REVIEW ARTICLE

Patients with atrial fibrillation and low risk of stroke: do they really need anticoagulation?

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ABSTRACT

KEY WORDS

anticoagulation, atrial fibrillation, stroke risk, thromboembolic risk

Atrial fibrillation (AF) significantly increases the risk of thromboembolic events, in particular the risk of stroke. Anticoagulation therapy has been shown to reduce this risk; therefore, the treatment should be lifelong. However, the risk in patients with nonvalvular AF is not equally distributed, and there is a population of patients at low risk. According to the current guidelines, the decision on the need of anticoagulation is primarily dependent on whether the patient is at low risk. The CHA, DS,-VASc is currently the most commonly recommended scheme for assessing thromboembolic risk in patients with nonvalvular AF. In a large group of nontreated patients with a CHA, DS,-VASc of 0 (1 in women), the annual risk of stroke was 0.49%; ischemic stroke, 0.43%; bleeding, 1.08%; intracranial bleeding, 0.15%; and death, 3.87%. In patients on warfarin, the frequency of ischemic stroke was similar. Patients with a CHA, DS,-VASc of 0 (1 in women) are low-risk patients who do not benefit from anticoagulation. The low-risk group is also defined as patients younger than 65 years of age without structural cardiovascular disease, regardless of sex. They represent from 6% to 10% of patients with nonvalvular AF. Thromboembolic risk in patients with a score of 1 (2 in women) is much more controversial, as reflected by several recently published cohort studies. In a Swedish study, the risk was found to be low, while in Danish and Taiwanese studies—as significantly higher. Another analysis has shown that the use of vitamin K antagonists is appropriate when the risk of stroke is higher than 1.7%/year. Owing to a lower risk of intracranial bleeding, anticoagulation with nonvitamin K antagonist oral anticoagulants may be considered already at an annual risk of stroke exceeding 0.9%. Patients at low risk do not require chronic anticoagulation.

nign arrhythmia. It may have various consequences, the most important of which is ischemic stroke. Every fifth stroke, and likely even more, is due to AF. Stroke secondary to AF is associated with 2-fold higher mortality, higher degree of disability, and 3-fold higher recurrence risk.¹⁻⁴ It is estimated that every 30 minutes in Poland 1 patient suffers from stroke secondary to AF.

Introduction Atrial fibrillation (AF) is not a be-

AF increases the risk of stroke 5-fold; however, in more complicated patients with other risk factors, it could be as high as >10% annually. Chronic oral anticoagulation significantly reduces this risk, but it is associated with complications, mainly bleeding, especially intracranial bleeding.⁵⁻¹² This is why the optimal estimation of thromboembolic risk and bleeding risk is so important in patients with AF. In patients with valvular AF (with postrheumatic valvular disease, especially with mitral stenosis, mechanical artificial valve, probably also biological artificial valve and postmitral valve repair) or in patients with hypertrophic cardiomyopathy, the thromboembolic risk is different, usually high, and they require chronic anticoagulation if there are no serious contraindications.^{2,13-17} The remaining patients with AF constitute a large and diverse group of so called nonvalvular AF.

Thromboembolic risk assessment scores in patients with nonvalvular atrial fibrillation Different schemes for assessing the risk of stroke and other thromboembolic events in patients with nonvalvular AF have been proposed, including CHADS₂, ATRIA, and CHA₂DS₂-VASc (TABLE 1).^{13,18,19} In the CHA₂DS₂-VASc, prior stroke, transient ischemic

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TABLE 1	Thromboembolic risk assessment scales in patients with nonvalvular	atrial
fibrillation		

Risk factor	CHA2DS2-VASc	CHADS ₂	ATRIA	
			prior stroke	no prior stroke
age ≥85 years	2	1	9	6
age 75–84 years	2	1	7	5
age 65–74 years	1	_	7	3
age <65 years	_	-	8	0
female sex	1	_	1	1
HF	_	1	1	1
HF or LVD	1	-	-	_
hypertension	1	1	1	1
albuminuria	_	-	1	1
eGFR <45 ml/ min/1.73 m ²	-	_	1	1
vascular disease	1	-	-	-
prior stroke/ peripheral embolism/TIA	2	2	-	-
total count	9	6	15	12

Abbreviations: eGFR, estimated glomerular filtration rate; HF, heart failure; LVD, left ventricular dysfunction; TIA, transient ischemic attack



FIGURE 1 Patients with nonvalvular atrial fibrillation at no need of anticoagulation (2012 European Society of Cardiology guidelines, modified) attack (TIA) or other thromboembolic event, and age \geq 75 years score 2 points. Heart failure or left ventricular dysfunction, hypertension, diabetes, vascular disease (prior myocardial infarction, peripheral artery disease, and aortic plaque), age of 65 to 74 years, and female sex score 1 point. Compared with the older CHADS₂ scale, the new factors are age of 65 to 74 years, vascular disease, and female sex.

The CHA_2DS_2 -VASc is currently the most commonly used scheme, recommended in the majority of guidelines and expert consensuses for thromboembolic risk assessment. The 2012 focused update of the European Society of Cardiology (ESC) guidelines for the management of AF advocate the use of this scheme (class I recommendation and level of evidence A). The 2014 United States and United Kingdom guidelines also recommend the use of the CHA_2DS_2 -VASc.^{2,13,20} Only in 2014 Canadian guidelines, the use of the $CHADS_2$ scheme is recommended, although modified by the addition of the age of ≥ 65 years as a risk factor.²¹ Canadian experts do not take female sex into account, and for patients with vascular disease as a single risk factor, they propose the use of acetylsalicylic acid (ASA) only.

Female sex as a risk factor is controversial. It has been demonstrated to increase risk when the other risk factors are present. In women younger than 65 years and without concomitant diseases, the risk is the same as in men.²²⁻²⁴

The most frequently recommended score to assess the risk of bleeding is HAS-BLED.¹³

Who is a low-risk patient at no need for anticoagulation? According to the widely available guidelines for nonvalvular AF, the initial step in stroke risk stratification is to identify low-risk patients.¹³ If the risk is low, the patient does not require anticoagulation. According to the 2012 ESC guidelines, in patients with nonvalvular AF with a CHA₂DS₂-VASc score of 0 or in patients younger than 65 years with lone AF regardless of sex should not receive anticoagulants. There is a significant discrepancy in this statement: the definition of lone AF requires that a patient is younger than 60 years old. Recently, experts in AF have stated that the term "lone AF" should no longer be used because there is increasing knowledge about the numerous risk factors and causes of AF as well as more precise diagnostic methods allowing to identify structural cardiac abnormalities in AF patients.²⁵ According to a recently modified recommendation, patients younger than 65 years old and without cardiovascular disease are at low thromboembolic risk, regardless of sex (FIGURE 1).¹¹

The question remains whether these patients are really at low risk and whether this risk, if present, is modified by anticoagulation. In 2010, the first CHA_2DS_2 -VASc validation was performed based on the data from the Euro Heart Survey on Atrial Fibrillation.¹⁸ In patients with a score of 0, the annual risk of thromboembolic events was 0%; however, the analysis included only 103 patients.

More recently, new data have been presented.^{26,27} Olesen et al²⁷ published the results of a Danish nationwide registry-based cohort study including 73 538 noncoagulated patients with nonvalvular AF. Among them, 16406 patients (22.3%) were categorized by CHADS, as being at low risk (score 0), but only 6369 patients (8.7%) had a CHA₂DS₂-VASc score of 0. In different studies, the frequency of a CHA₂DS₂-VASc of 0 was from 6% to 10%. In the Danish study, a thromboembolic event (ischemic stroke, peripheral embolism, or pulmonary embolism) after 1 year was reported in 1.67% of the patients with a CHADS, of 0 (1.47%–1.89%) and in 0.78% of the patients with a CHA₂DS₂-VASc of 0 (0.58%–1.04%). Among patients with a CHADS, of 0, moderate risk was observed in 39.5% and high risk in 21.7% when reassessed by the CHA₂DS₂--VASc scheme. In this study, the thromboembolic risk was compared in patients with and without chronic anticoagulation: the benefit of this therapy was proved in all patients except those with a CHA₂DS₂-VASc of 0.

TABLE 2 Event rates per 100 person-years according to a $CHA_2DS_2\text{-VASc}$ score and to treatment strategy 31

Event	CHA ₂ DS2-VASc = 0 (1 in women)		CHA_2DS_2 -VASc = 1 (2 in women)	
	no treatment	warfarin	no treatment	warfarin
stroke	0.49	0.88	1.55	1.06
ischemic stroke	0.43	0.75	1.50	1.02
bleeding	1.08	1.66	2.74	2.42
intracranial hemorrhage	0.15	0.16	0.36	0.44
death	3.87	2.20	11.3	4.00

In 2013, a new risk scheme, ATRIA, was proposed and compared with CHA_2DS_2 -VASc, also for identification of low-risk patients. Among 47 090 patients with an ATRIA score of 0 to 5, only 35% had a CHA_2DS_2 -VASc of 0 and the risk of stroke of 1.13%/year.²⁸ In other patients, the risk was much higher—from 2.94% to 6.94%/year.

An attempt was also made to determine whether the 2014 Canadian guidelines on AF could really allow to identify low-risk patients.²⁹ It was found that among patients not eligible for anticoagulation, there were patients with an annual stroke risk of 4.32%. An increased risk involved, among others, female patients younger than 65 years old, but with vascular disease.

One of the important validations of a CHA₂DS2-VASc of 0 was a study by Taillandier et al.³⁰ Among 8962 patients with AF, a score of 0 was found in 7%: 273 were anticoagulated, 145 were put on antiplatelet therapy, and 198 did not receive any therapy. In untreated patients, the annual risk of stroke or other thromboembolic event was 0.64%. The risk was not reduced in any of the treatment groups.

In 2015, the largest nonvalvular AF population with a CHA_2DS_2 -VASc of 0 and 1 from Denmark was presented by Lip et al.³¹ For a mean period of 5.9 years, the registries included 20 369 patients without risk factors except female sex (men, a CHA_2DS_2 -VASc of 0; women, a CHA_2DS_2 -VASc of 1). In 14115 patients, no prophylaxis was administered, 2182 patients were on ASA, and 4072 were on warfarin. Untreated patients had an annual risk of stroke of 0.49%; ischemic stroke, 0.43%; bleeding, 1.08%; intracranial bleeding, 0.15%; and death, 3.87%. In patients on warfarin, ischemic stroke was not reduced: 0.75%/year (TABLE 2).

Friberg et al³² analyzed the benefits of anticoagulation against bleeding in patients with AF. Net benefit was defined as the number of ischemic strokes avoided owing to anticoagulation minus the number of excess intracranial bleeding with a weight of 1.5 due to devastating consequences of this event. Only a CHA_2DS_2 -VASc of 0 was able to identify low-risk patients who derived no net clinical benefit or even experienced some disadvantage from anticoagulation.

Current data from the European surveys and registries suggest that more AF patients are anticoagulated, mainly because a wider implementation of the 2010 and 2012 ESC guidelines in clinical practice. However, it seems that patients with a CHA₂DS₂-VASc of 0 are still frequently treated with these agents. In the EURObservational Research Program Atrial Fibrillation (EORP-AF), 56.4% of patients with a score of 0 were anticoagulated (some of them because of planned cardioversion). In the PREvention oF thromboembolic events–European Registry in Atrial Fibrillation (PREFER in AF), the percentage was even higher: 62.6%.³³⁻³⁵

Importantly, in nonvalvular AF, patients with a CHA_2DS_2 -VASc of 0 (1 in women) are really at low risk and do not benefit from anticoagulation.

Do patients with a CHA, DS,-VASc of 1 require anticoagulation? In contrast to a CHA₂DS₂-VAS of 0, where there is no doubt for everyday practice, in patients with a CHA₂DS₂-VASc of 1, there are numerous controversies regarding risk assessment and optimal therapy. Most frequently, the risk is estimated as moderate but sometimes also as low. According to the 2012 ESC guidelines, anticoagulation should be considered after taking into account the bleeding risk and the patient's preference (class IIa recommendation, level of evidence A).¹³ However, in the 2014 United States guidelines for patients with a CHA₂DS₂-VASc of 1, anticoagulation, ASA, or no prophylaxis may be considered (class IIb recommendation, level of evidence C).²

It means that in every 10th patient (6%–15% according to some registries), the clinical decision is difficult. Older CHA_2DS_2 -VASc validations showed a broad range of thromboembolic risk calculated in this group of patients (from 0.55% to 2.94% annually). The differences were due to different definitions of outcomes: from ischemic stroke only to a composite endpoint of ischemic stroke, TIA, as well as systemic and pulmonary embolism.^{18,26,27,36}

In the Journal of American College of Cardiology, analyses from 3 different registries addressing this topic have been published in 2015. Friberg et al³⁶ analyzed data from Sweden: a registry of 140 420 patients with nonvalvular AF without anticoagulation. A CHA, DS, -VASc score of 1 was found in 12298 patients. Different definitions of a thromboembolic event were used: stroke, stroke + systemic embolism, additionally pulmonary embolism, additionally TIA. Isolated stroke was present in 0.1% to 0.2% of women and in 0.5% to 0.7% of men. The prevalence increased to 1.3% when a broader definition was applied. The study concluded that the risk of ischemic stroke in patients with a CHA₂DS₂-VASc of 1 is lower than previously estimated and these patients would not benefit from anticoagulation.

The outcomes of the Taiwan study were different: 186 570 patients with AF not receiving anticoagulation or ASA were studied.³⁷ They evaluated men with a CHA_2DS_2 -VASc of 1 (12 935) and women with a CHA_2DS_2 -VASc of 2 (7900). Among male patients, the annual risk of stroke was 2.75%

TABLE 3 Risk factor components of atrial fibrillation patients with a CHA_2DS_2 -VASc of 1 (excluding sex)^{31,37}

Risk factor	Taiwan cohort ³⁷		Danish cohort ³¹
	male patients $(n = 12935)$	female patients (n = 7900)	male + female patients (n = 9457)
age 65–74 years	38%	33%	56%
hypertension	31%	35%	32%
heart failure	16%	17%	3%
diabetes mellitus	8%	9%	5%
vascular disease	7%	6%	4%

 TABLE 4
 Risk factors for ischemic stroke, transient ischemic attack, or systemic embolism in patients with atrial fibrillation^{27,38}

Risk factor	Risk of ischemic stroke/transient ischemic attack/ systemic embolism: hazard ratios (95% CI)		
	Swedish cohort ³⁸	Danish cohort ²⁷	
age 65–74 years	2.97 (2.54–3.48)	3.07 (2.48–3.80)	
female sex	1.17 (1.11–1.22)	1.25 (0.96–1.63)	
vascular disease	1.14 (1.06–1.23)	2.04 (1.29–3.22)	
postmyocardial infarction	1.09 (1.03–1.15)		
post-CABG	1.19 (1.06–1.33)		
peripheral artery disease	1.22 (1.12–1.32)		
hypertension	1.17 (1.11–1.22)	2.32 (1.75–3.07)	
heart failure	0.98 (0.93–1.03)	3.39 (1.84–6.26)	
diabetes	1.19 (1.13–1.26)	3.31 (2.00–5.46)	

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval

(from 1.96%/year in vascular disease to 3.5%/year for patients aged 65–74 years); in women, the annual risk of stroke was 2.55% (from 1.91%/year in hypertension to 3.34%/year for patients aged 65–74 years). The stroke rates were much higher than those in the Swedish study, especially in patients aged 65 to 74 years. This finding could be attributed to racial differences.

Recently, Lip et al³¹ published an analysis of the Danish registry data. The risk criteria were similar to those in the Taiwan study: for men, a CHA₂DS₂-VASc of 1, and for women, a CHA₂DS₂-VASc of 2 (1 risk factor in addition to female sex). The study population consisted of 9457 patients with AF without anticoagulation or ASA, 3171 patients on ASA and 6403 patients on warfarin. In untreated patients, the annual rate of events was as follows: stroke, 1.55%; ischemic stroke, 1.50%; bleeding, 2.74%; intracranial bleeding, 0.36%; and death, 11.3%. Patients with a CHA₂DS₂-VASc of 1 (2 in women), when compared to those with a CHA₂DS₂-VASc of 0 (1 in women) showed an increase in the annual risk of stroke by 3.01-fold, bleeding by 2.35-fold, and death by 3.12-fold. In patients treated with warfarin, the annual incidence of stroke and death was lower than in those receiving ASA or in untreated patients (TABLE 2). The study confirmed that also in European patients with 1 risk factor (2 in women), the rates of events are significantly higher than in patients

with a CHA_2DS_2 -VASc of 0 (1 in women), but importantly, they are lower in patients on warfarin, especially regarding mortality. Differences in outcomes from various studies are surprising and hard to explain.

In patients with a CHA₂DS₂-VASc of 1 (2 in women), thromboembolic risk factors are not similarly distributed across study populations. Usually the most frequent risk factor is age of 65 to 74 years, followed by hypertension. Heart failure, vascular desease, or diabetes are less frequent factors affecting the CHA₂DS₂-VASc of 1 (TABLE 3). Thromboembolic risk for every single factor is different, and the results from studies are not consistent. The Swedish trial revealed that the risk of thromboembolic events (stroke, TIA, or peripheral emboli) was the highest for the age of 65 to 74 years.³⁸ The Danish study showed a significant effect of age as well as of diabetes and heart failure (TABLE 4).^{27,31,39} Inconsistent data require an individualized approach to a patient with a CHA₂DS₂-VASc of 1 when deciding on the need for anticoagulation.⁴⁰⁻⁴²

The decision on the use of anticoagulation is also based on bleeding risk assessment, usually with the HAS-BLED score. If the score is 3 or higher, the risk of bleeding is significant.¹³ It does not require discontinuation of anticoagulation, but the therapy needs to be modified to reduce the risk. In everyday practice, we should optimize hypotensive therapy, reconsider simultaneous antiplatelet therapy, discontinue nonsteroidal anti-inflammatory drugs if possible, or stop alcohol drinking.

The net benefit analysis of Friberg et al³² showed that patients with a CHA_2DS_2 -VASc of 1 benefit from anticoagulation. A similar net clinical benefit analysis has been recently performed by Lip et al⁴³ on the basis of the Danish AF cohort. This analysis supported the benefit of stroke prevention with oral anticoagultion compared with no therapy or with therapy with ASA among patients with AF who have a single stroke risk factor other than a sex factor. The benefit may be greater with nonvitamin K antagonist oral anticoagulants (NOACs) than with warfarin because of their better efficacy and safety compared with vitamin K antagonists in clinical trials.⁶⁻⁸

Eckman et al⁴⁴ performed a risk-modeling analysis, the results of which should be useful in decision making when considering anticoagulation treatment. The use of vitamin K antagonists is justified when the annual risk of stroke is higher than 1.7%. NOACs are associated with a lower risk of intracranial bleeding and should be considered when the annual risk of stroke exceeds 0.9%.⁶⁻⁸ Lower-risk patients, do not require chronic anticoagulation.

The presented data, which are highly inconsistent, come from retrospective but large registries. They were not designed to answer the question of whether patients with AF and low risk of stroke require anticoagulation, and the CHA₂DS₂-VASc was assessed post hoc. Patients with a score of 1 should be recruited to a randomized, prospective trial and compared with placebo; however, no such trial has been performed so far. We hope that the registries such as Global Anticoagulant Registry in the FIELD (GARFIELD) and Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation (GLORIA-AF) will explain whether patients with a CHA₂DS₂-VASc of 1 (2 in women) should be anticoagulated, and if not, who should receive anticoagulation.

In some disputable cases, other markers of thromboembolic risk, not included in the CHA_2DS_2 -VASc scheme, could be used, such as the size of the left atrium, presence of echogenic blood or thrombus on echocardiography, morphology of the left atrial appendage assessed by computed tomography (CT) or magnetic resonance imaging (MRI), presence of silent stroke signs on CT or MRI, biomarkers, coagulation markers, as well as the type and burden of AF.^{2,11,13,45}

Recently, the effect of left atrial appendage morphology on the risk of stroke has been examined. In a multicenter study, Di Biase et al⁴⁵ investigated the left atrial appendage by CT and MRI in 932 patients. They found that so called chicken-wing morphology (48% of patients) is the most favorable. In a multivariate analysis, the other morphologies carried a higher risk of stroke or TIA: cactus, 4-fold; windsock, 4.5-fold; and cauliflower, 8-fold. Based on these findings, a new algorithm for risk assessment for patients with a CHA₂DS2-VASc of 0 and 1 was proposed.⁴⁶ Patients with chicken-wing morphology could be left without anticoagulation; however, further studies are needed to confirm this finding.

Patients' preference is important when deciding on anticoagulation in patients with a CHA_2DS_2 -VASc of $1.^{2,13,47}$ Potential benefits and risk of therapy should be discussed thoughtfully during a detailed medical interview. Interestingly, data from questionnaires found that a considerable number of patients with nonvalvular AF will accept over 4 bleeding episodes to protect themselves from 1 stroke.⁴⁸

Summary Patients with nonvalvular AF and a CHA_2DS_2 -VASc of 0 (1 in women) have a very low risk of stroke and other thromboembolic events and do not benefit from anticoagulation therapy. Most of these patients do not require protection.

In patients with a score of 1 (2 in women), the decision is more complicated. Data on thromboembolic risk from recent trials are contradictory: in the Swedish study, it was found to be low but in the Danish and Taiwan studies—to be significantly higher. According to the ESC 2012 guidelines on AF, anticoagulation should be considered in this group of patients after the assessment of bleeding risk and patients' preference. The United States guidelines are more flexible. Therefore, decision making in individual patients can be sometimes difficult. The female patient without other risk factors should not be anticoagulated. From the practical point of view, the most frequent risk factor is the age of 65 to 74 years— the most important contributor to thromboembolic risk. Thus, these patients require anticoagulation. Owing to a dynamic nature of thromboembolic risk, patients should be reassessed on a regular basis.

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ARTYKUŁ POGLĄDOWY

Pacjenci z migotaniem przedsionków i małym ryzykiem udaru mózgu – czy rzeczywiście wymagają antykoagulacji?

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SŁOWA KLUCZOWE

STRESZCZENIE

antykoagulacja, migotanie przedsionków, ryzyko udaru mózgu, ryzyko zakrzepowo-zatorowe

Migotanie przedsionków (AF) istotnie zwiększa ryzyko powikłań zakrzepowo-zatorowych, szczególnie udaru mózgu. Udowodniono, że leczenie przeciwzakrzepowe redukuje to zagrożenie i dlatego powinno być stosowane przez całe życie. Jednak wśród chorych z niezastawkowym AF ryzyko jest niejednorodne i istnieje populacja pacjentów niskiego ryzyka. Zasady postępowania dotyczące decyzji o potrzebie antykoagulacji polegają na ustaleniu w pierwszej kolejności, czy nasz pacjent jest w grupie niskiego ryzyka. Skala CHA, DS,-VASc jest obecnie najpowszechniej zalecaną do oceny ryzyka zakrzepowo-zatorowego u chorych z niezastawkowym AF. W dużej grupie nieleczonych pacjentów z punktacją CHA, DS,-VASc = 0 (u kobiet 1) udar mózgu rejestrowano u 0,49%/rok, udar niedokrwienny u 0,43%/rok, krwawienie u 1,08%/rok, krwawienie śródczaszkowe u 0,15%/rok, a zgon u 3,87%/rok. U chorych leczonych warfaryną częstotliwość udaru niedokrwiennego była podobna. Pacjenci z punktacją 0 (kobiety 1) to chorzy niskiego ryzyka, którzy nie odniosą korzyści z antykoagulacji. Populację niskiego ryzyka definiuje się również jako osoby w wieku <65 lat bez choroby sercowo-naczyniowej, niezależnie od płci. Łącznie stanowi ona 6-10% pacjentów z niezastawkowym AF. Znacznie bardziej kontrowersyjną kwestią jest ryzyko zakrzepowo-zatorowe u chorych z punktacja 1 (kobiety 2), co znalazło odzwierciedlenie w kilku niedawno opublikowanych badaniach. W badaniu szwedzkim oceniono je jako małe, w badaniu tajwańskim i duńskim jako znacząco podwyższone. Inna analiza pokazała, że leczenie z zastosowaniem antagonisty witaminy K jest uzasadnione, gdy ryzyko udaru wynosi >1,7%/rok. Ze względu na mniejsze ryzyko krwawienia śródczaszkowego przy stosowaniu leków niebędących antagonistami witaminy K antykoagulacja jest zasadna już od poziomu ryzyka >0,9%. Mniejsze ryzyko oznacza brak potrzeby przewlekłej antykoagulacji.

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