible sources of bias. We did not use a criterion INR laboratory determination to assess the accuracy of the PT monitor INR values. However, in our opinion the comparison with INR values from four different laboratories is still acceptable and may better reflect the common clinical routine. The use of the thromboplastin reference standard is hampered by its limited supplies, and the tilt tube method to measure prothrombin time is rarely used routinely. In the majority of cases the local laboratory INR values are available as a comparison with monitor INR values.

The manufacturer provided different lots of cartridges in the instruction and surveillance phases. This may have introduced a further element of variability in the comparison of PT monitor INR values with laboratory INR values.

An AMT was performed to evaluate the cognitive level, and six patients were excluded from the study. Thus, monitor performance could be influenced by the patient's cognitive status, age, and sex. This may limit the transferability of the results to the general patient population. Evaluation of information-memory and concentration levels would be particularly important to identify those subjects that could safely monitor themselves with such portable devices.

From a clinical point of view, decisions about OAT dosing will be affected by small differences in the INR range between 1.5 and 3. In patients in the high therapeutic range (e.g., INR 3–4.5) subsequent OAT dosing based on the portable monitor might result in under-coagulation and an increased risk of thromboembolic events. In the surveillance phase of our study, however, only one patient suffered a thrombotic event (non-fatal acute myocardial infarction). Further studies are required to evaluate the feasibility and safety of home PT testing and OAT self-adjustment. Our results indicate that the portable monitor is accurate for INR values lower than 3.0, especially for values between 2.0 and 3.0. Accuracy of monitor performance is dependent on the expertise of different centers.

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Assessment of patient capability to self-adjust oral anticoagulant dose: a multicenter study on home use of a portable prothrombin time monitor (COAGUCHECK)

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ABSTRACT

***Background and Objectives*. Self-testing and self-monitoring with portable prothrombin time (PT) monitors has been shown to be feasible and safe. However the ability of patients on chronic oral anticoagulant therapy (OAT) to self-adjust their dose without specific training has never been properly evaluated. The aims of this study were to evaluate: 1) the ability of patients on chronic OAT to self-adjust their dose without specific training; 2) the integration of a portable PT monitor (Coagucheck, Roche Diagnostics, Germany) for home use into routine patient care in anticoagulation clinics.**

***Design and Methods.* A nested case-control study was conducted in four centers of the Italian Federation of Anticoagulation Clinics (FCSA). Patients (n=78) on stable OAT for at least 6 months (cases: 47 men, 31 women, age range: 18-75 years) were enrolled on a volunteer basis after passing an Abbreviated Mental Test and providing informed consent. After three instruction sessions on the use of Coaguchek, subjects performed the PT test at home, communicated the INR results to the Center and suggested the dose adjustment and date for next control as they thought appropriate. However, they were requested to follow the prescription made by the Center. Controls (78 subjects) matched by age (± 5 years), sex and therapeutic range with the cases, were selected from among those who attended the anticoagulation clinics and managed by usual care.**

***Results.* When compared with the dose prescribed by the Clinic, the dose suggested by warfarin and acenocoumarol users was equal to or within ± 6% of the mean weekly dose in 80% and 82% of suggestions, respectively. Time spent in the therapeutic range during the study was the same (80%) for cases and controls.**

***Interpretation and Conclusions*. Selected patients on chronic anticoagulant therapy can acquire a satisfactory ability for self-adjustment of OAT dose without specific training.**

Key words: oral anticoagulants, prothrombin time, point-of-care testing, venous thromboembolism, warfarin, acenocoumarol

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Patients on chronic oral anticoagulant therapy (OAT) require regular monitoring of the prothrombin time (PT) and mandatory individual dose adjustment to ensure that the PT remains within the therapeutic range.[1] To improve the efficacy and safety of OAT, outpatient clinics devoted entirely to oral anticoagulant control have been developed in several countries.[2-4] However, homebound patients, those who live far from a clinic and those with a regular job may find frequent testing difficult and time consuming. In patients with poor venous access, such as cancer patients and children even experienced phlebotomists may find it problematic to obtain adequate venipunctures. These difficulties may hamper satisfactory patient compliance and anticoagulation control, thus exposing patients to an increased risk of bleeding or thromboembolic complications.

Portable monitors, that perform coagulation tests from capillary blood, allow patients to test at home from a drop of whole blood obtained from a fingerstick.[5] Home PT monitoring has potential advantages over PT laboratory monitoring: 1) it may reduce the inconvenience of periodic visits to anticoagulation clinics; 2) it allows self-testing and self-adjustment of the anticoagulant dosage, which may improve patient compliance and anticoagulation control.

Several studies have shown that the accuracy of portable PT monitors is satisfactory[6] and that self-testing at home is feasible.[7] Randomized studies[8-12] have also shown the feasibility of patient self-monitoring after adequate instruction of the patients. Patients on chronic OAT who are managed by an Anticoagulation Clinic do not receive routine specific training on dose self-adjustment. However these patients may acquire such ability even without specific training during the time spent under the surveillance of an anticoagulation clinic. The ability of patients on chronic OAT to self-adjust their doses without specific training has not been properly evaluated yet. The aims of our study were the following: 1) to evaluate the ability of patients on chronic OAT to self-adjust the anticoagulant dose without specific training; 2) to evaluate the potential integration of a portable PT monitor with the routine work of anticoagulation clinics.

Experimental design

Nested case-control study in four Italian anticoagulation clinics (Centers) active in Bologna, Cremona, Milan, Padua, and belonging to the Italian Federation of Anticoagulation Clinics (FCSA, Federazione Centri Sorveglianza Anticoagulati).

Design and Methods

Study subjects

A random list of patients who regularly attended the four participating Centers and who were on stabilized OAT for at least 6 months was obtained from the electronic database available in each Center. After a telephone contact, consecutive patients were enrolled on a volunteer basis. Before enrollment in the study, the Hodkinson's Abbreviated Mental test (AMT)[13] was administered to each eligible patient to evaluate information-memory and concentration levels. Exclusion criteria were the following: 1) age less than 18 years and greater than 75 years, 2) failure at the AMT, 3) visual or manual impairment to perform self-testing (e.g. hand tremor), 4) failure to obtain informed consent. Controls, matched by age (± 5 y), sex and therapeutic range with the cases, were selected from among those who attended the Center regularly for chronic OAT therapy surveillance. In the participating centers, it is a routine procedure to instruct patients in the initial phase of treatment on the relevant aspects of OAT: mechanism of action, control of anticoagulation level and effects of over- or under-dosage, INR meaning, specific INR target and therapeutic ranges, habit and diet effects, drug interactions, etc. However, subjects enrolled in our study received no specific instructions or detailed algorithms to adjust the anticoagulant dose according to INR results.

Study intervention

The study consisted of a one-month instruction phase, followed by a six-month surveillance phase.

Instruction phase. The patients were instructed in the use of a portable PT monitor (Coagucheck, Roche Diagnostics, Germany) by physicians and nurses in each of the participating Centers. Three training sessions were conducted in each center. Patients were allowed to proceed with the study after the performance of the test had been judged satisfactory by the instructors in the last training session. No home practice between training sessions was allowed. Patients were then provided with the PT monitor Coagucheck, a finger stick device (Softclix II, Boehringer Mannheim, Mannheim, Germany), disposable sterile lancets and a box of 12 PT cartridges.

Anticoagulant therapy surveillance phase. On the day of each scheduled PT control the patients were required to perform the PT test by Coagucheck at home and then communicate the resulting INR value to the center preferably by fax, using a standard form to be filled in. The patients were requested to fill in the form with their suggestion about the weekly OAT dose (divided in 7 days) for the next period and the date for the next PT control as they thought appropriate on the basis of the obtained INR result. Patients were also asked to fill in a questionnaire regarding their general health conditions, any variation in OAT that might have occurred and any concomitant drug assumption. The physician in charge at the Center prescribed the anticoagulant dosage and scheduled the next PT control on the basis of the INR received from patients, without any knowledge of suggestions made by patients. Particular care was taken to avoid that the patients had prior knowledge of the dose and date for the next PT control indicated by the clinic. The patients were explicitly requested: a) to follow the prescription of the OAT dose and the date of the next control scheduled by the anticoagulation clinic, and b) to refer to the clinic directly (personally or by phone) whenever they thought it necessary. At the end of the study period, patients were asked to answer a self-administered questionnaire designed to determine their attitude toward the portable monitor.

Controls were managed by regular anticoagulation clinic care. The latter entails periodic visits and OAT dose adjustment by the clinic on the basis of INR results of PT measured by the anticoagulation clinic laboratory. The same physicians adjusted the dose for controls and for cases.

The study protocol was approved by the Ethics Committee of Research involving Human Subjects at each of the four centers involved in the study.

Study outcome measures

Anticoagulant therapy surveillance phase. The primary outcome measure was the ability of patients to self-adjust their OAT dose without specific training. The capability of patients for self-adjustment was evaluated by calculating the following: 1) the absolute and percent difference between the weekly dose suggested by the patients and the weekly dose prescribed by the Center; 2) the difference between the date of the next control suggested by the patients and the date scheduled by the Clinic.

For the purpose of this study, we chose to evaluate the differences between patient suggestions and clinic prescriptions on the basis of both an absolute difference cut-off and a percent difference cut-off.

Only 5 mg strength tablets of warfarin are available in Italy and all patients on acenocoumarol were using 4 mg strength tablets. Thus patients were accustomed to receive prescriptions of a minimum of a quarter of a tablet. As a result, the absolute difference which corresponds to the smallest possible variation in dosage was ±1.25 mg/week for warfarin and ±1 mg/week for acenocoumarol. Variations of 1 mg acenocoumarol may have a greater effect on the INR than variations of 1.25 mg warfarin, because the potency ratio between acenocoumarol and warfarin is approximately 2:1. As a result, an absolute difference of ±2.5 mg/week of warfarin was considered equivalent to a variation of ±1 mg/week of acenocoumarol. The percent difference between the weekly dose suggested by the patients and the weekly dose prescribed by the Center was considered significant when it was greater than ±6%. This percent difference cut-off was chosen arbitrarily.

The agreement between the dose suggested by the patients and the dose prescribed by the Clinic was also evaluated in relation to the mean weekly dose as prescribed by the Center.

The secondary outcome measure was quality of anticoagulant control. The latter was evaluated as the following: 1) the percentage of time the patients spent in the therapeutic range during the study period; 2) mean squared INR deviation. The latter was calculated as defined by Sawicki *et al*.[9] using the following equation: [INR-1/2 (upper value of target INR range + lower value of target INR range]2.

The percentage of time the patients spent in the therapeutic range during the 6 months of the study was compared with: a) the percentage of time spent in the therapeutic range by the same patients in the previous 6 months; b) the percentage of time spent in the therapeutic range by the controls during the study period.

The tertiary outcome measures were the following: 1) bleeding complications (classified as described elsewhere;[4] 2) thromboembolic events; 3) the mean number of INR determinations during the study period; 4) results of the self-administered questionnaire at the end of the study.

Statistical analysis

Data are expressed as mean ± 95% confidence intervals. Data analyses included Mann-Whitney U test, paired t-test, Fisher's exact test and the chi-squared test when appropriate. The percentage of time spent with the INR in the therapeutic range was calculated according to the method of Rosendaal *et al*.[14] using the software kindly donated by Dr. F.R. Rosendaal.

A two-tailed *p* value of less than 0.05 was considered statistically significant. The statistical analyses were conducted with the statistical package SOLO (BMDP Statistical Software, Los Angeles, CA, USA).

Results

Study subjects

Ninety-six subjects who were regularly attending the four anticoagulation clinics volunteered to participate in the study. Eighteen patients were excluded during the enrollment and instruction phases for the following reasons: failure at the Abbreviated Mental test (n=6), withdrawal of consent to participate (n=4); manual impairment (n=2); hospitalization (n=2); finger-stick impossible because of too thick skin (n=1); treatment suspension (n=1); diagnosis of cancer (n=1); positive HIV testing (n=1). Seventy-eight subjects were enrolled in the study and 78 subjects matched by age (± 5 years), sex and therapeutic range with the cases were selected as controls. Baseline characteristics of the study patients (cases) and controls are illustrated in Table 1. The mean age of cases and controls was 53.7 and 55.5 years, respectively (a non-significant difference). The mean duration of OAT therapy at the time of enrollment was 5.6 years (range: 9.6 months-17.5 years) for cases and 5.8 years (range: 6 months-22.5 years) for controls. The education level ranged from 8th grade to doctorate degree.

Surveillance phase

Ability of patients to self- adjust the OAT dose. Patients suggested a weekly dose in 86% of INR determinations (695/808). The patients were more willing to suggest a weekly dose when the INR was within (93% of the times) than when it was above (83%) or below (87%) the therapeutic range. The ability acquired by patients to self-adjust the dose was assessed by calculating the absolute difference between the dose suggested by the patients and that prescribed by the Center (Table 2). The weekly dose indicated by warfarin users was equal to the dose prescribed by the clinic in 28% of suggestions. The differences (under- or over-estimation) were within 1.25 mg/week in 47% of suggestions, between 1.25 and 2.5 mg/week in 11% of suggestions and greater than 2.5 mg/week in 13% of suggestions. Overall the weekly dose suggested by warfarin users was equal to or within ± 2.5 mg of the dose prescribed by the center in 86% of suggestions. The weekly dose indicated by acenocoumarol users was equal to the dose prescribed by the center in 53% of suggestions. The rate of concordance was significantly greater than in warfarin users ($p<0.0001$). The differences (under- or over-estimation) were within 1 mg/week in 37.8% of suggestions, between 1 and 2 mg/week in 5.5% of suggestions and greater than 2 mg/week in 3.7% of suggestions. Overall the weekly dose suggested by the patients was equal to or within ± 1 mg of the dose prescribed by the Center in 90.8% of suggestions.

The agreement between the dose suggested by the patients and the dose prescribed by the Center was also evaluated in relation to the mean weekly dose of anticoagulant prescribed by the Centre during the surveillance phase. Warfarin users were divided into three groups: those taking a weekly dose lower than 20 mg (7/49-14%), between 20 and 35 mg (19/49 - 39%) and greater than 35 mg (23/49-47%). The proportion of dose suggestions concordant or within ± 2.5 mg/week when compared with the dose pre-

Table 1. Baseline characteristics of study patients.

	Cases	*Controls*	*p*
Sex (M/F)	47/31	44/34	ns
Age range in years	18-75	25-75	
Mean age (95% CL)	53.7 (51.1-56.6)	55.5 (52.9-58.1)	ns
Duration of OAT years, mean (95% CL)	5.6 (4.7-6.5)	5.8 (4.7-6.9)	ns
OAT duration (range in y)	0.8-17.5	0.5- 22.5	
Targeted therapeutic range			
INR: 2-3.5	47/78=60%	52/78= 67%	ns
INR: 2.5-4.5	31/78=40%	26/78= 33%	
Acenocoumarol users	29/78= 37%	18/78= 23%	ns
Range 2-3.5	13/29= 45%	11/18= 61%	ns
Range 2.5-4.5	16/29= 55%	7/18= 39%	
Warfarin users	49/78= 63%	60/78= 77%	ns
Range 2-3.5:	34/49= 70%	41/60= 68%	ns
Range 2.5-4.5	15/49= 30%	19/60= 32%	
Indications for OAT therapy			
prosthetic heart valve	31	28	ns
venous thromboembolism	18	17	ns
atrial fibrillation	7	6	ns
other	22	27	ns

Table 2.

	Warfarin	*Acenocoumarol*	*p**
No. determinations:	493	315	
Dose suggestion in:	425/493 (86.2%)	270/315 (85.7%)	
Concordant:	28%	53%	<0.0001
Underestimation:			
</= 1.25 mg/w	26%	</= 1 mg/w	21.5%
1.25-2.5 mg/w	7%	1-2 mg/w	1.8%
> 2.5 mg/w	9 %	> 2 mg/w	1.5%
Overestimation:			
</= 1.25 mg/w	21%	</= 1 mg/w	16.3%
1.25-2.5 mg/w	4%	1 mg-2 mg/w	3.7%
> 2.5 mg/w	5%	> 2 mg/w	2.2%

**Fisher's exact test.*

Table 3. Agreement between the dose suggested by the patient and the dose prescribed by the center according to the mean weekly dose prescribed by the center over the study surveillance phase.

WARFARIN	*< 20 mg/wk (7 pts)*	*20-35 mg/wk (19 pts)*	*>35 mg/wk (23 pts)*
No difference or dose within ± 2.5 mg/week			
% of suggestions	86.8%	87.2%	88.8%
(n. of suggestions/total suggestions)	(53/61)	(137/157)	(184/207)*
No difference or dose within ± 6% of the weekly dose			
% of suggestions	54%	75.1%	90.3%
(n. of suggestions/total suggestions)	(33/61)	(118/157)	(187/207)**
ACENOCOUMAROL	*< 15 mg/wk (7 pts)*	*15-22 mg/wk (11 pts)*	*>22 mg/wk (11 pts)*
No difference or dose within ± 1 mg/week			
% of suggestions	91.2%	90%	91.5%
(n. of suggestion/total suggestions)	(52/57)	(96/107)	(97/106)§
No difference or dose within ± 6% of the weekly dose			
% of suggestions	63.1%	81.3%	92.4%
(n. of suggestion/total suggestions)	(36/57)	(87/107)	(98/106)#

*Wk: week. *χ^2 test: p= 0.22 among groups of warfarin users; **χ^2 test: p <0.001 among groups of warfarin users; §χ^2 test: p= 0.89 among groups of acenocoumarol users; #χ^2 test: p =<0.001 among groups of acenocoumarol users.*

Table 4. Suggestions for the date of the next control when compared to the date scheduled by the Center.

Suggestions: 83% (671/808)	
Concordant	27.1% (182/671)
Brought forward Mean 5 days	34.4% (231/671)
Postponed Mean 6 days	38% (255/671)

scribed by the Center was similar among these three groups (Table 3). However, the proportion of dose suggestions equal to or within ± 6% of the dose prescribed by the Center increased significantly from the lowest to the highest mean weekly dose group (chi-square p<0.0001).

Acenocoumarol users were divided into three groups: those taking a weekly dose lower than 15 mg (7/29 - 24%), between 15 and 22 mg (11/29-38%) and greater than 22 mg (11/29-38%). The proportion of dose suggestions concordant or within ± 1 mg/week when compared with the dose prescribed by the Center was similar among these three groups (Table 4). However, the proportion of dose suggestions equal to or within ± 6% of the dose prescribed by the Center increased significantly from the lowest to the highest mean weekly dose group (chi-square p <0.0001).

When patients omitted the dose suggestion (113 times), the monitor INR was above, below and within the therapeutic range in 29% (33/113), 30% (34/113) and 41% (46/113) of cases, respectively. Among the 33 monitor PT values above the therapeutic range, 11 were greater than 5 INR units and patients omitted a dose suggestion 6 out of 11 times (55%).

Difference between the date suggested by the patients for the next PT control and that scheduled by the clinic. A date for the next PT control was suggested by the patients 83% of the times (Table 4). The date indicated for next PT control was concordant with that scheduled by the Center in 27.1% suggestions, it was earlier (by a mean of 5 days) in 34% of suggestions and postponed (by a mean of 6 days) in 38% of suggestions.

Quality of anticoagulation control. During the study period, both cases and controls spent 80% of the time with an INR in the therapeutic range (Table 5). In the 6 months preceding the study, cases spent 80.5% of the time with an INR in the therapeutic range. The INR was above the therapeutic range in the cases for longer during the study than in the previous 6 months (6.4% vs. 5.5%) and for less time than in the controls (6.4% vs. 9.5%) but these differences were not significant. The time spent by cases with an INR below the therapeutic range during the study was higher than in controls (13.6% vs. 9.8%) but the difference was not significant. The mean INR square deviation was 0.89 (95% confidence limits: CL: 0.79-0.99) and 0.92 (95% CL: 0.77-1.06) for cases during the study and in the previous 6 months, respectively (p > 0.05). The mean INR square deviation during the instruction phase was 0.89 (95% CL: 0.79-0.99). The mean square INR deviation was 1.15 (95% CL: 0.82-1.47) for controls during the study and this was not significantly different from the mean square INR deviation for cases.

During the study period, the mean number of INR determinations was 11.7 for cases and 11.5 for controls, a non-significant difference.

Bleeding and thrombotic complications. No major bleeding events were recorded during the study. Among cases, two episodes of minor bleeding (epistaxis) were recorded. In one case the INR value was 1.47, in the other case INR was 2.7 but concomitant assumption of piroxicam was reported. Among controls, two

Table 5. Percentage of time spent within, below and above the therapeutic range.

	Group 1 Cases in previous 6 months	*Group 2 Cases during the study*	*Group 3 Controls during the study*
In range	80.5%	80%	80.5%*
Above	5.5%	6.4%	9.5%*
Below	14.5%	13.6%	9.8%*

**No difference between groups 1, 2 and 3.*

episodes of minor bleeding were also recorded: hematuria in a patient with an INR of 2.2 and epistaxis in one with an INR of 3.9. During the study period, one patient (case) experienced a non-fatal acute myocardial infarction. The following adverse events were also recorded during the study period: one case with a prosthetic heart valve had an aortic dissection and underwent surgery; one case had a limb amputation (due to worsening of peripheral obstructive arterial disease, INR values not available); a sudden death occurred in a case with known coronary artery disease (10 days after discontinuation of OAT therapy and start of anti-platelet therapy; post-mortem not performed).

Attitude of patients towards the portable monitor. Two patients withdrew their consent to participate in the study during the surveillance phase: one patient after two months because he was not feeling confident in the monitor results, the other after 5 months because she was getting too anxious to use the monitor.

The majority of patients (93%) judged the monitor easy to use and declared (76%) they were confident in the monitor results. However, 52% of patients were worried that the results given by the monitor could be very different from those given by the laboratory. About two-thirds (63%) declared that the monitor had made the treatment with OAT more acceptable and easier to comply with (65%). Twenty-seven percent of the patients declared they would be confident to self-adjust the OAT dose. The majority (80%), however, expressed the preference to keep the monitor for self-testing but have the dose prescribed by the clinic.

Discussion

Several studies have shown the feasibility of both self-testing and self-adjustment with Coagucheck. In particular, three randomized controlled studies have been performed in the Netherlands,[8] in Germany[9] and in Austria.[10] In all three studies patients were randomized to self-testing and self-monitoring after a structured teaching program. In the study by Cromheecke *et al*.[8] self-management of INR resulted in a degree of anticoagulation control that was equivalent to that obtained with management by the Thrombosis Service. In the studies by Watzke *et al*.[10] and Sawicki *et al.*[9], weekly self-testing and dosing resulted in better control of anticoagulation than that obtained with conventional care by specialized clinic and family physicians, respectively. In these three randomized studies a structured teaching program was implemented based on the use of either phenprocoumon or acenocoumarol.

In order to implement a structured teaching program in our clinics, we set out to examine the ability of selected patients on chronic OAT to self-adjust their dose without specific training. We also aimed to establish the feasibility of integrating the use of home PT monitoring with the routine surveillance activity of the anticoagulation clinic in selected patients.

Our data indicate that patients on chronic OAT therapy can acquire the ability to self-adjust their dose without specific training in self-adjustment.

We analyzed the relation between the ability of patients to suggest a dose adjustment in relation to their mean weekly dosage, as prescribed by the Center. When the agreement was expressed as a percentage difference, the concordance within ± 6% increased significantly with increasing mean weekly dose among both warfarin and acenocoumarol users. These findings indicate that dose self-adjustment might be more difficult for those patients more sensitive to warfarin or acenocoumarol and requiring a low weekly dose. Thus information about individual sensitivity to warfarin should be incorporated in a structured teaching program for self-monitoring and self-adjustment. This also implies that in the initial phase of oral anticoagulant therapy patients on self-adjustment should be advised that very careful monitoring and adjustment are required, because the information about individual sensitivity might not be completely available.

The results of this study should be interpreted in the light of several sources of potential bias. The lack of randomization of patients introduces selection bias. However patients were chosen randomly from the electronic database of the centers and then asked to participate in the study. We studied only patients who had been on OAT therapy for an average of 5.5 years. They were also selected on the basis of the results of information-memory testing and because of their regular attendance at the anticoagulation clinic and their high level of compliance. During the instruction phase of the study, they received instructions only on self-testing and no guidelines were given for self-adjustment. Thus their ability to suggest a weekly dose and the date for next PT control during the study may reflect: 1) the degree of theoretical knowledge on OAT therapy acquired at the education sessions given by anticoagulation clinics to all patients, and 2) the degree of practical knowledge acquired during the several years of duration of their therapy.

To minimize the possibility that patients would measure their PT at home more frequently than recommended by the anticoagulation clinic, the patients were supplied with monitor cartridges which were not on sale to the public. Thus it was necessary for them to refer to the anticoagulation clinic to obtain any further supply of cartridges.

Another source of potential bias is that some patients did not follow the prescription by the Clinic but decided to follow their self-adjusted dose. This is a possibility that cannot be excluded. However, this group of very well trained and selected patients was able to suggest a weekly dose which was concordant or differed by ± 2.5 mg for warfarin and by ± 1 mg for acenocoumarol in 86% and 90.8% of suggestions,

respectively.

Although 27% patients declared themselves confident about self-adjusting their OAT dose, the majority expressed the preference for self-testing with dose adjustment done by the Clinic. The patients' attitudes in this study are quite different from those reported in other studies. This difference might be due to the fact that patients were used to being under the surveillance of an Anticoagulation Clinic and that they were not specifically instructed to self-adjust their dose. As a result, they may have felt more confident in being managed by the Anticoagulation Clinic.

Home self-testing and self-management have important implications. Frequent testing at home may lead to better anticoagulation control and a reduction of the frequency of complications.

Therapeutic self-management should minimize patient inconvenience and enhance patient compliance. Thus further studies are needed to assess the possibility of patient self-management.

Contributions and Acknowledgments

BC co-ordinated the study, performed the collection and analysis of data and wrote the paper; GP designed the study, had the main responsibility for the study and revised the manuscript; MM,VP, ST co-ordinated the study in each center and revised the manuscript; MC, AB, GM and PR were responsible for the collection of data locally. The contribution of the clinicians and nurses in each center is gratefully acknowledged.

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Potential implications for clinical practice

- Our data indicate that selected patients on chronic oral anticoagulant therapy can acquire the ability to self-adjust their OAT dose without specific training. Our data confirm that Coagucheck can be integrated into the routine activity of an anticoagulation clinic for the surveillance of chronic anticoagulant therapy in selected patients after training in self-testing.

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Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison

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Summary

Background Vitamin K antagonist treatment is effective for prevention and treatment of thromboembolic events but frequent laboratory control and dose-adjustment are essential. Small portable devices have enabled patient self-monitoring of anticoagulation and self-adjustment of the dose. We compared this self-management of oral anticoagulant therapy with conventional management by a specialist anticoagulation clinic in a randomised cross-over study.

Methods 50 patients on long-term oral anticoagulant treatment were included in a randomised controlled crossover study. Patients were self-managed or were managed by the anticoagulation clinic for a period of 3 months. After this period the alternative strategy was followed for each patient. Prothrombin time (expressed as international normalised ratio [INR]) were measured at intervals of 1–2 weeks in both periods without knowledge of type of management. The primary endpoint was the number of measurements within the therapeutic range (therapeutic target value ±50·5 INR units).

Findings There was no significant difference in the overall quality of control of anticoagulation between the two study periods. Patients were for 55% and for 49% of the treatment period within a range of ±0·5 from the therapeutic target INR during self-management and anticoagulation clinic management, respectively (p=0·06). The proportion of patients who spent most time in the therapeutic target range was larger during self-management than during anticoagulation clinic-guided management. The odds ratio for a better control of anticoagulation (defined as the period of time in the therapeutic target range) during self-management compared with anticoagulation clinic-guided management was 4·6 (95% CI 2·1–10·2). A patient-satisfaction assessment showed superiority of self-management over conventional care.

Interpretation Self-management of INR in the population in this study is feasible and appears to result in control of anticoagulation that is at least equivalent to management by a specialist anticoagulation clinic. It is also better appreciated by patients. Larger studies are required to assess the effect of this novel management strategy on the incidence of thromboembolic or bleeding complications.

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Introduction

Oral anticoagulant treatment with vitamin K antagonists, such as warfarin or coumarin derivatives, has been shown to be effective for the prevention and treatment of thromboembolic events in various clinical circumstances.[1,2] Some patients need to be treated with vitamin K antagonists for a long time, even life-long, such as patients with mechanical prosthetic heart valves or patients with recurrent venous thromboembolism due to familial thrombophilia. The biological effect of these compounds—ie, inhibition of the synthesis of vitamin K-dependent coagulation factors—is extremely variable, both interindividually and intraindividually. Factors influencing this variability include fluctuating bioavailability, inconstant dietary vitamin K intake, changes in other drugs that the patient might be taking, and variable binding to plasma proteins.[2,3] To prevent under-treatment or overdosing, regular laboratory control (by means of the prothrombin time, expressed as and referred to throughout this paper as international normalised ratio [INR]) of the intensity of anticoagulation and dose-adjustments are necessary.[4] This management of oral anticoagulant therapy is often executed by hospital-based or specialised anticoagulation clinics, such as the "Thrombosis Service" in the Netherlands. Although this type of management is thought to be superior to less well-organised management of oral anticoagulation,[5,6] and despite a strong organisation, laboratory quality control, and automated, computerised dose-adjustments, for many patients the intensity of anticoagulation does not fall within the "therapeutic target range" for long periods.[7–10] Besides, the visits to the anticoagulation clinic are rather time-consuming and, for some patients, inconvenient.

Easy and reliable laboratory devices have become available, which allow the measurement of the prothrombin time (expressed as INR) from one drop of capillary whole blood.[11–13] Application of these devices may allow patient self-testing of the intensity of anticoagulation and self-adjustment of the warfarin dose.[14] Self-management of oral anticoagulant therapy may result in a more individualised approach, increased patient responsibility, and enhanced compliance, which may lead to improvement in the regulation of anticoagulation. An additional advantage could be that patients can do the test at home (saving travel and time during working hours) and are less dependent of the anticoagulation clinic. A potential disadvantage of self-management could be a poorer regulation of oral anticoagulant therapy, due to less professional guidance. Also, self-management of oral coagulation may theoretically be associated with increased anxiety of patients or even preoccupation with their disease.

Previous studies have shown the feasibility of self-testing and self-management of oral anticoagulation,[15–19] while two investigations showed the potential superiority of self-management over that of general practitioners.[20,21]

Self-management of anticoagulation has, however, so far not been compared with management by a specialised anticoagulation clinic. The aim of the present study was to directly compare the quality of self-management of oral anticoagulation with conventional care by the Thrombosis Service in the Netherlands in a randomised cross-over study.

Methods

Study design

The study was approved by the Institutional Review Board of the Academic Medical Centre of the University of Amsterdam, the Netherlands.

The study was done in two phases. In the first phase a direct comparison was made between self-measurement and self-dosing of vitamin K antagonists and anticoagulation-clinic-based management. The second phase of the study was done as a randomised cross-over study comparing self-management of oral anticoagulation with anticoagulation-clinic management.

In the first phase 15 patients on chronic (more than 6 months) anticoagulant therapy were educated and trained to measure their own INR and to adjust their dose of warfarin. Patients measured their INR at home at weekly intervals during a 6 week period. On the basis of this INR patients devised their own dosing schedule for the next week. Within 2 h they came to the anticoagulation clinic to have their INR measured using blood obtained by venipuncture. An experienced physician of the anticoagulation clinic then proposed a dosing scheme based on the anticoagulation-clinic INR value, in most cases with a computerised dosing program. This part of the study allowed us to establish the feasibility of self-measurement and self-dosing of anticoagulation by patients and the concordance between self-measured INR and clinic INR as well as between self-dosing of oral anticoagulation and physician-based dosing. The anticoagulation clinic INR and dosing scheme formed the basis for patient management.

In the randomised cross-over comparison (second phase) 50 patients on chronic anticoagulant therapy with oral agents were educated and trained to self-manage anticoagulation. Patients were then randomised (by sealed envelopes) to either 3 months of anticoagulation management by the specialised anticoagulation clinic (Thrombosis Service) or three months of self-management of anticoagulation. After 3 months, the alternative management strategy was used. To be able to assess the quality of anticoagulation in both study periods, the INR was measured at intervals of 1–2 weeks in all patients in both study periods by a central laboratory. These results were not made available to patients or managing physicians. The frequency of INR self-testing by patients during the self-management period and the frequency of INR determination by the Thrombosis Service during the anticoagulation clinic period was not more often than once weekly and at least once in 2 weeks. The primary endpoint of the study was the number of measurements that were within 0·5 INR units from the therapeutic target INR during each study period. Secondary endpoints included the percentage of time in the target range during the study period, the number of patients who were in the therapeutic target range for 0–100% of the time during each period, and the number of patients who achieved a better control of anticoagulation during one of the two management strategies.

Patients

Consecutive ambulant patients, seen at the outpatient departments of Cardiology and Internal Medicine of the Academic Medical Centre, Amsterdam, who received long-term anticoagulation and who were self-supporting were eligible for the study. The most important demographic and medical characteristics of the consenting patients are given in table 1. Indications for anticoagulation were prosthetic heart valves, prevention of arterial thrombosis (mostly in patients with atrial fibrillation), and secondary prevention of venous thromboembolism in patients with familial thrombophilia.

Education of patients

All patients underwent a structured educational programme to be able to do anticoagulation self-management. This educational programme was adapted from previously published educational programmes.[21,22] Briefly, the program consisted of two 2 h sessions. In the first session a small group of patients (four to six per group) received structured and interactive teaching on the function of the coagulation system, and the principles and monitoring of anticoagulant therapy. Instructions on self-measurement of the INR by means of a capillary finger stick and use of an automated device was given via a video presentation and live demonstration. Patients were then given the opportunity to measure their own INR (at least once or as many times as they wished) in the presence of an instructor. In the 10 days between the first and the second session, patients had the opportunity to measure their INR in their own environment and to report their experience in the second session. This second session was also used to learn and practise how to devise a proper oral-anticoagulant dosing scheme. For teaching purposes, a standard dose-adaptation nomogram was used, but patients were encouraged to adjust and tailor this nomogram according to their individual experience. After concluding the educational programme patients started self-management of anticoagulation. A 24 h help desk was set up to answer any questions or to assist with any problem that might arise.

Measurement of INR

Venous blood (9 vol) was collected in 3·2% sodium citrate (1 vol) and plasma was obtained by centrifugation at 1800×*g* for 20 min. The prothrombin time (PT) was measured in plasma by Tromborel-S reagent (Dade Behring, Leusden, Netherlands, ISI value 1.19) on a Elekra 1600 coagulometer (MLA, Pleasantville, NY). PT values were expressed as an INR according to international convention. Self-measurement of INR was done on capillary blood (obtained by a fingertip puncture, Softclix lancet system) on a Coaguchek coagulometer (Roche Diagnostics, Almere, Netherlands), with Coaguchek PT teststrips (Roche Diagnostics).[23,24]

Subjective quality of care assessment

A self-perceived assessment of the quality of care was made by patients using a structured questionnaire containing 32 items, which has been described previously.[21] This questionnaire measures patients' feelings about oral anticoagulation, general treatment topics, treatment satisfaction, self-efficacy, daily frictions and worries, and social issues. For each category a minimum of 1 point (total dissatisfaction) and a

maximum of 6 points (complete satisfaction) could be scored. This assessment has been validated in a previous study.[21] The questionnaire was submitted to the participating patients before and after they finished the period of self-management. A control group of patients on oral anticoagulation receiving regular anticoagulation-clinic-based care (matched for age, sex, and indication for anticoagulation) served as a reference population. The internal reliability coefficient of the questionnaire (Cronbach-α) was assessed as previously described.[25]

Sample size and statistical analysis

All data are presented as mean (SD). The agreement between self-measurements and laboratory measurements in the initial phase of the study was analysed as previously described.[26,27] The accuracy of the control of anticoagulation was assessed by evaluating the number of INR values within and outside the therapeutic target range and by measuring the length of time of adequate anticoagulation. The time in the therapeutic target range was calculated by means of linear interpolation.[28] The number of 50 patients for the randomised cross-over study was based on an assumption, as follows. From previous studies it can be concluded that, with Thrombosis-Service-managed anticoagulant therapy, at a given time about 20–40% of patients are not in the therapeutic target range.[7–9] On the assumption that if 20% of patients are not in the therapeutic target range during the observation period (ie, 120 occasions per period), a significant difference of 15% or more (α-error 0.05, power 0.8) in accuracy of anticoagulation will be detected between the two groups with a total study population of 50 patients. If no such difference was observed, the management strategies could be considered to be equivalent. For comparisons of groups the Wilcoxon signed-rank test and two-tailed Fisher's exact test were used.

Results

Feasibility and safety of self-management

In the first phase of the study a direct comparison of INRs (self-measured and measured at the anticoagulation clinic) and warfarin-dosing schemes (self-devised or clinic-based) was made for the 6-week study period. All patients were able to measure the INR at home and to devise a dosing scheme for the next week. There was an acceptable correlation between the self-measured INR and the clinic INR (figure 1). The mean difference between all self-measurements and all clinic measurements was 12·3% (SD 10·1), with a κ value for the agreement between the two methods of 0·64 (limits of agreement 0·08 [1·04], weighed κ 0·46). The intra-class correlation coefficient was 0·91 (95% CI 0·86–0·95). A difference of more than 0·5 and 1·0 units of the self-measured INR from the corresponding clinic value was seen in 21% and 5% of the measurements, respectively. When analysed to find to what extent such a deviation of the test result would lead to a different dosing scheme (according to the proposed dosing algorithm), this would have been the case in 2% of measurements. The relation between the self-measured INR value (y) and the reference laboratory value could be expressed by the linear regression equation $y=0{\cdot}993x-0{\cdot}057$. The correlation (r) between the self-measured INR and the anticoagulation clinic INR was 0·85. As suggested by figure 1, patients

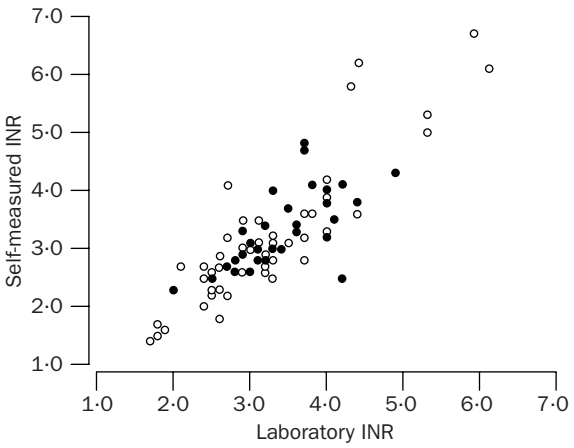

Figure 1: **Correlation between the self-measured INR from whole capillary blood at home and the virtually simultaneously measured laboratory INR from a venous blood sample**
The filled symbols and the open symbols represent measurements from patients taking phenoprocoumon or acenocoumarol, respectively.

who were using phenprocoumon had a smaller variability in INR values than those who were using acenocoumarol, but this difference did not reach significance. There was also no relevant difference in the percentage of values within the therapeutic range between these two groups.

A good agreement was observed between self-devised and anticoagulation-clinic-prescribed dosing schemes. A complete agreement in dosing scheme (total week's dose of anticoagulant agent and division of this dose over the days of the week) was seen in 68% of the cases. The mean difference in self-proposed versus clinic-based dosing schemes (expressed as total week's dose of oral anticoagulant agent) was 4% (SD 10). A difference of 10% or more in dose between the self-devised scheme and the clinic scheme was found in 13% and a difference of 15% or more between the schemes was present in 2%. There was no discrepancy concerning the dosing schemes in divergent directions (ie, patients proposing to take a higher dose and clinic physicians proposing to take a lower dose) in any of the dosing schedules.

Comparison between self-management and thrombosis service

The frequency of INR determination in the self-management period was once every 8·6 days, compared with a test frequency of once every 9·0 days in the Thrombosis Service period.

Of the 50 patients included in this phase of the trial, one patient turned out to be unable to self-manage anticoagulation due to progressive visual impairment. All other patients were able to self-manage their anticoagulation during the study and the help-desk was infrequently consulted (0·3 times per patient in 3 months). In the remaining 49 patients the mean difference of all measured INRs from the therapeutic target value was 10% (SD 20) during the 3 months of self-management compared with 12% (22) in the period managed by the thrombosis service. There was no significant difference in the control of anticoagulation between the two study periods (figure 2). During self-management 55·0% of the measurements were less than 0·5 from the intended therapeutic target INR, whereas this figure was 49% in the Thrombosis Service management period (p=0·06, odds ratio 1·2, 95% CI

1·0–1·6). In particular, in patients in whom the control of anticoagulation was fairly good, the percentage of time in the target range was larger for patients on self-management than during management by the thrombosis service (figure 2). The number of patients having more than 50% of the time in the therapeutic target range (defined as the therapeutic target value ±0·5) was 29 (60%) in the self-management period versus 25 (52%) in the thrombosis service period. The number of patients with more than 75% of the time in the therapeutic target range was 13 (27%) during self-management versus 6 (12%) in the thrombosis-service period (2·5, 1·0–6·7). Of the 49 patients 34 had a better control of anticoagulation (defined as the period of time in the therapeutic target range) during self-management than during anticoagulation clinic-guided management (4·6, 2·1–10·2). In five of 49 patients there was no difference and in ten of 49 patients the anticoagulation-clinic management resulted in a better control of anticoagulation than self-management. The number of dose adjustments was equal in both study periods and also the magnitude of the dose-adjustments was not significantly different between the two study periods. Serious under-anticoagulation or over-anticoagulation (INR <1·5 or >5·0) occurred during 3·5% of the self-management period and during 5·3% of the anticoagulation-clinic-management period (p=0·07).

No relation between a better control of anticoagulation and age, educational level, or indication for anticoagulation could be established.

No major bleeding episodes (defined as bleeding requiring hospital admission or transfusion or any central-nervous-system bleeding) were seen in either management group during the observation period. In the anticoagulation clinic-management group three minor bleedings occurred (one joint bleeding after minor trauma at an INR of 7·5, one minor calf-muscle bleeding at an

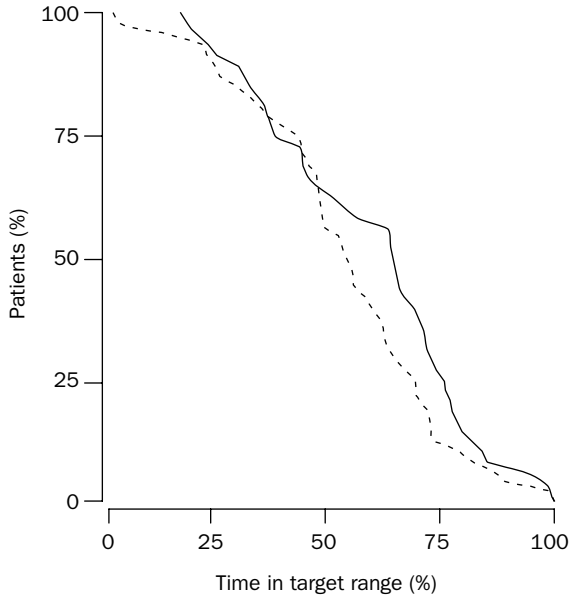

Figure 2: **Comparison of control of anticoagulation (expressed as percentage of the time in the therapeutic target range) in patients during self-management (unbroken line) and during anticoagulation clinic-guided management (broken line)**
Overall, there is no significant difference but the proportion of patients more than 50% of the time in the therapeutic target range is larger during self-management than during anticoagulation-clinic-based management (p<0·05).

	Phase I (n=15)	Phase 2 (n=50)
Age (years)	39 (range 19–58)	42 (range 22–71)
M/F ratio	7/8	29/20
Indication for anticoagulation		
Artificial heart valve	5 (33%)	23 (46%)
Arterial thromboembolism	4 (27%)	12 (24%)
Venous thromboembolism	6 (40%)	15 (30%)
Angicoagulant agent		
Acenocoumarol	10 (67%)	32 (64%)
Phenprocoumon	5 (33%)	18 (36%)
Aimed target range INR		
2·0–3·0	3 (20%)	3 (6%)
2·5–3·5	5 (33%)	16 (32%)
3·0–4·0	5 (33%)	25 (50%)
3·5–4·5	2 (14%)	6 (12%)

Table 1: **Characteristics of patients in the INR comparison study (phase I) and in the cross-over comparison (phase II)**

INR of 4·2, and one episode of recurrent nose bleeding at an INR of 6·5), whereas in the self-management period one minor nose bleeding (INR 2·4) occurred. In the anticoagulation-clinic-management period there was one episode of clinically suspected recurrent venous thrombosis (though not confirmed by objective testing) at an INR or 1·4 and one patient with a prosthetic aortic valve suffered from a transient ischaemic attack. During self-management there were no symptoms and signs of thrombotic complications. The differences in clinical outcome were not significant. The order of management in the study did not affect any of the outcome factors; in other words a carry-over effect could not be shown.

Subjective quality-of-care assessment

The quality-of-care questionnaire was completed by 45 participants at the start and the end of the self-management study period. A total of 44 patients on Thrombosis Service anticoagulation, matched for age, sex,

	Self-management group (n=45)	Conventional-care group (n=44)	p	Cronbach-α
Age	42 (16)	42 (12)	. .	. .
M/F ratio	28:17	25:19	. .	. .
Indication for anticoagulation				
Artificial heart valve	23 (51%)	21 (48%)		
Arterial thromboembolism	12 (24%)	10 (23%)		
Venous thromboembolism	10 (22%)	12 (27%)		
Target range INR				
2·0–3·0	2 (4%)	2 (5%)		
2·5–3·5	13 (29%)	16 (36%)		
3·0–4·0	24 (53%)	22 (50%)		
3·5–4·5	6 (13%)	4 (9%)		
Years on anticoagulant treatment	3·9 (2·2)	4·1 (2·1)		
Highest school education				
University/advanced education	20 (44%)	19 (43%)		
Intermediate education	21 (47%)	21 (48%)		
Primary education	4 (9%)	4 (9%)		
General treatment satisfaction	4·8 (1·2)	4·0 (1·5)	0·015	0·74
Self-efficacy	5·4 (0·6)	4·5 (1·0)	<0·001	0·70
Daily worries	1·8 (0·5)	2·6 (0·5)	<0·001	0·83
Distress	2·5 (0·8)	2·9 (1·1)	0·022	0·76
Social issues	1·7 (0·6)	2·7 (0·9)	<0·001	0·79

The comparison is made between patients participating in the cross-over study at the end of the self-management period and a matched control group receiving conventional care, ie, management of oral anticoagulation by the specialised anticoagulation clinic. Values are mean (SD).

Table 2: **Patients' characteristics and comparison of subjective quality-of-care assessment**

and indication for anticoagulation, formed the control group. Results from patients at the start of the self-management period were not different from the results obtained in the control group. There were no differences between the two groups in INR target ranges, number of years on anticoagulant treatment, and the degree of education (table 2). The internal reliability of the questionnaire was acceptable as indicated by the Cronbach-α values. There were significant differences in all five categories of the questionnaire in favour of the self-management group (table 2). Scores for general treatment satisfaction and self-efficacy were higher in the self-management group, whereas the score for daily anxieties, distress, and strain were significantly lower.

Discussion

Oral anticoagulation with warfarin is an effective measure for the treatment and prevention of arterial and venous thromboembolism. However, the substantial interindividual and intraindividual variation in the biological effect of vitamin K antagonists renders many patients outside the therapeutic target range over long periods of time. This is cumbersome for several reasons. First, clinical studies show that under-coagulation and over-coagulation enhance the risk of adverse clinical outcomes—ie, thromboembolism and bleeding, respectively.[29–31] For example, the annual incidence of major bleeding in patients on vitamin K antagonists for various indications is 0·9–2·5% and this risk increases several-fold in patients with higher INRs. Hence, the variability in the intensity of anticoagulation necessitates frequent laboratory control and dose-adjustment, which constitutes a second drawback of oral anticoagulation. Previous studies have shown that anticoagulation management by specialised anticoagulation clinics results in better control of anticoagulation compared with control in general practice.[5,6] However, in certain areas this may even amplify the practical problem of frequent checks. Self-management of anticoagulation may overcome the need for frequent visits to an anticoagulation clinic, may achieve maximal individualisation, and improved compliance, which are all factors that have been shown to improve the quality of anticoagulation.[29–32] In our study we show that self-management of oral anticoagulation results in a control of anticoagulation that is at least as good and potentially superior to control by a specialised anticoagulation service in a randomised cross-over trial. Patients appeared to be able to measure their INR adequately and to devise appropriate dosing schemes for their warfarin. Some variation between the INR values obtained with the portable self-testing device and laboratory INRs was detectable. This is in accordance with previous reports, but in fact the variation was not larger than the variation that may be encountered between different laboratories measuring an INR value from a single sample.[23,33] There was a slight benefit in the control of anticoagulation during the self-management period in comparison with the period that anticoagulation was managed by the anticoagulation clinic. In addition, patient-independence of the clinics considerably improved patient satisfaction with their anticoagulant treatment in comparison to patients receiving conventional care, which confirms identical findings in one of the previous studies.[21] Previous studies have also shown the feasibility of self-management of oral anticoagulation and a number of retrospective cohort studies have indicated that self-management of anticoagulant treatment was equivalent or superior to conventional care.[1§6–18] Part of this effect may be explained by the feasibility of more frequent control of the INR. In multicentre prospective randomised trials it was shown that control of anticoagulation was better in patients who managed their anticoagulation themselves compared with patients who had their anticoagulation managed by a general practitioner.[20,21] The present report is the first to indicate that self-management is at least as effective as management of anticoagulation by specialised anticoagulation centres.

In the present study the adequacy of anticoagulant control was expressed in terms of being in the therapeutic target range. In fact, the incidence of bleeding or thrombotic episodes would provide a potentially more revelant outcome assessment. However, the size and the design of our study did not permit us to establish a significant difference in these factors. Nevertheless, clinical studies show that there is a clear relation between adequate control of anticoagulation and a lower incidence of bleeding and thrombotic complications in patients on oral anticoagulants.[9,29] Hence, the small improvement during self-management of oral anticoagulation, as shown in our study, may potentially be extrapolated to a beneficial effect of this management strategy on clinical outcome.

Although we did not specifically select patients for our study, a certain degree of selection cannot be excluded. Indeed, young patients or patients with a busy working or social life might be over-represented in our study group. Strictly speaking, we can limit our conclusions only to the feasibility of self-measurement of INR and self-dosing to the type of patients included in our study. However, others have found that all patients who are able to lead an independent and self-supporting life are in principle capable of self-management of anticoagulation, irrespective of education and social status. Other education and self-management programmes for patients, such as self-control and self-management of insulin-dependent diabetes mellitus, have been similar in this respect.[34] In our practice, limiting factors for self-measurement of the INR with the Coaguchek device were mainly physical factors, such as visual impairment. Another limitation of our study is that the results apply only to patients on chronic anticogulant therapy and not to those just starting oral anticoagulant agents.

Despite the ability of patients to self-manage oral anticoagulation, adequate support remains necessary. Ongoing education, counsel in case of sustained dysregulation of anticoagulation, or advice on interruption of therapy in case of bleeding or the need to undergo an invasive procedure are, among others, issues that need to be taken care of. In the organisation of such support the anticoagulation clinics should play a major role. Nevertheless, self-management of anticoagulation may be a cost-effective approach, as was shown in a previous analysis.[35]

In conclusion, we have shown that self-management of oral anticoagulant therapy is feasible and at least as effective as management by a specialised anticoagulation clinic. In addition, self-management was well accepted and appreciated by the participating patients. Self-

management of anticoagulation may be considered as a novel, patient-friendly, and effective strategy to improve long-term treatment with anticoagulant agents.

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DOCUMENTO Nº 6

Anticoagulation management in primary care: a trial-based economic evaluation

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Summary. The demand for anticoagulation management is increasing because of a widening of the indications of treatment. A primary care clinic using near-patient testing and computer decision support software is one model of care to meet this increased demand. The study aimed to determine the cost and cost-effectiveness of primary care-based anticoagulation management in comparison with 'traditional' hospital care-based provision by means of a cost-effectiveness analysis using data from a Birmingham-based multicentre randomized controlled trial. The costs per patient per year in primary care were £170 [95% confidence interval (CI) £149–190] vs. £69 (95% CI £57–81). Sensitivity analysis demonstrated that the cost in primary care could be reduced to under £100 per patient per year under plausible changes in the variables. Primary care provides similar levels of control to secondary care for patients on anticoagulation therapy. There is an increased cost of managing patients in primary care and at no point did primary care become a lower cost option than secondary care. Local decision-makers need to assess the increased cost of primary care anticoagulation management in terms of the potential reductions in high-cost serious adverse events.

Keywords: economic evaluation, anticoagulation, warfarin, primary care, secondary care.

The continuing expansion of clinical indications for warfarin (particularly non-rheumatic atrial fibrillation) has greatly increased the pressure on hospital anticoagulation management services (Sudlow *et al*, 1995; Sweeney *et al*, 1995). In response, various efforts have been undertaken to provide care in non-hospital settings. Studies have demonstrated that care within non-hospital settings can be at least as good as hospital care in terms of International Normalized Ratio (INR) control and the incidence of adverse events (Pell *et al*, 1993; Radley, 1995; Fitzmaurice *et al*, 1997). There has been little research, however, into the cost implications of devolving anticoagulation care into the community. This paper provides a report of an economic evaluation of one new model of care: a practice nurse-led, primary care clinic utilizing near-patient testing for INR testing combined with a computerized decision support system to assist with warfarin dosing (hereafter primary care) which was compared with conventional hospital management.

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METHODS

The economic evaluation used data from a Birmingham-based multicentre randomized controlled trial which is reported in full elsewhere (Fitzmaurice *et al*, 2000). Patients were randomized either to the primary care intervention arm or to the hospital control arm. The clinical study was powered to detect a 20% difference in INR control at 5% significance, and analysis was on an intention-to-treat basis. For the economic evaluation power calculation, a £25 difference in the cost per patient per annum was taken to be a significant cost difference, which at 80% power and 5% significance required 63 patients in each arm of the trial. Effectiveness was measured by the proportion of time patients spent in their target therapeutic range using Rosendaal's method, assuming a linear change in INR, within a specific software package (BAP-PC, University of Birmingham) and by the percentage of patients whose INR fell within a target range (point prevalence). The primary care arm consisted of 122 patients (45% female; 9% domiciliary) and the hospital arm 102 patients (42% female; 16% domiciliary). The mean patient ages were 67 years [95% confidence interval (CI) 64–69 years] and 68 years (95% CI 66–71 years) respectively. There were no significant baseline differences between the groups in terms

Table I. Study results.

	Primary care arm	Hospital arm
Mean follow-up in days (95% CI)	261 (240–283)	249 (227–270)
Mean number of visits (95% CI)	10 (9–10)	7 (6–7)
Mean percentage of time spent in range (95% CI)	69 (66–73)	57 (50–63)
Mean INR point prevalence (%) (95% CI)	71 (63–79)	62 (52–71)
Mean per patient cost (1996 £) (95% CI)	169 (151–190)	69 (59–82)

of general health or clinical indication, with the commonest indication being atrial fibrillation.

In the primary care arm, all elements of care were provided by the practice nurse, with general practitioner support available when required. The blood sample was tested using a Thrombotrak near-patient testing device (Nycomed, UK) and 'Coventry' computer decision support software helped to provide the dosage (Ryan *et al*, 1989). Patients received their dosage information before leaving the clinic. Administration was included in the appointment duration.

In comparison, hospital management involved multiple staff. The number of patients observed in a regular hospital clinic varied between 70 and 100 patients. The estimate of annual volume on which we based our calculations was 15 000 visits per year at 150 clinics, i.e. 100 patients per clinic. Patients were seen by a consultant for their initial appointment and by a consultant/senior registrar for their subsequent follow-up appointments. Patients left the clinic after their appointment. Blood samples were tested in large batches in the clinic laboratory using a Sysmex CA-1000 coagulation analyser (Sysmex Corporation) by a medical laboratory scientific officer (MLSO). Interpretation of the result and dosage was carried out by a senior registrar. Dosage information was subsequently posted out to the patient. Administration of the clinic was provided by a full-time clinic manager. Housebound patients in the primary care arm received a domiciliary service and in the hospital they were transported to the clinic. Initial appointments were longer in both arms to include patient education.

The economic evaluation conducted was a cost-effectiveness analysis (Drummond *et al*, 1997). In the analysis, the cost perspective adopted was that of the National Health Service. Monetary valuation of resource use was undertaken by attaching unit costs at 1996–7 prices. Costs to the patient and family will be discussed elsewhere. Key resource items such as the number of visits were collected on all trial patients. Observational data were used to estimate the mean time that staff were involved in each activity. Staff costs were then calculated on the basis of salary scale mid-points plus an additional 40% for employer costs. Capital costs were based on purchase prices and were amortized over a 5-year period using HM Treasury's recommended 6% discount rate (HM Treasury, 1997). Straight line depreciation and no residual value were assumed. Room rental costs for both primary and secondary care were based on an estimate provided by one of the practice managers.

Table II. Resource use.

	Mean cost per patient per year	
	Primary care arm ($N = 122$)	Hospital arm ($N = 102$)
Software	38·92	0·00
Coagulation machine	23·35	1·79
Computer maintenance	24·59	0·00
Training	5·31	0·00
Test consumables	3·88	5·84
Staff – initial visit	4·90	8·40
Staff – follow-up visit	21·31	13·07
Staff – administration	0·00	12·86
Staff – GP	7·48	0·00
Overheads	22·28 ($N = 111$)	6·66 ($N = 86$)
Postage	0·00	1·36
Quality assessment	14·46	0·22
Domiciliary – additional costs	56·27 ($N = 11$)	120·31 ($N = 16$)
First visit	25·41 ($N = 111$)	13·89 ($N = 86$)
Follow-up visit	20·18	6·62
Domiciliary first visit	22·36 ($N = 11$)	31·39 ($N = 16$)
Domiciliary follow-up visit	19·21	24·12

Table III. The impact of changes of number of practice patients on the average total cost (ATC) of primary care provision per patient per year.

No of anticoagulation patients	ATC per patient per year (£) 10 visits	ATC per patient per year (£) 10 visits*	ATC per patient per year (£) 10 visits†
5	304·09	218·63	194·89
10	191·65	148·91	137·04
12	172·90	137·29	127·40
14	159·52	129·00	120·51
16	149·48	122·77	115·35
18	141·67	117·93	111·33
20	135·42	114·06	108·12
25	124·18	107·08	102·34
30	116·68	102·44	98·48
35	111·33	99·12	95·73
40	107·31	96·63	93·66
45	104·19	94·69	92·05
50	101·69	93·14	90·77

*With machine cost at £400 and computer and software at £1000.
†With machine cost at £400 and software only at £500.

Cost data were expected to be skewed with a few patients having very large management costs. The approach adopted was to use the arithmetic mean along with a 95% confidence interval around the mean. This confidence interval was then compared with a confidence interval derived using the non-parametric bootstrap approach (Barber & Thompson, 1998). Significance tests of difference between means were carried out using unpaired *t*-tests (Hill & Hill, 1991). Sensitivity analysis was used to consider the robustness of the results to plausible changes in the variables. Using one-way analysis, the costs of the equipment were altered to reflect the continuing price deflation of computers, software and of near-patient anticoagulation machines. The number of patients utilizing the primary care service was also varied to provide a more generalizable estimate of the cost per patient in primary care. This also allows a threshold sensitivity analysis to consider the level at which primary care becomes financially viable in comparison with the practice sending their patients to the hospital clinic.

RESULTS

The study results are summarized in Table I. At 12-month follow-up, the primary care arm demonstrated at least as good levels of control as the secondary care arm, with improved control as measured by percentage of time spent in range and similar levels of control as measured by point prevalence. Significantly more patient visits were made in the primary care arm (on average, three more per patient; $P < 0{\cdot}01$).

A breakdown of the costs is given in Table II. Mean per patient hospital anticoagulation management costs, £69·08 (SE 5·95), were significantly lower ($P < 0{\cdot}001$) than primary care costs, £169·62 (SE 10·17). Similarly, the cost per first visit and follow-up visits were significantly less ($P < 0{\cdot}001$): £13·89 (SE 0·00) compared with £25·41 (SE 3·13) and £6·62 (SE 0·00) compared with £20·18 (SE 3·13). However, in providing anticoagulation for domiciliary patients, primary care was significantly cheaper for both first and follow-up visit: £22·36 (SE 0·57) compared with £31·39 (SE 0·00) and £19·21 (SE 0·57) compared with £24·12 (SE 0·00); $P < 0{\cdot}001$.

Sensitivity analysis was carried out on the costs (Table III). Secondary care costs due to large patient numbers were not sensitive to plausible cost changes. Primary care costs were reconsidered for 5–50 patients to consider the cost implications for practices with only a few patients up to practices with a relatively large number of patients on anticoagulation management. For a practice with 40 patients being managed, the incremental cost (primary care cost minus hospital cost) was reduced to £38 per patient per year or £1500 for all patients. Two scenarios of reduced capital costs were also considered; the first assumed a machine cost of £400 and a computer and software cost of £1000, and the second used the same machine cost and a software only cost of £500, which assumes that a current computer is available and is currently underused. For a primary care practice with 40 patients, this reduced the incremental cost per patient to £27·50 and £24·50, respectively, with a cost per follow-up visit of £9·14 and £8·84 respectively.

DISCUSSION

This study reports one of the first instances of economic evaluation alongside a clinical trial of primary care anticoagulation. The results show that although primary care had better levels of control measured by the time spent in range (and at least as good levels of control measured by point prevalence) it was also likely to be associated with a higher cost in providing the service. A judgement is required by the local decision-maker as to whether the improvement in effectiveness justifies this additional cost.

The higher cost per patient in primary care was related to

three factors: clinic sizes, the number of visits and the level of contact time. The large cost difference is primarily a result of less efficient use of fixed costs in primary care. The numbers of patients per practice in the primary care arm ranged from two to 19 patients (mean of 12 patients). In the sensitivity analysis, increasing the number of patients per primary care practice reduced the average cost. However, if the higher number of visits per patient in primary care is maintained then primary care will always cost more than the observed hospital model; such that there will be no threshold at which primary care becomes more cost-effective, i.e. better clinical outcomes and lower cost. Financial viability will again be a consideration of the local decision-maker. It is feasible that the costs of the software and near-patient testing equipment will be reduced further, which will again help to reduce the cost difference.

Primary care anticoagulation is unlikely, on average, to be cheaper than hospital-based anticoagulation, but the cost difference may be small. In response to this finding and to the extent that the greater time spent in therapeutic range translates to fewer serious events, any higher cost in terms of management must be balanced against the potential for reductions in high-cost serious adverse events, particularly stroke. There is a need therefore for more accurate routine collection of data on the overall incidence of haemorrhagic and thrombotic events associated with warfarin therapy.

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DOCUMENTO Nº 7

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A capillary whole blood method for measuring the INR

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Summary This study describes a method of measuring the INR on native whole blood capillary samples using Innovin recombinant thromboplastin. Modification of the reagent was necessary to compensate for the nonoptimal level of calcium in the sample/reagent mixture.

Ninety-five percent of results obtained by the capillary blood method were no more than 0.42 INR higher or 0.38 INR lower than the venous blood method. The effect of changes in haematocrit was minimal. Significant differences in results were found between the Innovin and Thrombotest capillary blood methods.

Provided the reagent was properly stored, there was no reagent drift and satisfactory results were obtained on samples supplied by UKNEQAS (coagulation) from previous trials. The method described is a convenient, simple and accurate method of measuring the INR using native capillary whole blood and Innovin recombinant thromboplastin.

Keywords INR, Innovin recombinant thromboplastin, capillary blood, calcium, haematocrit.

Introduction

Since the introduction of the original method for prothrombin time (PT) measurement (Quick 1935), a variety of different thromboplastin reagents have become available. These reagents contain tissue factor (TF) and lipids and are manufactured from crude tissue extracts (usually brain) of both human and animal origin.

As an alternative to the tissue extract thromboplastins, recent scientific advances have resulted in the development of thromboplastins containing recombinant tissue factor (rTF) which have been relipiditated to allow expression of coagulation activity. Two of these reagents have been produced commercially for several years and are marketed as Recombiplastin (Ortho, Amersham, UK Diagnostics Ltd Clinical); (Roussi *et al.* 1994; Tripodi *et al.* 1994) and Innovin (Dade Behring, Marburg, Germany Bader *et al.* 1994). It has been demonstrated that some important differences exist between INRs that are measured using Innovin, Recombiplastin and those using conventional (tissue extract) thromboplastins (Kitchen *et al.* 1996).

Most INR measurements are made using citrated plasma obtained from venous blood samples, but a significant and consistent number of centres are registered with the UK National External Quality Assessment Scheme for

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Blood Coagulation (UKNEQAS) as using methods employing capillary blood samples. Some of these methods employ conventional tissue thromboplastins such as Thrombotest (Organon Tecknika Ltd, Cambridge, UK), Manchester Capillary Reagent (Thrombosis Reference Centre, Manchester, UK) and Diagen Reagent (Diagnostics Ltd, Thame, UK). Others use methods employing thromboplastins in 'dry chemistry' form designed for use with particular types of coagulometers such as Coagu-Chek (Roche Diagnostics, Welwyn Garden City, UK) and Rapidpoint Coag Monitor (Bayer plc Diagnostics Division, Newbury, UK).

When testing whole blood samples the method of clot detection used in the analyser must be based on a system other than an optical system that responds to changes in turbidity.

Because many centres use capillary blood testing methods for INR in addition to methods using citrated plasma obtained from venous blood samples, it is important that the same reagents are used for both methods. The aim of this study was to develop a method for INR measurement using native capillary whole blood samples and Innovin recombinant thromboplastin.

Materials and Methods

Summary of study design

The study design is based on protocols recommended by the Medical Devices Agency of the Department of Health (Giddings *et al.* 1989; Mackie & Gardiner 1998). Although designed for the evaluation of automated coagulometers, there are elements of the protocols that can be applied to the testing of coagulation reagents.

Investigations were performed to establish the following:

Mean normal prothrombin time (MNPT)

For both the venous and capillary methods, samples were collected from 20 ambulant apparently healthy subjects and calculations made to provide the geometric mean normal prothrombin time (MNPT) and degree of skewness and kurtosis.

Calculation of ISI of the thromboplastin

The ISI was calculated using the WHO recommended procedure (WHO Expert Committee on Biological Standardization. 33rd Report 1983). Ten normal and 30 patients' samples were tested on 5 separate days (eight per day) over a period of 2 weeks.

Calculation of the INR

The INR on each sample was calculated using the formula:

$$\mathrm{INR} = \left[\frac{\mathrm{PT}}{\mathrm{MNPT}}\right]^{\mathrm{ISI}}$$

Within run precision

Twenty samples with a normal INR value and 20 samples with a high INR value were assayed and the geometric mean (M), standard deviation (SD) and coefficient of variation (CV) calculated. Within run precision tests were performed using citrated whole blood samples (Table 2).

Between run precision

Samples with a normal INR value and samples with a high INR value were repeatedly assayed each day for one month. Both measures of precision were performed using plasma samples due to the impracticability of using whole

Table 1. Correction factors that may be applied to INR values based on results obtained using artificially produced anaemic and polycythaemic venous blood samples

Haematocrit (l/l)	Factor (xINR)
0.2	1.15
0.3	1.05
0.4	Nil
0.5	0.9

Table 2. Between run precision tests on samples at two levels of INR

Sample	INR = 1.0	INR = 4.5
Number	20	20
Mean (sec)	10.5	46.5
SD (sec)	0.41	2
CV (%)	4.1	4.3

Table 3. Within run precision tests on samples at two levels of INR

Sample	INR = 1.0	INR = 3.5
Number	20	20
Mean (sec)	10.03	36
SD (sec)	0.34	1.62
CV (%)	3.4	4.5

blood. For the between run precision the test plasmas were frozen as aliquots at −20 °C (Table 3).

Comparability

Comparability between the methods was evaluated using the Student's paired *t*-test and Wilcoxon Rank Sum test with levels of significance at $P < 0.05$.

The correlation coefficient and regression analyses were calculated together with an analytical method for assessing agreement between the two methods (Bland & Altman 1986). Samples were taken from volunteers receiving coumarin therapy attending the outpatient's anticoagulant clinics. A minimum of 10 samples were tested in each of the 0.5 INR intervals within the INR range:

1.0 – > 4.5; 1.0–1.5; 1.5–2.0; 2.0–2.5; 2.5–3.0; 3.0–3.5; 3.5–4.0; 4.0–4.5; > 4.5

In order to make the samples as representative as possible, approximately half of the patients in the above ranges were male and half were female. Hct values ranged from 0.323 l/l to 0.525 l/l with a mean of 0.412 l/l.

Reagent drift

Reagent drift was assessed by simultaneously analysing freshly frozen aliquots of control plasmas (normal INR and high INR) at timed intervals using the same reagent vials. One vial of reagent was stored at 4 °C and the other vial stored at 37 °C. Aliquots of the reagent were also kept in an open carousel chamber at 37 °C and similarly analysed. The procedure was performed on two separate occasions.

Effect of changes in haematocrit (Hct)

Venous blood samples obtained from volunteers within various ranges of INR were modified by the addition and/or removal of the red cells or plasma to artificially produce a range of Hct values from low to high. The INR values of these samples were measured using the capillary method under test. Forty samples with Hct > 0.45 l/l were analysed and 11 with Hct < 0.35 l/l.

Analysis of samples used in the UK National Quality Assessment Scheme for Blood Coagulation (UKNEQAS)

Fifteen lyophilized citrated plasma samples (some from previous trials but the majority from current trials) kindly supplied by UKNEQAS, were analysed using the venous and capillary blood methods and the percentage deviation calculated, based on the reagent median INRs obtained in each trial.

Costs of analysis

The costs of the analyses (on 1st June 1999) using the capillary and venous blood methods were estimated from the known reagents and consumables, instrument and servicing, laboratory overheads and laboratory staff costs (Table 4).

Instrumentation and materials

The INRs using citrated plasma were measured using a Sysmex CA-1000 coagulometer (Sysmex UK Ltd, Milton Keynes, UK) and the capillary blood INR's using a Biomatic 2000 coagulometer (Sarstedt Ltd, Beaumont Eys, UK). The Hcts were estimated using a Coulter MAXM blood count analyser (Beckman Coulter Ltd, High Wycombe, UK). The capillary blood samples were obtained using the Ames Minilet system (Bayer) and the samples measured using 100 μl Blauband capillary tube pipettes (Scientific Laboratory Supplies Ltd, Nottingham, UK).

Table 4. Comparison of costs for capillary blood method and venous blood method for measuring the INR as at 01/06/1999

Method	Capillary	Venous
Reagents/consumables	47p	46p
Instruments/service	13p	9p
Other equipment	–	6p
Laboratory overheads	92p	92p
Biomedical scientist time	70p	24p
Phlebotomist time	–	60p
Total	£2.22	£2.37

Innovin thromboplastin reagent

The analyses were performed using Innovin reagent batch number TFS 659 which had been assigned an ISI of 0.99 by the manufacturers for analysis on the Sysmex CA-1000 coagulometer. The thromboplastin was used in accordance with the manufacturers instructions for the venous blood samples but the reagent needed to be modified for use with capillary blood (*vide supra*). The reagent had been calibrated, by the manufacturer, against RBT 90.

Thrombotest reagent

Capillary blood analyses were performed using Thrombotest reagent (batch number 710050) reconstituted with distilled water in line with the manufacturer's instructions. The ISI for capillary blood samples assigned by the manufacturer was 1.00. The reagent had been calibrated, by the manufacturer, against OBT/79. The recommended method was employed using 50 μl of capillary whole blood and 250 μl of Thrombotest reagent.

Control plasmas

Two levels of Ci-Trol (Dade) control plasmas (normal range Ci-Trol 1, lot number COL1E-400; lower therapeutic range Ci-Trol 3, lot number COL3E-401) were used to control both the venous and capillary methods.

Normal subjects

Venous blood samples from 20 ambulant healthy subjects were collected into Vacutainers (Becton Dickinson Ltd, Cowley, UK) containing 0.105 M buffered trisodium citrate in the ratio of nine parts blood to one part trisodium citrate. The samples were centrifuged at 2000 ***g*** at room temperature within 30 min of collection and analysed immediately in the original tubes using the Sysmex CA-1000 coagulometer. Similarly capillary blood samples were collected from 20 healthy subjects and analysed using the Sarstedt Biomatic 2000 coagulometer.

Test subjects

The routine method for measuring the INR on outpatients is by testing a capillary blood sample using Thrombotest reagent. Patients attending the outpatient anticoagulant clinics were tested using Innovin as well as Thrombotest. In addition, two venous blood samples were taken into Vacutainers, one containing 0.105 M buffered trisodium citrate and the other NaEDTA. Plasma obtained from the citrated sample was used to measure the INR with Innovin using the venous blood method and the EDTA sample was used to perform a blood count in order to obtain the Hct.

Measurement of prothrombin time (PT)

When measuring the PT of citrated plasma with Innovin the recommended volumes used were 100 μl of citrated plasma and 200 μl of Innovin (or proportionate volumes).

Because native whole blood was used for the capillary method, adjustments of these volumes was necessary to compensate for the cell volume (Hct) of the sample.

Based on an average Hct of 0.400 l/l, the volumes were adjusted to 100 μl of whole blood and 120 μl of Innovin.

Results

Preliminary tests using the above volumes performed on citrated venous blood samples obtained from patients receiving coumarin therapy, showed good agreement between the whole blood and citrated plasma methods with a correlation coefficient (r) of 0.996 and no significant difference using paired *t*-test and Wilcoxon Rank Sum paired test ($P = > 0.05$).

The mean prothrombin times were 29.2 s and 29.7 s for the citrated plasma and citrated whole blood methods, respectively.

Slightly inferior results were found when native whole blood capillary blood samples obtained by finger-prick were substituted for the whole blood venous samples. Although the results were statistically acceptable according to the paired *t*-test, the Wilcoxon Rank Sum paired test indicated a significant difference between the results ($P = < 0.05$). Using the regression line value the ISI of the thromboplastin was calculated as 1.07 for the capillary blood compared with 0.99 for the venous blood samples suggesting a reduction in sensitivity of the thromboplastin

It was concluded that the calcium present in the Innovin reagent in addition to the normal physiological calcium present in the native whole blood sample resulted in a level of calcium ions outside the limits necessary for optimum coagulation (Lovelock & Porterfield 1952). The calcium contained in the Innovin reagent was neutralized by the addition of a calculated volume of 0.105 M trisodium citrate obtained from Vacutainer tubes normally used for venous blood coagulation tests (20 ml Innovin + 1.8 ml 0.105 m trisodium citrate). The modified reagent

was prepared immediately before use and stored, capped at 4 °C. Because of the addition of the trisodium citrate, the final volume of citrated Innovin was adjusted for use in measuring the PT.

Technique for measuring the prothrombin time

Modified Innovin reagent – 130 μl:

Incubate for 1 minute (max 30 min) at 37 °C.

Capillary whole blood –100 μl:

The coagulometer starts the timing process as the blood sample is added.

The clotting time was recorded.

Mean normal prothrombin time (MNPT)

The geometric mean of the PTs of 20 apparently normal subjects was calculated as 9.92 s. The distribution was slightly positively skewed (measure of skewness 0.28) and kurtosed (– 0.87).

Calculation of the ISI

There was a tight correlation between the venous and capillary methods (Figure 1) giving a slope = 0.99 and the venous blood ISI = 0.99. The capillary blood ISI = 0.98 (0.99 × 0.99). The coefficient of variation for the ISI was 1.85% (Figure 1).

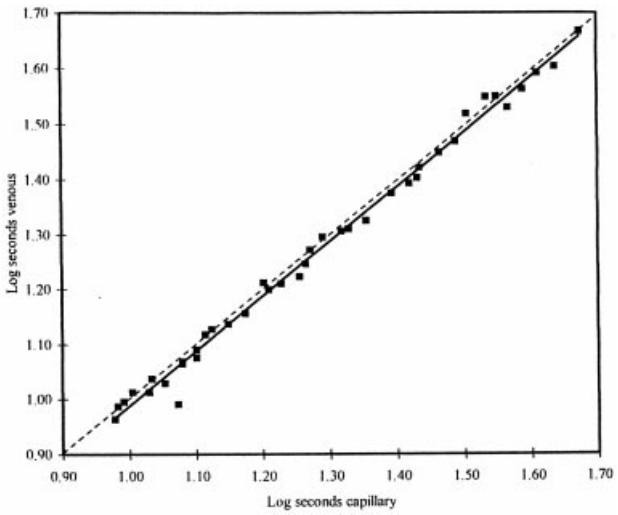

Figure 1. The ISI for the capillary blood method following modification of the Innovin reagent (slope = 0.99).

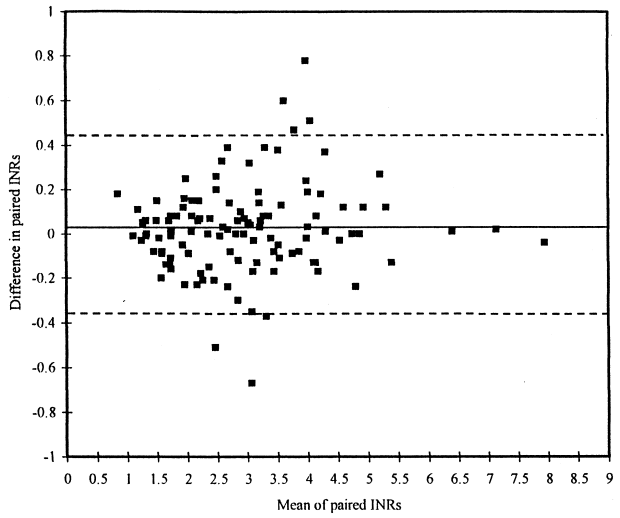

Figure 2. Plot of the differences between the capillary whole blood and venous blood methods against the mean of the paired methods. The average difference is shown by the solid line (mean difference = 0.02) and the ± 2 SD shown as the dotted lines. 95% of the capillary blood method will be within +0.42 or −0.38 INRs of the venous blood method.

Tests of comparability

There was no significant difference between the two methods using the paired *t*-test and the Wilcoxon rank sum paired test and the correlation coefficient and regression analysis indicated close agreement. One sample had an INR of 15.2 using the capillary method and 15.4 using the venous blood method. Analysis of the differences between the methods in the same subjects indicate that 95% of the results obtained using the capillary whole blood method will be no more than 0.42 INR higher or 0.38 INR lower than results obtained using the venous blood method. These limits would be regarded as being clinically acceptable (Figure 2).

Similar analyses were performed on the results obtained using the Innovin and Thrombotest capillary blood methods. Significant differences were found using the paired *t*-test and the Wilcoxon rank sum paired test ($P = < 0.05$). However analysis of the differences between the two methods indicate that 95% of the Innovin capillary blood method will be no more than 0.61 INR higher or 1.69 INR lower than the Thrombotest capillary blood method (Figure 3).

Reagent drift

There was no apparent drift with the reagents stored in capped vials at either 4 °C or 37 °C. A significant differ-

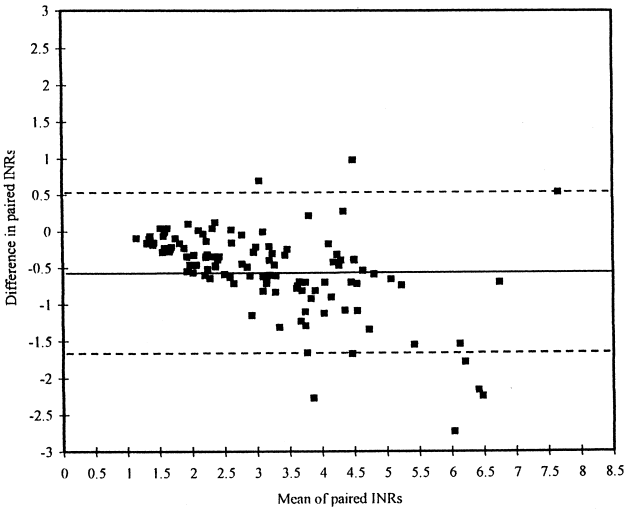

Figure 3. Plot of the differences between the Innovin and Thrombotest capillary whole blood methods against the means of the paired methods. The average difference is shown by the solid line (mean difference = 0.54) and the ± 2 standard deviations are shown by the dotted lines. 95% of the Innovin method will be within +0.61 or −1.69 INRs of the Thrombotest method.

ence was seen after one hour with the reagent kept in an open carousel at 37 °C.

Effect of changes in haematocrit (Hct)

Higher INR values were found in the polycythaemic samples and lower INRs in the anaemic samples. Based on the values obtained, a range of correction factors was calculated which might be applied to correct the INR results for changes in Hct (Table 1).

The patients results indicated that on samples with higher Hct levels 95% of the INR results from the capillary method would be no more than 0.45 INR above or 0.39 INR below results obtained with the venous blood method ($P = > 0.05$). In the case of the samples with lower Hct levels these figures are 0.30 INR above or 0.42 INR below, respectively ($P = > 0.05$). In both these instances the results would be clinically acceptable. The INR results were less influenced by changes in the Hct level using native capillary whole blood compared with those obtained using artificially manipulated samples. There is the possibility that the results obtained by the venous blood method (used as the reference) might be influenced by variations in the concentration of trisodium citrate in the samples (Duncan *et al.* 1994; Adcock *et al.* 1997; Charangkul *et al.* 1998). In practice, the application of correction for haematocrit would only be necessary for patients with severe anaemia or polycythaemia.

Results of samples used in the UK National Quality Assurance Scheme for Blood Coagulation (UKNEQAS)

Apart from the first sample (98/01) where both results were above the 15% limit of acceptability, all other results were within acceptable limits, with the Sysmex showing an average deviation of 7.4% and the Sarstedt showing 7.2%.

Discussion

Despite the improvement in standardization, the development of recombinant thromboplastins has highlighted differences in results between this type of reagent and conventional tissue thromboplastins (Kitchen *et al.* 1996). The significant differences that were found in results between the Innovin and Thrombotest whole blood capillary methods support this finding. For centres wishing to employ a method of INR measurement using native capillary whole samples in addition to citrated venous blood samples, it is essential that the same type of thromboplastin be used for both techniques (Kitchen *et al.* 1994). This study was designed to develop a method of measuring the INR on native capillary whole blood samples using Innovin recombinant thromboplastin. The native capillary whole blood sample is tested immediately with no risk of factor V depletion due to storage. Patients receiving anticoagulant treatment invariably have normal or possibly raised fibrinogen levels (Munro 1993), although this finding may be due to over-estimation when using the prothrombin time derived fibrinogen method (De Cristofaro & Landolfi 1998).

Using whole blood as opposed to citrated plasma, necessitated adjustment of the sample to reagent volumes to compensate for the presence of blood cells in the sample based on a Hct level of 0.40 l/l. Modification of the Innovin reagent by the addition of tri-Sodium citrate to neutralize the excess calcium in the blood sample, resulted in an ISI of 0.98, closely approximating that for citrated plasma.

The geometric mean was calculated as being 9.95 s with a slightly positively skewed distribution. Within run and between run precision results were within acceptable limits.

The INR was calculated employing the recommended formula using the test/normal time ratio raised to the power of the ISI.

Test for comparability showed good correlation and agreement between the two methods. Results indicated that in 95% of cases the capillary method would be no more than 0.42 INR higher or 0.38 INR lower than the

venous blood method. The INR results were minimally effected by changes in Hct levels with 95% of results obtained with the capillary blood method being no more than 0.45 INR higher or 0.39 INR lower than the venous method on samples with Hct of > 0.45 l/l.

On samples with Hct of < 0.35 l/l, 95% of the results obtained with the capillary method were no more 0.30 INR higher or 0.42 INR lower than the venous method. These ranges would not be considered to be clinically significant.

There was no apparent reagent drift when the Innovin reagent was stored capped at 4 °C or 37 °C. Significant changes in results were seen when the Innovin was stored in open carousels at 37 °C.

Performance in the UKNEQAS (Coagulation) scheme performed on 15 samples was satisfactory with the whole blood capillary method showing an average deviation of 7.2% against the venous blood method with an average deviation of 7.4%.

A cost analysis based on laboratory involvement in obtaining and testing the blood sample only, showed the capillary blood method costing £2.22 per test.

Described is a method for determining the INR using native capillary whole blood and modified Innovin recombinant thromboplastin. The method proved to be precise and accurate and provides an added option to the range of near patient testing and capillary blood methods for the rapid testing of patients for INR levels.

The results obtained in this study require confirmation on other batches of reagent and using different coagulometers suitable for use with whole blood samples.

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The authors wish to express their gratitude to the physicians and surgeons at Neath General Hospital for their permission to approach the patients under their care.

We wish to acknowledge the helpful advice on statistical analysis provided by Keith Morris at the University of Wales Institute of Science and Technology. We would also like to thank the Steering Committee of the UK National Quality Assessment Scheme for Blood Coagulation for kindly supplying us with samples from previous trials and for permitting us to publish the relevant data.

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British Journal of Haematology

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GUIDELINES ON ORAL ANTICOAGULATION: THIRD EDITION*, [dagger]

[Guideline]

DOCUMENTO Nº 8

Outline

Graphics

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1. INTRODUCTION

The revision of the 1990 oral anticoagulant guidelines by the British Committee for Standards in Haematology (BCSH) (British Committee for Standards in Haematology, 1990) [12] has been undertaken to reflect changes in the current medical literature and to incorporate the outcomes of medical audit. Guidelines on heparin were published by the BCSH in 1993 (British Committee for Standards in Haematology, 1993b) [14]. These present guidelines include indications for oral anti-coagulation and suggested arrangements for the management of an anticoagulant service.

These new guidelines aim to take account of the current practical difficulties involved in the safe monitoring of the rapidly expanding numbers of patients on long-term anti-coagulant therapy. With patient numbers more than doubling in most anticoagulant clinics in the past 5 years and the trend set to continue, the organizational problems are immense (Baglin, 1994; Rose, 1996) [6,95]. However, it remains the haematologist's responsibility to ensure that local arrangements for laboratory testing and dosage of oral anticoagulant therapy are satisfactory. This involves regular participation in national/regional quality assessment schemes and audit of clinical practice.

The third edition of these guidelines has been prepared by the Haemostasis and Thrombosis Task force of the British Society for Haematology. The document has been circulated to members of the British Committee for Standards in Haematology. Relevant scientific papers from systematic literature review were identified from Medline for 1965 to July 1996 using the index terms oral anticoagulation or warfarin and venous thromboembolism, deep vein thrombosis, pulmonary embolus, stroke, heart valve(s), prosthesis, atrial fibrillation, peripheral vascular disease, grafts, coronary artery, myocardial infarction, coronary artery graft, angioplasty and stents, central venous catheters and chemotherapy. Further publications were obtained from the references cited and reviews known to members of the Task Force. Evidence and graded recommendations are according to the US Agency for Health Care Policy and Research (US Department of Health and Human Services, Public Health Service and Agency Care Policy and Research, 1992) [120] (Table VII).

A (Evidence levels Ia, Ib)	Requires at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (Evidence levels IIa, IIb, III)	Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation
C (Evidence level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities; indicates absence of directly applicable studies of good quality

Levels of evidence

Ia. Meta-analysis of randomized controlled trials
Ib. At least one randomized controlled trial
IIa. At least one well-designed controlled study without randomisation
IIb. At least one other type of well-designed quasi-experimental study
III. Well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case–control studies
IV. Expert committee reports or opinions and/or clinical experience of respected authorities

Table VII. Appendix I. Graded recommendations.

2. TARGET INR

The international normalized ratio (INR) is a recommended method for reporting prothrombin time results for control of oral anticoagulation (British Committee for Standards in Haematology, 1990) [12]. Since adoption of the INR system it has been usual practice to adjust the dose of warfarin, or other oral vitamin K antagonist, to maintain the INR within a therapeutic range. The range was often one INR unit, e.g. INR between 2.0 and 3.0. However, in practice many clinicians and computer support systems regulate dosage according to deviation of INR from a single target taken as the midpoint of the designated range, e.g. target INR of 2.5 for a range of 2.0-3.0. Furthermore, extensive audit indicates that only 50% of INRs in a population of patients taking warfarin are usually within the range at any one time, i.e. 0.5 INR units of the target (Rose, 1996), [95] whereas 80% of patients are within 0.75 INR units of the target. With this experience it now seems more practical to designate a target INR and encourage dose adjustment dependent on deviation of INR from the target and also individual patient characteristics such as reason for anticoagulation, stability of INRs over time, previous bleeding and thrombotic events.

In view of this we have elected to recommend target INRs throughout these guidelines. We recommend that appropriate dose adjustment is made dependent on deviation of INR from the target. An INR within 0.5 INR units of the target is generally satisfactory and deviations of 0.5 and 0.75 INR units can be used as standards for audit (see also section 11).

3. INDICATIONS FOR ANTICOAGULATION

The indications for oral anticoagulation and recommended target INRs are summarized in Table I for ease of access. The evidence basis for these recommendations is summarised within the document.

Indication	Target INR	Grade of recommendation
Pulmonary embolus	2·5	A
Proximal deep vein thrombosis	2·5	A
Calf vein thrombus	2·5	A
Recurrence of venous thromboembolism when no longer on warfarin therapy	2·5	A
Recurrence of venous thromboembolism whilst on warfarin therapy	3·5	C
Symptomatic inherited thrombophilia	2·5	C
Antiphospholipid syndrome	3·5	B

Antiphospholipid syndrome	3·5	B
Non-rheumatic atrial fibrillation	2·5	A
Atrial fibrillation due to rheumatic heart disease, congenital heart disease, thyrotoxicosis	2·5	C
Cardioversion	2·5	B
Mural thrombus	2·5	B
Cardiomyopathy	2·5	C
Mechanical prosthetic heart valve	3·5	B
Bioprosthetic valve	Not indicated	A (see text)
Ischaemic stroke without atrial fibrillation	Not indicated	A (see text)
Retinal vessel occlusion	Not indicated	C (see text)
Peripheral arterial thrombosis and grafts	Not indicated	A (see text)
Coronary artery thrombosis	Not indicated	A (see text)
Coronary artery graft thrombosis	Not indicated	A (see text)
Coronary angioplasty and stents	Not indicated	A (see text)

Table I. Indications for oral anticoagulation, target INR and grade of recommendation.

3.1. Venous thromboembolism in non-pregnant patients

First event of pulmonary embolus or proximal vein thrombosis: INR 2.5 for 6 months (grade A, level Ib). Calf vein thrombosis in non-surgical patients with no persistent risk factors: INR 2.5 for 3 months (grade A, level Ib). Post-operative calf vein thrombosis without persistent risk factors: INR 2.5 for 6 weeks (grade A, level Ib). Continued treatment should be considered if risk factors are persistent (grade B, level IIb). A recurrence after stopping warfarin requires a further episode of treatment, INR 2.5. A recurrence on treatment requires intensification of treatment, INR 3.5 (grade C, level IV), or alternative anticoagulant treatment.

Initial anticoagulation with heparin and a period of at least 6 weeks oral anticoagulant therapy is necessary dependent on the extent of thrombus, on whether the thrombotic event was triggered by a precipitating event, such as surgery, and on the existence of risk factors for recurrence (Hull et al, 1979; Francis, 1994; Weinmann & Salzman, 1994) [50,36,125].

Pulmonary embolus is strongly associated with proximal deep vein thrombosis of the lower limb (Sandler

& Martin, 1989) [98] but occurs infrequently when thrombosis remains confined to the calf (Hirsh, 1990; Ginsberg, 1996) [47,42]. There has been no randomized study to determine the optimum intensity or duration of oral anticoagulant therapy after an episode of pulmonary embolism. Recommendations are therefore derived from the results of treatment of proximal vein thrombosis in the lower limb where pulmonary embolism is typically regarded as an endpoint in interventional studies. Fatal recurrence of pulmonary embolism is extremely rare when deep vein thrombosis is treated with heparin initially followed by a prolonged period of treatment with warfarin (Coon et al, 1969; Hull et al, 1979; Carson et al, 1992; Schulman et al, 1995) [24,50,18,102]. An INR of 2.0-3.0 gives the lowest recurrence and bleeding rates (Hull et al, 1982) [51] and is the recommended range for venous thromboembolism.

Retrospective studies gave conflicting results as to the optimal duration of oral anticoagulant therapy ranging from 6 weeks (Petiti et al, 1986) [84] to 6 months (Coon et al, 1969) [24]. A series of small studies showed no difference in recurrence rates for patients treated for 4 weeks (Holmgren et al, 1985) [49] or 6 weeks (O'Sullivan, 1972) [79] compared to 6 months therapy, but not all patients had an objectively confirmed diagnosis. In addition, these studies either combined or did not distinguish patients with proximal thrombosis from those with thrombus confined to the calf. A review of duration of therapy in 1988 recommended at least 6 weeks therapy and indicated the need for prospective randomized studies. This review did not indicate the methods used for evaluating studies but stated that the confidence intervals for recurrence rates after only 6 weeks therapy were wide (Fennerty et al, 1988) [32]. Since then two prospective studies have randomized patients with proximal vein thrombosis to different durations of anticoagulation, one comparing 4 weeks with 3 months (Levine et al, 1995) [69] and one comparing 6 weeks with 6 months (Schulman et al, 1995) [102]. In the 4-week/3-month study recurrence rates were 8.6% in the 4-week group compared to 0.9% in the 3-month group (OR = 10.1, 95% CI 1.3-81.4) (Levine et al, 1995) [69]. In the 6-week/6-month study recurrence rates after 2 years were 18.1% after 6 weeks treatment and 9.5% after 6 months treatment (OR = 2.1, 95% CI 1.4-3.1). In the 6-week group there was a sharp increase in the recurrence rate immediately after cessation of oral anticoagulant therapy (Schulman et al, 1995) [102]. Further clarification of the optimal duration of therapy will be obtained from the Duree Optimale du Traitement Antivitamine K (DOTAVK) study in which patients with proximal deep vein thrombosis are randomized to 3 or 6 months therapy. Therefore the present recommendation for duration of treatment of proximal deep vein thrombosis or symptomatic pulmonary embolism is 6 months (grade A recommendation, level Ib evidence). There is an opinion based on subgroup analysis that a period of 6 weeks therapy is adequate for proximal vein thrombosis in patients without permanent risk factors (grade C, level IV) (Hirsh, 1995; Ginsberg, 1996) [48,42].

Thrombi below the level of the popliteal vein are not usually detected by compression ultrasound examination. Although these calf vein thrombi do not typically cause symptomatic pulmonary emboli they may extend into the popliteal and femoral veins and then cause significant emboli (Hirsh, 1990) [47]. Calf vein thrombi detected by contrast venography should either be treated with anticoagulant therapy or monitored with serial non-invasive tests, such as compression ultrasound examination (Cogo et al, 1998) [22] and treated as for a proximal thrombus if extension occurs. Untreated symptomatic calf vein thrombosis in non-surgical patients is associated with a recurrence rate of >25% and the risk of proximal extension and pulmonary embolization (Lagerstedt et al, 1985; Lohr et al, 1991; Raskob, 1996) [62,70,92]. Treatment with warfarin to maintain an INR of 2.0-3.0 for 3 months reduces these risks to 7.6% or less (Lagerstedt et al, 1985; Research Committee of the British Thoracic Society, 1992) [62,94]. This rate is lower than that achieved with 4 weeks (12.4%) (Research Committee of the British Thoracic Society, 1992) [94] or 6 weeks anticoagulation (11.8%) (Schulman et al, 1995) [102] and comparable to that achieved with 6 months treatment (5.8%) (Schulman et al, 1995) [102]. Therefore the best general

recommendation at the present time is that symptomatic calf vein thrombosis in non-surgical patients without predisposing factors, such as cancer or thrombophilia, should be treated for 3 months (grade A, level Ib).

Post-operative calf vein thrombosis is also associated with proximal extension and pulmonary embolus (Kakkar et al, 1969; Pellegrini et al, 1993) [57,81]. However, a shorter period of anticoagulation appears to be sufficient to prevent recurrence after the initial precipitating event. In the BTSRC (British Thoracic Society Research Committee) study recurrence rates in surgical patients were low in patients assigned to 4 weeks (1.7%) as well as 3 months treatment (1.8%) (Research Committee of the British Thoracic Society, 1992) [94]. However, 26% of patients randomized to 4 weeks treatment actually received 6 weeks therapy, so it is prudent to recommend 6 weeks therapy until the results of further randomized studies are available (grade A, level Ib).

Continued treatment should be considered for patients with persistent risk factors for recurrence, e.g. cancer, thrombophilia (grade B, level IIb) (Research Committee of the British Thoracic Society, 1992; Hirsh, 1995; Levine et al, 1995; Schulman et al, 1995) [94,48,69,102].

Patients with recurrent venous thromboembolism after stopping warfarin require further treatment with warfarin to maintain an INR of 2.5. The risk of further recurrence is high and the optimum duration of therapy is currently unknown (Schulman et al, 1997) [101]. Patients who have a recurrence whilst anticoagulated with warfarin should be considered for higher intensity therapy with warfarin, INR 3.5 (British Committee for Standards in Haematology, 1990) [12] (grade C, level IV), or alternative anticoagulant therapy and evaluation for carcinoma or the antiphospholipid syndrome (Ginsberg, 1996) [42].

3.2. Inherited thrombophilia

No episode of thromboembolism-antithrombotic prophylaxis for high-risk periods (grade C, level IV). After an episode of venous thromboembolism evidence of thrombophilia lowers the threshold for long-term anticoagulant therapy: INR 2.5 (grade C, level IV).

For these guidelines the term thrombophilia is used to refer to inherited disorders of the haemostatic system that result in an increased risk of venous thromboembolism (Cavenagh & Colvin, 1996; De Stefano et al, 1996; Lane et al, 1996), [19,25,64] namely deficiencies of antithrombin, protein C, protein S and the factor V Leiden mutation (FV:R506Q). Acute thrombotic events should be treated with initial heparinization and oral anticoagulation to achieve an INR of 2.5 (Cavenagh et al, 1996; De Stefano et al, 1996; Lane et al, 1996) [19,25,64]. It is not yet known if after the initial treatment episode this level of anticoagulation is required long term or whether lower intensity warfarin regimens or aspirin will give equivalent protection. Until this information is available a target INR of 2.5 is recommended for those patients receiving anticoagulant therapy (grade C, level IV). Recommendations on the duration of therapy cannot be given as this will vary with the genetic defect, whether more than one defect is present, whether previous events were precipitated, and whether other family members with the defect are thrombosis-prone. Guidelines on the investigation and management of thrombophilia are currently being prepared by the Haemostasis and Thrombosis Task Force.

3.3. Antiphospholipid syndrome

Guidelines on the investigation and management of the antiphospholipid syndrome are currently being prepared by the Haemostasis and Thrombosis Task Force. It should be noted, however, that patients with arterial thrombosis associated with this syndrome should be treated immediately with heparin initially and then warfarin (grade C, level V) (Greaves & Preston, 1991) [44]. The target INR has not been clarified. A target of 2.5 has often been used but a non-randomized comparative study reported a target of 3.5 (Khamashta et al, 1995) [60] (grade B, level III).

3.4. Atrial fibrillation

3.4.1. Non-rheumatic atrial fibrillation

INR 2.5 (grade A, level Ia)

In five randomized primary prevention trials comparing oral anticoagulation to placebo or no treatment anticoagulation prevented two-thirds of fata or disabling strokes due to major thromboembolism (Peterson et al, 1989; The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, 1990; Connolly et al, 1991; Stroke Prevention in Atrial Fibrillation Investigators, 1991; Ezekowitz et al, 1992; Atrial Fibrillation Investigators, 1994) [83,113,23,108,31,5]. In these studies the target INR ranged from 1.5 to 4.5. Thromboembolic event rates were relatively higher with INRs <2.0 (European Atrial Fibrillation Trial Study Group, 1995) [30]. These studies indicate a beneficial effect of warfarin in carefully selected patients in whom anticoagulation is expertly controlled.

The Atrial Fibrillation Investigators established a common database to identify subgroups of patients whose risk of stroke was so low that warfarin is not justified. They identified patients under 65 years of age without diabetes, a history of hypertension or a previous stroke or transient ischaemic attack (TIA) as low risk. These patients had an annual event rate of 1.0% which was not reduced by warfarin (European Atrial Fibrillation Trial Study Group, 1993; Hylek et al, 1996) [29,55]. SPAF II (Stroke Prevention in Atrial Fibrillation, second study) was the first primary prevention study in which patients were randomized to either anti-coagulation (target INR 2.0-4.5) or aspirin 325 mg/d and overall aspirin was as effective as warfarin (Stroke Prevention in Atrial Fibrillation Investigators, 1994) [109]. However, the rate of intracranial haemorrhage in patients >75 on warfarin was higher than in previous studies and it is not clear if the results of SPAF II were due to patient characteristics or chance.

In SPAF III patients at high risk of thromboembolism (congestive heart failure, left ventricular dysfunction on echocardiography, previous thromboembolism, systolic hypertension at enrollment or being a women over 75 years) had a lower primary event rate with adjusted dose warfarin (INR 2.0-3.0) compared to combined low-dose warfarin and aspirin (Stroke Prevention in Atrial Fibrillation Investigators, 1996) [110].

Warfarin should be considered as first-line therapy in patients with atrial fibrillation and at least one risk factor (previous thromboembolism, hypertension, heart failure, abnormal left ventricular function on echocardiography) for thromboembolism. However, patients should be reviewed as the benefit/risk ratio may alter with increasing age or the development of additional illness. Low-risk patients may be treated with aspirin alone (grade A, level Ia). The Dutch PATAF study and AFASAK II will further evaluate the effectiveness of aspirin and different intensities of anticoagulant therapy (Laupacis & Albers, 1995) [66].

3.4.2. Rheumatic heart disease

INR 2.5 (grade C, level IV)

The risk of stroke is 3 times greater in patients with atrial fibrillation with mitral stenosis than in those without valve disease (Wolf et al, 1978) [128]. Based on its apparent effectiveness in non-randomized studies and its effect in non-rheumatic atrial fibrillation, warfarin is usually given to maintain an INR of 2.5.

3.4.3 Congenital heart disease and thyrotoxicosis

INR 2.5 (grade C, level IV)

The risk of embolic stroke in patients with atrial fibrillation due to these disorders is unknown. Given the benefit in other patients with atrial fibrillation, warfarin is usually given to prevent stroke.

3.4.4. Cardioversion

INR 2.5 for 3 weeks before and 4 weeks after cardioversion (grade B, level III)

No randomized study has determined if anticoagulation reduces the risk of systemic embolization when atrial fibrillation is terminated, although non-randomized reports indicate a reduced risk with anticoagulant therapy (grade B, level III) (Bjerkelund & Orning, 1969; Weinberg & Mancini, 1989; Arnold et al, 1992) [11,124,4]. Embolic risk is associated with both electrical and pharmacological termination of atrial fibrillation. Therefore warfarin is typically given for 3 weeks prior to, and 4 weeks after, termination of fibrillation (Laupacis, 1996) [65].

3.5. Heart valve disease without atrial fibrillation

Mitral valve prolapse, mitral annular calcification and aortic valve disease in the absence of atrial fibrillation or previous embolic events are associated with a low risk of stroke and are not routine indications for anticoagulant therapy. Rheumatic mitral valve disease is associated with a high risk of stroke even in the absence of atrial fibrillation and is an indication for anticoagulation, INR 2.5 (Levine et al, 1992) [67] (grade C, level IV).

3.6. Mural thrombus

INR 2.5 for 3 months (grade B, level III)

Patients with mural thrombus after myocardial infarction are at greatest risk of embolization in the first 3 months, especially in the presence of a left ventricular aneurysm. Following initial heparin therapy, warfarin is recommended for 3 months to achieve an INR of 2.5 (Schecter et al, 1996) [100] (grade B, level III).

3.7. Cardiomyopathy

INR 2.5 (grade C, level IV)

Dilated cardiomyopathy is associated with a 30-50% risk of thrombus formation and a high risk of

systemic embolisation (Fuster et al, 1981) [38]. Prolonged anticoagulant therapy is recommended (Schecter et al, 1996) [100] (grade C, level IV).

3.8. Heart valve prostheses

3.8.1. Mechanical prosthetic valves

INR 3.5 (grade B, level IIa)

The recommended intensity of anticoagulation varies with different consensus statements (British Committee for Standards in Haematology, 1990; Ad Hoc Committee of the Working Group on Valvular Heart Disease European Society of Cardiology, 1993; Stein et al, 1995) [12,1,107]. Recent recommendations for INR ranges of 2.0-3.0 (Ad Hoc Committee of the Working Group on Valvular Heart Disease European Society of Cardiology, 1993) [1] and 2.5-3.5 (Stein et al, 1995) [107] are based on prospective randomized studies but these studies have limitations (Turpie, 1996) [118] and none had a group of patients randomized to a range of 2.0-3.0 without additional antiplatelet therapy. An effective relatively low intensity regimen (INR 3.0-4.0) is supported by the latest analysis of a large Dutch study equating actual INRs to events (Cannegieter et al, 1995) [17] (grade B, level IIa). This study also indicated the need to allow for the significant number of patients who are inadequately anticoagulated when the target INR is low. There was a clear relationship between event rates and actual INRs with a sharp rise in embolism rates with an INR <2.5 and haemorrhagic rates with an INR >5.0. Actual INRs were lower than the target range 31% of the time, so the target should be above 2.5. A target of 3.5 would maintain the majority of patients >2.5 and <5.0 and therefore maximize efficacy. The position and age of the prosthesis are also factors that determine thrombotic risk.

3.8.2. Bioprosthetic valves

Long-term warfarin not required in absence of atrial fibrillation (grade A, level Ib).

Oral anticoagulants are not required for valves in the aortic position in patients in sinus rhythm, although many centres anticoagulate patients for 3-6 months after any tissue valve implant (Turpie, 1996) [118]. Patients with bioprostheses in the mitral position should receive oral anticoagulants to achieve an INR of 2.5 for the first 3 months (Turpie et al, 1988) [119] (grade A, level Ib). After 3 months, patients with atrial fibrillation should receive lifelong therapy to achieve an INR of 2.5. Patients with bioprosthetic valves with a history of systemic embolism and those with intracardiac thrombus should also be anticoagulated to achieve an INR of 2.5. Patients who do not require oral anticoagulants after the first 3 months may be considered for antiplatelet therapy, e.g. aspirin (Nunez et al, 1984; Stein et al, 1992) [78,106].

3.9. Ischaemic stroke (see also 8.2 Stroke as a contraindication to warfarin)

Aspirin should be considered as secondary prophylaxis (grade A, level Ia).

Anticoagulant therapy reduces the risk of stroke in patients with atrial fibrillation (see section 3.4) but it has also been considered for patients without atrial fibrillation who suffer transient ischaemic attacks (TIAs), stroke in evolution and completed stroke.

There have been no randomized double-blind studies to evaluate the effect of oral anticoagulants in patients with TIAs. Several small studies have given insignificant and contrasting results. Given the clear

risk reduction with aspirin therapy warfarin should not be given as first-line therapy (del Zoppo, 1994; Hart et al, 1996) [26,46] unless there is a potential cardiac source of embolism. There is no evidence for a beneficial effect of warfarin in patients with carotid artery stenosis.

No recommendation can be given for warfarin for stroke in evolution as appropriately sized randomized trials have not been performed (del Zoppo, 1994; Hart et al, 1996) [26,46].

There is no evidence to support the use of warfarin in completed stroke. In a small randomized study the outcome of patients receiving anticoagulants was worse than those receiving placebo, with more episodes of further stroke and death due to intracerebral haemorrhage (Baker et al, 1962) [8]. The results of other small studies support the observation that warfarin does more harm than good in patients with stroke (Genton et al, 1977; Sherman et al, 1992) [41,103].

If warfarin is given the recommended INR is unknown. Given the effectiveness of low-intensity anticoagulation, INR 2.0-3.0, in patients with atrial fibrillation and other cardiac sources of emboli and the effectiveness of an INR >3.0 in patients with coronary thrombosis it is reasonable to adopt an INR between 2.0 and 4.0 if patients are to receive warfarin (grade C, level IV). Evidence-based guidelines may be facilitated by results from ongoing trials such as SPIRIT (Stroke Prevention in Reversible Ischaemia Trial, warfarin to INR of 3.0-4.5 versus aspirin 30 mg daily) and WARS (Warfarin-Aspirin Reinfarction Study, warfarin to INR of 1.4-2.8 versus aspirin 325 mg).

3.10. Retinal vein thrombosis

The value of anticoagulant therapy in retinal vein thrombosis has not been evaluated. When retinal vein thrombosis complicates the antiphospholipid syndrome anticoagulation is recommended (grade C, level V, see section 3.3).

3.11. Peripheral arterial thrombosis and grafts

Aspirin should be considered as secondary prophylaxis (grade A, level Ia).

Uncontrolled surveys suggest that oral anticoagulants may reduce the risk of acute thrombotic arterial occlusion without any effect on the progress of atherosclerosis (Tillgren, 1965; Gallus, 1988) [116,39]. Likewise the effect of anticoagulation following peripheral arterial reconstructive surgery is not established but may be beneficial (Kretschmer et al, 1988) [61]. Based on the intensity of anticoagulation required to prevent coronary artery thrombosis, an INR of 3.5 is usually recommended if warfarin is given (grade C, level IV). However, these patients have widespread atherosclerosis and treatment with aspirin should be considered as the risk of acute peripheral arterial occlusion, coronary thrombosis and ischaemic stroke are reduced by one third (Antiplatelet Trialists Collaboration, 1994) [3]. Large-scale studies comparing anticoagulation with aspirin after bypass surgery are now being conducted (Clagett, 1992) [21].

3.12. Coronary artery thrombosis (see also 3.6 Mural thrombus)

Aspirin should be considered as secondary prophylaxis (grade A, level Ia).

Oral anticoagulant therapy to achieve an INR >2.8 reduces the risk of reinfarction following a first event (Report of the Sixty-Plus Reinfarction Study Research Group, 1980; Smith et al, 1990; Anticoagulants in

the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group, 1994) [93,105,2] (level Ib). Earlier meta-analysis had revealed a 20% reduction in mortality with anticoagulant therapy during the immediate post-infarction period (Chalmers et al, 1977), [20] but the management of myocardial infarction has changed dramatically with the widespread adoption of thrombolysis and aspirin therapy, and at the moment oral anticoagulation cannot be generally recommended in preference to aspirin except in patients with mural thrombus (Vaitkus & Barnathan, 1993) [121]. The effect of warfarin to achieve an INR >3.0 is not apparently superior to the beneficial effect of aspirin and bleeding rates in anticoagulated patients are higher (The EPSIM Research Group, 1982) [114]. All patients at present should receive aspirin at 150 mg daily following coronary thrombosis or the development of angina. Low-dose warfarin (INR 1.5) to reduce factor VII coagulant activity as primary prevention of infarction is being evaluated, but no recommendation can yet be given (Meade et al, 1988) [75]. A large number of randomized studies combining anticoagulant and antiplatelet therapy are now being conducted (Becker & Ansell, 1996) [9] and further meta-analysis by the Antithrombotic Trialists Collaboration will become available. At the present time if warfarin is given an of INR 3.5 is recommended (grade A, level Ib).

3.13. Coronary artery graft thrombosis

Aspirin should be considered as secondary prophylaxis (grade A, level Ib).

Vein graft occlusion occurring in the first month is due to thrombosis. The frequency of thrombosis is 10-20% and this is reduced by aspirin, but warfarin has not been shown to be effective (Van der Meer, J., et al, 1993) [123]. Late occlusion is due to atherosclerosis with superimposed thrombosis. Although aspirin plus oral anticoagulation may reduce the risk of late occlusion, the value of warfarin alone is not known and anticoagulation is not routinely recommended (Pfisterer et al, 1989) [85]. If warfarin is given an INR of 3.5 is recommended based on the results of reinfarction studies. A lower intensity of anticoagulation has not been evaluated.

3.14. Coronary angioplasty and coronary stents

Aspirin should be considered as first-line therapy (grade A, level Ib).

Both aspirin and heparin reduce the risk of acute occlusion following angioplasty. Oral anticoagulation has not been shown to reduce the incidence of late stenosis (Thorton et al, 1984) [115]. Coronary stents do not require oral anticoagulation, but aspirin is recommended after angioplasty and stent insertion to prevent coronary and other thrombotic events in this high-risk population.

3.15. Vena caval filters

Filters are used to prevent pulmonary emboli in patients in whom anticoagulation is contraindicated or in whom it has failed. The use of anticoagulation in patients with filters must be determined by individual risk-benefit analysis. There are no prospective randomized studies. Vena cava thrombosis can occur in up to 20% of patients, and therefore in the absence of either bleeding or high bleeding risk anticoagulation is justified (Elliott & Eklof, 1996) [28]. Contraindications to anticoagulation may resolve after insertion of a filter allowing introduction of warfarin with a target INR of 2.5 at that stage (grade C, level IV).

3.16. Low-dose warfarin

Minidose warfarin has been evaluated in gynaecological and orthopaedic surgery. It did reduce the risk of DVT in a small study of patients having gynaecological surgery (Poller et al, 1987) [87] but it did not reduce the risk of venous thrombosis in hip replacement surgery (Fordyce et al, 1991) [35]. A two-step warfarin regimen has been shown to be effective in hip surgery but was not monitored with INR (Francis et al, 1983) [37]. The effectiveness of fixed minidose warfarin at 1 mg/d to reduce the risk of central venous catheter associated thrombosis is unproven. In a randomized study of 121 patients final analysis was only available for 80 patients. These patients were not representative of the complete group and no recommendation can be given until further studies are completed (Bern et al, 1990) [10]. A very-low-dose warfarin regimen to keep the INR at 1.3-1.9 has been used to reduce the risk of venous thromboembolism in patients with advanced breast cancer (Levine et al, 1994) [68].

Absolute recommendations on the indications, duration and intensity of low-dose warfarin regimens cannot be given at present.

4. COMMENCEMENT OF ORAL ANTICOAGULANT THERAPY

It is important to confirm objectively the diagnosis for which anticoagulant treatment is to be given. However, this should not delay the start of therapy. Where possible, routine blood samples for prothrombin time (PT) and activated partial thromboplastin time (APTT), platelet count and liver function tests should be taken before starting treatment, but the results are rarely needed immediately (McLinley et al, 1993) [74]. Oral anticoagulation can be commenced on day 1 in conjunction with heparin in most patients with deep venous thrombosis. 5 d of heparin treatment is as effective as a longer period of heparin in patients with venous thromboembolism (grade A, level Ib) (Gallus et al, 1986; Rosiello et al, 1987; Hull et al, 1990; Mohiuddin et al, 1992) [40,96,52,76]. As the initial period of treatment with warfarin may be associated with a procoagulant state due to a rapid reduction in protein C levels, it is recommended that patients receive heparin therapy for at least 4 d and it should not be discontinued until the INR has been in the therapeutic range for 2 consecutive days (Ginsberg, 1996) [42] (grade C, level IV). In patients with large thromboses a longer period of heparin up to 10 d may be administered (Hull et al, 1990; Mohiuddin et al, 1992) [52,76]. A standard protocol for the commencement of anticoagulant treatment is recommended (grade B, level IIb) (Fennerty et al, 1984) [33] (Table VIII).

Day	INR	Warfarin dose (mg)
First	< 1·4	10
Second	< 1·8	10
	1·8	1
	> 1·8	0·5
Third	< 2·0	10
	2·0–2·1	5
	2·2–2·3	4·5
	2·4–2·5	4
	2·6–2·7	3·5

	2·6–2·7	3·5
	2·8–2·9	3
	3·0–3·1	2·5
	3·2–3·3	2
	3·4	1·5
	3·5	1
	3·6–4·0	0·5
	>4·0	0
		(Predicted maintenance dose)
Fourth	<1·4	>8
	1·4	8
	1·5	7·5
	1·6–1·7	7
	1·8	6·5
	1·9	6
	2·0–2·1	5·5
	2·2–2·3	5
	2·4–2·6	4·5
	2·7–3·0	4
	3·1–3·5	3·5
	3·6–4·0	3
	4·1–4·5	Miss out next day's dose then give 2 mg
	>4·5	Miss out 2 d doses then give 1 mg

Table VIII. Appendix II. Warfarin loading schedule.

A specific anticoagulant treatment chart is recommended for in-patient anticoagulation which contains the treatment protocol, the results of coagulation tests (INR and APTT ratios) and the prescribed doses based on these results. This chart can then form the basis of the anticoagulant referral form for out-patient follow-up. A standard chart is being prepared by the task force.

Modifications to the oral anticoagulant loading dose may be necessary if base-line coagulation results are abnormal. Some patients may be particularly sensitive to warfarin. These include the elderly and those with high-risk factors such as congestive cardiac failure and liver disease or those on drug therapy known to potentiate oral anticoagulants. A loading dose of <10 mg daily is recommended under these circumstances.

For rapid anticoagulation with warfarin, daily INR measurement for a minimum of 4 d is recommended (Table VIII). Having achieved an INR in the desired therapeutic range, the INR should continue to be monitored weekly until control is stable. Thereafter the frequency of recall can be extended. Extension of recall up to 12 weeks is acceptable. In the outpatient setting or the community when rapid anticoagulation is not required, loading doses of <10 mg daily are recommended. A slow induction of anticoagulation with warfarin can be achieved by starting at a dose of 2 mg daily and increasing this slowly until the target INR is achieved (grade C, level IV).

It is important that discharge arrangements for anticoagulant follow-up are detailed in the hospital notes and that patients receive the yellow Department of Health anticoagulant booklets (obtained from DHSS Stores, No. 2 Site, Manchester Road, Heywood, Lancashire OL10 2PZ, or SHHD (Div. IIID), Room 9, St Andrews House, Edinburgh EH1 3DE). At discharge an appointment should be made for further INR measurement (this should not normally exceed 7 d). Responsibility for the discharge arrangements lies with the clinician referring the patient.

4.1 Thrombophilia

Patients with protein C deficiency are at risk of developing skin necrosis during commencement of oral anticoagulation. Introduction of warfarin therapy should proceed without a loading dose of warfarin even when heparin is given. Patients with protein S deficiency may also be at risk. Skin necrosis has not yet been reported in patients with resistance to activated protein C. It would be prudent to introduce anticoagulation with warfarin slowly in all patients and to withdraw warfarin slowly at the end of treatment (grade C, level IV).

5. MANAGING ANTICOAGULATION IN THE PERI-OPERATIVE PERIOD

Stop anticoagulation or perform surgery with the INR <2.5. If there is a risk of dangerous bleeding, e.g. internal, then stop anticoagulation at least 3 d before surgery or reverse anticoagulation with low-dose vitamin K (see section 6) (grade B, level III).

The short-term risk of thromboembolism in patients with mechanical heart valves when not anticoagulated is very small. Therefore these patients should be managed in the same way (grade B, level IIb).

In rare circumstances where it is necessary to continue anticoagulation, e.g. life-threatening thromboembolism in patients with adenocarcinoma, then reduce INR to <2.5 and start heparin (see heparin guidelines (British Committee for Standards in Haematology, 1993b) [14]) (grade C, level IV).

For minor surgical procedures the oral anticoagulant dose should be stopped or adjusted to achieve a target INR of approximately 2.0 on the day of surgery (Taberner et al, 1978; Francis et al, 1983) [111,37] (grade B, level III). The INR should be checked pre-operatively and if <2.5 the patient can proceed to surgery. If the INR is >2.5 the surgeon and haematologist must decide if the level of anticoagulation is safe for surgery to take place.

Prevention of bleeding with oral tranexamic acid mouthwash (4.8%) can be achieved after dental extraction without dose modification of oral anticoagulants (Ramstrom et al, 1993) [91] (grade A, level Ib).

For major surgery, oral anticoagulants should be stopped at least 3 d prior to surgery, and depending on

the thrombotic risk of the condition for which the patient is receiving anticoagulant therapy, the INR can be monitored and if necessary heparin instituted once the INR is below the lower limit of the therapeutic range (e.g. <2.0 for a target of 2.5) (grade C). After warfarin is stopped it typically takes about 4 d for the INR to reach 1.5 (White et al, 1995) [126]. The threshold for institution of heparin and the dose required will depend on the underlying condition, e.g. secondary prevention of venous thrombosis is low risk after the first month of anticoagulation and warfarin could be replaced with low-dose subcutaneous heparin preoperatively. A caged-ball metal mitral valve prosthesis is relatively high risk and warfarin might be replaced with a continuous infusion of heparin once the INR is <3.0. There is, of course, a risk of bleeding associated with heparin during surgery, and some experts consider that the risk of heparin is greater than the risk of stopping anticoagulation for 4 d before surgery and restarting as soon as possible after surgery in patients with mechanical heart valves (Kearon & Hirsh, 1997) [59] (and see below).

The timing for reinstitution of oral anticoagulants will depend on the risk of post-operative haemorrhage. The 48-72 h delay for achievement of anticoagulation with oral vitamin K antagonists will also influence this decision. In many instances oral anticoagulants can be started again as soon as the patient has an oral intake.

Certain types of surgery, such as neurosurgery, are particularly high risk for bleeding complications, and a period without any anticoagulant is preferable (Cannegieter et al, 1994) [16] (grade B). Anticoagulant therapy in patients with metal heart valve prostheses can be temporarily discontinued. A meta-analysis of studies covering a period of 53 647 patient-years indicated that the risk of all thromboembolic events when not on oral anticoagulant therapy was only 8 per hundred patient-years. This equates to a risk of <0.2% over a 7 d period (Cannegieter et al, 1994) [16]. However, this study did not specifically address the peri-operative period when the risk may be higher due to the prothrombotic state associated with surgery. In a retrospective analysis of 180 non-cardiac operations in 159 patients with valve prostheses (170 Starr-Edwards, 59 mitral and 108 aortic), 153 operations were performed >12 months after valve replacement. In 62% of patients anticoagulation was discontinued 1-3 d before surgery and in 23% more than 3 d before. Anticoagulation was resumed 1-3 d later in 60% and after 4 d in 24%. Total peri-operative cessation averaged 6.6 d. No post-operative thromboembolic events occurred in relation to the surgical procedure (level III) (Tinker & Tarhan, 1978) [117]. In another study in which patients with metal prostheses underwent non-cardiac surgery with cessation of oral anticoagulation, two of 10 procedures in patients with mitral prostheses were complicated by perioperative thromboembolism compared with 0 of 25 procedures in patients with aortic prostheses (level III) (Kathol et al, 1976) [58].

6. MANAGING BLEEDING AND EXCESSIVE ANTICOAGULATION

Bleeding while on oral anticoagulants increases significantly with INR results >5.0 (Eckman et al, 1993; Cannegieter et al, 1995) [27,17]. Therapeutic decisions are dependent on the INR and whether there is minor or major bleeding. The dose of vitamin K used to reverse over-anticoagulation depends on the INR (Shetty et al, 1992) [104]. Recommendations for management are given in Table II.

3·0 < INR < 6·0 (target INR 2·5) 4·0 < INR < 6·0 (target INR 3·5)	(1) reduce warfarin dose or stop (2) restart warfarin when INR < 5·0	
6·0 < INR < 8·0, no bleeding or minor bleeding	(1) stop warfarin (2) restart when INR < 5·0	
INR > 8·0, no bleeding or minor bleeding	(1) stop warfarin (2) restart warfarin when INR < 5·0 (3) if other risk factors for bleeding give 0·5–2·5 mg of vitamin K (oral)	Level III, grade B
Major bleeding	(1) stop warfarin (2) give prothrombin complex concentrate 50 units/kg or FFP 15 ml/kg (3) give 5 mg of vitamin (oral or i.v.)	Level III, grade B

Table II. Recommendations for management of bleeding and excessive anticoagulation.

INR >8.0, no bleeding or minor bleeding.

Stop oral anticoagulants. If no other risk factors for haemorrhage stop treatment until INR <5.0. If risk factors for haemorrhage or minor bleeding (e.g. age >70 years, previous bleeding complications, epistaxis) give vitamin K. Due to near complete absorption, oral vitamin K is as effective as intravenous with the delay in action hardly influenced by the absorption time. However, only 0.5 mg is required to reduce the INR from >5.0 to a target level of 2.0-3.0 (Shetty et al, 1992) [104]. Vitamin K tablets usually contain >5 mg which will completely reverse anticoagulation. Therefore, when partial correction is required it may be necessary to give intravenous vitamin K or alternatively give the intravenous preparation orally. Allergic reactions following intravenous administration are rare with new preparations of vitamin K. If the INR is still too high at 24 h the dose of vitamin K can be repeated.

Major bleeding.

Resuscitate and transfer to hospital for reversal of anticoagulation with vitamin K and prothrombin complex concentrates (PCC) or fresh frozen plasma. Anticoagulation can be effectively reversed with 50 units/kg prothrombin complex concentrate, PCC (factors II, VII, IX and X or factor II, IX and X concentrate and factor VII concentrate) (Makris et al, 1996) [73] and vitamin K 5 mg by slow intravenous injection (grade B, level III). However, patients receiving warfarin may have an underlying hypercoagulable state and infusion of prothrombin complex concentrate may exacerbate this. Further studies are required to determine the minimum dose of concentrate required to restore thrombin generation to normal and the safety of concentrates used for this purpose. In the absence of available concentrate licensed for this use emergency, treatment with 15 ml/kg of FFP and intravenous vitamin K 5 mg will partially reverse anticoagulation, though the levels of individual factors will typically remain <20% (Makris et al, 1996) [73] and larger doses should be given if possible.

For patients with prosthetic heart valves, full reversal of oral anticoagulants with vitamin K may result in prolonged oral anticoagulant resistance and the possibility of valve thrombosis and thromboemboli. The degree of reversal must therefore be decided on an individual basis. All patients with bleeding should be evaluated to identify if there is a local anatomical reason for bleeding.

Bleeding may occur when patients are not over-anticoagulated. In these circumstances it may still be necessary to reverse anticoagulation and identify the cause of bleeding.

7. DRUG INTERACTIONS

If the drug change lasts <5 d either no change, minor dose reduction or omit one complete dose of warfarin if known potentiating drug given (grade C, level IV). If the drug change lasts >5 d check INR after start of new drug and adjust warfarin dose on basis of result (grade C, level IV).

Almost any drug can interact with oral anticoagulants, the majority potentiating the anticoagulant effect (notable exceptions which reduce the effect are anti-epileptics, barbiturates, sucralfate, Rowachol, rifampicin). For further details see relevant appendix in the current British National Formulary. When prescribing, a non-interacting drug should be chosen when possible.

For short courses of new drug therapy, oral anticoagulant dose adjustment is not essential but a slight dose reduction or omission of one dose could be recommended if a known potentiator is prescribed (grade C). If medication is for >5 d the INR should be checked 1 week after commencement and the oral anticoagulant dose adjusted accordingly, returning to the normal maintenance dose after stopping the new drug.

8. CONTRAINDICATIONS TO ANTICOAGULATION

These are seldom absolute. The risk of haemorrhage is multifactorial, though increasing age is often found to be associated with an increased risk of major bleeding (Landefeld et al, 1989; Fihn et al, 1993; van der Meer, F., et al, 1993; Hylek & Singer, 1994; Stroke Prevention in Atrial Fibrillation Investigators, 1994; Palareti et al, 1996) [63,34,122,54,109,80]. The following situations deserve specific mention.

8.1. Pregnancy

Organogenesis occurs during the 6th to 12th weeks of gestation and exposure to warfarin at this time may be associated with embryopathy (Hall et al, 1980; Iturbe-Alessio et al, 1986; Wong et al, 1993) [45,56,129]. However, due to immaturity of the fetal liver there is a continuing risk of fetal bleeding throughout pregnancy. Avoiding oral anticoagulants reduces the risk of embryopathy, but heparin can cause maternal osteoporosis and thrombocytopenia. Furthermore, heparin may not be as effective during pregnancy in preventing thromboembolic events in patients with mechanical valves (Sbarouni & Oakley, 1994) [99]. Patients receiving warfarin should be told of the risk before conception and advised to have early pregnancy tests to detect pregnancy before 6 weeks gestation. The possible need for alternative treatment with heparin in the first trimester and for 2-3 weeks before delivery (British Committee for Standards in Haematology, 1993a; Ginsberg & Barron, 1994) [13,43] should be explained in advance (British Committee for Standards in Haematology, 1993a) [13] Guidelines on management of anticoagulant therapy in pregnancy have been published (British Committee for Standards in Haematology, 1993a) [13].

8.2. Stroke

Haemorrhagic stroke is a contraindication to oral anticoagulant therapy (Lowe, 1996) [71]. In patients with ischaemic strokes anticoagulation increases the risk of secondary haemorrhage into the infarcted brain. In patients with atrial fibrillation long-term warfarin therapy is beneficial, but the risk of early recurrent embolism is low and initial heparin is not required. Start warfarin 48 h to 14 d after ischaemic stroke without initial heparin therapy dependent on size of infarct and blood pressure. In patients with large embolic strokes or uncontrolled hypertension anticoagulation should be postponed for 14 d. Patients with small- to moderate-sized ischaemic strokes without evidence of haemorrhage on CT scanning 48 h after the onset of the event can be anticoagulated without delay.

9. ORGANIZATION

Responsibility for ensuring a safe anticoagulant service and organizational procedures should be documented. The level of personnel involved in an anticoagulant service will be determined by local circumstances. Increasingly pharmacists, nurses, clinical scientists and technologists are involved in providing anticoagulant care. With the development of local guidelines and computer decision support systems some duties may be devolved at the discretion of the local hospital or Trust. The following organizational issues are recommended.

A lead clinician should be nominated who should be in charge of the anticoagulant service. Responsibilities are outlined in Table III.

1. Receive referrals and approve need for anticoagulation
2. Give advice on duration and intensity of anticoagulation
3. Ensure system is in place for patients to receive urgent medical advice relating to anticoagulation
4. Ensure participation in national laboratory quality assurance scheme and monitor performance
5. Ensure regular clinical audit
6. Ensure anticoagulant guidelines are available, including the management of over-anticoagulation
7. Provide general practitioners involved in anticoagulant care with advice and guidelines
8. Approve computer assisted management programmes prior to implementation
9. Ensure adequate training is available for all personnel
10. Provide written approval for personnel, detailing levels of responsibility

Table III. Responsibilities of lead clinician for anticoagulant service.

Where non-medical personnel are involved in anticoagulant care they should have a strong clinical background with appropriate clinical qualifications, e.g. nurse practitioner, senior pharmacist. Recommendations regarding non-medical personnel are listed in Table IV.

1. Personnel should be responsible to the lead clinician organizing the anticoagulant service
2. Personnel should have received adequate training and should be approved prior to commencement of duties
3. Dose recommendations and recall should be made according to written protocols or computer assisted guidelines
4. Recommendations should be available for review by the clinician
5. The clinician should be alerted to patients with an INR > 8 and those with bleeding problems
6. Personnel should provide patient education regarding anticoagulant therapy

Table IV. Recommendations for non-medical personnel involved in anticoagulant service.

The development of anticoagulant services away from a hospital setting, using a postal service for collection of samples and return of dosage recommendations, has been practised for many years in some areas. Particular care is needed, however, to ensure patients can be quickly contacted regarding any change of dose. It is essential that patients managed in this way know how to report any complications of treatment and how to get urgent clinical advice. A system using trained staff to provide a peripatetic service to the home or general practice maintains a direct route for good communication with the patient. All previous patient results should be readily accessible with full documentation of the clinical condition and duration of treatment before further instructions are given. Records should be regularly audited.

10. COMPUTER SUPPORT SYSTEMS

The computerization of anticoagulant management offers practical benefits to the laboratory and clinical staff, with standardization and continuity of recommendations. The standardization of anticoagulant control according to previous BCSH guidelines has been achieved using computer programs (Ryan et al, 1989; Hunt, 1993) [97,53]. Table V indicates facilities for inclusion when considering implementing a computer system.

1. Rapid retrieval of data to screen or printer
2. Data storage in chronological order
3. Dosage recommendations according to algorithm or guidelines approved by consultant in charge of the service; this should include evaluation of results over the full range of INR results
4. An alerting system for patient results which fall outside defined criteria
5. A facility to over-ride computer recommendations
6. Patient recall for testing according to agreed criteria based on previous stability with invalid date alerts
7. An alerting system for non-attendees
8. An alerting system for discontinuation of treatment
9. A prompt system to check for bleeding problems when high INR values are obtained
10. A system to record bleeding/thrombotic events or other rare side-effects
11. A facility to audit results

Table V. Recommendations for implementation of computer-assisted anticoagulation.

Organizational advantages may include automatic generation of clinic lists, transport lists and letters to GPs/colleagues regarding commencement and discontinuation of treatment. A database of drug interactions with warfarin is an additional helpful facility.

11. CLINICAL AUDIT

Routine audit of clinic management with review of over-anticoagulated patients should be an integral part of the anticoagulant service. Review of patient outcome of INR values >8 (Philips et al, 1993), [86] or patients requiring therapeutic interventions to reverse anticoagulant effect, are useful criteria for audit. Potential outcomes of audit may include better use of consultant time, reduction of in-patient stay to achieve stable anticoagulation, reduction in surgery-related tromboembolic problems, reduction in near-miss events and potential litigation problems. Table VI indicates some standards for audit.

1. Provision of adequate data for safe transfer of anticoagulant follow-up
2. Provision of anticoagulant cards for patients on hospital discharge
3. Patient information: awareness of need for anticoagulation and possible side-effects of treatment
4. Hospital notes contain information that the patient is currently on warfarin
5. The use of heparin/warfarin dosage schedules in hospital setting (see Appendix II)
6. Follow-up arrangements for patients failing to attend appointments
7. Achievement of target INR: 50% of INRs within 0·5 INR units and 80% within 0·75 INR units of target

Table VI. Standards for audit.

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12. LABORATORY CONTROL

The INR system is used to standardize variability of response of different thromboplastin reagents to warfarin (WHO Expert Committee on Biological Standardisation, 1983) [127]. The INR is calculated from the prothrombin time ratio at test plasma to the geometric mean normal prothrombin time (GMNPT), to the power of the international sensitivity index (ISI) of the thromboplastin.

$$INR = (\text{patient PT}/\text{GMNPT})^{ISI}$$

Two important sources of variability remain in the INR calculation: the measurement of the GMNPT and

the ISI determination of the thromboplastin reagent (Taberner et al, 1989; Peters et al, 1991) [112,82]. The GMNPT should be derived from the geometric of 20 healthy adult plasma samples, or the use of validated lyophilized normal control plasma. Low ISI thromboplastins are recommended for monitoring oral anticoagulant therapy (Moriarty et al, 1988) [77]. Local estimation of ISI values is not recommended, and ISI values of each thromboplastin batch should be assigned by manufactures by comparison with an international standard. Unfortunately there remains a problem partly due to the source of reference material (human or non-human) used in the calibration. Furthermore, problems with coagulometers producing shorter PT times than manual methods are well recognized (Poller et al, 1989) [88]. Local calibration of coagulometers can be achieved by using plasma calibrants with manually certified PT values (Poller et al, 1995) [89]. Participation in a CPA (Clinical Pathology Accreditation) accredited External Quality Assurance Scheme for anticoagulation is essential for monitoring laboratory performance (Preston, 1995) [90]. Participants are encouraged to discuss technical problems with the EQAS co-ordinators.

There is no clinically significant change in INR when analysis is delayed for up to 3 d. Off-site blood sampling can accommodate a large increase in patient workload without a major revenue increase in primary care and with continued totally quality management and central expert advice (Baglin & Luddington, 1997) [7].

13. NEAR-PATIENT TESTING

There are now several near-patient testing systems available for monitoring oral anticoagulant control (Machin et al, 1996) [72]. These have generally shown a good correlation with manual and automated methods. The advantages include a rapid result without centrifugation of samples, using portable equipment easy to use by non-scientific staff. The monitoring of quality control may be more difficult due to lack of appropriate quality control material. Furthermore, the ISI values of some reagents incorporated in the disposable cards are higher than recommended. When near patient testing is to be used it is recommended that this is established in conjunction with local pathology services, in order to overview quality control (British Committee for Standards in Haematology, 1995) [15].

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[dagger] Although the advice and information contained in these guidelines is believed to be true and accurate at the time of going to press, neither the authors nor the publishers can accept any legal responsibility or liability for any errors or omissions.

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