

Oral Anticoagulation Management in Primary Care With the Use of Computerized Decision Support and Near-Patient Testing

A Randomized, Controlled Trial

David A. Fitzmaurice, MD; F. D. Richard Hobbs, FRCGP; Ellen T. Murray, MSc; Roger L. Holder, BSc; Teresa F. Allan, MSc; Peter E. Rose, MD

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.

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THE EXPANSION of clinical indications for treatment with warfarin sodium¹⁻⁵ has heightened concerns over the process of warfarin monitoring.^{6,7} The significance of this issue for all health care systems with aging populations can be estimated from data showing that, of patients with identified atrial fibrillation, only one third are currently receiving anticoagulation therapy.⁸ Furthermore, in the absence of screening programs, probably 60% of patients with atrial fibrillation remain unidentified.⁷ On the basis of these data, the service requirements for anticoagulation monitoring may be predicted to increase by a factor of 5.

This issue is particularly problematic for primary care, with lack of resources for monitoring⁶ and perceptions of inadequate expertise in anticoagulation care.⁹ The use of computerized decision support systems (CDSSs) may overcome lack of ex-

perience, having demonstrated significant improvement in dosing and recall decisions based on the international normalized ratio (INR) result when used in primary care¹⁰ and hospital settings.¹¹ A CDSS can reduce the reliance on specialist delivery of anticoagulation care, enabling other health care professionals to manage clinics.¹² The use of near-patient testing (NPT) for INR estimation alongside CDSS offers the possibility of full devolution of warfarin management to primary care.^{13,14} Reliable machines for INR monitoring are available that have been rigorously evaluated within laboratory settings.¹⁵⁻¹⁷

This study was therefore designed to test the efficacy, cost-effectiveness, and safety of using a novel complete care package comprising NPT and CDSS for oral anticoagulation monitoring within nurse-led primary care clinics. The hypothesis was that anticoagulation care can be provided at least as well within this primary

From the Department of General Practice, Medical School, The University of Birmingham, Birmingham, England (Drs Fitzmaurice and Hobbs, Mss Murray and Allan, and Mr Holder); and Pathology Department, Warwick Hospital, Warwick, England (Dr Rose).

SUBJECTS AND METHODS

Twelve practices, of the 248 practices within Birmingham, England, were randomly selected by means of random numbers from a list of 21 practices that had expressed interest in the study. The list of practices encompassed large and small practices, in a variety of inner-city, urban, and rural locations. Randomization was stratified by practice size to ensure that the population base was large enough to meet the sample size criterion. No practices were excluded from randomization. Nine practices were randomized to intervention and 3 to control.

The study used 2 control populations: patients individually randomly allocated as controls in the intervention practices (intrapractice controls) and all patients in the control practices (interpractice controls). Interpractice controls were included to allow an estimate of any Hawthorne effect that might have occurred among the intrapractice control patients. The Hawthorne effect describes the potential for taking part in research to itself influence routine practice and thus alter (improve) care in control patients within study practices.

In intervention practices, patients taking warfarin, identified from validated practice lists, were randomized individually, by means of computer-generated random codes, to continue current follow-up arrangements (hospital care) or monitoring within the practice by nurse-led NPT and CDSS. No patients were excluded from randomization at this stage.

Three local hospital laboratories provided laboratory support. Four methods were used to compare INR results. Blood samples were delivered to the hospitals by routine collection. In hospital 1, the INR was estimated on 2 machines: Thrombotrak (Nycomed UK, Birmingham), using Thrombotest (Nycomed UK) from the same batch as that used by the practices (method 1a); and Automated Coagulation Laboratory (ACL) machine (International Laboratories, Cheshire, England), using International Laboratory (IL) (PT

FIBHS Plus) reagent (International Laboratories) (method 1b). The international sensitivity index (ISI) of the ACL/IL combination, 1.15, was derived by the laboratory by means of an orthogonal regression calibration procedure, comparing manual and machine values obtained from 20 plasma samples from healthy subjects and 80 samples from patients treated with warfarin. As hospital 1 is accredited as a regional reference laboratory, the INR derived by means of the ACL/IL combination is taken as the criterion standard (method 1b).

In hospital 2, INR was estimated by a KC-10 machine (Amelung GmbH, Lemgo, Germany) using Manchester reagent with an ISI of 1.04 (method 2). In laboratory 3, INR was obtained manually by means of Manchester reagent with an ISI of 1.03 (method 3). These ISIs were provided by the manufacturer, with no local calibration undertaken. Hospitals 1 and 2 provided routine anticoagulation management for the control patients. In hospital 1, patients were sent dosing and recall advice by mail after a dosing decision had been made by a physician. In hospital 2, patients were seen by a physician with their INR result and given dosing and recall advice during the visit. Hospital 2 changed to using a CDSS (Dawn AC; 4S Information Systems, Cumbria, England) during the study, and patients were then seen only by a technician (a medical laboratory science officer).

Anticoagulation Management Support System (Softop Information Systems, Warwick, England)^{10,11,18} was chosen as the CDSS for this study, as it had been validated in secondary¹¹ and primary¹⁰ care settings. All dosing decisions within the practice-based clinic were recorded on the CDSS. Dosing recommendations made by the CDSS were based on the current INR in relation to individual therapeutic range, based on the British Society of Haematology guidelines, with the 2 main ranges being 2.0 to 3.0 and 3.0 to 4.5.⁵ All recommendations could be overridden, and nurses were advised to check with medical staff if a change of dose was recommended. This was also necessary for patients for whom clinical indications might interfere with their control, for example, concomitant medication.

care model as with routine hospital management. The outcome measures included a wide variety of previously validated, and novel, clinical measures. This article describes the main clinical outcomes, including degrees of therapeutic INR control.

RESULTS

Intervention practices had a mean population of 7000. A total of 224 patients were recruited, comprising 122 intervention and 102 intrapractice controls and 143 interpractice controls (**Figure**). Forty patients discontinued the study before 12 months, including 11 patients randomized to intervention who returned to hospital care (**Table 1**). Eighteen patients declined to enter the study. On an intention-to-treat basis, there were 254 patient-years of follow-up. There were no significant differences between intervention and control groups in age or sex distribution (55% male, 45% female), comorbidity, or concomitant drug history. The most common clinical indication for warfarin treatment in all groups was atrial fibrillation (intervention group, 45%; control group,

53%), with no significant difference between groups in terms of indication (**Table 2**).

INR CONTROL AND CLINICAL OUTCOMES

Data for the proportion of tests undertaken and point prevalence INR showed no significant differences between the 2 intervention populations and external (Hawthorne) control patients (**Table 3** and **Table 4**). These data indicate that it is unlikely that a significant Hawthorne effect occurred among control patients in the intervention practices. Since this was the reason for the inclusion of these external controls, no further data on these patients are presented. Analysis of data from the patients who declined to enter the study demonstrated results similar to those of the control population.

The proportion of time spent in the target INR range was calculated with assumption of a linear change between consecutive INR results^{20,21} (**Table 5**). Only patients with 3 or more INR results (n=202) were included in this analysis. A significant difference in percentage of time spent in range was found between the 2 groups during the

Thrombotrak was the NPT used in the study since it was, at that time, the only NPT for INR with a positive Department of Health evaluation. The thromboplastin used for the NPT was Thrombotest, a World Health Organization reference (and therefore criterion standard) thromboplastin. No practice had previous experience of either CDSS or NPT for anticoagulation.

The primary outcome of INR control was determined by point prevalence of patients achieving individual therapeutic INR targets (the routine method used to report INR control in England) and individual proportion of time spent within the therapeutic target INR range. Point prevalence results were calculated for all patients in the study, with the last result carried forward for patients who left the study for any reason (n=346), and for patients in the study for the whole study period (n=254), and for patients commencing warfarin treatment during the study period (n=322).

The percentage of time spent in the target range was calculated by means of all INR data for all patients having 3 or more INR results. Secondary outcome measures included adverse events, particularly hemorrhagic and thromboembolic episodes, and patient satisfaction.

The study commenced in February 1995, with intervention for 12 months. Ethical approval was received from the local ethical committees. All patients aged 18 years and older receiving warfarin therapy were invited to participate in the study. Informed consent was obtained. Retrospective INR data for all patients (intervention and control) were collected from either patient-held or hospital records. Patients who declined to enter the study were monitored through the hospital clinic. New patients receiving warfarin after study commencement were identified through the practices' standard mechanisms and were allocated to the intervention or control group by means of computer-generated randomization codes. All new patients were stabilized in a hospital clinic before inclusion in the study.

INTERVENTION AND CONTROL PATIENTS

The dedicated practice clinics were managed by practice nurses who had a morning of theoretical training on indications for anticoagulation and issues relating to the monitoring, including the role of the INR, measures of control, and quality assurance. The afternoon session provided practical instruction in the use of the CDSS and NPT. After training, 1 on-site visit was conducted by 2 of us (D.A.F. and E.T.M.) to ensure practical skills within the practice clinic. Where the CDSS suggested a change of dose, or if there were clinical indications such as a break in treatment, the nurses had to check with a general practitioner before advising the patients. One practice employed a medical laboratory science officer for the study.

Internal quality assurance was performed before the start of each clinic. Intervention practices were required to perform external quality assurance, with reagents supplied by one of the local laboratories every 2 months. Citrated venous blood samples were used for INR estimation. The NPT INR result in the practice was entered into the CDSS, which advised on warfarin dosing and the date for the next appointment. Control patient data were monitored through the hospital clinics.

STUDY POWER AND EFFECT SIZE

The study, powered for equivalence of effect of 10% on the basis of INR control,¹⁹ in terms of point prevalence, in the intervention and control groups at 90% power and 5% significance, required 101 patients in each arm. Data for intervention and control patients were transferred onto an Access database (Microsoft Inc, Seattle, Wash) for analysis. A commercially available software package (SPSS; SPSS Inc, Chicago, Ill) and Minitab (Minitab Inc, State College, Pa) were used for statistical analysis. Individual statistical tests included McNemar test for dependent proportions, χ^2 , and log-linear modeling.

study period ($P < .001$), with a significant improvement in proportion of time spent in range for intervention patients (paired t test, $P = .008$). There was also an improvement in both control populations, and, when the improvements were compared across the 3 populations, there were no significant differences in these improvements in the proportion of time spent in range.

There was no significant difference between the groups in terms of overall death rates (**Table 6**) or serious adverse events (**Table 7**). One fatal cerebrovascular accident occurred in the intervention group and was classified in the hospital notes as "massive intracerebral hemorrhage" with INR of 1.9 on admission. The patient had no computed tomographic scan to confirm the cause.

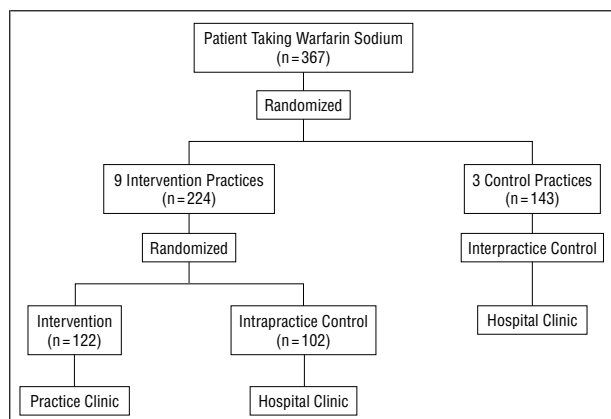
There were no significant differences in overall adverse event rates between the groups. For the total study population (including both control populations), in terms of hemorrhagic adverse incidents, there were 39.8 minor, 0.4 major, and no fatal events per 100 patient-years, and for thromboembolic incidents, there were 10 serious events (3.9 per 100 patient-years), of which 2 were fatal (0.79 per 100 patient-years).

ECONOMIC ANALYSIS

Health economic analysis (which will be reported in more detail in a separate article) demonstrated that the intervention cost, on average, was approximately £100 (\$160) per patient per year more than for controls, principally because of the capital costs of setting up the practice-based clinics and the increased frequency of testing found within the practices (Table 3). The practice-based costs were significantly affected ($P < .001$) by practice size, with larger practices sustaining lower mean costs. The practice-based costs ranged from £80 to £350 per patient per year, with a mean of £169 (\$270), while the mean hospital costs were £69 (\$110) per patient per year.

COMMENT

These primary care practices encompassed variations in list size, demography, and budget-holding status. The prevalence of practice patients receiving warfarin ranged from 0.2% to 0.7%. There were no significant differences between the 2 study populations in terms of de-



Study design.

Table 1. Reasons for Leaving Study

Reason	Intervention, No.	Control, No.			Total, No.
		Intrapractice	Interpractice	Total	
Moved away	3	3	3	6	9
Too ill or non-compliant	3	0	0	0	3
Returned to hospital clinic	8	NA*	NA	NA	8
Died	3	3	3	6	9
Completed therapy	6	11	9	20	26
Total	23	17	15	32	55

*NA indicates not applicable.

Table 2. Clinical Indication for Warfarin Sodium Therapy and Therapeutic Range*

Condition/Therapeutic Range†	Intervention, No. (%)	Control, No. (%)			Total, No. (%)
		Intrapractice	Interpractice	Total	
Atrial fibrillation/2.0-3.0	55 (45)	53 (52)	68 (48)	121 (49)	176 (48)
Mechanical prosthetic valves/3.0-4.5	17 (14)	14 (14)	27 (19)	41 (17)	58 (16)
Recurrent DVT and/or PE/2.0-3.0	17 (14)	15 (15)	17 (12)	32 (13)	49 (13)
TIA/CVA caused by thromboembolic event/2.0-3.0	5 (4)	3 (3)	8 (6)	11 (5)	16 (4)
Cardiomyopathy/2.0-3.0	4 (3)	6 (6)	3 (2)	9 (4)	13 (4)
DVT treatment/2.0-3.0	5 (4)	4 (4)	3 (2)	7 (3)	12 (3)
Mitral or aortic stenosis/2.0-3.0	7 (6)	1 (1)	2 (1)	3 (1)	10 (3)
Systemic embolus/2.0-3.0	2 (2)	3 (3)	2 (1)	5 (2)	7 (2)
PE/2.0-3.0	2 (2)	1 (1)	4 (3)	5 (2)	7 (2)
Prevention of DVT/PE in MI/2.0-3.0	3 (2)	0 (0)	3 (2)	3 (1)	6 (1)
Recurrent DVT and/or PE during warfarin therapy/3.0-4.5	4 (3)	0 (0)	2 (1)	2 (1)	6 (2)
Arterial disease including MI/3.0-4.5	0 (0)	2 (2)	2 (1)	4 (2)	4 (1)
Coronary artery bypass/2.0-3.0	0 (0)	0 (0)	2 (1)	2 (1)	2 (1)
Xenograft heart valve replacement/2.0-3.0	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)
Total	122 (100)	102 (100)	143 (100)	245 (100)	367 (100)

*Because of the rounding, percentages may not all total 100. DVT indicates deep venous thrombosis; PE, pulmonary embolism; TIA, transient ischemic attack; CVA, cerebrovascular accident; and MI, myocardial infarction.

†Therapeutic range of international normalized ratio.

mographics, illnesses requiring warfarin therapy, and general health. The most common indication for warfarin therapy in both groups was atrial fibrillation, reflecting recent recommendations for thromboprophylaxis in atrial fibrillation.² Variation in practice size, status, and location enabled a legitimate analysis for this model of primary care management, with results being generalizable to other primary care settings.

The primary outcome measure reported is the degree of INR control, based on point prevalence, an established method of comparing therapeutic control between different oral anticoagulation clinics.¹⁹ Study data showed no difference in therapeutic control between the intervention and control populations.

Analysis of INR by percentage of time spent within the therapeutic range showed significant improvement for the intervention, but the magnitude of this improvement was not significantly different from that seen in the 2 control populations. As this method of analysis takes into account all patients recruited and reflects patient, time, and therapeutic control factors, it represents a more

robust method of comparing the performance of clinics than the traditional point prevalence method.²¹

Although the study CDSS was designed for large hospital clinics, feedback showed that practice staff valued the confidence the program gave. This clinical benefit overcame the practical deficiencies in the software, which included the inability to import and export patient data from existing clinical systems. Such problems have resulted in limited use of CDSS in other clinical settings because of staff frustration.²² The fact that the staff valued the CDSS despite the extra time and duplication of data recording involved demonstrates that expert systems do have important primary care applications in discrete clinical situations.¹²

The study NPT (Thrombotrak) was found not to be ideal for general practice, principally because of the need for pipetting skills to reconstitute reagents. It was not easily portable, precluding its use for home visits. The Thrombotrak can perform INR estimation on capillary or thumb-prick samples, which would reduce the operator-dependent variables inherent in pipetting blood

Table 3. Proportion of Tests in Range*

Patient Group	Tests in Range			
	Study Entry Data		Study Data	
	No. (%)	95% CI	No. (%)	95% CI
Intervention (n = 122)	366 (61)	55-67	1181 (62)	58-66
Intrapractice control (n = 102)	271 (51)	43-58	660 (53)	48-59
Interpractice control (n = 143)	209 (61)	53-68	1040 (62)	58-66
Total control (n = 245)	480 (55)	44-66	1700 (58)	51-65

*CI indicates confidence interval.

Table 4. INR Results Within Range Point Prevalence*

Patient Group	Results in Range			
	Study Entry Data		Study Data	
	No. (%)	95% CI	No. (%)	95% CI
Intervention	118 (63)	54-71	121† (71)	63-79
Intrapractice control	102 (50)	40-60	102 (62)	52-71
Interpractice control	142 (54)	46-62	143 (66)	58-73
Total control	244 (53)	46-59	245 (64)	51-65

*INR indicates international normalized ratio; CI, confidence interval.
†One value missing.

Table 5. Percentage of Time Spent Within INR Target Range*

Patient Group	Patients in Range			
	Study Entry Data		Study Data	
	No. (%)	95% CI	No. (%)	95% CI
Intervention	113 (57)	50-63	110 (69)	66-73
Intrapractice control	83 (52)	44-60	92 (57)	50-63
Interpractice control	91 (62)	53-70	138 (65)	61-70
Total control	174 (57)	46-69	230 (62)	54-70

*INR indicates international normalized ratio; CI, confidence interval.

samples. Having stated these reservations, the practice staff using the NPT overcame these difficulties and performed well within the external quality assurance scheme. Furthermore, reliable and portable machines are now available, with few operator-dependent variables, albeit at higher reagent costs.¹⁵⁻¹⁷

The principal outcome measures for any oral anticoagulation clinics are prevention of thrombotic events and avoidance of hemorrhagic events. There are limited data regarding absolute and relative risks of oral anticoagulation, and comparison between studies is problematic because of the differing definitions used for major and minor adverse events. For this study, we based our definitions on 3 previous studies.²³⁻²⁵ These data compare favorably with earlier studies that produced figures of 0.25 to 0.64 fatal and 1.1 to 2.7 major bleeding events

Table 6. Causes of Death

Cause of Death	Intervention, No.	Control, No.			Total, No.
		Intrapractice	Interpractice	Total	
Stroke	1	0	1	1	2
Congestive cardiac failure	1	0	1	1	2
Ischemic heart disease	0	0	1	1	1
Left ventricular failure	0	1	0	1	1
Renal failure	0	1	0	1	1
Carcinoma	1	1	0	1	2
Total	3	3	3	6	9

Table 7. Serious Adverse Effects*

Description	Intervention, No.	Control, No.			Total, No. (%)
		Intrapractice	Interpractice	Total	
DVT	1	0	0	0	1 (8)
TIA	0	1	3	4	4 (31)
Fatal CVA	1	0	1	1	2 (15)
Nonfatal CVA	0	1†	3‡	4	4 (31)
Saddle embolus	0	1	0	1	1 (8)
Epistaxis	1	0	0	0	1 (8)
Total	3	3	7	10	13 (100)
Patient-years	87.3	68.4	97.3	165.7	253.0

*DVT indicates deep venous thrombosis; TIA, transient ischemic attack; and CVA, cerebrovascular accident.
†Classified as cerebral infarct.
‡One unclassified, 1 cerebellar stroke, and 1 occipital lobe stroke.

per 100 patient-years.^{23,25} Intervention patients tended toward fewer serious adverse events, with 1.14 serious bleeding incidents and 2.28 serious thrombotic events per 100 patient-years.

Given the difficulties in extracting clinical data, particularly from hospital case records, the incidence of adverse events may be greater in the control group than was recorded in the study. These data, however, suggest that the annual risk of stroke or transient ischemic attack in a homogeneous population taking warfarin is 8%.

In conclusion, this study has demonstrated that a primary care model of nurse-led anticoagulation clinics can be developed with the use of CDSS and NPT. These data only support the effectiveness of the complete package of care, and it is not possible to determine whether individual elements (nurse-led, CDSS, or NPT) contributed most to the positive results. Using this model of care would be feasible in most primary health care settings in many countries, with the potential for improved clinical outcomes in terms of therapeutic INR control.

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Reprints: David A. Fitzmaurice, MD, Department of General Practice, Medical School, The University of Birmingham, Birmingham B15 2TT, England (e-mail: D.A.Fitzmaurice@bham.ac.uk).

REFERENCES

1. Lowe GDO. Anti-thrombotic treatment and atrial fibrillation. *BMJ*. 1992;305:1445-1446.
2. Sweeney KG, Pereira-Gray D, Steele R, Evans P. Use of warfarin in non-rheumatic atrial fibrillation: a commentary from general practice. *Br J Gen Pract*. 1995;45:153-158.
3. Gustafsson C, Asplund K, Britton M, Norrving B, Olsson B, Marke LA. Cost effectiveness of primary prevention in atrial fibrillation: Swedish national perspective. *BMJ*. 1992;305:1457-1460.
4. Sandercock P, Bamford J, Dennis M, et al. Atrial fibrillation and stroke: prevalence in different types of stroke and influence on early and long term prognosis (Oxfordshire Community Stroke Project). *BMJ*. 1992;305:1460-1465.
5. British Society for Haematology, British Committee for Standards in Haematology Haemostasis and Thrombosis Task Force. Audit of oral anticoagulant treatment. *J Clin Pathol*. 1993;46:1069-1070.
6. Taylor F, Ramsey M, Voke J, Cohen H. GPs not prepared for monitoring anticoagulation [letter]. *BMJ*. 1993;307:1493.
7. Sudlow CM, Rodgers H, Kenny RA, Thomson RG. Service provision and use of anticoagulants in atrial fibrillation. *BMJ*. 1995;311:558-561.
8. Sudlow M, Rodgers H, Kenny RA, Thomson R. Population based study of use of anticoagulants among patients with atrial fibrillation in the community. *BMJ*. 1997;314:1529-1530.
9. Shakespeare J. Anticoagulation in patients with atrial fibrillation: GPs struggle to meet demand [letter]. *BMJ*. 1994;308:415.
10. Fitzmaurice DA, Hobbs FDR, Murray ET, Bradley CP, Holder R. Evaluation of computerised decision support for oral anticoagulation management in primary care. *Br J Gen Pract*. 1996;46:533-535.
11. Ryan P, Gilbert M, Rose PE. Computer control of anti-coagulant dose for therapeutic management. *BMJ*. 1989;299:1207-1209.
12. Hobbs FDR, Delaney BC, Fitzmaurice DA, et al. A review of near patient testing in primary care. *Health Technol Assess*. 1997;1(5):i-iv, 1-229.
13. Rink E, Hilton S, Szczepura A, et al. Impact of introducing near patient testing for standard investigations in general practice. *BMJ*. 1993;307:775-778.
14. Hobbs FDR. Near patient testing in primary care. *BMJ*. 1996;312:263-264.
15. Kapiotis S, Quehenberger P, Speiser W. Evaluation of the new method Coaguchek for the determination of the prothrombin time from capillary blood: comparison with thrombotest on KC-1. *Thromb Res*. 1995;77:563-567.
16. Sanders KJ, Lewis SM, Cooper S, England JM. *An Evaluation of the Nycomed Thrombotrak Coagulation System*. London, England: NHS Procurement Directorate; 1989.
17. Oberhardt BJ, Dermott SC, Taylor M, Alkadi ZY, Abruzzini AF, Gresalfi NJ. Dry reagent technology for rapid, convenient measurements of blood coagulation and fibrinolysis. *Clin Chem*. 1991;37:520-526.
18. Poller L, Wright D, Rowlands M. Prospective comparative study of computer programs used for management of warfarin. *J Clin Pathol*. 1993;46:299-303.
19. van den Besselaar AMPH. Recommended method for reporting therapeutic control of oral anticoagulant therapy. *Thromb Haemost*. 1990;63:316-317.
20. Rosendaal FR, Cannegieter SC, van der Meer FJM, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost*. 1993;69:236-239.
21. Azar AJ, Deckers JW, Rosendaal FR, et al. Assessment of therapeutic quality control in a long-term anticoagulant trial in post-myocardial infarction patients. *Thromb Haemost*. 1994;72:347-351.
22. Hobbs FDR, Delaney BC, Carson A, Kenkre JE. A prospective controlled trial of computerized decision support for lipid management in primary care. *Fam Pract*. 1996;13:133-137.
23. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). *Lancet*. 1996;348:423-428.
24. Fihn SD, McDonell M, Martin D, et al. Risk factors for complications of chronic anticoagulation. *Ann Intern Med*. 1993;118:511-520.
25. van der Meer FJM, Rosendaal FR, Vandenbroucke JP, Briet E. Bleeding complications in oral anticoagulant therapy. *Arch Intern Med*. 1993;153:1557-1562.