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The prognostic value of various carotid ultrasound parameters in patients at high and very high cardiovascular risk☆

Vadim V. Genkel [a,*], Alla S. Kuznetsova [b], Veronika S. Sumerkina [c], Alexey O. Salashenko [d], Igor I. Shaposhnik [d]

[a] Department of Internal Medicine, Federal State Budgetary Educational Institution of Higher Education "South-Ural State Medical University" of the Ministry of Healthcare of the Russian Federation, Vorovskogo st. 64, 454092 Chelyabinsk, Russia.
[b] Department of Hospital Therapy, Federal State Budgetary Educational Institution of Higher Education "South-Ural State Medical University" of the Ministry of Healthcare of the Russian Federation, Vorovskogo st. 64, 454092 Chelyabinsk, Russia.
[c] Central Research Laboratory, Federal State Budgetary Educational Institution of Higher Education "South-Ural State Medical University" of the Ministry of Healthcare of the Russian Federation, Vorovskogo st. 64, 454092 Chelyabinsk, Russia.
[d] Department of Internal Medicine, Federal State Budgetary Educational Institution of Higher Education "South-Ural State Medical University" of the Ministry of Healthcare of the Russian Federation, Vorovskogo st. 64, 454092 Chelyabinsk, Russia.

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ABSTRACT

Background: According to the current guidelines the visualization of atherosclerotic plaques in the carotid arteries is the only option that carotid ultrasound provides for the assessment of cardiovascular risk (CVR). The direction devoted to the development and implementation of markers based on the quantification of atheroma, is promising. The aim of the study was to evaluate the prognostic value of various carotid ultrasound parameters in patients at high and very high CVR.

Methods: Patients at high and very high CVR were included. All patients underwent carotid ultrasound. We evaluated carotid intima-media thickness (cIMT), carotid plaque, carotid plaque score (cPS) and carotid total plaque area (cTPA). The combined endpoint was cardiovascular death, non-fatal myocardial infarction or unstable angina, non-fatal stroke and coronary revascularization.

Results: The study included 100 patients. The duration of the follow-up period was 24.4 (14.1–34.3) months. Endpoint events occurred in 34.0% patients. cIMT and cPS were not significantly associated with the risk of cardiovascular events. The presence of carotid plaque in accordance with Cox regression after adjusting for possible confounders was associated with an increase in the relative risk of cardiovascular events by 10.5 times (95% CI 1.27–86.5; $p = 0.008$). CTPA ≥69 mm^2 according to adjusted analysis was associated with an increase in the risk of cardiovascular events by 5.86 times (95% CI 2.09–16.4; $p = 0.001$).

Conclusion: In patients at high and very high CVR among carotid atherosclerosis markers only carotid plaque and cTPA had an independent predictive value regarding the development of adverse cardiovascular events.

1. Introduction

Duplex ultrasound scanning (DUS) of the carotid arteries is a recognized tool for assessing cardiovascular risk (CVR) in various patient populations [1]. For a long time, the assessment of the carotid intima-media thickness (cIMT) of the common carotid arteries (CCA), as well as the assessment of the presence of atherosclerotic plaques in carotid arteries was used as predictors of adverse cardiovascular events and CVR reclassifiers [2]. However, for a number of compelling reasons, first in the 2013 ACC/AHA guideline on the assessment of CVR, and then in the 2016 European Guidelines on cardiovascular disease prevention in clinical practice, cIMT measuring with a view to stratifying the risk of cardiovascular complications is not recommended in clinical practice (class - III; level - A) [1,3].

Thus, the visualization of atherosclerotic plaques in the carotid arteries is the only option that DUS of the carotid arteries provides for the assessment of CVR. The direction devoted to the development and implementation of clinical markers based on the quantitative assessment of atheroma, is promising [4]. This should allow increasing the predictive value of carotid ultrasound beyond plaque presence.

A quantitative assessment of the carotid plaque burden can now be carried out using such indicators as the total height of the plaques (carotid plaque score (cPS)) and the total area of plaques (carotid total plaque area (cTPA)). The measurement of both indicators is quite simple, does not take much time and can be performed within the framework of the standard study protocol. Currently there are limited data

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: South-Ural State Medical University, Vorovskogo st. 64, 454092 Chelyabinsk, Russia.
E-mail address: henkel-07@mail.ru (V.V. Genkel).

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on the predictive value of the above indicators. In the work of H. Tada et al. in patients with familial hypercholesterolemia, cPS was independently associated (in contradistinction to cIMT) with the presence of coronary artery disease (CAD) (relative risk (RR) 1.22; 95% confidence interval (CI) 1.10–1.37; $p = 0.00036$) [5]. Similar results were obtained by S. Akazawa et al. on a population of asymptomatic patients with diabetes mellitus [6]. In a study by T. Hirata et al. the independent predictive value of cPS was established for cardiovascular death in elderly patients without established cardiovascular disease (CVD) [7]. The use of such indicator as cTPA in addition to the Framingham Risk Score in H.A. Perez et al. allowed stratifying 24.1% of patients in the high risk group and 13.6% in the low risk group [8].

In view of the data published to date, further research is needed to clarify the prognostic value of various markers of carotid atherosclerosis in the category of high and very high risk patients. Aim of the study to assess the prognostic significance of various carotid ultrasound parameters (carotid plaque, cIMT, cPS, cTPA) in relation to the development of adverse cardiovascular events in patients at high and very high CVR.

2. Methods

The study included patients aged 40–75 years at high and very high CVR, determined in accordance with 2016 European Guidelines on cardiovascular disease prevention in clinical practice [1]. A necessary condition for the inclusion of patients in the study was signed informed consent. The study protocol was approved by the Ethics Committee of South-Ural State Medical University. The criteria for non-inclusion in the study and/or exclusions from the study were the following clinical conditions: acute coronary syndrome; acute stroke; severe liver and kidney dysfunction (reduction in estimated glomerular filtration rate (eGFR) of ≪30 ml/min/1.73 m^2); malignant tumors; mental illnesses; abuse of alcohol and psychoactive substances.

All patients underwent fasting blood sampling. The following lipid metabolism parameters were determined: total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL—C), triglycerides (TG). The state of carbohydrate metabolism was assessed by the level of glycated hemoglobin (HbA1c). To assess the functional status of the kidneys, serum creatinine was determined with the subsequent calculation of eGFR using CKD-EPI formula. In addition, the concentration of highly sensitive C-reactive protein (hsCRP) was determined.

The combined endpoint was cardiovascular death, non-fatal myocardial infarction or unstable angina (which required hospitalization), non-fatal stroke, and coronary revascularization.

2.1. Ultrasound examination

All patients underwent carotid DUS. The following vessels were inspected from both sides in longitudinal and cross-section views: common carotid arteries (CCA) with bifurcation of CCA, internal carotid arteries (ICA), external carotid artery (ECA) from the anterior, lateral and posterior accesses. The study was carried out with a linear transducer with a frequency of 10 MHz on a digital ultrasonic multifunctional diagnostic scanner of expert class "Samsung Medison EKO7" (Republic of Korea). All diagnostic studies were carried out by a single operator with 5 years of clinical experience.

The cIMT was determined in automatic mode (AutoIMT function) on both sides in the distal third of CCA 1 cm proximal to CCA bifurcation within a region free of plaque from the front access. Mean cIMT ($cIMT_m$) was determined by the formula: $cIMT_m = (cIMT_{left} + cIMT_{right})/2$.

Atherosclerotic plaque was considered a focal thickening of the intima-media complex ≫1.5 mm or 0.5 mm more than the circumflex cIMT, or 50% more than the cIMT of the adjacent CCA areas [9].

The percentage of stenosis was measured planimetrically in the B-mode by the diameter in the cross section of the vessel. The percentage of stenosis was determined according to the ECST (The European Carotid Surgery Trial) method [10]. In the case of plaque, lumen stenosis, the total value of carotid stenosis, which is the sum of percent of all stenoses of the carotid arteries on both sides, was calculated, and the maximum percentage of stenosis of the carotid arteries in a particular patient was determined [11].

Parameters reflecting the carotid plaque burden were evaluated. The cPS was determined as the total height of all plaques visualized in the carotid arteries, without regard to their length [6,12]. The cPS was calculated by summing the maximum plaque thickness measured on the near and far wall of four divisions from both sides of the carotid wall. cTPA was estimated in the longitudinal position, which allows to achieve the best visualization of plaque, the area of plaque was measured in the manual trace mode. These measurements were performed for each rendered plaque, followed by the calculation of the total value [13,14]. Intraobserver reliability was calculated using Bland–Altman statistics with 95% limits of agreement. A good interobserver reproducibility was observed for the cTPA (Bland-Altman plot are presented in the supplementary materials).

Measurement of ankle-brachial index (ABI) was carried out in accordance with scientific statement from the American Heart Association [15]. Systolic blood pressure was measured in the Doppler mode.

2.2. Statistical analysis

Statistical analysis of the data was performed using the Microsoft Excel software and the IBM SPSS Statistics version 18 statistical analysis package. Qualitative variables were described by absolute and relative frequencies (percentages). Quantitative variables were described with the following statistics: mediana (Me) and 25th and 75th percentiles (LQ, UQ) in case of nonnormal distributed variables. For indicators with normal distribution, mean value (M) and standard deviation (SD) were used. In order to establish the optimal threshold values of the studied parameters, ROC analysis was performed with determination of sensitivity and specificity, as well as calculation of the area under the characteristic curve (AUC) with a 95% CI. Analysis of survival in groups was performed using the Kaplan-Meier method, and a log-rank test was used to compare the two curves. Observations, in which the studied outcome came, were designated as completed. Considered to be censored observations in which the outcome did not come at the time of the end of the study. In order to identify risk factors for survival, Cox regression step-by-step analysis was used. At the same time, the time before the outcome was considered a dependent (predicted) variable, and the factors under study were independent. Differences were considered as statistically significant if error level $p \ll 0.05$.

3. Results

The study included 100 patients at high and very high risk. High CVR was established in 20 (20.0%) patients: in 7 (7.00%) patients, a reduction in eGFR of ≪60 ml/min/1.73 m^2 was diagnosed; 7 (7.00%) had markedly elevated single risk factors (severe hypertension or hypercholesterolemia); 6 (6.00%) – had SCORE ≥ 5% and ≤10%. Very high CVR was

Table 1
Clinical, laboratory and instrumental characteristics of patients.

Characteristics	Patients ($n = 100$)
Age, years, (Me [LQ; UQ])	62.0 (55.0–67.0)
Male (n, %)/Female (n, %)	51 (51.0)/49 (49.0)
BMI (kg/m^2, Me (LQ; UQ))	27.0 (25.0–31.3)
Obesity (n, %)	37 (37.0)
Abdominal obesity (n, %)	71 (71.0)
Smoking (n, %)	28 (28.0)
Coronary artery disease (n, %)	73 (73.0)
Myocardial infarction (n, %)	31 (31.0)
Coronary artery revascularization (n, %)	26 (26.0)
Stroke (n, %)	5 (5.00)
Intermittent claudication, (n, %)	26 (26.0)
Type 2 diabetes mellitus (n, %)	43 (43.0)
Hypertension (n, %)	87 (87.0)
Chronic heart failure (n, %)	64 (64.0)
Antiplatelets (n, %)	76 (76.0)
Beta-blockers (n, %)	60 (60.0)
ACE inhibitors (n, %)	74 (74.0)
Diuretics (n, %)	20 (20.0)
Statins (n, %)	71 (71.0)
Oral antidiabetic medications (n, %)	28 (28.0)
Insulin (n, %)	15 (15.0)
TC (mmol/l, Me [LQ; UQ])	4.95 (3.80–5.58)
LDL-c (mmol/l, Me [LQ; UQ])	2.77 (1.95–3.81)
HDL-c (mmol/l, Me [LQ; UQ])	1.20 (1.01–1.61)
Triglycerides (mmol/l, Me [LQ; UQ])	1.38 (1.04–1.92)
hsCRP (mg/l, Me [LQ; UQ])	2.38 (1.26–5.66)
HbA1c (%, Me [LQ; UQ])	5.30 (4.80–6.35)
eGFR (ml/min/1.73 m^2, Me [LQ; UQ])	57.5 (50.0–68.0)
$cIMT_m$ (mm, M [SD])	0.89 (0.19)
cIMT ≥0.9 mm (n, %)	60 (60.0)
Carotid plaque (n, %)	78 (78.0)
cPS (mm, Me [LQ; UQ])	3.34 (1.59–5.02)
cTPA (mm^2, Me [LQ; UQ])	36.0 (11.0–60.0)
Maximum stenosis of CA (%, Me [LQ; UQ])	36.0 (25.0–45.0)
Overall stenosis of CA (%, Me [LQ; UQ])	63.0 (25.0–129)
Maximum stenosis of ICA (%, Me [LQ; UQ])	24.5 (0.00–44.5)
Carotid stenosis ≥50% (n, %)	20 (20.0)
Ankle-brachial index ≪0.9 (n, %)	21 (21.0)

BMI = body mass index; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; eGFR = estimated glomerular filtration rate; hsCRP = high-sensitivity C-reactive protein; ACE = angiotensin-converting-enzyme; HbA1c = glycated hemoglobin; $cIMT_m$ = mean carotid intima-media thickness; cPS = carotid plaque score; cTPA = carotid plaque score; cTPA = carotid total plaque area; CA = carotid artery.

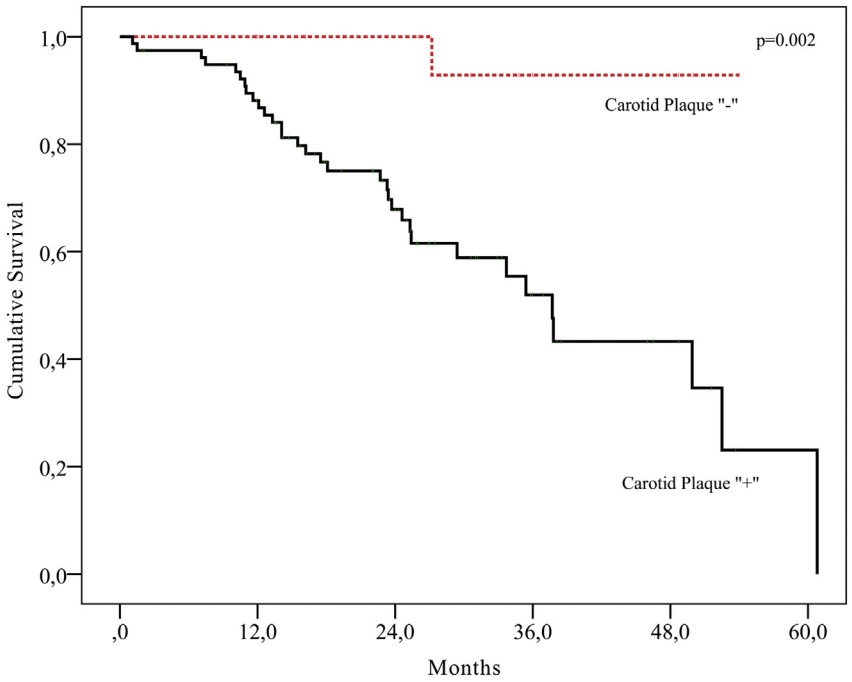

Fig. 1. Kaplan–Meier curves of cardiovascular events according to the carotid plaque presence. *P* values were calculated using log-rank tests.

established in 80 (80.0%) patients: 73 (73.0%) patients suffered from CAD; 7 (7.00%) patients were diagnosed with type 2 diabetes mellitus (T2DM) in combination with major risk factors. Table 1 shows the clinical characteristics and the results of carotid DUS and the measurement of ABI of the patients included in the study.

As shown in Table 1, carotid plaques were detected in 78% of patients, while the median carotid stenosis was 36.0%, and ≫50% of stenoses of the carotid arteries were diagnosed in 20%.

The duration of the follow-up period was 24.4 (14.1–34.3) months. The events constituting the combined endpoint occurred in 34 (34%) patients: cardiovascular death was recorded in 7 (7%) patients; nonfatal myocardial infarction or stroke in 3 (3%) patients; unstable angina, which required hospitalization in 24 (24%) patients, while emergency coronary angiography was performed in 8 (8%) patients, coronary artery stenting was performed in 3 (3%) cases. Data relating to the analysis of survival and patient status (time-to-event-or-censoring and censor status) are presented in the supplementary materials.

We carried out an analysis aimed at assessing the prognostic significance of various markers of carotid atherosclerosis in relation to the development of cardiovascular events. There were no statistically

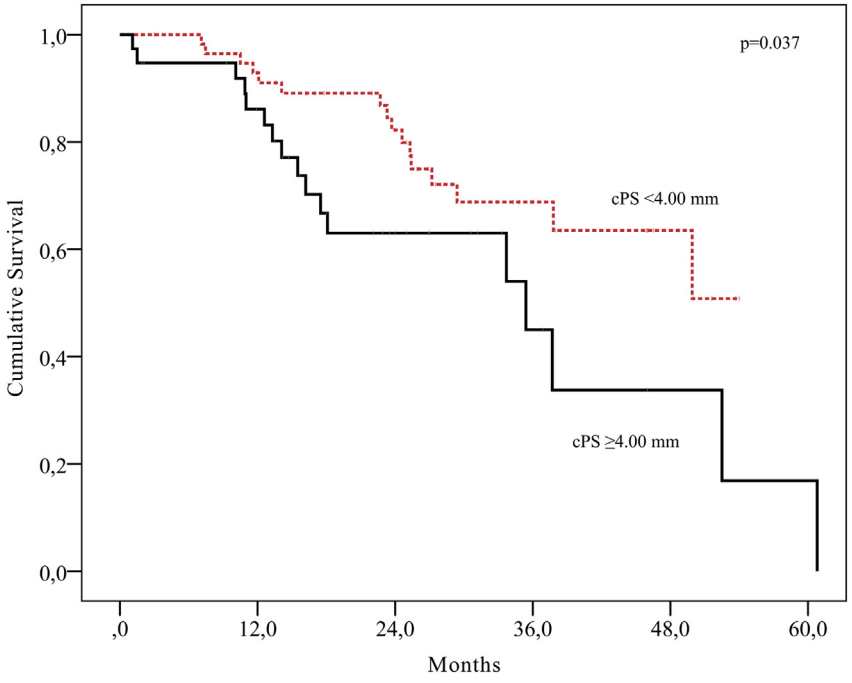

Fig. 2. Kaplan–Meier curves of cardiovascular events according to cPS. P values were calculated using log-rank tests.

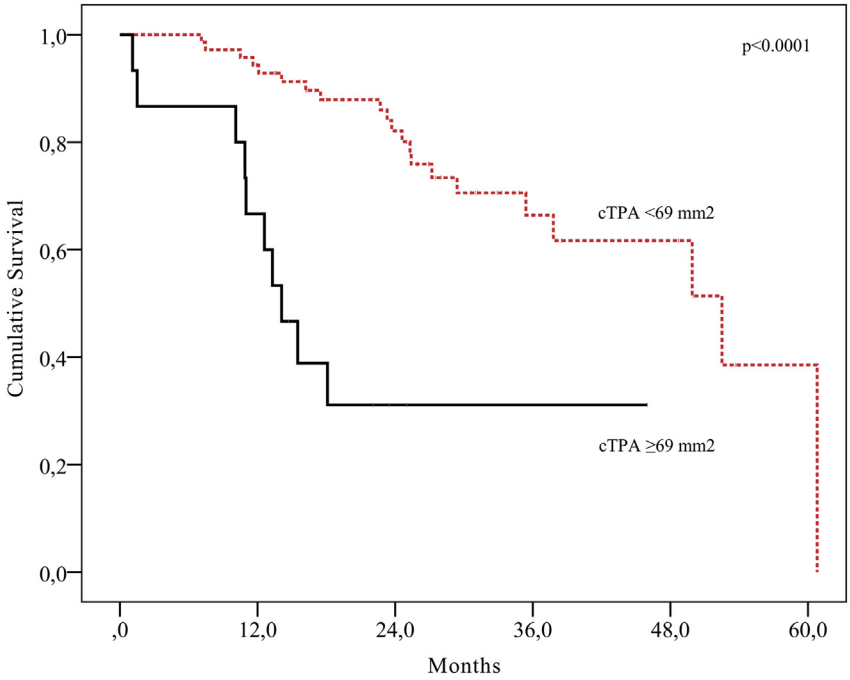

Fig. 3. Kaplan–Meier curves of cardiovascular events according to cTPA. P values were calculated using log-rank tests.

significant associations between an increase in cIMT ≥0.9 mm and adverse cardiovascular events (RR 1.13; 95% CI 0.53–2.39; $p = 0.750$). Also, there were no statistically significant associations between carotid arteries stenosis and adverse cardiovascular events (RR 1.29; 95% CI 0.61–2.76; $p = 0.504$).

In contrast, the presence of carotid plaque in accordance with Cox regression without adjusting for possible interfering factors was associated with an increase in the RR of adverse cardiovascular events 12.0 times (95% CI 1.64–88.3; $p = 0.014$). After adjusting for factors such as sex, age, smoking, hypertension, BMI, eGFR, LDL-c and HbA1c, RR was 10.5 (95% CI 1.27–86.5; $p = 0.008$; see Fig. 1).

According to ROC analysis, the optimal cut-off values of cPS and cTPA were determined, allowing to predict the development of adverse cardiovascular events: cPS ≥4.00 mm (sensitivity – 69.7%, specificity – 77.8%) and cTPA ≥69 mm^2 (sensitivity – 71.0%, specificity – 89.8%). The overall diagnostic accuracy of these indicators, as measured by AUC, and ROC curves, are presented in the supplementary materials.

According to Cox regression data without adjusting for potential interfering factors, an increase in cPS ≥4.00 mm was associated with an increase in RR of the development of events included in the combined endpoint by 2.07 times (95% CI 1.03–4.17; $p = 0.041$; see Fig. 2).

However, during regression analysis adjusted for sex, age, smoking, hypertension, BMI, eGFR, LDL-c, HbA1c, associations between cPS and cardiovascular events were not statistically significant (RR 1.56; 95% CI 0.69–3.54; $p = 0.281$).

In contrast, an increase in cTPA ≥69 mm^2 corrected for sex, age, smoking, hypertension, BMI, eGFR, LDL-c, HbA1c, and the presence of carotid plaque was associated with an increase in the RR of adverse cardiovascular events by 5.86 times (95% CI 2.09–16.4; $p = 0.001$; see Fig. 3).

4. Discussion

The study and implementation of novel imaging biomarkers of atherosclerosis and atherosclerotic CVD into clinical practice should help improve the prediction of adverse cardiovascular events among various patient categories [16]. Ultrasound examination of peripheral arteries is considered today as an informative and accessible method for diagnosing atherosclerosis and evaluating CVR [17,18]. Ultrasound markers whose predictive value for cardiovascular events is currently being studied include indicators such as atherosclerotic plaque in carotid and femoral arteries, plaque score, total plaque area and volume, structure of atherosclerotic plaque, and others [19–22].

Results of the studies that have demonstrated the independent predictive value of cPS and cTPA are currently limited. In a study by T. Kawai et al. in patients with hypertension, an increase in cPS was an independent predictor of stroke, but not cardiovascular death [23]. Thus, the increase in cPS ≫5.0 was associated with an increase in RR of the stroke by 3.86 times ($p = 0.002$) corrected for sex, age, blood pressure and hyperlipidemia. In the work of T. Nakahashi et al. in patients with acute coronary syndrome, the increase in cPS ≥9.8 was associated with an increase in RR of major adverse cardiovascular events by 1.52 times (95% CI 1.01–2.31) over 4 years of follow-up [24].

In the work of M. Matangi et al. an increase in cTPA of ≫23.8 mm^2 in patients without established CVD was associated with a decrease in event-free survival compared with patients whose cTPA was ≪23.8 mm^2–96.5% versus 86.1% ($p \ll 0.0001$) [25]. C. Mitchell et al. found that the increase in cTPA of 24.7 mm^2 was associated with an increase in the RR of myocardial infarction, cardiovascular death, cardiac arrest (with successful resuscitation), and first-time angina in patients without established CVD 1.23 times (95% CI 1.11–1.36; $p \ll 0.001$) [16].

In our study, a cohort of high (20%) and very high (80%) CVR patients among carotid atherosclerosis markers had independent predictive value for the development of adverse cardiovascular events, carotid plaque and cTPA, but not cIMT and cPS. It is interesting to note that among indicators that quantify carotid plaque burden, cTPA but not cPS was an independent predictor of cardiovascular events. In our opinion, this may be due to the varying ability of these markers to represent the plaque burden. While cPS takes into account only the height of atheroma, cTPA allows to quantify the length of plaque and the characteristics of its shape [26].

In our experience, measuring cTPA does not require significant time from the operator, incl. in comparison with PS. However, the possibility for obtaining of the additional prognostic information assesses cTPA as

one more preferable over other markers of carotid atherosclerosis beyond plaque presence. In the future, the widespread introduction of three-dimensional ultrasound will allow for a more accurate assessment of plaque burden by measuring the volume of an atheroma in the carotid arteries [27].

5. Conclusion

In patients at high and very high cardiovascular risk among carotid ultrasound parameters only the presence of carotid plaque and cTPA had an independent predictive value regarding the development of adverse cardiovascular events. An increase in cTPA of ≫69 mm^2 was associated with an increase in the RR of cardiovascular events over 2 years of follow-up 5.86 times (95% CI 2.09–16.4; $p = 0.001$).

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Declaration of Competing Interest

All authors declare no conflict of interest.

Appendix A. Supplementary data

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