ORIGINAL ARTICLE

Correlations of C-reactive protein, von Willebrand factor, and carotid artery intima-media thickness with CHA_2DS_2-VASc in patients with acute atrial fibrillation

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KEY WORDS

atrial fibrillation, C-reactive protein, intima-media thickness, stroke risk, von Willebrand factor

ABSTRACT

INTRODUCTION The risk of stroke in patients with atrial fibrillation (AF) seems to be independent of the presence or duration of arrhythmia at a given moment. However, there is no single approved measurable parameter that would allow to predict the risk of stroke in patients with newly diagnosed AF.

OBJECTIVES We aimed to determine the levels of von Willebrand factor (vWF) and high-sensitivity C-reactive protein (hs-CRP) as well as to measure the intima-media thickness (IMT) in patients in the first hours of an AF episode and compare these markers with predicted risk of stroke.

PATIENTS AND METHODS The study group consisted of 60 consecutive adult patients with symptomatic AF lasting less than 48 hours. In all patients, vWF and hs-CRP levels as well as IMT were measured and compared with the calculated CHA_2DS_2-VASc score.

RESULTS We found a significant difference in the levels of the measured markers (vWF, 110.3% [range, 92.3%–124.2%] vs 170.2% [range, 111.1%–219.5%], $P < 0.005$; hs-CRP, 1.08 mg/l [range, 0.46–2.49 mg/l] vs 3.43 mg/l [range, 1.59; 5.95 mg/l]; $P < 0.005$) and IMT (0.62 mm [range, 0.56–0.71 mm] vs 0.75 mm [range, 0.63–0.81 mm], $P = 0.01$) between patients with a CHA_2DS_2-VASc score of less than 2 and those with a score of 2 or higher. Using the receiver operating characteristic curves, we determined the optimal cut-off points for hs-CRP (1.27 mg/l), vWF (153.25%), and IMT (0.65 mm), which allowed us to identify patients requiring oral anticoagulation.

CONCLUSIONS The tested parameters allow, with moderate sensitivity and specificity, to predict the presence of indications for chronic oral antithrombotic prophylaxis in patients with newly diagnosed AF. In order to determine the real ability of these parameters to predict stroke, a prospective long-term follow-up is required.

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INTRODUCTION Atrial fibrillation (AF), the most common sustained arrhythmia affecting primarily patients already burdened with cardiovascular diseases,[1,2] is associated with an increased risk of thromboembolic complications, of which ischemic stroke is the major clinical manifestation. The incidence of ischemic stroke in patients with nonrheumatic AF is approximately 5% per year, which is 4- to 5-fold higher than in the population with sinus rhythm.[3,4] It is recognized that actually every fifth stroke is associated with AF.[5] Asymptomatic AF episodes are considered to be one of the major causes of cryptogenic stroke.[6,7] Ischemia of the central nervous system caused by AF is associated with a 2-fold higher mortality rates than for other reasons, and the neurological defect caused by this type of stroke is generally deeper, leading to more severe disability and 1.5-fold higher costs of poststroke care.[8,9] Also the relationship between both symptomatic and asymptomatic AF and the pathogenesis of vascular dementia is being considered.[10]

Regardless of the leading role of flow disturbances in the left atrial appendage and

cardioembolic mechanisms, a different pathogenesis of stroke in patients with AF is possible. The presence of a thrombus in the left atrial appendage was confirmed in only 21% to 23% of patients with stroke complicating acute onset of AF.[11] Even every fourth stroke in patients with AF may be due to cerebrovascular disease, atherosclerosis of the aorta, and embolization from other cardiac causes.[12] The majority of elderly patients with AF suffer from arterial hypertension,[13] and every eighth patient suffers from previously unrecognized carotid artery stenosis.[14] Atherosclerosis is also a recognized independent risk factor for stroke in AF.

Interestingly, there was no difference in the incidence of stroke between patients with paroxysmal and persistent or permanent AF.[15] Furthermore, it has been shown that among patients with paroxysmal AF, a significant proportion of strokes occurs during sinus rhythm (in the Canadian Atrial Fibrillation Trial of 8 in 9 strokes).[16] The phenomenon of atrial stunning may partially explain the above data. However, it appears that the tendency for thromboembolism is characteristic of patients with a history of AF regardless of the presence of active arrhythmia and could be connected with general inflammatory burden, prothrombotic state,[17] and endothelial dysfunction.

Research that formed the basis for the development of the CHA_2DS_2-VASc risk scale indicates that the risk of stroke depends more on age, sex, and comorbidities affecting the cardiovascular system rather than on the characteristics of the arrhythmia. Generally, it must be acknowledged that the search for simple biochemical factors that allow us to predict prognosis in patients with AF has not brought spectacular effects so far.[18,19] In particular, no single measurable parameter constituting a considered predictor of stroke in patients with AF has been previously described. Therefore, we aimed to assess the levels of high-sensitivity C-reactive protein (hs-CRP) and von Willebrand factor (vWF) as well as to measure the intima-media thickness (IMT) of the common carotid arteries in patients with an acute onset of AF and compare these markers with the calculated CHA_2DS_2-VASc score.

PATIENTS AND METHODS We included 60 consecutive adult patients from the Clinical Department of Internal Diseases and Geriatrics, University Hospital in Krakow, Poland, with a symptomatic onset of AF lasting less than 48 hours and scheduled for pharmacological cardioversion (and therefore classified as having persistent AF according to the European Society of Cardiology guidelines). The exclusion criteria were as follows: hemodynamic instability, acute coronary syndrome, acute or chronic inflammatory disease, cancer, or lack of consent to participate in the study.

All patients underwent a physical examination for the presence of inclusion and exclusion criteria. Atrial fibrillation was confirmed by electrocardiography. The time of arrhythmia onset was established on the basis of a medical interview and considering only symptoms that may be associated with arrhythmia (such as palpitations, anxiety in the precordial area, and others). Patients with symptoms not necessarily related to arrhythmia (such as malaise, worse exercise tolerance, and others) were excluded. The presence of inflammatory disease or cancer was excluded on the basis of the patient's medical history and records, physical examination, and other relevant tests if necessary.

Data obtained from patients in the interview, complemented by information from the available medical records, were systematized using a questionnaire consisting of basic demographic data and concomitant diseases. The CHA_2DS_2-VASc score was calculated for every patient, with 1 point scored for age from 65 to 74 years, female sex, presence of heart failure, hypertension, diabetes, and vascular disease (peripheral artery disease, previous myocardial infarction, aortic plaque) and 2 points scored for age of 75 years or older and a history of stroke or transient ischemic attack or thromboembolism.

Blood samples were drawn from antecubital veins into EDTA tubes from all patients in the fasting state. The levels of hs-CRP were measured using routine methods. Each patient had the levels determined twice within a 7-day interval, and the average from the 2 measurements was considered as the result. To measure vWF levels, the samples were centrifuged for 15 minutes at 3500 rpm. The supernatant was frozen at –70°C until the analysis. After collection, the set of samples was thawed at the Diagnostic Unit of the University Hospital, and the levels of both markers were determined. Plasma human concentrations of vWF (Stago Diagnostic S.A.S., Nanterre, France) were measured using a commercially available enzyme-linked immunosorbent assay kit. Each measurement was performed according to the manufacturer's instructions. The concentration of vWF was expressed as the percentage of the mean plasma concentration in healthy population.

All patients had their IMT measured. Methodology was based on the recommendations of the Mannheim consensus. A bilateral carotid ultrasound in the presentation of B-mode was performed using a GE Vivid 3 Ultrasound linear 10 MHz probe (GE Medical System, Milwaukee, Wisconsin, United States). Patients were examined in the supine position with the head laid in a deviation of approximately 45° relative to the sagittal plane of the body. The artery was visualized on both sides in the longitudinal dimension, from the anterior-oblique, lateral, or posterior-oblique angle, depending on the best presentation of the intima-media complex. IMT was assessed at the distal wall of the common carotid artery at a distance of 1 centimeter before the bifurcation. The fragment of the wall with a well-visible intima-media complex, without atherosclerotic plaques, was analyzed. For this purpose, the following

TABLE 1 General characteristics of the study groups based on the presence of risk factors used in the CHA_2DS_2-VASc risk scale

Parameter	CHA_2DS_2-VASc <2	CHA_2DS_2-VASc ≥2	*P* value
n	17	43	–
age, y	55.82 ±10.51	68.84 ±8.46	<0.005
male sex	14 (82)	19 (44)	<0.05
hypertension	7 (41)	43 (100)	<0.005
heart failure	1 (6)	16 (37)	<0.005
diabetes	1 (6)	11 (26)	<0.005
history of stroke	0 (0)	6 (14)	<0.005
vascular disease	4 (24)	30 (70)	<0.005

Data are presented as mean ± standard deviation or number (percentage) of patients.

definitions were used: 1) IMT on ultrasound was a structure composed of 2 parallel lines corresponding to the limits: lumen/intima and media/adventitia; and 2) atheromatous plaque on ultrasound is a focal structure bulging into the lumen of at least 0.5 mm or constituting the extension of the surrounding intima-media complex by at least 50%, as well as the corresponding enlargement of the intima-media complex of more than 1.5 mm.

The whole study was synchronized with electrocardiography. A still image in the final phase of diastole, attributable to the R wave, was then evaluated using the original device software, GE Vivid 3 Ultrasound (GE Medical System). As the final value, the average of the measurements on both external carotid arteries was calculated.

All statistical analyses were performed with the Statistica 10 software (StatSoft Inc., Tulsa, Oklahoma, United States). Data were presented as a mean ± standard deviation or as a median and interquartile range in the case of non-normal distribution. The 2 independent groups of variables were compared using the nonparametric Mann–Whitney test.

Using the receiver operating characteristic (ROC) curve, we identified the optimal cut-off points for the tested parameters that allowed to predict the presence of indications for oral anticoagulation. To assess this ability of the test panel, we calculated the area under the ROC curve. A *P* value of less than 0.05 was considered statistically significant.

RESULTS The study group consisted of 60 patients aged from 26 to 88 years (mean age, 65.15 ±10.76 years; 27 women [45% of the patients]). The mean CHA_2DS_2-VASc score was 2.82 ±1.77. The characteristics of the study group are shown in **TABLE 1**.

The median plasma levels of vWF were 135.5% (range, 102.5%–210.1%), and of hs-CRP, 2.15 mg/l (range, 1.01–4.79 mg/l). The median IMT was 0.71 mm (range, 0.61–0.81 mm). We found several differences in the levels of individual markers depending on the presence of individual risk factors (**FIGURE 1A–C**). In addition, we observed significant differences in the levels of the measured markers between patients with a $CHADS_2$-VASc score of less than 2 and those with a score of 2 or higher (which are considered an optional and mandatory indication for chronic oral anticoagulation, respectively). The levels were as follows: vWF, 110.3% (range, 92.3%–124.2%) vs 170.2% (range, 111.1%–219.5%), P <0.005; hs-CRP, 1.08 mg/l (range, 0.46–2.49 mg/l) vs 3.43 mg/l (range, 1.59–5.95 mg/l), P <0.005; and IMT, 0.62 mm (range, 0.56–0.71 mm) vs 0.75 mm (range, 0.63–0.81 mm), P = 0.01.

Using the ROC curves, we determined the optimal cut-off points for hs-CRP, vWF, and IMT that allowed to identify patients requiring oral anticoagulation (**FIGURE 2**). The tested parameters were characterized by moderate sensitivity and specificity in predicting the indications for anticoagulation (**TABLE 2**). As cut-off points, we selected the values with the highest sensitivity and specificity. However, it is worth noting that the vWF level exceeding 182.7% had a specificity of 100% in predicting indications for anticoagulation, but the corresponding sensitivity was only 46.3%.

TABLE 2 Sensitivity and specificity of the tested parameters in predicting indications for chronic oral anticoagulation

Parameter	Cut-off	Sensitivity	Specificity	AUC	95% CI
hs-CRP, mg/l	1.27	78.0%	68.7%	0.756	0.619–0.893
vWF, %	153.25	58.5%	94.1%	0.752	0.630–0.873
IMT, mm	0.65	72.5%	66.7%	0.726	0.583–0.868

Abbrevations: AUC, area under the curve; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; IMT, intima-media thickness; vWF, von Willebrand factor

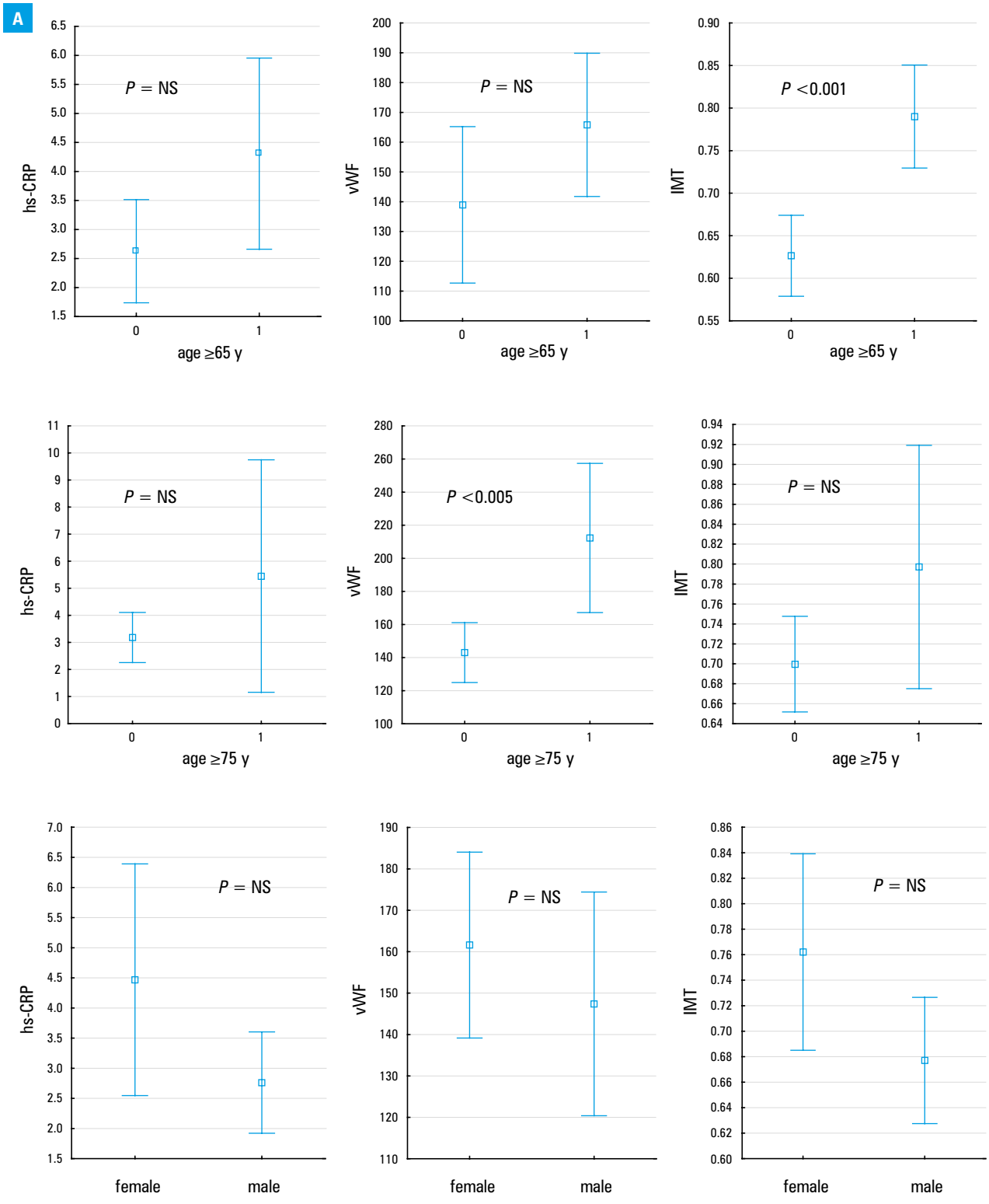


FIGURE 1 **A** – levels of high-sensitivity C-reactive protein, von Willebrand factor, and intima-media thickness in the subgroups of patients divided by the presence of particular risk factors according to the CHA_2DS_2-VASc risk scale
Data presented as mean ± standard deviation.
Abbreviations: NS, nonsignificant; others, see **TABLE 2**

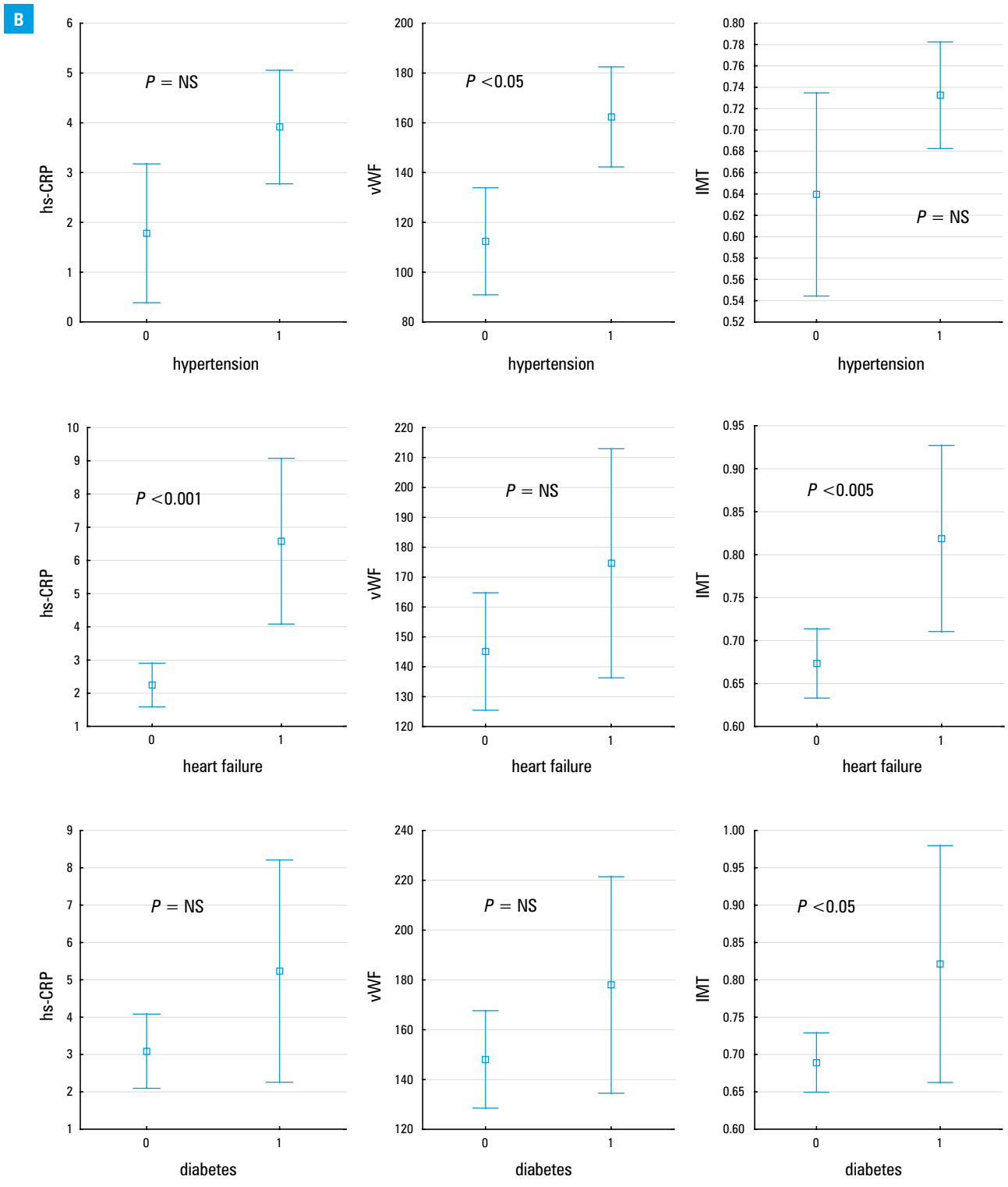


FIGURE 1 **B** – levels of high-sensitivity C-reactive protein, von Willebrand factor, and intima-media thickness in the subgroups of patients divided by the presence of particular risk factors according to the CHA_2DS_2-VASc risk scale
Data presented as mean ± standard deviation.
Abbreviations: see **FIGURE 1 A**

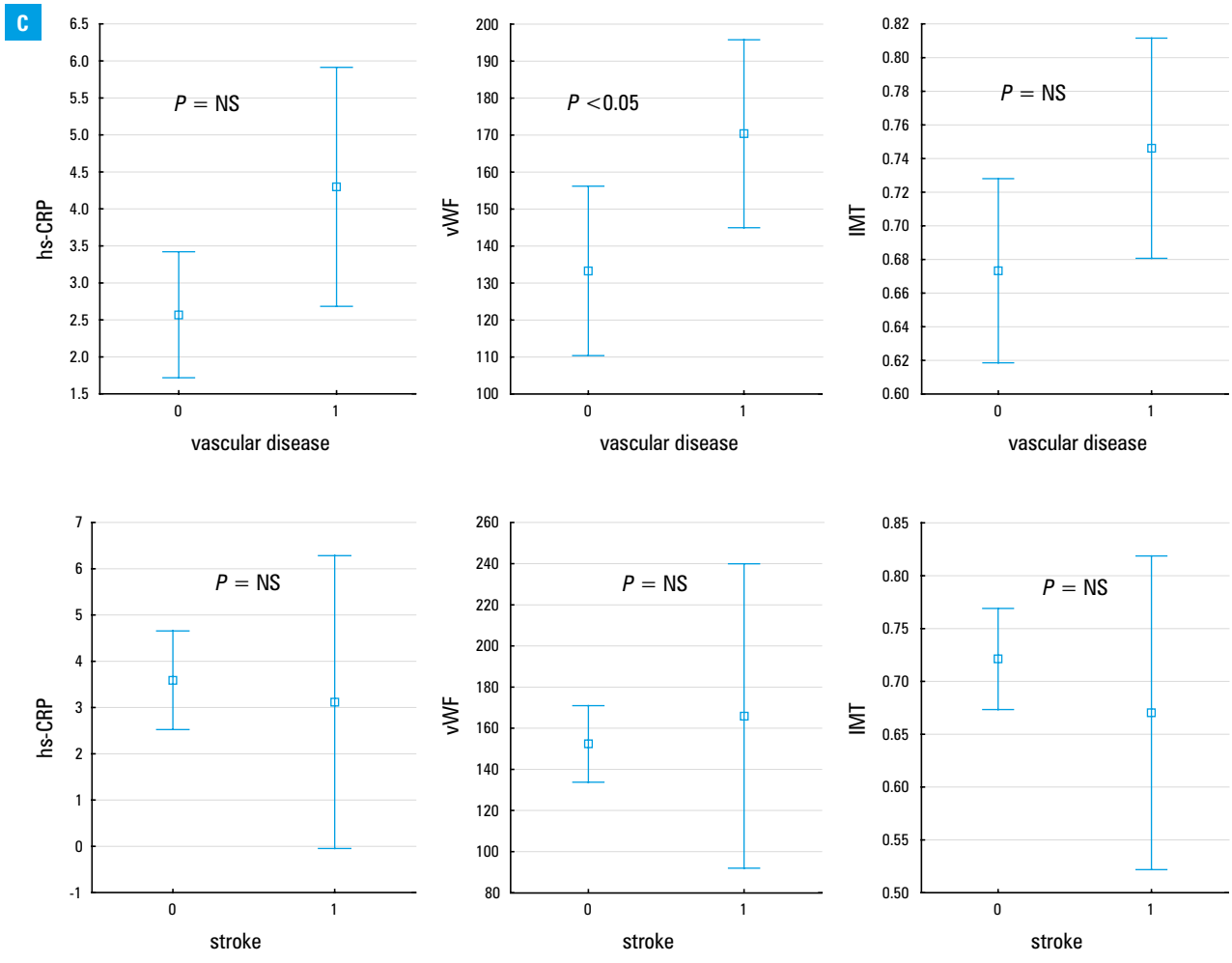


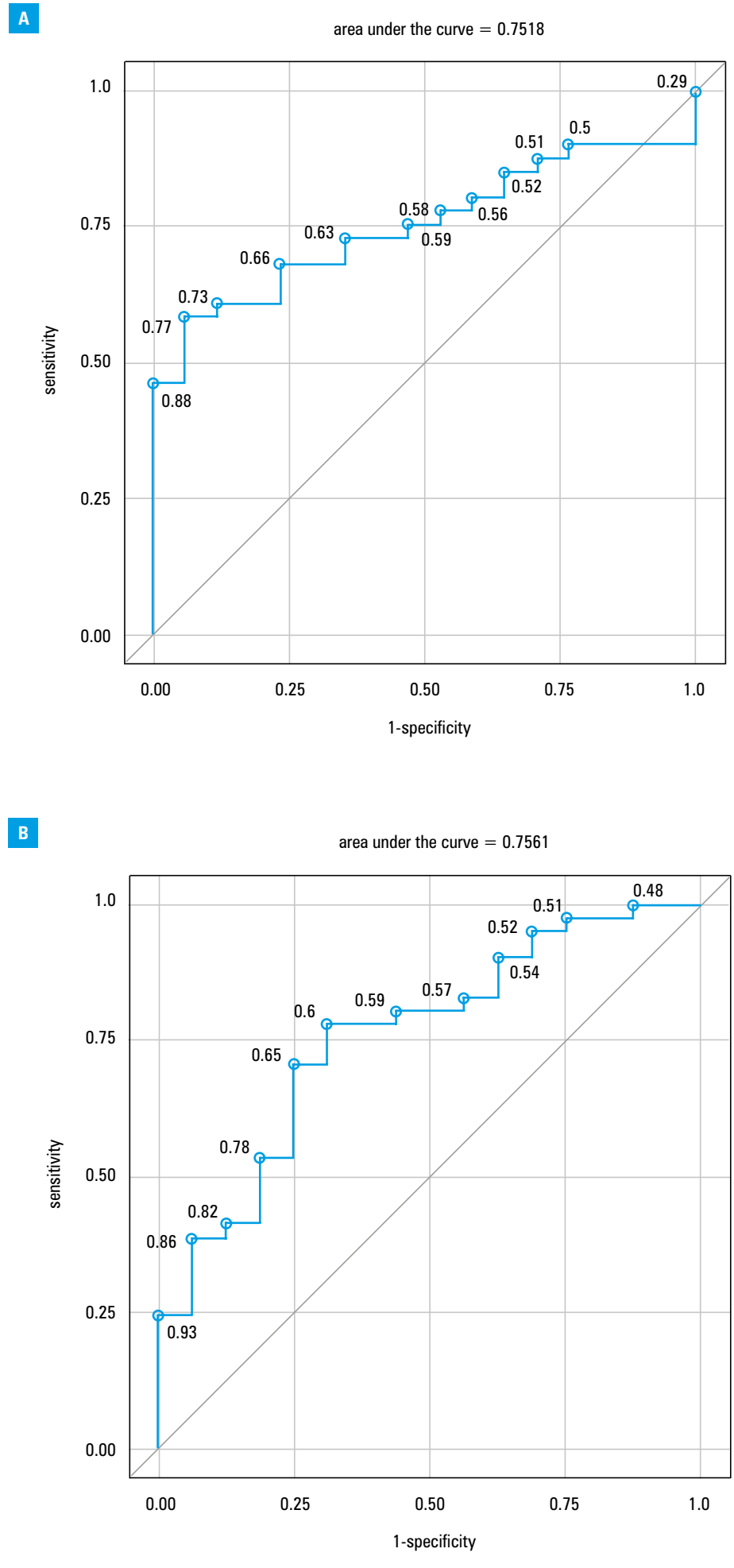
FIGURE 1 C – levels of high-sensitivity C-reactive protein, von Willebrand factor, and intima-media thickness in the subgroups of patients divided by the presence of particular risk factors according to the CHA_2DS_2-VASc risk scale
Data presented as mean ± standard deviation.
Abbreviations: see **FIGURE 1 A**

DISCUSSION The decision to introduce antithrombotic therapy has a greater impact on the outcome of patients with AF than the decision to restore sinus rhythm. A method using measurable, biochemical, or imaging studies to determine the risk of stroke in patients with AF has not been developed so far. The available risk scales are based on clinical judgment and the presence of several comorbidities. They are simple to use and widely accessible, but in practice they cause numerous difficulties.[20,21] The aim of this study was to assess the possibility of using the selected parameters as surrogate markers of venous thromboembolic risk in patients with newly diagnosed AF. If measurable differences in hs-CRP levels, vWF levels, and IMT were confirmed, this finding might serve as the basis for further prospective studies on the role of these markers as indicators of the need for anticoagulant treatment in patients with unclear medical history, borderline risk, or unusual health burdens. Our study demonstrated that the biochemical markers of endothelial function (vWF) and inflammatory activation (hs-CRP) as well as the ultrasound measurement of atherosclerosis progression (IMT) may be used to differentiate patients with low and high risk of stroke.

Heppell et al[22] were the first to link the markers of endothelial function with the risk of cardioembolic complications in AF. They showed that a high concentration of vWF is an independent risk factor for left atrial thrombus formation in this group of patients.[22] vWF, as a molecule linking endothelial dysfunction with activation of the coagulation system, constitutes a part of the hypercoagulability pathomechanism in AF. The role of this compound was further confirmed by Conway et al[23] in the SPAF III study. In a large group of more than 1300 patients with permanent AF, they showed that the concentration of vWF increases in subgroups classified on the basis of their own stroke risk stratification system (including age, sex, presence of hypertension, heart failure, and a history of thromboembolic event). These results were later confirmed in a smaller subgroup of patients treated with aspirin.[24]

Similar findings were reported by Roldan et al[25] in a group of 200 patients. vWF levels were

FIGURE 2 Receiver operating characteristic curves for von Willebrand factor (**A**), high-sensitivity C-reactive protein (**B**), and intima-media thickness (**C**, see p. 842) in the prediction model of CHA_2DS_2-VASc ≥2 points



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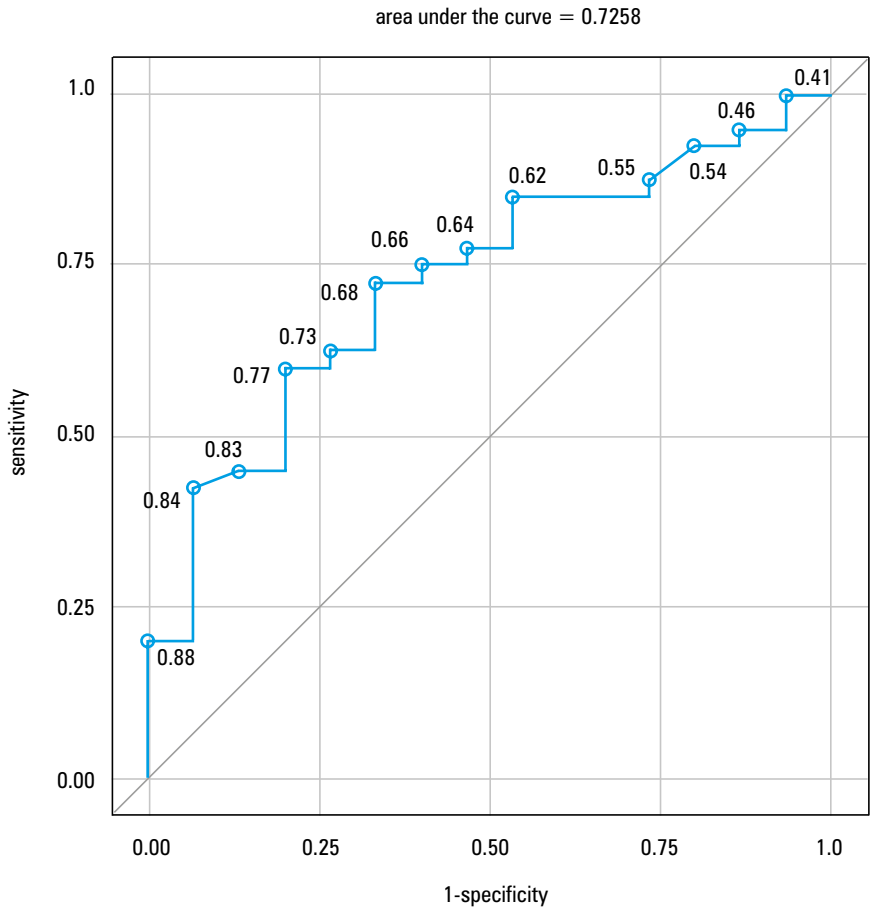

shown to correlate with the $CHADS_2$ and Framingham risk scores. No correlation was observed for E-selectin, which indicates that not all markers of endothelial dysfunction are associated with the risk of stroke. On the other hand, Lip et al[26] found that the inclusion of vWF levels can improve the prognostic value of $CHADS_2$ and Birmingham scales in predicting stroke and vascular events.[26] The cut-off point for vWF was established at a level of 158 IU/dl. Recently, in a prospective study, Ehrlich et al[27] reported that in patients with AF, vWF levels exceeding 0.7 U/ml are a risk factor for an adverse cardiovascular event or death. However, this finding lost significance in a multivariate analysis. vWF levels are also higher in stroke patients with AF than in those without AF and correlate with the severity, outcome, and infarct size of stroke.[28] Of note, the majority of the above studies included patients with chronic AF, with the exception of Ehrlich et al[27] who included patients with different forms of AF. To our knowledge, our study is the first to have investigated the association between vWF levels and a projected risk of stroke in patients with acute onset of AF.

A little more is known about the relationship of hs-CRP levels with stroke in patients with AF. A study by Lip et al,[29] who assessed the concentration of this marker in patients with nonvalvular chronic AF, found a positive correlation beetween hs-CRP levels and the estimated risk of stroke calculated with $CHADS_2$, Nice, and SPAF III scales. This was mainly due to a higher concentration of hs-CRP in patients with diabetes, hypertension, heart failure, ischemic heart disease, and peripheral vascular disease, which suggests that a similar effect could be achieved for the CHA_2DS_2-VASc risk score, which is the current standard in clinical practice. Ederhy et al[30] suggested that the inclusion of hs-CRP levels in risk stratification using the commonly available scales allows to better predict the presence of thrombus in the left atrium.[30] We have not identified any study in the available literature that would evaluate hs-CRP levels and endothelial function for prognostic purposes in patients with AF. However, there has been a report by Huang et al[31] who indicated that a simultaneous assessment of flow-mediated dilation and hs-CRP levels in patients with sinus rhythm can better predict the risk of adverse cardiovascular events, including stroke.[31]

In our study, IMT showed the weakest predictive ability. However, the association of carotid IMT with the presence of risk factors included in the CHA_2DS_2-VASc scale is unquestionable. On the other hand, according to our knowledge, there have been no studies evaluating the prognostic value of IMT in predicting stroke in patients with AF. However, interestingly, Chlumsky et al[32] studied only patients with a history of stroke and, paradoxically, observed a smaller size of IMT in patients with AF compared with those in sinus rhythm. In the majority of previous studies evaluating IMT as a predictor of stroke, AF was

treated as an exclusion criterion because investigators generally believed that the pathogenesis of ischemic stroke in patients with AF was clearly different. In light of studies showing a significant incidence of noncardioembolic neurological events in AF, we should verify this approach in a prospective study and attempt to determine the significance of IMT in stroke prediction also in this group of patients.

In conclusion, vWF, hs-CRP, and IMT allow, with moderate sensitivity and specificity, to predict the presence of indications for chronic oral anticoagulant therapy in relation to clinical risk scores. In order to determine the real ability of these parameters to predict stroke, a prospective long-term follow-up is required.

Contribution statement KR and TG conceived the idea for the study and contributed to the design of the research project as well as analysis of the results. KR was involved in data acquisition and preparation of the manuscript. Both authors edited and approved the final version of the manuscript.

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ARTYKUŁ ORYGINALNY

Korelacja poziomu białka C-reaktywnego, czynnika von Willebranda oraz grubości kompleksu *intima-media* tętnic szyjnych ze skalą CHA_2DS_2-VASc u pacjentów ze świeżym napadem migotania przedsionków

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SŁOWA KLUCZOWE

białko C-reaktywne, czynnik von Willebranda, grubość kompleksu *intima-media*, migotanie przedsionków, ryzyko udaru mózgu

STRESZCZENIE

WPROWADZENIE Ryzyko wystąpienia udaru mózgu u pacjentów z migotaniem przedsionków (*atrial fibrillation* – AF) wydaje się niezależne od obecności lub czasu trwania arytmii w danym momencie. Nie ma jednak pojedynczego, uznanego i mierzalnego parametru, który pozwalałby przewidzieć ryzyko wystąpienia udaru mózgu u pacjentów z nowo rozpoznanym AF.

CELE Celem badania było oznaczenie poziomu czynnika von Willebranda (*von Willebrand factor* – vWF) i białka C-reaktywnego oznaczonego metodą o dużej czułości (*high-sensitivity C-reactive protein* – hsCRP), a także pomiar grubości kompleksu *intima-media* (*intima-media thickness* – IMT) u pacjentów w pierwszych godzinach trwania napadu AF i porównać je z przewidywanym ryzykiem udaru.

PACJENCI I METODY Grupę badaną stanowiło 60 kolejnych dorosłych pacjentów z objawowym AF trwającym krócej niż 48 godzin. U wszystkich chorych zmierzono IMT oraz poziomy vWF i hsCRP, a następnie porównano je z obliczoną wartością CHA_2DS_2-VASc.

WYNIKI Stwierdzono istotną różnicę w poziomach mierzonych markerów (vWF: 110,3% [przedział międzykwartylowy: 92,3–124,2%] *vs* 170,2% [111,1–219,5%], $p < 0,005$; hsCRP: 1,08 mg/l [0,46–2,49 mg/l] *vs* 3,43 mg/l [1,59–5,95 mg/l], $p < 0,005$) oraz IMT (0,62 mm [0,56–0,71 mm] *vs* 0,75 mm [0,63–0,81 mm], $p = 0,01$) między pacjentami z wynikiem CHA_2DS_2-VASc <2 oraz ≥ 2. Następnie za pomocą krzywych ROC ustaliliśmy optymalne punkty odcięcia dla hsCRP (1,27 mg/l), vWF (153,25%) i IMT (0,65 mm) pozwalające rozpoznać pacjentów wymagających doustnej antykoagulacji.

WNIOSKI Badane parametry pozwalają z umiarkowaną czułością i swoistością przewidzieć obecność wskazań do przewlekłej doustnej profilaktyki przeciwzakrzepowej u pacjentów ze świeżo wykrytym AF. Aby ustalić rzeczywistą zdolność tych parametrów do przewidywania udaru mózgu potrzebna jest prospektywna obserwacja długoterminowa.

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