

# Thromboembolic and Bleeding Complications in Patients With Mechanical Heart Valve Prostheses

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**Background** Patients with mechanical heart valve prostheses may experience valve thrombosis and subsequent systemic embolism for which they are treated with oral anticoagulant therapy. It is essential to know reliable estimates of the risks and benefits of this therapy in order to answer a number of clinical questions rationally. We sought to obtain more precise estimates of the risks and benefits by combining the data from individual studies by using meta-analysis.

**Methods and Results** We searched for studies in which the incidences were reported of embolic or bleeding complications in patients with mechanical heart valve prostheses. They were collected from the Medline and Current Contents database and by cross-references between 1970 and 1992. Since most studies vary greatly in many respects, we used a number of inclusion criteria, thus selecting comparable studies of acceptable quality only. The influence of antithrombotic therapy, valve position, and valve type was analyzed by univariate and by multivariate analysis with Poisson regression techniques. Forty-six studies were found, including 13 088 patients studied

for 53 647 patient-years. We found an incidence of major embolism in the absence of antithrombotic therapy of 4 per 100 patient-years. With antiplatelet therapy this risk was 2.2 per 100 patient-years, and with cumarin therapy it was reduced to 1 per 100 patient-years. This risk varied with the type and the site of the prosthesis. A prosthesis in mitral position increased the risk almost twice as compared with the aortic position. Tilting disc valves and bileaflet valves showed a lower incidence of major embolism than caged ball valves. An incidence of major bleeding was found in patients treated with cumarin derivatives of 1.4 per 100 patient-years. The incidence of bleeding became significantly higher with the addition of antiplatelet therapy, although this did not decrease the risk of thromboembolism any further.

**Conclusions** These data provide a reference for future studies and give adequate risk estimates for clinical decision making. (*Circulation*. 1994;89:635-641.)

**Key Words** • meta-analysis • anticoagulants • aspirin • thrombosis • embolism

In March 1960, the first successful replacement of an aortic valve was performed by Harken.<sup>1</sup> In the following years, many modifications have been made and new designs introduced to address specific deficiencies in these early devices. Most modern prostheses now offer good durability and hemodynamic characteristics. The main problem still remaining is the thromboembolic potential of these valves.

Implantation of an artificial device places a large foreign surface in contact with the bloodstream. Thrombus formation on the valve may be influenced—according to Virchow's triad—by surface characteristics of the prosthesis (material and design), blood flow (cardiac output, turbulence, and stagnation), and characteristics of the blood constituents of the patient (hypercoagulability). Clinically, this may result in significant disruption of valve function, a life-threatening event. Likewise, parts of the thrombus may embolize to peripheral arterial sites. These emboli usually involve the central nervous system, resulting in a spectrum of effects ranging from transient to sometimes fatal events. To prevent

these complications, life-long oral anticoagulation therapy is recommended in all patients.<sup>2</sup> However, this treatment introduces a risk of severe or fatal bleeding.<sup>3</sup>

In the past 20 years, many reports have been published on the risks of thromboembolic and bleeding complications. Unfortunately, the reported results vary greatly because of differences in patient selection, definitions of end points, methods of follow-up and statistical analysis, and type, intensity, and efficacy of anticoagulation therapy.<sup>4</sup> Besides, the quality of the reports is often inadequate. McGoon<sup>5</sup> examined 51 reports on this subject and concluded that none of these gave complete information. Consequently, from the information of the individual studies, it is hardly possible to establish the risks of thromboembolism and bleeding with any reliability. Assessing the influence of factors such as position and model of the valve is even more difficult.

Many clinical questions cannot be answered rationally without reliable estimates of the risks and benefits of oral anticoagulation: what is the optimal intensity of anticoagulation for various groups of patients; what is the risk of temporarily interrupting anticoagulation in patients who have recurrent bleeding complications or in patients who require surgery; which patients should receive bioprostheses instead of mechanical prostheses, etc. In addition, it is important to know the extent of these risks in the design of clinical trials in which the optimal therapy is investigated.

We have set out to obtain reliable estimates of the risks of thromboembolic and bleeding complications in

Received June 11, 1993; revision accepted October 19, 1993.

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TABLE 1. Studies Included in This Review

	Patients	Patient-Years	References
<b>Anticoagulation</b>			
None	460	1225	40, 45-50
Antiplatelet	595	1226	11, 16, 46, 47, 49, 51-55
Cumarin	11 213	49 494	10-40
Cumarin and antiplatelet	820	1702	41-44
<b>Valve position</b>			
Aorta	4679	24 582	10, 12, 15-17, 25, 26, 30, 31, 34, 38-40, 45-50, 52-55
Mitral	1555	9618	12, 21, 25, 27, 38
Both	534	2837	12, 25, 26, 36
Not stated/mix	6320	16 610	11, 13, 14, 18-20, 23, 24, 28, 29, 32, 33, 35, 37, 41-44, 51
<b>Valve model</b>			
Starr-Edwards	821	1945	34, 40, 45-47, 53, 54
Björk-Shiley	5344	28 468	17, 19, 25-27, 30, 36, 38, 42, 51
St Jude	2011	6984	10, 14, 16, 20, 28, 31, 32, 34, 55
Medtronic-Hall	1517	4711	12, 23, 32, 33
Lillehei-Kaster	750	4933	21, 22, 30, 39, 48, 52
Omniscience	835	1743	13, 18, 24, 41, 44
Omnicarbon	354	555	29
Smeloff-Cutter	294	1586	15, 49
Duromedics	508	1064	35
Bicer	99	93	43
Not stated/mix	555	1565	11, 37, 40, 50

patients with mechanical heart valves to provide an adequate basis for answering these questions. We combined the data from individual studies by using meta-analysis, a systematic and quantitative reviewing strategy.<sup>6,7</sup> To minimize the problems of variability between studies caused by differences in methodological strength or completeness of information, we used rigorous inclusion criteria.

## Methods

### Data Collection

We searched for original studies with data on the incidences of thromboembolic complications, bleeding complications, or both in patients with mechanical heart valve prostheses. These were collected from the Medline and Current Contents database and by cross-references. We initially selected all studies published in English between 1985 and 1992. The reports were only included if the following criteria were stated and met: duration of follow-up; type of anticoagulation and number of patients treated; possibility to discriminate, according to the following definitions, between thrombosis (valve-related clotting impairing the function of the valve, diagnosed at operation or autopsy); major embolism (causing death, residual neurological deficit, or peripheral ischemia requiring surgery); minor embolism (transient cerebral or peripheral ischemia); major bleeding (intracranial bleeding, bleeding causing death or necessitating hospitalization); minor bleeding (all other bleeding); and results reported separately by model or position of the valve or by type or intensity of anticoagulation therapy.

In addition to studies that did not fulfill these criteria, reports were excluded that concerned selected patient groups only (such as children, elderly patients only, additional coronary bypass surgery in all patients, etc); included biopros-

theses without separate analysis of these valves; studied a patient group already included in reports published later; and studied triple valve replacement only.

In this set of studies (published after 1985), most patients received cumarin therapy. Since we were interested in the risk of thromboembolic complications in the absence of such treatment, we extended our search to all studies published in English after 1970 in which no anticoagulation therapy was given or only antiplatelet treatment was given. The same inclusion criteria were applied.

A standardized data form was used to extract information on position and type of the valve, type and level of anticoagulation, number of patients and patient-years, and number of complications for each report.

If a study contained information on more than one series of patients with differences in valve position, valve type, or type of anticoagulation, these series were analyzed as if they were separate studies.

### Statistical Analysis

We used two methods to obtain summary results: First, averages of the results of the individual series, weighted by study size, were calculated. Ninety-five percent confidence intervals (CI) were calculated with the assumption of a Poisson distribution of the outcome of interest.<sup>8</sup> Second, since valve position and valve type were not distributed equally over the different anticoagulation groups, we performed a multivariate analysis by Poisson regression techniques.<sup>9</sup> For instance, in most studies in which no anticoagulation was given, older valve types such as Starr-Edwards were used, often in aortic position. Analyzing these variables in a univariate way may lead to confounded results. With multivariate analysis, it is possible to determine the effect of one variable while the other variables are adjusted for. Since studies were compared

**TABLE 2. Incidence Rates of Valve Thrombosis and Major and Total Embolisms: Effect of Antithrombotic Treatment**

Anticoagulation	Incidence Rates per 100 Patient-Years (95% Confidence Intervals)		
	Valve Thrombosis	Major Embolism	Total Embolism*
None	1.8 (0.9-3.0)	4.0 (2.9-5.2)	8.6 (7.0-10.4)
Antiplatelet	1.6 (1.0-2.5)	2.2 (1.4-3.1)	8.2 (6.6-10.0)
Dipyridamole	4.1 (1.9-7.2)	5.4 (2.8-8.8)	11.2 (7.3-15.9)
Aspirin†	1.0 (0.4-1.7)	1.4 (0.8-2.3)	7.5 (5.9-9.4)
Cumarin	0.2 (0.2-0.2)	1.0 (1.0-1.1)	1.8 (1.7-1.9)
Cumarin and antiplatelet	0.1 (0.0-0.3)	1.7 (1.1-2.3)	3.2 (2.4-4.1)

\*This category includes all reported incidences (valve thrombosis, major embolism, and minor embolism).

†Aspirin alone or in combination with dipyridamole or pentoxifylline.

that sometimes differed 10 to 20 years in age, we wanted to eliminate a possible effect of the period of publication. We therefore performed this analysis first for all studies and subsequently only for the studies that were published after 1980.

## Results

### Data

We found 160 reports published between 1985 and 1992. Twenty reports were published between 1970 and 1985 that dealt with patients who received no anticoagulation or antiplatelet therapy only. Of these 180, only 46 studies satisfied all our inclusion criteria. Most reports (39) were excluded because a distinction between major and minor complications could not be made. Twenty-nine reports studied a selected patient group and were therefore excluded. Thirty-seven studies were excluded according to one of the other criteria, and 29 reports were excluded because of missing information about two or more items.

Of the 46 reports that could be used, cumarin treatment only was given in 31.<sup>10-40</sup> In four studies, antiplatelet treatment was given additionally to cumarin derivatives.<sup>41-44</sup> Seven studies were found in which no antithrombotic treatment was administered.<sup>40,45-50</sup> In 10 reports, only antiplatelet treatment was given (aspirin, dipyridamole, or both; in one study, aspirin plus pentoxifylline).<sup>11,16,46,47,49,51-55</sup> Therefore, in 6 reports, more than one regimen was described.

The studies included 13 088 patients in total, studied for 53 647 patient-years. Table 1 shows the number of patients and patient-years for the different regimens, valve positions, and valve models.

### Thromboembolism: Antithrombotic Therapy

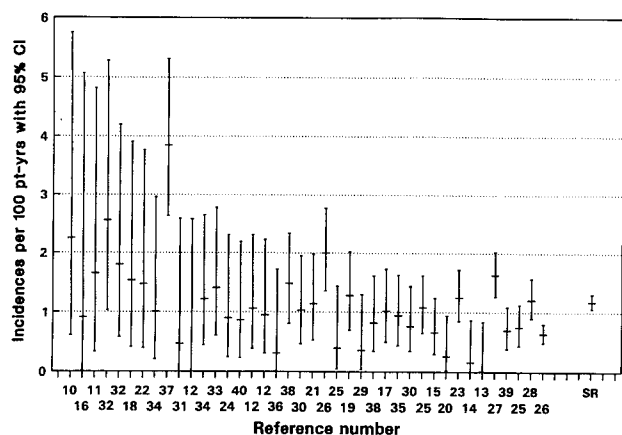
The incidence rates of thrombosis on the valve and major and total embolism are shown in Table 2. These are expressed as number of events per 100 patient-years (this corresponds to percent occurrence annually).

With cumarin therapy, the incidence of valve thrombosis was 0.2 per 100 patient-years (95% CI, 0.2 to 0.2). The incidence of major embolism was 1.0 (95% CI, 1.0 to 1.1) (Figure), and that of total embolism was 1.8 (95% CI, 1.7 to 1.9). In the "no treatment" category, these incidences were at least four times higher. They were not effectively reduced with antiplatelet therapy (Table 2).

In the antiplatelet category, dipyridamole alone was given in one study (123 patients, 241 patient-years).<sup>51</sup> In this study, incidence rates were found that were as high as those without antithrombotic treatment. These figures affect the average results of the antiplatelet category, so we reported separately the results of aspirin (either alone or in combination with dipyridamole) and those of dipyridamole alone (Table 2). The incidence of total embolism in patients treated with aspirin alone did not differ from that when aspirin in combination with dipyridamole was given.

### Multivariate Analysis

The results in Table 2 were obtained by calculating averages of the results of the individual studies, weighted by study size. With multivariate analysis, we found similar results (Table 3). These are expressed as rate ratios, which show the ratio of the incidence rates for each particular factor, whereas the other variables are adjusted for. For example, a rate ratio of 3.7 when no anticoagulation is compared with cumarin therapy reflects a 3.7-fold increase of the risk of embolism without anticoagulation. This corresponds with the in-



Graph shows incidence rates of major embolism reported in all studies in which cumarin therapy was given. These are expressed in incidences per 100 patient-years (pt-yrs) with 95% confidence intervals (CI) and ordered by width of the 95% CI. If an article contained information on more than one series of patients with different valve positions or valve types, these series were analyzed as separate studies. SR indicates summary result, obtained by calculating the average of the results of the individual series weighted by study size.

**TABLE 3. Multivariate Analysis With Poisson Regression Techniques**

	Major Embolism		Total Embolism	
	Rate Ratio†	95% CI‡	Rate Ratio†	95% CI‡
No anticoagulation	3.7	2.5-5.6	5.6	4.2-7.5
Antiplatelet treatment	1.9	1.3-2.9	4.8	3.8-6.0
Cumarin+antiplatelet	1.3	0.9-2.0	1.4	1.0-1.8
Cumarin	1.0*	...	1.0*	...
Mitral position	1.8	1.4-2.2	2.4	2.0-2.8
Aortic and mitral positions	1.9	1.3-2.7	1.9	1.4-2.5
Aortic position	1.0*	...	1.0*	...
Tilting disk valves	0.7	0.5-1.0	0.7	0.5-0.9
Bileaflet valves	0.6	0.4-0.9	0.5	0.4-0.7
Caged ball valves	1.0*	...	1.0*	...

\*Reference category.

†Incidence rate ratios for major and total embolisms are shown for different treatment regimens, valve positions, and valve types. The rate ratio may be interpreted as the risk relative to the reference category, with its corresponding 95% confidence interval (CI).

‡A 95% CI that does not include unity denotes statistical significance at the .05 level.

cidence of major embolism of 1.0 (95% CI, 1.0 to 1.1) per 100 patient-years with cumarin therapy compared with the incidence of 4.0 (95% CI, 2.9 to 5.2) without, as was found with univariate analysis (Table 2).

Antiplatelet therapy was associated with a twofold higher risk of major embolism than cumarin therapy, as we also found in univariate analysis. Cumarin derivatives combined with antiplatelet therapy did not appear to be superior to cumarin therapy alone (the 95% CI includes 1, the rate ratio of the reference group).

#### Position of the Valve

Unfortunately, in the studies in which no antithrombotic treatment or antiplatelet treatment only was given, it was not possible to analyze separately for the aortic and mitral positions with univariate analysis because in most studies, either an aortic valve was used or the position of the valve was not stated at all. However, in the studies in which the patients were treated with cumarin derivatives, the position of the valve was stated often enough to calculate incidence rates for the different valve positions (Table 4). The incidence rate of the mitral valve compared with that of the aortic valve was five times as high for valve thrombosis and about 1.5 times as high for embolism. With multivariate analysis, the effect of the position of the valve was similar as with univariate analysis (Table 3), ie, a higher risk for the mitral position.

#### Valve Model

We defined three broad categories of valve models: the caged ball types (Starr-Edwards and Smeloff-Cutter), the tilting disc valves (Björk-Shiley, Medtronic-Hall, Lillehei-Kaster, Omniscience, Omnicarbon, and Bicer), and bileaflet valves (St Jude and Duromedics).

In the studies in which no anticoagulation was given, the most commonly used valve type was the Starr-Edwards ball valve. No difference in the incidence of either thrombosis or embolism was found between the Starr-Edwards and other valve models (all in aortic position). The same applied for the antiplatelet group. In the cumarin treatment group, no differences between the different valve types could be demonstrated.

However, using multivariate analysis to adjust for other variables, we found a higher risk for the caged ball valves compared with the tilting disc and bileaflet valves (Table 3). In this analysis, we also included the studies in which the position or the model of the valve was not stated or in which a mixture was used. Since the outcome of the analysis has no meaning for these groups, these results are not reported. They had to be included in the analysis, however, in order to use all information on the other variables optimally.

We performed a subgroup analysis within the caged ball valve studies to examine a possible difference between cloth-covered and non-cloth-covered valves. With multivariate analysis, we found a rate ratio of

**TABLE 4. Incidence Rates of Valve Thrombosis and Major and Total Embolisms With Cumarin Therapy: Effect of Valve Position**

Valve Position	Incidence Rates per 100 Patient-Years (95% Confidence Intervals)		
	Valve Thrombosis	Major Embolism	Total Embolism*
Aortic	0.1 (0.1-0.2)	0.8 (0.7-0.9)	1.1 (1.0-1.3)
Mitral	0.5 (0.3-0.7)	1.3 (1.1-1.5)	2.7 (2.3-3.0)
Both	0.4 (0.2-0.7)	1.4 (1.0-1.9)	2.1 (1.6-2.7)

\*This category includes all reported incidences (valve thrombosis, major embolism, and minor embolism).

TABLE 5. Incidence Rates of Cerebral, Major, and Total Bleeding

Anticoagulation	Incidence Rates per 100 Patient-Years (95% Confidence Intervals)		
	Cerebral Bleeding	Major Bleeding	Total Bleeding†
Antiplatelet	NDA*	NDA*	0.5 (0.1-1.2)
Cumarin	0.5 (0.4-0.7)	1.4 (1.2-1.5)	1.9 (1.7-2.0)
Antiplatelet and cumarin	NDA*	NDA*	4.6 (3.1-6.4)

\*NDA indicates no data available.

†This category includes all reported incidences (cerebral bleeding, major bleeding, and minor bleeding).

cloth-covered compared with non-cloth-covered valves of 1.4 (95% CI, 0.6 to 3.2) for major embolism and a rate ratio of 1.3 (95% CI, 0.8 to 3.2) for total embolism. No clear difference could be demonstrated.

To eliminate a possible effect of the publication period, the multivariate analysis was also performed with the studies published after 1980 only. This led to similar results (data not shown).

### Bleeding

The incidence rates of cerebral, major, and total bleeding are shown in Table 5. None of the reports in the "no treatment" category reported the incidence of bleeding. Placebo-controlled trials have never been carried out in these patients, so data on the incidence of bleeding in the absence of antithrombotic treatment are lacking. In the reports of the antiplatelet studies, the number of bleedings was not always stated. In the studies in which it was, major bleeding could not be analyzed separately.

Treatment with oral anticoagulation therapy gave rise to an incidence of major bleeding of 1.4 per 100 patient-years (95% CI, 1.2 to 1.5). The addition of antiplatelet treatment to cumarin derivatives appeared to increase the bleeding risk: We found an incidence of total bleeding of 4.6 per 100 patient-years (95% CI, 3.1 to 6.4), which was higher than that of cumarin therapy only (this series of studies was too small to calculate the incidence of major bleeding separately).

### Mortality

In the studies in which no anticoagulation or antiplatelet therapy was given, the late mortality was stated only occasionally, so this could not be analyzed for these groups.

The total late mortality (more than 30 days after valve implantation) in the studies in which cumarin therapy was given was 4.6 per 100 patient-years (95% CI, 4.3 to 4.8). No difference in mortality was found according to valve position (aortic valve, 4.5 [95% CI, 4.2 to 4.9]; mitral, 4.6 [95% CI, 4.1 to 5.0]; and both valves, 4.8 [95% CI, 3.6 to 6.1] per 100 patient-years).

### Discussion

Thromboembolism and anticoagulant-related bleeding remain the most frequent complications of mechanical heart valve prostheses.<sup>56</sup> Many reports have been published on the risks of these complications. However, the reported results differ enormously, and the quality of the studies is often inadequate.<sup>4,5</sup> Therefore, from the information of the individual studies, it is not possible to

answer many clinical questions rationally. This variability results first of all from the lack of standardization of definitions of complications. Of the 180 studies initially selected, a distinction in minor, major, and lethal complications could not be made in 39, which distinction is of the utmost importance. Assessment of major events that require hospitalization or cause death will be more objective than assessment of minor events. Besides, patients are inclined to forget transient events, especially when follow-up was retrospective or prospective, with long intervals between contacting the patient. This has been demonstrated recently by Bodnar and Horstkotte.<sup>57</sup> Two publications give guidelines for reporting valve-related complications<sup>58,59</sup>; surprisingly, neither advises distinguishing between minor and major embolisms. We strongly recommend adding this distinction when using these guidelines to increase the comparability among the different studies. Other causes of incomparability are differences in patient selections, methods of follow-up, and type and efficacy of anticoagulation therapy.

To minimize the differences between the individual studies and to select studies of similar quality, we used a number of inclusion criteria as stated in "Methods." The Figure gives an overview of the incidences of major embolism found in the included studies in which cumarin therapy was given with 95% CI. All valve types and positions are included in the graph. Still, the variability among these incidences is not as large as described by Grunkemeier and London,<sup>4</sup> who compared a series of studies without the application of inclusion criteria. Apparently, our inclusion criteria did improve the comparability of the information and thus the validity of the end result.

One study, however, stands out: namely, the study performed by Saour et al.<sup>37</sup> They found an incidence rate of major embolism of 3.85 per 100 patient-years, which is much higher than the incidence rate reported in any other study. Actually, this incidence rate is similar to that usually found in the absence of treatment (Table 2). We have no satisfactory explanation for this finding.

We pooled the data from the included studies and calculated the incidences of valve thrombosis, major embolism, and total embolism. Because the most comparable and reliable figure is that of major embolism, only this figure will be discussed.

Without anticoagulation, the risk of major embolism is about 4 per 100 patient-years. Aspirin reduces the risk of major embolism by about 40% compared with no treatment but is only about half as effective as cumarin

therapy. Dipyridamole does not appear to have any effect on the prevention of thromboembolism either alone or when given in combination with aspirin.

Cumarin therapy reduces the incidence of major embolism by approximately 75% to an annual risk of about 1%. The addition of antiplatelet treatment to cumarin derivatives does not further decrease this risk. In fact, there even appears to be a tendency toward an increased risk. This may be due to the fact that these patients possibly received less intense anticoagulant therapy (because they were given antiplatelet therapy in addition). These data leave little doubt about the benefit of cumarin treatment in these patients, whereas that of aspirin and dipyridamole is obviously not sufficient.

The risk of major bleeding caused by cumarin therapy will be less than 1.4% annually, so the benefit of cumarin therapy in these patients clearly outweighs the risk. Still, it should be possible to minimize both embolic and bleeding complications by optimizing the intensity of this treatment. It is reasonable to assume that the risk of embolism decreases with higher intensities of anticoagulation while the risk of bleeding increases. The optimal intensity will be the level at which the sum of both risks is minimal.<sup>60</sup>

To examine the possibility of fine-tuning this optimal intensity according to site and type of the prosthesis, we calculated the effect of these variables with univariate and multivariate analyses. In patients who took cumarin therapy, an apparent effect of the position of the valve on the incidence of major embolism was found. This risk is almost twofold higher with valves in the mitral position than in the aortic position. The same result was found with multivariate analysis, which means that this effect is largely independent from other factors.

An effect of the valve model could not be established with univariate analysis. With multivariate regression analysis, however, we found that both tilting disc valves and bileaflet valves showed a lower incidence of major embolism than the caged ball valves. In a second analysis, we excluded the studies that were published before 1980. No major differences were found, so this finding was not caused by the fact that the ball valves were used mainly in the older studies. It may reflect a real increased thrombogenicity of this valve model.

In most reports, basic information on the treatment with oral anticoagulant therapy was lacking. In only five studies was the target range stated as International Normalized Ratio (INR). In the other reports, the target range was not stated at all or reported in such a way that the INR could not be derived from the provided information (except for one study in which the target prothrombin time was mentioned and the type of thromboplastin provided). Information on quality control of the treatment, eg, the percentage of prothrombin times within the target ranges, was only sporadically provided. Our summary results therefore could not be related to anticoagulation levels. This considerable lack of elementary information probably reflects the fact that in many centers, anticoagulation monitoring has not been considered as important as it should be. Thus, efforts to reduce both embolic and bleeding complications to a minimum should not only include the search for the optimal intensity but also and foremost, the optimization of treatment monitoring.

An important clinical question that may be answered more rationally on the basis of this study concerns the risk of interrupting anticoagulation in patients with recurrent bleeding complications or in patients who require surgery. Without anticoagulation, we found a risk of major embolism of about 4 per 100 patient-years and a risk of valve thrombosis of 1.7 per 100 patient-years. Although this is a high risk on a yearly basis, for 1 day it will only be  $(4+1.7)/365=0.016\%$  (ie, 1.6 in 10 000). Therefore, short interruption of anticoagulation may not be as dangerous as is often presumed. The risk of severe damage to organs by bleeding when anticoagulation is not fully interrupted is probably much higher in these situations.

The aim of this study has been to provide a reference for future studies and to give adequate estimates of risks for clinical decision making. By using inclusion criteria, we selected comparable information and could therefore calculate reliable and valid summary results. The data show that cumarin treatment reduces the incidence of major embolism in patients with mechanical heart valves by approximately 75% from about 4% to 1% yearly. This offsets the incidence of major bleeding of 1.4% yearly, induced by cumarin therapy. Obviously, both risks will be influenced by the intensity of anticoagulation therapy. The optimal intensity may differ according to the type and site of the prosthesis, since the risk of embolism is influenced by these variables.

To minimize both embolic and bleeding complications in patients with mechanical heart valves, the monitoring of cumarin treatment should be optimized, and the optimal intensity should be sought.

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