Optimal Level of Oral Anticoagulant Therapy for the Prevention of Arterial Thrombosis in Patients With Mechanical Heart Valve Prostheses, Atrial Fibrillation, or Myocardial Infarction

A Prospective Study of 4202 Patients

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Background: Oral anticoagulant therapy is effective for the prevention of arterial thromboembolism in various patient groups. The increased risk of hemorrhage remains the major drawback to this therapy and is associated with the intensity of anticoagulation. Finding the optimal intensity at which the overall incidence rate of both bleeding and thromboembolic events is minimized represents a way to improve the safety of oral anticoagulant treatment.

Methods: We evaluated all patients visiting the Leiden Anticoagulation Clinic with mechanical heart valve prostheses, atrial fibrillation, or myocardial infarction from 1994 to 1998. Untoward events were major thromboembolism and major hemorrhage. We calculated intensity-specific incidence rates of untoward events to assess the optimal intensity per indication of treatment. We enrolled 4202 patients for a total of 7788 patient-years.

Results: A total of 3226 hospital admissions were reported, 306 owing to an untoward event. Incidence rates of untoward events were around 4% per year for all indications: 4.3 (95% confidence interval [CI], 3.1-5.6) for patients with mechanical heart valve prostheses, 4.3 (95% CI, 3.7-5.1) for patients with atrial fibrillation, and 3.6 per year (95% CI, 3.0-4.4) for patients treated after a myocardial infarction. The optimal intensity of anticoagulation for patients with mechanical heart valve prostheses was an international normalized ratio (INR) of 2.5 to 2.9; for patients with atrial fibrillation, an INR of 3.0 to 3.4; and for patients after myocardial infarction, an INR of 3.5 to 3.9.

Conclusion: Our study suggests target INRs of 3.0 for patients with mechanical heart valve prostheses and atrial fibrillation and 3.5 after myocardial infarction as a starting point in future clinical trials.

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FOR OVER HALF A CENTURY, oral anticoagulant therapy with vitamin K antagonists has proven its value in the primary and secondary prevention of arterial thromboembolism. Patients with mechanical heart valve prostheses are protected from valve thrombosis and ischemic stroke,[1] whereas treatment in patients with atrial fibrillation[2] or with ischemic heart disease prevents ischemic stroke and (recurrent) myocardial infarction.[3-5] Despite the development of new anticoagulants as direct thrombin inhibitors, vitamin K antagonists remain the keystone of anticoagulant therapy in most patients.

Now that in the aging Western society a growing number of patients are treated with vitamin K antagonists, the necessity to improve the safety of this therapy gains more and more importance. The major drawback of oral anticoagulant therapy is the increased risk of hemorrhage, which is associated with the intensity of anticoagulation and patient characteristics such as age and sex. The incidence of hemorrhage increases with higher intensities of anticoagulation,[6,7] whereas the thromboembolic risk increases with lower intensities.[8,9] Hence, the intensity level that provides the lowest incidence of all combined bleeding and thromboembolic events is regarded as the optimal intensity for treatment with vitamin K antagonists. The determination and implementation of the optimal intensity represents a way to improve the safety of oral anticoagulant therapy.

We previously developed a method to determine the optimal intensity level in observational studies,[10] which was subse-

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quently applied for various indications.[11-14] Some of the studies, however, were ad hoc analyses within randomized trials and could be criticized because of the small numbers of events on which the optimal intensity was based[11,15] or the incompleteness of the data.[12]

We therefore designed a large study among patients using oral anticoagulants because they had mechanical heart valve prostheses, atrial fibrillation, or had experienced a myocardial infarction. We calculated incidences of major hemorrhage and thromboembolism and assessed the optimal intensity of treatment with vitamin K antagonists by calculating international normalized ratio (INR)-specific incidence rates.

METHODS

ORAL ANTICOAGULANT CONTROL

In the Netherlands, all outpatients who are treated with vitamin K antagonists are referred to regional anticoagulation clinics to have their treatment monitored. Patients visit the anticoagulation clinic regularly or are visited at home. During each visit, a trained nurse fills in a short medical questionnaire addressing intercurrent diseases, changes in medication, hospital admissions, future interventions, and the occurrence of bleeding and thromboembolic events. A venous blood sample is taken in which the prothrombin time is measured. Prothrombin times are expressed as an INR. Laboratory procedures and materials do not change substantially during follow-up. Specialized physicians subsequently prescribe the anticoagulant dose and determine the date of the next visit. The national target INR ranges at the start of our study were 3.6 to 4.8 (for patients with a mechanical heart valve prosthesis) and 3.0 to 4.5 (for patients who had experienced a myocardial infarction and for atrial fibrillation). In 1996, after the publication of several studies of the optimal intensity oral anticoagulation,[9,12,13] the target ranges were adjusted and set at INRs of 3.0 to 4.0 (for those who had a mechanical heart valve prosthesis or myocardial infarction) and 2.5 to 3.5 (for those with atrial fibrillation).

PATIENTS

The Leiden Anticoagulation Clinic is a regional clinic in the Netherlands, serving an area with 450 000 inhabitants. The clinic annually treats over 6000 patients. In the period of 1994 to 1998, we included all patients of the Leiden Anticoagulation Clinic who were treated with vitamin K antagonists for mechanical heart valve prostheses, atrial fibrillation, or after a myocardial infarction.

DATA COLLECTION

The Leiden Anticoagulation Clinic routinely keeps a computerized medical record for each patient, containing all medical information that is collected through interviews at regular visits and by consulting general practitioners and medical specialists. The following data were retrieved from these records: indication for anticoagulant therapy, date of birth, sex, duration of treatment, all INR measurements with the corresponding date, hospital admissions, and death. In addition, we collected all discharge letters for the reported hospital admissions. When relevant, we also gathered results of laboratory tests, radiographs, computed tomographic (CT) scans, and autopsy reports. In this way, all thromboembolic and bleeding events that required hospital admission were registered.

OUTCOME EVENTS

Major hemorrhage and major thromboembolism were considered outcome events. Definitions of these events were adopted from previous studies.[13,16] Major hemorrhage consisted of intracranial, spinal, and extracranial bleeding events. Intracranial and spinal hemorrhage was defined as neurological impairment of sudden or subacute onset, confirmed by CT scan, surgery, or autopsy. Extracranial major hemorrhage was defined as blood loss, inward or outward, leading to hospital admission for observation or treatment, or death. Bleeding events that occurred while the patient was already admitted for a different reason or admissions for diagnostic purposes only were not taken into account.

Major thromboembolism consisted of ischemic stroke, myocardial infarction, and peripheral thromboembolism. The diagnosis of ischemic stroke required an acute neurological deficit confined to the blood supply of a single brain artery and confirmed by CT scan or autopsy. Myocardial infarction was defined by 2 of the following: a history of chest discomfort, a typical rise in the level of specific cardiac enzymes above the upper limit of the reference range, or the development of new Q waves on the electrocardiogram. Peripheral thromboembolism was diagnosed as sudden peripheral ischemia, proven by duplex scanning, angiography, surgery, or autopsy.

To weigh the severity of different untoward events, we adjudicated all outcome events as serious, life threatening, or fatal. Cerebrovascular accidents (ischemic and bleeding) were considered to be life threatening when invasive procedures like surgery or angiography were needed or if they led to a modified Rankin score higher than 2 three weeks after the event occurred. The modified Rankin score measures disability after stroke on a scale of 0 to 5, at which the loss of independence in daily life begins at grade 2.[17,18] Extracranial bleeding was considered to be life threatening if surgery or angiography was required or if it led to irreversible damage such as blindness or to 2 of the following: severe blood loss, hypotension (systolic blood pressure, $<$90 mm Hg) or severe anemia (hemoglobin level, $<$6.4 g/dL; to convert to grams per liter, multiply by 10.0). Life-threatening myocardial infarctions required thrombolysis or percutaneous transluminal catheter angioplasty, leading to an increase of the creatine kinase muscle-brain (MB) fraction higher than 500 U/L or to heart failure, ventricular rhythm disturbances, or hypotension. Events were considered to be fatal when the patient died as a direct consequence of the event. All other events were considered to be serious.

An expert panel classified all events according to the definitions given herein. The panel members—a neurologist (W.L.E.M.B.), cardiologist (E.E.v.d.W.), internist, and clinical epidemiologist (F.R.R.)—were at all times blinded to the intensity of oral anticoagulation at the time of the event.

OPTIMAL INTENSITY

The optimal intensity of oral anticoagulation is defined as the INR level that provides the lowest overall incidence of untoward events. We calculated INR-specific incidence rates as the ratio of the number of events that occurred at a certain INR level and the number of patient-years that this intensity level had been reached by the total patient population. The INR-specific incidence rates were computed per INR interval of 0.5, using the method of Rosendaal et al.[10] Follow-up of the cases stopped when the event of interest occurred. The 95% confidence intervals (CIs) of the incidence rates were obtained by standard calculations, presuming a Poisson distribution of the number of events. To obtain

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the INR value most representative of the one at which the untoward events occurred, we collected the INR value from the hospital record on admission. If the INR was not measured on hospital admission or if the test result could not be retrieved, we used the last INR measurement at the anticoagulation clinic if the test had been performed within 8 days before the event. If no INR value was available, the event was disregarded for the calculation of INR-specific incidence rates.

RESULTS

PATIENT CHARACTERISTICS

We included 4202 patients who received coumarin therapy at the Leiden anticoagulation clinic for one of the study indications: 483 patients (12%) with a mechanical heart valve prosthesis (1149 patient-years), 2111 (50%) with atrial fibrillation (3476 patient-years), and 1608 (38%) who were treated because of myocardial infarction (3163 patient-years). Most patients (2820 [67%]) were already prescribed vitamin K antagonists when the study started, and 1382 patients (33%) entered the study later on when they started treatment. A total of 542 patients (13%) died during follow-up.

Table 1 presents the main patient characteristics according to the indication for anticoagulant treatment. There was a preponderance of men among patients who were treated because of a myocardial infarction (78% compared with 54% and 55% for the 2 other indications) and an older age in patients treated for atrial fibrillation (63% > 70 years compared with 41% [myocardial infarction] and 32% [mechanical heart valve prosthesis]).

HOSPITAL ADMISSIONS

In the follow-up period, 1774 patients were admitted to hospital (3226 admissions in total). Most patients were admitted for internal diseases. About one-third underwent surgery. A minority had neurologic disorders. Complete clinical information could be obtained in 3188 admissions (99%). The expert panel identified 306 outcome events that fulfilled the predefined criteria. We retrieved INRs from the day the event had occurred in 278 cases (91%). Another 10 INRs could be obtained from the medical records of the anticoagulation clinic because they had been measured within 8 days before the event. In 18 cases (6%), no INR had been measured or the test result could not be retrieved.

ANTICOAGULANT CONTROL

During the 3 years of follow-up, 122 946 INR measurements were performed at the anticoagulation clinic in the 4202 participating patients. The mean interval between 2 measurements was 3 weeks. Approximately 63% of the total follow-up time was spent within the target range, 19% below this range, and 18% above. A total of 344 person-years (4.4% of the total follow-up time) were not allocated to an INR interval because the duration between 2 measurements exceeded 8 weeks.[10]

Table 1. Patient Characteristics

Characteristic	No. (%)		
	Mechanical Heart Valve	Atrial Fibrillation	Myocardial Infarction
Patients, No.	483	2111	1608
Patient-years, No.	1149	3476	3163
Sex			
Men	268 (55)	1195 (57)	1251 (78)
Women	215 (45)	916 (43)	357 (22)
Age, y			
<60	164 (34)	268 (13)	410 (26)
60-70	165 (34)	503 (24)	532 (33)
>70	154 (32)	1340 (63)	666 (41)

MECHANICAL HEART VALVE PROSTHESES

Outcome Events

Table 2 presents an overview of the primary outcome events. In patients with a mechanical heart valve prosthesis, the incidence rate of all major outcome events combined was 4.3 (95% CI, 3.1-5.6) per 100 patient-years.

Thirty-eight patients experienced a major bleeding event (3.4 per 100 patient-years; 95% CI, 2.4-4.6) of which 4 were fatal (0.3 per 100 patient-years; 95% CI, 0.1-0.8); all 4 caused by intracranial hemorrhage. The incidence of nonfatal bleeding events was 3.1 per 100 patient-years (95% CI, 2.1-4.2).

Nine patients experienced a thromboembolic event (0.8 per 100 patient-years; 95% CI, 0.4-1.4), of which 2 myocardial infarctions were fatal (0.2 per 100 patient-years; 95% CI, 0.0-0.5). The incidence of nonfatal thromboembolic events was 0.6 per 100 patient-years (95% CI, 0.2-1.2).

Nine of the 34 nonfatal hemorrhages were life threatening (2 intracranial, 7 extracranial), as were 4 of the 7 nonfatal thromboembolic events (2 ischemic strokes, 2 myocardial infarctions). Therefore, the combined incidence of fatal and life-threatening events was 1.1 per 100 patient-years (95% CI, 0.6-1.9) for hemorrhage and 0.5 per 100 patient-years (95% CI, 0.2-1.0) for thromboembolism.

Optimal Intensity

The **Figure** shows the INR-specific incidence rates of all combined untoward events and their 95% CI per INR level. The lowest incidence was found at an INR of 2.5 to 2.9: 2.0 per 100 patient-years (95% CI, 0.2-5.7). At higher INRs (≤4.5), incidence rates increased only slightly to a maximum of 2.6 events per 100 patient-years for an INR of 4.0 to 4.5. In contrast, incidence rates rose rapidly from 6.7 per 100 patient-years (95% CI, 0.6-19.4) for an INR of 2.0 to 2.4, up to 51.8 per 100 patient-years for an INR of 1.0 to 1.4, and from 4.7 per 100 patient-years (95% CI, 1.4-9.8) for an INR of 4.5 to 4.9, up to 55.3 per 100 patient-years (95% CI, 28.0-91.9) for an INR greater than 5.5.

In addition, we calculated INR-specific incidence rates exclusively for the most severe untoward events (life threatening or fatal). As shown in **Table 3**, the anticoagulant intensity that provided the lowest incidence rate of untoward events remained the same.

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Table 2. Primary Outcome Events

Event	Mechanical Heart Valve		Atrial Fibrillation		Myocardial Infarction	
	Events, No.	Incidence,[a] 1149 Patient-Years (95% CI)	Events, No.	Incidence,[a] 3476 Patient-Years (95% CI)	Events, No.	Incidence,[a] 3163 Patient-Years (95% CI)
All events	47	4.3 (3.1-5.6)	146	4.3 (37-5.1)	113	3.6 (3.0-4.4)
Hemorrhage						
Fatal						
Intracranial	4	0.3	11	0.3	4	0.1
Extracranial	0		3	0.1	1	0.0
Nonfatal						
Intracranial	4	0.3	10	0.3	6	0.2
Extracranial[b]	30	2.7	73	2.1	42	1.3
Total	**38**	3.4 (2.4-4.6)	**97**	2.9 (2.3-3.5)	**53**	1.7 (1.3-2.2)
Thromboembolism						
Fatal						
Cerebral infarction	0		0		0	
Myocardial infarction	2	0.2	9	0.3	13	0.4
Nonfatal						
Cerebral infarction	4	0.3	15	0.4	4	0.1
Myocardial infarction	2	0.2	24	0.7	42	1.3
Peripheral embolism	1	0.1	1	0.0	1	0.0
Total	**9**	0.8 (0.4-1.4)	**49**	1.4 (1.0-1.9)	**60**	1.9 (1.5-2.4)

[a] Incidences are expressed as events per 100 patient-years. Because follow-up ended when the end point of interest occurred, the denominators differ slightly between end points.

[b] Nonfatal extracranial bleeding for patients with mechanical heart valve prostheses consisted of intracranial (4 patients), gastrointestinal (12 patients), intra-abdominal (1), muscle and skin (11), urogenital (3), nose (2) and respiratory (1) bleeding; for patients with atrial fibrillation, it consisted of intracranial (10), gastrointestinal (32), muscle and skin (16), urogenital (11), respiratory (6), nose (5), intra-abdominal (2), and eye (1) bleeding; and for patients with myocardial infarction, it consisted of intracranial (6), spinal (1), gastrointestinal (29), muscle and skin (4), urogenital (2), respiratory (4), and nose (2) bleeding.

ATRIAL FIBRILLATION

Outcome Events

The combined incidence rate of all major outcome events in patients treated because of atrial fibrillation was 4.3 events (95% CI, 3.7-5.1) per 100 patient-years (Table 2). Ninety-seven patients had experienced a major bleeding event (2.9 events per 100 patient-years; 95% CI, 2.3-3.5), of which 14 were fatal (0.4 events per 100 patient-years; 95% CI, 0.2-0.6): 11 caused by intracranial bleeding, 3 caused by extracranial bleeding. The incidence of nonfatal hemorrhages was 2.4 events per 100 patient-years (95% CI, 1.9-2.9).

Forty-nine patients experienced a thromboembolic event (1.4 events per 100 patient-years; 95% CI, 1.0-1.9). Nine were fatal, all caused by myocardial infarction (0.3 events per 100 patient-years; 95% CI, 0.1-0.5). The incidence of nonfatal thromboembolic events was 1.2 events per 100 patient-years (95% CI, 0.8-1.5).

Seventeen of the 83 nonfatal hemorrhages were life threatening vs 13 of the 40 nonfatal thromboembolic events. The incidence of fatal and life-threatening events combined was 0.9 events per 100 patient-years (95% CI, 0.6-1.2) for hemorrhage and 0.6 per 100 patient-years (95% CI, 0.4-0.9) for thromboembolism.

Optimal Intensity

We found the optimal intensity of oral anticoagulant treatment in patients with atrial fibrillation to be an INR of 3.0 to 3.4 (Figure). In this intensity range, the incidence rate of untoward events was 2.4 events per 100 patient-years (95% CI, 1.5-3.5). Lower INRs led to higher incidence rates: from 2.6 events per 100 patient-years (95% CI, 1.5-4.0) for INRs of 2.5 to 2.9, up to 32.9 per 100 patient-years (95% CI, 10.1-68.9) for INRs less than 1.5. High intensities yielded incidence rates of 2.6 events per 100 patient-years (95% CI, 1.6-3.9) for INRs of 3.5 to 3.9, 9.0 per 100 patient-years (95% CI, 4.6-14.9) for INRs of 4.5 to 4.9, and up to 42.3 per 100 patient-years (95% CI, 29.2-57.8) for INRs greater than 5. When we excluded myocardial infarction as an outcome event, arguing that patients with atrial fibrillation are treated with anticoagulation agents because of their risk of ischemic stroke, not myocardial infarction, the optimal intensity stayed the same. When we limited the untoward events to life-threatening and fatal cases (Table 3), the incidence rates were lower at INRs of 2.0 to 3.0 (0.6 events per 100 patient-years; 95% CI, 0.2-1.2) compared with an INR of 3.0 to 4.0 (1.0 events per 100 patient-years; 95% CI, 0.6-1.6).

MYOCARDIAL INFARCTION

Outcome Events

The incidence rate of all untoward events in patients treated after a myocardial infarction was 3.6 (95% CI, 3.0-4.4) per 100 patient-years (Table 2). Fifty-three bleeding events occurred (1.7 per 100 patient-years; 95% CI, 1.3-2.2), of which 5 were fatal (0.2 per 100 patient-years; 95% CI, 0.0-0.3). The incidence of nonfatal hem-

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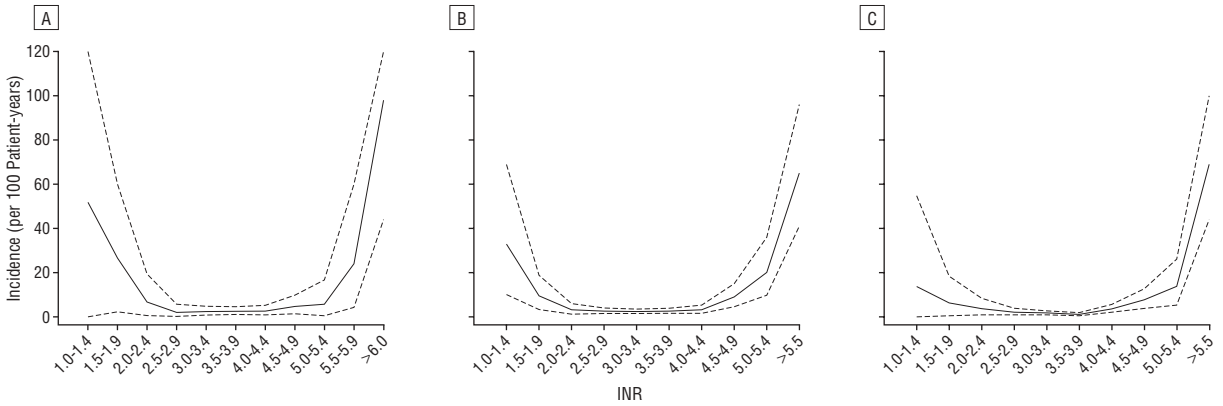

INR Interval	Patient-years, No.	Events, No.	Incidence (per 100 patient-years)
1.0-1.4	1.9	1	51.8
1.5-1.9	7.5	2	26.6
2.0-2.4	30.0	2	6.7
2.5-2.9	102.4	2	2.0
3.0-3.4	248.8	6	2.4
3.5-3.9	315.9	8	2.5
4.0-4.4	230.9	6	2.6
4.5-4.9	106.7	5	4.7
5.0-5.4	35.0	2	5.7
5.5-5.9	12.5	3	24.0
6.0-6.4	5.2	2	38.3
>6.5	4.0	7	176.8

INR Interval	Patient-years, No.	Events, No.	Incidence (per 100 patient-years)
1.0-1.4	15.2	5	32.9
1.5-1.9	63.4	6	9.5
2.0-2.4	220.1	7	3.2
2.5-2.9	662.2	17	2.6
3.0-3.4	968.2	23	2.4
3.5-3.9	767.7	20	2.6
4.0-4.4	376.9	12	3.2
4.5-4.9	133.4	12	9.0
5.0-5.4	47.9	10	20.9
5.5-5.9	20.0	3	15.0
6.0-6.4	8.8	4	45.5
>6.5	6.1	18	295.1

INR Interval	Patient-years, No.	Events, No.	Incidence (per 100 patient-years)
1.0-1.4	7.3	1	13.7
1.5-1.9	31.7	2	6.3
2.0-2.4	106.8	4	3.7
2.5-2.9	376.5	8	2.1
3.0-3.4	909.6	15	1.6
3.5-3.9	902.7	10	1.1
4.0-4.4	471.4	17	3.6
4.5-4.9	156.7	12	7.7
5.0-5.4	50.9	7	13.8
5.5-5.9	18.4	8	43.5
6.0-6.4	7.3	6	82.2
>6.5	10.3	14	135.9

Figure. International normalized ratio (INR) specific incidence rates. Rates are shown for patients with a mechanical heart valve (A), atrial fibrillation (B), and myocardial infarction (C). Dashed lines indicate 95% confidence intervals.

orrhage was 1.5 events per 100 patient-years (95% CI, 1.1-2.0).

Sixty thromboembolic events occurred (1.9 per 100 patient-years; 95% CI, 1.5-2.4). Thirteen recurrent myocardial infarctions were fatal (0.4 events per 100 patient-years; 95% CI, 0.2-0.7); the incidence rate of nonfatal thromboembolic events was 1.5 per 100 patient-years (95% CI, 1.1-2.0).

Eleven hemorrhages (3 intracranial and 8 extracranial) were life threatening, as were 25 myocardial infarctions. The incidence of life-threatening and fatal events combined therefore became 0.5 per 100 patient-years (95% CI, 0.3-0.8) for hemorrhage and 1.2 per 100 patient-years (95% CI, 0.8-1.6) for arterial thromboembolism.

Optimal Intensity

We found the lowest incidence of untoward events to be an INR of 3.5 to 3.9 INR (Figure), yielding an incidence rate of 1.1 per 100 patient-years (95% CI, 0.5-1.9). Lower intensity levels yielded higher incidence rates, varying from 1.6 events per 100 patient-years (95% CI, 0.9-2.6) for INRs of 3.0 to 3.4, up to 13.7 events per 100 patient-years (95% CI, 0-54.8) for INRs of less than 1.5. Higher intensities led to incidence rates of 3.6 events per 100 patient-years (95% CI, 2.1-5.6) for INRs of 4.0 to 4.4, up to 40.3 per 100 patient-years (95% CI, 27.8-55.0) for INRs of 5 or greater. When we analyzed only life-threatening and fatal events, the position of the optimal intensity did not change (Table 3).

COMMENT

We performed a cohort study among patients of a Dutch anticoagulation clinic to calculate incidence rates of bleeding and thromboembolic events and to identify the optimal intensity of oral anticoagulant therapy for patients with cardiac sources of arterial thrombosis: mechanical heart valve prostheses, atrial fibrillation, and myocardial infarction. The incidence rate of all untoward events was similar for all 3 indications, around 4% per year. To date, these numbers have been stable. The optimal intensity of anticoagulation, at which the overall incidence rate of both bleeding and thromboembolic events is lowest, did not differ much among the 3 indications. It was located at an INR of 2.5 to 2.9 for patients with mechanical heart valve prostheses, at an INR of 3.0 to 3.4 for patients with atrial fibrillation, and at an INR of 3.5 to 3.9 for patients treated after a myocardial infarction.

Before suggesting optimal target levels for oral anticoagulation in daily practice, 2 additional issues have to be addressed. First, it should be assessed whether the protective effects of oral anticoagulants outweigh the introduced bleeding risk because we would otherwise just exchange one risk for the other. Within the ranges with the lowest incidence rates, the incidence of all major untoward combined events was 2.0 per 100 patient-years for patients with mechanical heart valve prostheses, 2.4 per 100 patient-years for patients with atrial fibrillation, and

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Table 3. Incidence Rates of Untoward Events According to Severity

INR	All Events, Incidence[a] (95% CI)	Life-Threatening and Fatal Events, Incidence[a] (95% CI)
Mechanical heart valve		
<2.0	31.9 (5.7-79.4)	10.6 (0.0-42.6)
2.0-2.4	6.7 (0.6-19.4)	3.3 (0.0-13.3)
2.5-2.9	2.0 (0.2-5.7)	1.0 (0.1-4.4)
3.0-3.9	2.5 (1.3-4.0)	1.1 (0.4-2.1)
4.0-4.9	3.3 (1.6-5.5)	1.8 (0.6-3.5)
≥5.0	24.7 (13.3-39.7)	5.3 (0.9-13.2)
Atrial fibrillation		
<2.0	14.0 (6.8-23.7)	7.6 (2.7-15.1)
2.0-2.9	2.7 (1.7-3.9)	0.6 (0.2-1.2)
3.0-3.4	2.4 (1.5-3.5)	1.0 (0.5-1.8)
3.5-3.9	2.6 (1.6-3.9)	1.0 (0.4-1.9)
4.0-4.9	4.7 (3.0-6.8)	1.4 (0.5-2.6)
≥5.0	42.3 (29.2-57.8)	15.7 (8.2-25.6)
Myocardial infarction		
<2.0	7.7 (1.4-19.1)	5.1 (0.4-14.9)
2.0-2.9	2.5 (1.3-4.1)	1.7 (0.7-3.0)
3.0-3.4	1.6 (0.9-2.6)	0.7 (0.2-1.3)
3.5-3.9	1.1 (0.5-1.9)	0.6 (0.2-1.2)
4.0-4.9	3.1 (3.1-6.5)	2.5 (1.4-4.0)
≥5.0	27.8 (27.8-55.0)	12.7 (6.2-21.4)

Abbreviations: CI, confidence interval; INR, international normalized ratio.
[a] Per 100 patient-years.

1.1 per 100 patient-years for patients after a myocardial infarction. The incidences of major thromboembolism in these patient groups without anticoagulant therapy have been estimated at 5.8 per 100 patient-years,[1] 4.5 per 100 patient-years,[2] and 6.9 per 100 patient-years,[12] respectively, indicating that the use of oral anticoagulants is beneficial in all 3 indications. It is important to note that the concomitant use of vitamin K antagonists and antiplatelet agents was highly uncommon in the Netherlands because of the increased bleeding risk.

Second, the severity of thromboembolic and bleeding events may not be judged as similar. Therefore, we weighed all outcome events as serious, life threatening, or fatal and separately analyzed the most severe events only. The position of the intensity range with the lowest incidence of these untoward events did not change for patients with mechanical heart valve prostheses or for those after myocardial infarction but tended to be lower for patients with atrial fibrillation.

The data presented herein suggest the following target levels for oral anticoagulation in the prevention of arterial (thrombo)embolism: an INR of 3.0 for patients with mechanical heart valve prostheses, 3.0 for patients with atrial fibrillation, and 3.5 for patients after myocardial infarction.

Still, it is important to realize that the optimal (target) levels we found should be interpreted cautiously because the design of our study has its limitations. Despite the large patient groups and substantial follow-up period of 3 years, the absolute number of untoward events remains relatively small. Although clear patterns are shown, the statistical precision of the outcomes is therefore limited. Another shortcoming of the study design might be that few patient characteristics or individual clinical parameters were taken into account. One might argue, therefore, that although the study results apply to the group as a whole, individual patients may have different risks at different intensities. Although this is undoubtedly true, very large studies would be required to estimate these individual risks. It is highly uncertain if such studies will ever be performed.

Yet, the study design has major advantages as well. The important features are that we used actually achieved INR levels to calculate the optimal target intensities irrespective of the targets used. Furthermore, we performed a study in the routine setting of an anticoagulation clinic, preventing bias from nonroutine, more intense monitoring. For this reason, the study results can easily be applied to day-to-day practice.

Now that we have defined the presumed optimal intensity of oral anticoagulation for patients with mechanical heart valve prostheses, atrial fibrillation, and after myocardial infarction, testing these ranges in new clinical trials should be considered. These trials could compare current target ranges with the optimal intensity levels we found and provide us with a final answer as to which INR level is safest for patients at high risk of arterial thromboembolism.

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