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CARDIOLOGY  
JOURNAL

ISSN: 1897-5593

e-ISSN: 1898-018X

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**Authors:** Maciej Haberka, Andrzej Kubicius, Monika Starzak, Małgorzata Patryka, Zbigniew Gašior

**DOI:** 10.5603/CJ.a2021.0134

**Article type:** Original Article

**Submitted:** 2021-01-17

**Accepted:** 2021-07-02

**Published online:** 2021-10-25

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## **Adiposity, fat depots and the prediction of stroke**

Maciej Haberka et al., Adiposity and stroke

Maciej Haberka<sup>1</sup>, Andrzej Kubicius<sup>2</sup>, Monika Starzak<sup>3</sup>, Małgorzata Partyka<sup>4</sup>, Zbigniew Gąsior<sup>1</sup>

<sup>1</sup>Department of Cardiology, SHS, Medical University of Silesia, Katowice, Poland

<sup>2</sup>Department of Cardiology, Upper Silesia Medical Center, Katowice, Poland

<sup>3</sup>Department of Cardiology, General Hospital No. 4, Gliwice, Poland

<sup>4</sup>Department of Diagnostic Imaging, City Hospital, Chorzow, Poland

Address for correspondence: Maciej Haberka, MD, PhD, Department of Cardiology, SHS, Medical University of Silesia, ul. Ziołowa 45/47, 40–635 Katowice, Poland, tel: +48 32 2527407, fax: +48 32 2523032, e-mail: mhaberka@op.pl

### **Abstract**

**Background:** Despite the progress in research, the utility of clinical assessment for the prediction of stroke is limited. The aim herein, was to evaluate the predictive values of major ultrasound indexes of carotid artery and fat depots for stroke in patients with high and very high cardiovascular (CV) risk.

**Methods:** The study group included 364 patients (age:  $61.3 \pm 7.2$  years old) with typical CV risk factors scheduled for elective coronary angiography (2012–2013). A comprehensive baseline assessment included the following ultrasound indexes: carotid artery intima-media thickness (IMT), extra-media thickness (EMT), epicardial (EFT) and pericardial fat thickness (PFT), abdominal subcutaneous (ASF) and visceral fat (AVF) and combined Periarterial Adipose Tissue Intima Media Adventitia (PATIMA) index. Afterwards, all patients were followed for  $80.9 \pm 7.1$  months.

**Results:** There were 23 strokes and 25 cases with new-onset atrial fibrillation during follow-up. Receiver operating characteristics (ROC) analysis showed, that selected clinical parameters (age, waist circumference [WC], waist hip ratio [WHR]) and ultrasound indexes

(EFT: area under curve [AUC] 0.672,  $p < 0.01$  and PATIMA index: AUC 0.658,  $p < 0.01$ ) were predictive for stroke. However, their predictive values showed no significant differences ( $p = \text{NS}$ ). The baseline body mass index (BMI) was the only parameter, which showed a prediction for new-onset atrial fibrillation (BMI  $> 33 \text{ kg/m}^2$ : sensitivity 65%, specificity 76%).

**Conclusions:** It was found that age, WC and echocardiographic EFT revealed significant predictive values for stroke. Both WC and EFT showed a very high NPV suggesting that they should be implemented into the clinical practice as a tool affirming a very low risk of stroke.

**Key words:** epicardial fat, extra-media thickness, intima media thickness, atrial fibrillation, stroke

## INTRODUCTION

Cerebrovascular disease is an important cause of disability and mortality in developed countries [1]. Atrial fibrillation (AF) is one of the major causes of ischemic stroke [2] and cardioembolism is the most frequent cause of cryptogenic events [3]. Obesity is another world-wide medical problem increasing the risk of several cardiovascular (CV) diseases and complications [4]. However, the estimation of CV risk in patients with several comorbidities is difficult. Obesity has a few phenotypes, which are associated with different risk, especially in patients with chronic CV diseases [5]. This is explained by fat depots with a more or less active role in metabolism or local pathophysiology of arterial wall or heart muscle [6]. Previous studies showed that perivascular fat thickness is associated with cardiometabolic risk [7–9], peripheral atherosclerosis [10] and the severity of coronary artery disease [11, 12]. Whereas abdominal visceral adipose tissue is more associated with metabolic risk [9, 10].

Despite the great progress in research, the utility of clinical assessment for the prediction of stroke is still limited. Therefore, the aim herein, was to evaluate the predictive values of major ultrasound indexes of carotid artery and fat depots for stroke in patients with high and very high CV risk.

## METHODS

### Study group

All the consecutive patients (age: 50–75 years old) scheduled for CV diagnostics in the Department of Cardiology (2012–2013) were recruited to the study group. The following exclusion criteria were used at the screening: heart failure, significant heart valve defects,

chronic inflammatory diseases, neoplastic diseases in the prior 5 years, secondary causes of obesity or prior interventions in obesity, a 10% unintentional weight loss, a poor carotid artery image quality and a genetic predisposition for CV diseases.

Subjects completed the study at the Department of Cardiology at the Medical University of Silesia (SUM). The protocol was approved by the SUM Ethics Committee. This work was supported by a research non-commercial grant from the Medical University of Silesia (KNW-1-029/N/8/K).

### **Clinical characteristics**

A comprehensive clinical assessment and the following ultrasound indexes were obtained in all patients: abdominal subcutaneous fat (ASF), abdominal visceral fat (AVF), carotid intima-media thickness (IMT), carotid extra media thickness (EMT), epicardial fat thickness (EFT), pericardial fat thickness (PFT) and the periarterial adipose tissue intima media adventitia (PATIMA) index.

Hyperlipidemia was determined based on plasma lipid levels or prior diagnosis and current treatment [13]. The diagnosis of hypertension was confirmed by the office blood pressure or prior diagnosis and current treatment [13]. Diabetes mellitus (DM) was reported in patients with prior diagnosis or abnormal fasting plasma glucose concentration ( $\geq 126$  mg/dL) or HbA1c ( $\geq 6.5\%$ ) or 2-h post-load plasma glucose ( $\geq 200$  mg/dL) in case of discrepancies [14, 15].

Obesity was classified according to body mass index ( $BMI = \text{body mass (kg)} / \text{height (m)}^2$ ) as normal weight (18.5–24.9 kg/m<sup>2</sup>), overweight (25.0–29.9 kg/m<sup>2</sup>) and obesity ( $\geq 30.0$  kg/m<sup>2</sup>): class 1 (30.0–34.9 kg/m<sup>2</sup>), class 2 (35.0–39.9 kg/m<sup>2</sup>) and class 3 ( $\geq 40.0$  kg/m<sup>2</sup>). Chronic kidney disease was determined based on estimated glomerular filtration rate ( $< 60$  mL/min/1.73 m<sup>2</sup>) or prior diagnosis and treatment. Waist circumference (WC: midpoint between the lowest rib and the iliac crest) and hip circumference (HC) were measured with a tape at the end of expiration. Coronary artery disease was defined as stenosis  $\geq 50\%$  in any major coronary artery assessed in coronary angiography. Finally, CV risk was estimated for each of the study patients based on the European Society of Cardiology guidelines [13].

### **Ultrasound indexes**

All the ultrasound scans were analyzed offline blinded to the patient's data with the intra- and interobserver variability as shown previously [11].

### **Carotid artery indexes: IMT and EMT**

All the patients were in a supine position at the ECG-gated ultrasound examination of both carotid arteries (GE Vivid 9, Milwaukee, US — linear transducer 9–12 MHz). All the images were recorded by an experienced researcher using constant settings and once the recruitment was finished, images with the region of interest were analyzed offline blinded to patient's data. Common carotid artery IMT was measured according to the Mannheim Consensus guidelines on a 10 mm-length segment starting 5 mm proximally to the carotid bulb using a semi-automated GE software [16]. Carotid IMT was an average value of both sides' carotid arteries.

Carotid EMT was measured in the images obtained in an alternative (to IMT) scanning of the carotid vessels and the method was described in our previous studies [11]. In brief, EMT is the distance between the carotid media-adventitia border and the jugular wall-lumen interface averaged from both common carotid arteries (CCA) with visualization of the zoomed interface between the near wall of the distal segment of the CCA and the neighboring jugular vein. It is measured manually in a standardized protocol including a 7 mm segment starting 3 mm proximal to the bulb. The mean EMT values were averaged from the serial measurements taken at end-diastole (5 consecutive beats) in both sides' carotid arteries.

### **Cardiac fat: EFT and PFT**

Epicardial adipose tissue (EFT) was evaluated using transthoracic echocardiography according to the most frequent and accepted method [17, 18]. Two-dimensional long and short axis parasternal views were obtained and recorded using GE Vivid 9 ultrasound machine with a 1.5–4.5 MHz transducer. The EFT was identified as an area between epicardium and visceral layer of the pericardium. The PFT was determined as an area between the visceral layer and parietal pericardium layer. Both (EFT and PFT) were measured perpendicularly to the right ventricle free wall at the level of the aortic annulus. The maximum values were measured both at the end-diastole during 5 consecutive beats and a mean value was obtained.

### **Abdominal fat: ASF and AVF**

The transducer (7.5 MHz for ASF or 3.5 MHz for AVF) was placed on the skin (1 cm above umbilicus; transverse view) as lightly as possible to prevent compression of the layers and to perform a breath-hold measurements. The ASF was measured as the distance between the skin and external surface of the rectus abdominis muscle. The AVF was determined as the

space between the internal surface of the rectus abdominis muscle and anterior wall of the aorta [7].

### **Ultrasound combined indexes**

All the ultrasound indexes (carotid IMT and EMT, cardiac EFT) were used in analysis as separate mean values. Each of them represents various tissue components and may correspond to different aspects of cardiovascular risk. Therefore, combined indexes (PATIMA) were used. The PATIMA index was developed recently [11] and it was calculated according to the following formula:  $PATIMA [u] = (EMT/BMI \times 35) + IMT + (EFT \times 60)$ .

### **Clinical follow-up**

All the clinical characteristics and ultrasound indexes were obtained prospectively at the time of enrollment (2012–2013). Afterwards, the Regional Branch of the National Health System (NHS) provided medical data regarding all the study patients. Data included inpatients and outpatients with the main diagnosis, concomitant diseases and treatment in the time period up to the end of 2019. A stroke was determined if it was either the main or concomitant diagnosis or a cause of death reported by the hospital or outpatient. A new-onset AF (NOAF) was determined if AF was reported in the follow-up time and was not present at the time of the study enrollment (2012–2013). Finally, NHS medical data regarding mortality was also collected.

### **Statistical analysis**

All results presented in the text, tables and figure are expressed as means  $\pm$  standard deviation or number and percentage. The results' normal distribution was analyzed with the Kolmogorov-Smirnov test. Associations between parameters were assessed using the Pearson correlation analysis. To determine the best cut-off of particular clinical parameters or ultrasound indexes, the receiver operating characteristic (ROC) curves were used providing sensitivity, specificity, positive (PPV) and negative (NPV) predictive values for a stroke and a NOAF. Moreover, multivariable logistic regression models were employed to identify variables independently associated with follow-up events. A value  $p < 0.05$  was considered statistically significant. Statistical analysis was undertaken using MedCalc (version 18.5, MedCalc Software).

## RESULTS

### Study group characteristics

The study group included 364 patients (age:  $61.3 \pm 7.2$  years old) with high or very high CV risk. All the patients used a standard pharmacotherapy, including beta-blockers (95%), acetylsalicylic acid (95%), lipid lowering treatment (100%) — statins (95%), fibrates (3%), ezetimibe (2%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (86%), diuretics (30%), calcium channel blockers (26%) and nitrates (18%).

The study patients revealed several CV risk factors as follows: dyslipidemia (100%), hypertension (89%), obesity (49%), diabetes (35%), and smoking (29%). Most patients had CAD (70%), one fifth (22%) had peripheral artery disease and carotid artery stenosis ( $\geq 50\%$ ) was found in 51 patients. Furthermore, 42 patients were found to have AF at baseline and medical history revealed prior myocardial infarction in 21% and stroke in 6% of the cases (Table 1).

The mean measures of ultrasound indexes are presented in Table 2.

The baseline carotid IMT showed a weak association with carotid EMT ( $r = 0.25$ ,  $p < 0.0001$ ), PFT ( $r = 0.1$ ,  $p = 0.01$ ) and AVF ( $r = 0.1$ ,  $p < 0.01$ ). None of the other ultrasound indexes showed a significant association. Moreover, EFT showed a weak association with BMI ( $r = 0.2$ ;  $p < 0.01$ ) and no correlation with WHR ( $p = 0.8$ ) or WC ( $p = 0.2$ ). The PATIMA combined index also showed a weak association with BMI ( $r = 0.2$ ;  $p = 0.001$ ) and no association with WHR ( $p = 0.5$ ) or WC ( $p = 0.8$ ).

### Clinical prognosis and follow-up

The baseline clinical characteristics and ultrasound indexes were used in the ROC analysis in prediction of stroke and NOAF. All the study patients were followed for  $80.9 \pm 7.1$  months. There were 50 deaths in the primary study group during follow-up. There were 23 strokes in 23 patients (4 patients died) and 25 cases with NOAF during the follow-up. The ROC analysis showed, that selected clinical parameters (age, WC, WHR) and ultrasound indexes (EFT and PATIMA combined index) were predictive for stroke. Their predictive values showed no significant differences ( $p = \text{NS}$ ). However, a multivariable logistic regression model including those five parameters showed that only EFT (odds ratio [OR] 1.4; 95% confidence interval [CI] 0.5–2.3;  $p = 0.04$ ) and PATIMA combined index (OR 2.1; 95% CI 1.01–4.22;  $p = 0.04$ ). Finally, baseline BMI was the only parameter, which showed a prediction for NOAF, which occurred during a follow-up (BMI  $> 33 \text{ kg/m}^2$ : sensitivity 65%, specificity 76%, PPV 14%, NPV 97%; Table 3, Fig. 1).

## DISCUSSION

This was the first prospective study providing a complete analysis of clinical risk factors and major ultrasound indexes in the prediction for stroke among patients with at least high CV risk.

All the major ultrasound indexes were used, which are related to various tissue components, including subcutaneous or visceral adipose tissue, perivascular fat or various layers of the arterial wall. The associations between baseline single ultrasound indexes were either statistically or clinically not significant, which suggests that they are related to different aspects of CV risk. The echocardiography EFT was the only single ultrasound index, which predicted strokes during a 7-year prospective follow-up. Although the combined PATIMA index was also found to have significant predictions for strokes, it is a derivative of the EFT measure and its predictive value was not superior to the EFT alone. Finally, the baseline BMI was the only parameter with a prediction for NOAF and ultrasound indexes failed to predict AF.

According to available research, the present study is the first to show that increased EFT (> 2.8 mm) was predictive for stroke in a prospective follow-up. Three small and cross-sectional studies found a significantly higher EFT in patients with acute ischemic stroke compared to control groups [19–21]. Noteworthy, increased EFT was also found in young patients with embolic stroke of undetermined source [22]. Kyoung-Im et al. [23] showed that patients with ischemic stroke and AF had higher EFT compared to subjects with stroke, but without AF. In the current study, EFT had a high sensitivity and a very high NPV suggesting that values lower than 2.8 mm indicate a very low risk of stroke. Given that epicardial fat is involved in various atherosclerotic diseases, increased EFT is not specific only for increased risk of stroke. Moreover, the present study showed that obesity has an important relation with AF and strokes. Although central obesity was found to be predictive for stroke, baseline BMI was the only parameter of adiposity with a predictive value for NOAF. All the ultrasound indexes failed to predict NOAF. The current study did not confirm the predictive value of EFT for AF, which was found in some other studies [24, 25].

A few major ultrasound indexes were used, which failed to predict NOAF or strokes. So far, carotid IMT was evidenced to have some predictive value for strokes [26, 27]. There were no previous studies, which assessed other fat depots in relation to stroke. Despite the link between visceral fat and stroke, the present study did not confirm the relation between abdominal visceral adipose tissue (AVF) and the risk of stroke.



## **Epicardial fat and stroke**

Epicardial adipocytes originate from brown adipose tissue and they have been shown to produce various types of cytokines [28, 29]. It has the same blood supply as the myocardium, with a close anatomic and functional relationship as well. It is a fat depot related not only to local ventricle mass or function, but it is also related to visceral adiposity and cardiometabolic risk [30, 31]. Epicardial fat is also involved in the pathogenesis of insulin resistance through endothelial function, insulin-mediated vasoreactivity, and muscle perfusion [32]. The EFT may be increased as a consequence of adipocytes' dysfunction and muscle proliferation [33]. Visceral obesity and an increasing number of adipocytes may induce a hypoxia and a pro-inflammatory state [33]. Moreover, increased release of pro-inflammatory cytokines induce lipolysis, oxidative stress and apoptosis within various depots of visceral adipose tissue [34]. Finally, excessive serum fatty acids link epicardial adipocytes, altered cardiac repolarization and arrhythmias [23]. Previous studies also suggest a link between EFT and the development of left atrial myopathy, increasing the risk of AF [35, 36]. Recent studies have shown that increased epicardial adiposity can directly modulate the electrophysiological properties of the heart and ion currents, causing higher arrhythmogenesis in left atrial myocytes, which contributes to an increased risk of AF [37]. There is also a well-established relation between general obesity, left atrial enlargement and changes in the histology of the atrial wall [38].

## **Limitations of the study**

The present data regarding prospective clinical follow-up originated from the National Health System which collects reports from all the medical centers. There was no prospective visit or active testing for unknown AF in the study. Therefore, some patients of the study could have undetected AF, which could have affected the present results. There is also a possibility that an undiagnosed stroke could have been a cause of death, which was not known, reported to NHS and was included in the analysis. However, this is also true for other similar studies.

## **CONCLUSIONS**

This is the first study providing important results based on a comprehensive assessment of various ultrasound indexes reflecting vascular indexes or fat depots and a prospective follow-up. It was found that age, WC and echocardiographic EFT revealed significant predictive values for stroke. Both WC and EFT showed a very high NPV

suggesting that they should be implemented into the clinical practice as a tool affirming a very low risk of stroke.

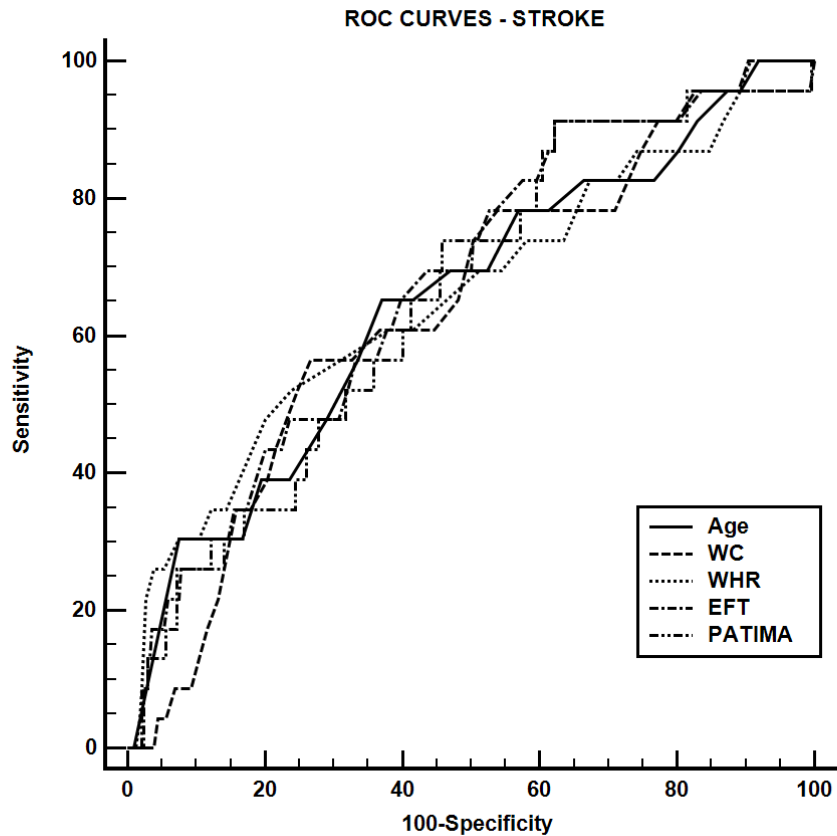
**Conflict of interest:** None declared

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**Figure 1.** The receiver operating characteristics (ROC) curves representing selected clinical parameters and ultrasound indexes with significant prediction of stroke; EFT — epicardial fat thickness; PATIMA — periarterial adipose tissue intima media adventitia, WC — waist circumference; WHR — waist-hip ratio.

**Table 1.** Clinical characteristics of the study group.

	Mean ± SD or no. (%)
Age [years]	61.3 ± 7.2
Female/male	131 (36%)/233 (64%)
Diabetes	130 (36%)
Lipid-lowering treatment	364 (100%)
Total cholesterol [mg/dL]	175 ± 45
LDL-C [mg/dL]	102 ± 41
HDL-C [mg/dL]	44 ± 12

Triglycerides [mg/dL]	141 ± 84
Hypertension	325 (89%)
Chronic kidney disease	17 (5%)
Coronary artery disease	255 (70%)
Prior myocardial infarction	77 (21%)
Peripheral artery disease	82 (22%)
Carotid artery stenosis ≥ 50%	51 (14%)
Prior stroke	22 (6%)
Smoker or ex-smoker	258 (71%)
Body mass index [kg/m <sup>2</sup> ]	30.8 ± 6
Obesity	182 (50%)
Risk factors	4.8 ± 1.5
Very high/high CV risk	302 (83%)/62 (17%)

CV — cardiovascular; LDL-C — low density lipoprotein cholesterol; HDL-C — high density lipoprotein cholesterol; SD — standard deviation

<b>Table 1.</b> Ultrasound indexes of cardiovascular risk.	
	<b>Mean ± SD or no. (%)</b>
Abdominal visceral fat [mm]	76 ± 26
Abdominal subcutaneous fat [mm]	27.5 ± 11
Carotid intima media thickness [μm]	915 ± 360
Carotid extra media thickness [μm]	793 ± 124
Epicardial fat thickness [mm]	3.51 ± 1.53
Pericardial fat thickness [mm]	9 ± 6.3
PATIMA combined index [u]	211 ± 96

PATIMA — periarterial adipose tissue intima media adventitia; SD — standard deviation

**Tables 3.** The baseline characteristics and ultrasound indexes in prediction of clinical events in the receiver operating characteristics (ROC) analysis.

	Stroke		Atrial fibrillation	
	AUC	P	AUC	P
Age	<b>0.661</b>	<b>0.002</b>	0.557	0.32
Total number of CV risk factors	0.535	0.57	0.5	0.98
LDL-C	0.571	0.2	0.527	0.62
Triglycerides	0.636	0.1	0.501	0.9
Body mass index	0.542	0.45	<b>0.694</b>	<b>0.001</b>
Body fat	0.517	0.8	0.555	0.38
Waist circumference	<b>0.640</b>	<b>0.01</b>	0.602	0.09
Waist-hip ratio	<b>0.659</b>	<b>0.01</b>	0.515	0.8
Abdominal visceral fat	0.577	0.15	0.540	0.47
Abdominal subcutaneous fat	0.526	0.6	0.6	0.09
Carotid intima media thickness	0.591	0.13	0.538	0.52
Carotid extra media thickness	0.540	0.5	0.503	0.95
Epicardial fat thickness	<b>0.672</b>	<b>&lt; 0.01</b>	0.556	0.45
Pericardial fat thickness	0.513	0.8	0.520	0.7
PATIMA combined index	<b>0.658</b>	<b>&lt; 0.01</b>	0.563	0.39

AUC — area under curve; CV — cardiovascular; LDL-C — low density lipoprotein cholesterol; PATIMA — periarterial adipose tissue intima media adventitia