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Optimal Intensity of Oral Anticoagulant Therapy After Myocardial Infarction

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Objectives. **This study attempted to determine the optimal intensity of anticoagulant therapy in patients after myocardial infarction.**

Background. **Treatment with oral anticoagulant therapy entails a delicate balance between over- (risk of bleeding) and under-anticoagulation (risk of thromboemboli). The optimal intensity required to prevent the occurrence of either event (bleeding or thromboembolic) is not known.**

Methods. **A method was used to determine the optimal intensity of anticoagulant therapy by calculating incidence rates for either event associated with a specific international normalized ratio. The numerator included events occurring at given international normalized ratios, and the denominator comprised the total observation time.**

Results. **The study population included 3,404 myocardial infarction patients enrolled in the ASPECT (Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis) trial. Total treatment was 6,918 patient-years. Major bleeding occurred in 57 patients (0.8/100 patient-years), and thromboembolic complications in 397 (5.7/100 patient-years). The incidence of the combined outcome (bleeding or thromboembolic complications) with international normalized ratio <2 was 8.0/100 patient-years (283 events in 3,579 patient-years), with international normalized ratios between 2 and 3, 3.9/100 patient-years (33 events in 838 patient-years); 3.2/100 patient-years (57 events in 1,775 patient-years) for international normalized ratios between 3 and 4; 6.6/100 patient-years (37 events in 564 patient-years) for international normalized ratios between 4 and 5; and 7.7/100 patient-years (14 events in 182 patient-years) for international normalized ratios >5. After adjustment for achieved international normalized ratio levels, significant predictors were higher levels of systolic blood pressure and age.**

Conclusions. **If equal weight is given to hemorrhagic and thromboembolic complications, these results suggest that the optimal intensity of long-term anticoagulant therapy for myocardial infarction patients lies between 2.0 and 4.0 international normalized ratio, with a trend to suggest an optimal intensity of 3.0 to 4.0.**

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Findings of the three most recently performed trials following myocardial infarction demonstrated that intensive anticoagulant therapy reduced the rate of reinfarction by 34% to 55%, stroke by 40% to 55% and total mortality by 10% to 26% (1–3). In these investigations, a high quality of anticoagulation was achieved, because 63% to 74% of the prothrombin time measurements were within the therapeutic international normalized ratio range between 2.5 and 5.0.

Although the investigations demonstrated beneficial effects of anticoagulant treatment in myocardial infarction survivors, these trials have not established the optimal intensity of anticoagulant therapy for two major reasons. First, the intensity of anticoagulant therapy actually achieved was not taken into account, and, second, the target level of anticoagulation was chosen arbitrarily. For the same reasons, randomized trials conducted to compare two intensities of oral anticoagulant therapy offered little information on the optimal intensity of anticoagulant therapy (4). Therefore, it is not known what intensity of anticoagulant therapy offers the optimal benefit-risk ratio, that is, the optimal balance between prevention of thromboembolic events and bleeding complications.

To determine this optimal intensity of anticoagulant therapy, we quantitatively evaluated the occurrence of hemorrhagic as well as arterial thromboembolic complications with respect to the international normalized ratio level preceding the event, thereby enabling the calculation of international normalized ratio-specific incidence event rates. The study population comprised 3,404 myocardial infarction patients randomized to anticoagulant therapy or placebo.

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Methods

Patients. The ASPECT (Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis) subjects comprised the study group. This trial has been described in detail elsewhere (3,5). In short, ASPECT was a randomized, double-blind, placebo-controlled, multicenter, clinical trial that compared anticoagulant therapy with placebo on mortality and cardiovascular events in myocardial infarction patients. This trial demonstrated that anticoagulant therapy targeted at international normalized ratio 2.8 to 4.8 reduced the rates of recurrent myocardial infarction by 53% and intracranial events by 40%. The present analysis was planned as an ancillary one before study termination.

Hospital survivors of acute myocardial infarction were screened for eligibility just before hospital discharge. After giving informed consent, patients were randomly assigned to treatment with oral anticoagulant therapy or matching placebo. From September 1, 1986 until December 31, 1991, 3,404 patients entered the trial. Their mean age was 61 years, 20% were women (mean age 65 years), fewer than 8% had diabetes, 25% had been treated with thrombolytics, and 95% of the patients were in Killip class I or II during hospitalization. Fewer than 2% of the patients had undergone a revascularization before study entry, and 9% had suffered a previous myocardial infarction. Medication at hospital discharge included beta-adrenergic blocking drugs in 50% and angiotensin-converting enzyme inhibitors in 9%. Because the present analysis considered only the period under trial medication, the mean follow-up per patient was 2.1 years.

Oral anticoagulation and dose adjustment. The target anticoagulant range was 2.8 to 4.8 international normalized ratio (6–9). Individual dose adjustments were guided by the prothrombin time measurements obtained at regular intervals at 1 of the 19 participating anticoagulant clinics. Anticoagulant treatment consisted of phenprocoumon, acenocoumarol or matching placebo tablets. Double-blinding was maintained at the anticoagulant clinics by use of a computerized dosage algorithm that automatically converted prothrombin times to sham values within therapeutic range in placebo-treated patients.

At each follow-up visit to the anticoagulant clinic, a short history was taken, and a blood sample was drawn for determination of the Thrombotest, a modified prothrombin time test (10). Patients were seen at the initial (randomization) visit and on a weekly basis thereafter until the prothrombin time measurements were within the specified target range. The interval between visits was subsequently prolonged up to a maximum period of 9 weeks. Patients requiring frequent dosage adjustments were seen more regularly. At the end of trial in June 1992, trial medication was discontinued in all patients.

Definition of clinical events. The following clinical events were considered: major bleeding or thromboembolic complications. Bleeding was considered major if it 1) led to death, 2) was clinically suspected or proven intracranial (cerebrovascular event leading to death within 24 h was considered to be caused by intracranial bleeding unless the findings on computed axial tomography scanning indicated otherwise; in all other instances, the diagnosis of an intracranial hemorrhage had to be confirmed by findings on CAT scan (11), or 3) led to hospital admission for treatment of bleeding (hospital admission for diagnostic purposes only was not considered a criterion for major bleeding).

Thromboembolic complications included 1) instantaneous or sudden death occurring within 1 h after onset of symptoms; (2) recurrent myocardial infarction documented by at least two of the following (12,13): a) history of chest discomfort of at least 30 min duration; b) serial enzyme pattern typical for myocardial infarction with at least one cardiac enzyme exceeding twice the upper limit of normal; or c) the development of new Q-waves (lasting >0.03 s or of Q-wave equivalent [R >0.03 s in V_1 and R/S >1 in V_2]) on the standard 12-lead electrocardiogram (ECG); myocardial infarction was also diagnosed when death occurred within 28 days after hospitalization for recurrent myocardial infarction; 3) cerebral infarction, classified according to internationally accepted criteria and diagnosed on the basis of the CAT-scan findings (11); and 4) other arterial thromboembolic complications.

Information on clinical events was obtained directly from the patients when they visited the anticoagulant clinic or from their general practitioners. In case of hospitalization, additional information was retrieved from the hospital records. The diagnosis and classification of clinical events were established by the Mortality and Morbidity Classification Committee of the ASPECT trial, who independently reviewed the clinical course of each case on the basis of a review of a standardized patient report before study termination. The committee members were unaware of treatment assignment and were not informed of actual prothrombin time measurements.

Assessment of optimal intensity. Incidence rates were calculated for different achieved intensities of anticoagulant therapy (4). Intervals of 1.0 international normalized ratio were used. As the lowest reference interval, we used international normalized ratio <2, which includes the patient-time of all patients on placebo and actual measurements of international normalized ratio <2 in patients receiving anticoagulant drugs (5%). This reference category represents absence of treatment. Only those international normalized ratio measurements that were obtained during the trial medication period were considered. The optimal intensity of anticoagulant therapy will lie at the level at which the incidence of bleeding or thromboemboli is lowest, that is, where the incidence of complications, whatever their type, is lowest. This approach has been explained in detail previously (4).

Numerator data: events. The numerator of the international normalized ratio-specific incidence rate was composed of events (bleeding or thromboembolism) occurring at a given international normalized ratio intensity. If the international normalized ratio measurement for the date of event was not available, the last international normalized ratio measurement obtained within a maximum period of 28 days before the event

Table 1. Selected Demographic, Baseline and Randomization Characteristics

	Anticoagulant	Placebo	Total
No. of patients (%)	1,700 (100)	1,704 (100)	3,404 (100)
Mean age, years (SD)	61 (11)	61 (11)	61 (11)
Gender (%)			
Male	1,370 (81)	1,350 (79)	2,270 (80)
Female	330 (19)	354 (21)	684 (20)
Trial medication (%)			
Phenprocoumon	930 (55)	935 (55)	1,865 (55)
Acenocoumarol	770 (45)	769 (45)	1,539 (45)
Mean SBP, mm Hg (SD)	119 (16)	119 (16)	119 (16)

SBP = systolic blood pressure at hospital discharge.

Table 2. Incidence of Major Bleeding During Follow-Up

	Anticoagulant (n = 1,700)	Placebo (n = 1,704)	Total
Number of patient-years	3,430	3,488	6,918
Intracranial bleeding	14	1	15
Fatal	7	0	7
Nonfatal	7	1	8
Extracranial bleeding	37	5	42
Fatal	2	0	2
Nonfatal	35	5	40
Total major bleeding*	51 (1.5/100 py)	6 (0.2/100 py)	57 (0.8/100 py)

*Intracranial or extracranial bleeding, whichever occurred first. py = patient-years.

was taken from the hospital records. International normalized ratio measurements were considered missing in all other instances. Patients who were treated with placebo were included in the analysis because their achieved international normalized ratio intensity corresponding to "lack" of anticoagulation is of course known and corresponds to an international normalized ratio of 1 at the time of an event as well as at all other times. In a subsequent, stricter analysis, we only included events for which an international normalized ratio measurement obtained no more than 3 days before the event was available, whereas all others were considered missing (except for the placebo patients).

Patients were censored when an event was reached after cessation of trial medication or at the end of follow-up, on June 30, 1992, whichever occurred first. In case patients experienced more than one event, only the first was considered. Four patients with major bleeding from an invasive interventional procedure during hospitalization were not included in the analysis.

Denominator data: international normalized ratio-time. The denominator of the international normalized ratio-specific incidence rate comprised the sum of patient-days within specific international normalized ratio intervals (4). In order to calculate the time each patient was within an international normalized ratio-specific range, we assumed a linear interpolation between adjacent international normalized ratio measurements (5). In addition, in case the interval between two consecutive international normalized ratio measurements exceeded 56 days, this time period was not included in the present analysis, because a linear change over this long period of time becomes unrealistic. Patients who used placebo were considered to have international normalized ratio measurements below 2 during the total period of follow-up.

Poisson regression analysis. The relative risk of bleeding or thromboembolic events associated with international normalized ratio-specific intervals after adjustment for age, sex, type of coumarin congener and blood pressure was calculated with Poisson regression analysis (14). The Poisson was used to model incidence rates for grouped data. Age and systolic blood pressure, measured during hospitalization for the index myocardial infarction, were categorized on the basis of the median value (below or above 60 years of age and 120 mm Hg, respectively). The incidence rate ratios obtained from the model may be viewed as relative risks, that is, the risk for an event relative to the reference risk factor category controlling for the other risk factors. The 95% confidence intervals were obtained from the Poisson distribution.

Results

A total of 1,700 patients were randomized to anticoagulant therapy (with 3,430 patient-years of follow-up), and 1,704 to placebo (with 3,488 patient-years of follow-up); 55% of the patients received phenprocoumon, and 45% acenocoumarol (Table 1).

The incidence of major bleeding is shown in Table 2. Fifty-seven cases of major bleeding (0.8/100 patient-years) occurred, 51 in the anticoagulant (1.5/100 patient-years) and 6 in the placebo group (0.2/100 patient-years). This results in a relative risk for major bleeding of 8.6 with a 95% confidence interval of 3.7 to 20.1. Fatal bleeding (nine patients) was observed only in the anticoagulated group (0.3/100 patient-years). The most frequent sites of major extracranial bleeding were the gastrointestinal tract (26 with anticoagulation and 2 with placebo) and muscular hematoma in 10 of the anticoagulated group.

The incidence of thromboembolic events is presented in Table 3. A total of 397 thromboembolic complications (5.7/100 patient-years) occurred, of which 118 were fatal. One hundred twenty-seven thromboembolic events (3.7/100 patient-years) were observed in the anticoagulation group, and 270 with placebo (7.7/100 patient-years), resulting in a relative risk for major thromboembolic complications of 0.48 with a 95% confidence interval of 0.39 to 0.59. The major thromboembolic events included sudden death (69 patients), recurrent myocardial infarction (293 patients) and cerebral infarction (34 patients).

International normalized ratio measurements obtained at hospital admission or within 3 days before the occurrence of major bleeding were available in 42 cases (6 of 6 placebo and 36 of 51 anticoagulation patients) and in 55 patients (6 of 6

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Table 3. Incidence of Thromboembolic Events During Follow-Up

	Anticoagulant (n = 1,700)	Placebo (n = 1,704)	Total
Number of patient-years	3,430	3,488	6,918
Sudden death	35	34	69
Recurrent MI	86	207	293
Fatal	16	31	47
Nonfatal	70	176	246
Cerebral infarction	6	28	34
Fatal	0	2	2
Nonfatal	6	26	32
Other arterial thromboemboli	1	4	5
Total major thromboemboli*	127 (3.7/100py)	270 (7.7/100py)	397 (5.7/100py)

*Sudden death, recurrent myocardial infarction (MI), cerebral infarction, other arterial thromboemboli, whichever event occurred first. py = patient-years.

placebo and 49 of 51 anticoagulation patients) within a time frame of 28 days. International normalized ratio measurements within 3 days from thromboembolic complication were obtained in 294 patients (270 of 270 placebo and 24 of 127 anticoagulation patients) and within 28 days in 375 patients (270 of 270 placebo and 105 of 127 anticoagulation patients). The total number of patient-years within international normalized ratio-specific intervals for the combined event (bleeding or thromboemboli) were 3,559 patient-years (international normalized ratio <2), 838 patient-years (international normalized ratio 2 to 3), 1,775 patient-years (international normalized ratio 3 to 4), 564 patient-years (international normalized ratio 4 to 5) and 182 patient-years (international normalized ratio >5) for international normalized ratio measurements obtained within 3 or 28 days from the event.

International normalized ratio-specific incidence rates based on measurements obtained within 28 days of major bleeding and thromboembolic complication are presented in Figure 1 and in Table 4. The international normalized ratio-specific incidence rate of bleeding was lowest, 0.2 per 100 patient-years (8 events in 3,603 patient-years), at anticoagulant intensities less than 2 international normalized ratio and was highest, 7.9 per 100 patient-years (12 events in 151 patient-years), at anticoagulant intensities exceeding the value of 5. On the other hand, the incidence of thromboembolic complications was highest, 8.0 per 100 patient-years (282 events in 3,509 patient-years), for anticoagulant intensities less than 2 international normalized ratio and was lowest, 1.6/100 patient-years (2 events in 126 patient-years) for international normalized ratio intensities exceeding the value of 5.

Figure 1. International normalized ratio (Inr)-specific incidence rates for bleeding and thromboembolic complications. py = patient-years.

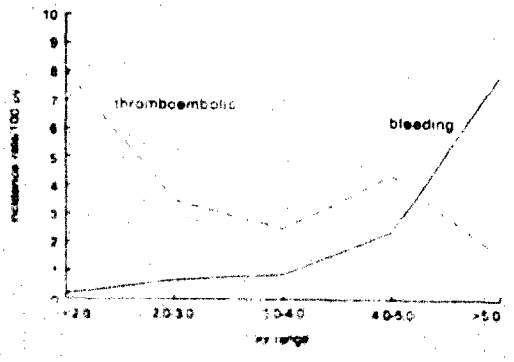

Table 4. Incidence of Events Within the Specific International Normalized Ratio Intervals

INR	Events	Patient-Years	Incidence Rate
	Hemorrhagic		
<2	8	3,603	0.2/100py
2–3	5	757	0.7/100py
3–4	16	1,811	0.9/100py
4–5	14	576	2.4/100py
>5	12	151	7.9/100py
	Thromboembolic		
<2	282	3,509	8.0/100py
2–3	27	771	3.5/100py
3–4	41	1,654	2.5/100py
4–5	23	528	4.4/100py
>5	2	126	1.6/100py
	Hemorrhagic or Thromboembolic		
<2	283	3,559	8.0/100py
2–3	32	838	3.8/100py
3–4	57	1,775	3.2/100py
4–5	37	564	6.6/100py
>5	14	182	7.7/100py

INR = international normalized ratio; py = patient-years.

The optimal anticoagulant intensity. The incidence of the combined outcome (bleeding or thromboembolic complications) occurred in 423 cases (6.1/100 patient-years). The incidence was lowest, 3.2/100 patient-years (57 events in 1,775 patient-years), at international normalized ratio values between 3 and 4. International normalized ratio-specific incidence rates with corresponding 95% confidence intervals, based on international normalized ratio measurements obtained within 28 days from event, are presented in Figure 2, for the combined events of bleeding as well as thromboemboli. The incidence of complications was highest at international normalized ratio values below 2 and above 5. The intensity at which the international normalized ratio-specific incidence rates of the curve is lowest is the optimal intensity: between 3 and 4 international normalized ratio. Similar results were obtained when the analysis was repeated for international normalized ratio measurements obtained within 3 days from the event.

Poisson regression analysis was performed to determine the independent risk of event (bleeding or thromboembolic) asso-

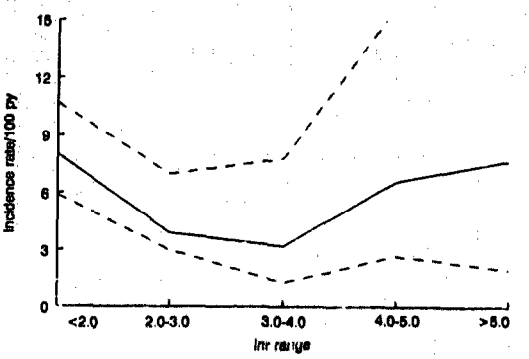

Figure 2. International normalized ratio (Inr)-specific incidence rates for the combined event (bleeding or thromboembolic complications). **Dashed lines** indicate 95% confidence interval.

ciated with age, sex, systolic blood pressure at discharge and type of coumarin congener; results, after controlling for achieved international normalized ratio intensities, are presented in Table 5. Significant predictors for major bleeding or thromboemboli included higher systolic blood pressure and more advanced age. The risk of bleeding was higher in women.

Discussion

The optimal intensity, the intensity of anticoagulation at which the incidence of hemorrhages as well as thromboembolism was lowest, appeared to be located between international normalized ratio 2.0 and 4.0, with a trend to suggest an optimal intensity between 3.0 and 4.0 international normalized ratios. In this range, the risk of bleeding was relatively low, amounting to 5 major bleeding complications per 1,000 treatment-years.

Table 5. Multivariate Analysis of Other Risk Factors for Hemorrhagic and Thromboembolic Complications*

	Hemorrhagic Events RR (95% CI)	Thromboembolic Events RR (95% CI)
Age (years)		
<60†	1.0	1.0
≥60	1.5 (0.8–2.8)	1.6 (1.2–2.1)
Gender		
Male†	1.0	1.0
Female	1.7 (0.9–3.2)	1.1 (0.8–1.5)
Anticoagulant congener		
Phenprocoumon†	1.0	1.0
Acenocoumarol	0.9 (0.5–1.6)	1.0 (0.7–1.5)
SBP (mm Hg)		
≤120†	1.0	1.0
>120	2.0 (1.1–3.6)	3.3 (2.2–4.9)

*Adjusted for achieved international normalized ratio intensities. †Reference group risk set at 1.0. CI = confidence interval; RR = rate ratio; SBP = systolic blood pressure at hospital discharge.

while the reduction in thromboembolic complications, relative to international normalized ratio intensities below 2, was 70%. Such a narrow range for optimal anticoagulation could be achieved in only approximately 20% of patient-years in this study, although the quality of long-term anticoagulant therapy achievable in the Netherlands on a population basis is probably unique. The broader range (international normalized ratio 2.0 to 4.0) could be attained in 75% of patient-years and was almost as effective. Such levels may be more readily achievable in general.

Intensity of anticoagulation and risk of bleeding. The risk of bleeding associated with anticoagulant therapy in patients with as well as without coronary heart disease is well recognized and has led to the conduct of several trials that compared the efficacy of different intensities of oral anticoagulant therapy (15–17). So far, however, these trials have been unable to provide the "true" optimal anticoagulant intensity. The main reason, of course, is that achieved anticoagulant intensity is not constant and will invariably fluctuate around the prespecified target level hinging on particular characteristics of the patient under treatment as well as on extraneous features related to the administration and monitoring of the therapy.

Given the acknowledged relation between incidence of bleeding complications and high anticoagulant intensities (15–22), it is surprising that few attempts have been made to quantify this association. In one recent population study (23) in which the achieved intensity of anticoagulant therapy was analyzed in 6,814 patients, a 42% increase in the risk of major bleeding was reported for every rise of 1.0 in the international normalized ratio. In another recent analysis, a nested case-control study of 565 patients starting outpatient therapy with warfarin by Landefeld et al. (20), the odds ratio for major bleeding increased with increasing prothrombin time to control ratios. In the present analysis, the risk of major bleeding increased gradually with elevation in the intensity of anticoagulation achieved. The risk was increased 80% when international normalized ratio intensities were between 4 and 5 as compared to intensities below 2 international normalized ratio, while the risk was increased almost fivefold when international normalized ratio intensity exceeded 5.

Intensity of anticoagulation and risk of thromboembolic complications. Although it seems reasonable to assume an increased risk of thromboembolic events with less intense anticoagulation, this conclusion cannot easily be extracted from the literature. In addition to the previously mentioned methodological issues, the relatively small size of some studies is another limiting factor. Evidence for strong effects of anticoagulant therapy on thromboembolic complications were obtained in the three most recently conducted placebo-controlled trials: the Sixty-Plus (1), WARIS (2) and ASPECT (3). The intensity of treatment in these was characterized by a prothrombin time prolongation of 2.5 to 5.0 international normalized ratio. These trials convincingly demonstrated that a substantial reduction in myocardial infarctions and cerebrovascular events can be achieved with this type of therapy.

Limitations of our study. A drawback of our analysis is that we were unable to obtain international normalized ratio measurements at the time of the event in every instance, in particular for the thromboembolic events. Prothrombin time measurement at the moment of the event was not specifically required by the study protocol and, therefore, was not always reported by the investigator. In bleeding patients on oral anticoagulant therapy, an international normalized ratio measurement will be performed far more often than in a patient with a myocardial infarction. This is unfortunate but affects only the power of the study, not the validity, because it is not conceivable that the decision to perform or not perform an international normalized ratio in a patient with myocardial infarction is dependent on his or her (known) international normalized ratio. It should be noted that double-blinding was still maintained at the time of hospital admission. When we restricted the analysis to events with an international normalized ratio at or shortly before (<3 days) the event, international normalized ratio data were available in only about 34% of the patients taking anticoagulants (and all placebo patients). When a less stringent criterion was used, and international normalized ratio measurements up to 28 days before the event were accepted as representing the international normalized ratio at the event, we had information on 87% of the anticoagulation patients (and again in all placebo patients). Although both analyses are obviously suboptimal, they lead to the same result of a nadir of events at international normalized ratio values between 2 and 4. Although these findings will need to be confirmed in larger series, these first analyses of the achieved intensity of anticoagulant therapy in myocardial infarction patients point to an optimal intensity of 2 to 4 international normalized ratio, with a trend to suggest that the optimum intensity lies between 3 and 4 international normalized ratio.

In this analysis, the optimal intensity of anticoagulant therapy was defined as the level at which the incidence of the sum of bleeding or embolic complications was lowest, and they were equally considered. We realize that this is not always realistic, and it is dependent on the severity of the actual complication, cardiac or neurologic. The actual rate of embolic as well as hemorrhagic complications is therefore given here.

Prediction of events. In line with findings reported by others, the current analysis confirmed the independent contribution of higher systolic blood pressure to increased bleeding tendency during anticoagulation therapy (24). High blood pressure was also associated with increased thromboembolic complications. Our results confirm a recent observation of a higher bleeding incidence in elderly and female patients (23–25). In contrast to findings of another analysis that employed the same quantitative approach as currently described (23), we were unable to confirm the association of the use of acenocoumarol with increased bleeding tendency.

Conclusions. In conclusion, the optimal therapeutic range for long-term oral anticoagulant therapy in myocardial infarction patients has been a matter of intense debate for more than 30 years (26). Findings in this large cohort provide a quantitative basis to locate the optimal therapeutic anticoagulant intensity within the international normalized ratio range of 2.0 and 4.0, assuming that equal weights are given to hemorrhagic and thromboembolic complications, with a trend to suggest an optimal intensity of 3.0 to 4.0. In this range, somewhat lower than the targeted anticoagulant intensity in the most recent secondary prevention trials (27), the incidence of major bleeding during long-term anticoagulant therapy is relatively small, and a substantial reduction in the rate of thromboembolic events is achieved.

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