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High prevalence of inherited thrombophilia and antiphospholipid syndrome in myocardial infarction with non-obstructive coronary arteries: Comparison with cryptogenic stroke☆,☆☆

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ABSTRACT

Background: A role of thrombophilia in myocardial infarction with non-obstructive coronary arteries (MINOCA) is unclear. We investigated thrombophilic factors in MINOCA patients versus those following cryptogenic stroke (CS), a well-established indication for thrombophilia screening.

Methods: In a prospective cross-sectional study, we assessed 84 consecutive patients (median age: 45.5 years) at least 3 months after MINOCA. Age-matched CS patients (n = 84) and published data on general population served as controls. Thrombophilia screening involved inherited thrombophilia (factor V Leiden, prothrombin G20210A mutation, deficiency of protein C, protein S or antithrombin), antiphospholipid syndrome (APS), along with factor VIII >150%, homocysteine ≥15 μM and lipoprotein (a) >30 mg/dl.

Results: Compared to CS, MINOCA were more often males (60.7 vs 33.3%, P < 0.001), obese (34.5 vs 17.9%, P = 0.014), smokers (51.2 vs 35.7%, P = 0.043) and had family history of myocardial infarction (27.4 vs 6.0%, P < 0.001). Inherited thrombophilia occurred in 20 (23.8%) MINOCA patients and in 13 (15.5%) with CS (P = 0.17), without any difference in the parameters except for elevated lipoprotein (a) that was less common in MINOCA (21.4 vs 39.3%, P = 0.012). APS was found in 13 (15.5%) of MINOCA patients, mostly in a single-positive form. APS was diagnosed less frequently in STEMI (2.5 vs 27.3% for NSTEMI, P = 0.002) and MINOCA patients aged ≤50 years (5.7 vs 32.3% for older subjects, P = 0.003).

Conclusions: MINOCA patients exhibit high prevalence of thrombophilia including APS, similar to that in CS. Our first comprehensive thrombophilia testing in MINOCA supports its clinical relevance and the need for long-term anticoagulation for some abnormalities, especially APS.

1. Introduction

Myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA) is clinically defined by general criteria for MI with the absence of obstructive coronary artery disease [1]. Large registries showed that MINOCA represents 1–13% of patients with MI [2–4]. A systematic review involving 28 publications showed that compared with obstructive MI patients, those with MINOCA were more likely to be younger and female but less often had hyperlipidemia [5]. Moreover, the prognosis of patients with MINOCA is likely to be more favourable as suggested by in-hospital all-cause mortality (0.9 vs 3.2%; odds ratio (OR) 0.37; 95% confidence interval (CI) 0.2–0.67) compared with obstructive MI [5].

The etiology of MINOCA remains unclear. Several potential mechanisms, such as vasospasm, spontaneous coronary dissection, microcirculation dysfunction, takotsubo cardiomyopathy or myocarditis have been proposed so far [6]. It has been also postulated that MINOCA

Abbreviations: MINOCA, myocardial infarction with non-obstructive coronary arteries; MI, myocardial infarction; FVL, factor V Leiden; APS, antiphospholipid syndrome; PC, protein C deficiency; PS, protein S deficiency; AT, antithrombin deficiency; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; VTE, venous thromboembolism; VKA, vitamin K antagonist; NOAC, non-vitamin K antagonist oral anticoagulant.

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results from in situ thrombus formation with the subsequent lysis, thereby resulting in a morphologically normal angiogram [6]. A prothrombotic state, both inherited or acquired, may lead to such a sequence of pathological events [7]. In the latest MINOCA position paper of the European Society of Cardiology (ESC), a diagnostic flow chart includes imaging methods with a key role of cardiac magnetic resonance, invasive investigations (intravascular ultrasound (IVUS), optical coherence tomography (OCT), provocative spasm testing) and laboratory assays, including thrombophilia screening [1,8] as previously suggested [7]. Individual thrombophilic disorders differ in their prevalence in the general population and their effect on prothrombotic potential – from a 50–100 fold higher thrombosis risk in homozygous factor V Leiden (FVL) to only a mild impact of protein S deficiency (PS) in terms of venous thromboembolism (VTE), the most common indication for such testing [9]. To our knowledge, there has been no single study exploring all known thrombophilias of established clinical relevance in patients with MINOCA. A few small studies yielded inconsistent results [10–13]. In the largest systemic review including 8 available reports involving 378 MINOCA patients who underwent partial thrombophilia screening, thrombophilia disorders were found in 14% and as expected the most common thrombophilia was FVL detected in 12% [5].

A common indication for thrombophilia screening is cryptogenic stroke, defined as symptomatic cerebral infarcts for which no probable cause is identified after adequate diagnostic evaluation [14]. Despite the relatively small groups of cryptogenic stroke patients, significantly higher frequencies of antiphospholipid syndrome (APS) [15] as well as similar trend in case of FVL [16] in comparison to healthy controls were described. Thrombophilic disorders can be detected among 44% of patients with cryptogenic stroke based on extended thrombophilia panel [17]. APS is a well-known independent prothrombotic risk factor for the first and recurrent ischemic stroke especially in young adults [18]. No consistent association between ischemic stroke and FVL, prothrombin G20210A mutation as well as rare deficiencies of protein C (PC), PS or antithrombin (AT) has been demonstrated so far [19–23]. Taken together, solely APS is a well-established risk factor for ischemic stroke at a younger age, which is routinely assessed.

We hypothesized that patients with MINOCA have a significant prevalence of thrombophilia including APS which is similar to that observed for cryptogenic stroke. Therefore, we sought to investigate thrombophilia in MINOCA as compared to that detected in cryptogenic stroke.

2. Material and methods

In this prospective cross-sectional study, we enrolled consecutive ambulatory patients with MINOCA and cryptogenic stroke who were referred for further clinical and laboratory work-up between March 2014 and October 2018. Patients were eligible if 3 months or more (up to 18 months) elapsed from the event. Exclusion criteria were as follows: signs of acute infection on the day of blood collection, known malignancy, hemodialysis, current anticoagulant therapy, other documented thromboembolic event within the three preceding months. MINOCA was defined as MI (positive cardiac biomarkers - rising and/or falling in serial levels, with at least one value above 99th percentile upper reference limit and at least one clinical evidence of infarction) without angiographic obstructive coronary artery disease (no lesions ≥50% in coronary angiography) [1]. Patients with ST-segment elevation in at least two contiguous leads were classified as ST-segment elevation MI (STEMI). In contrast, patients without ST-segment elevation at presentation are designated as non-ST-segment elevation MI (NSTEMI) [8]. The age-matched control group represented patients who experienced ischemic stroke confirmed by brain imaging that was not referred to definite cardioembolism, large artery atherosclerosis or small artery disease despite a standard vascular, cardiac and serologic (international normalized ratio (INR), activated partial thromboplastin time (APTT), complete blood count, platelet count) evaluation as described previously [14,24,25].

Comorbidities and cardiovascular risk factors were analyzed. The diagnosis of obesity was established based on body mass index (BMI) over 30 kg/m^2. Hyperlipidemia was defined as total cholesterol (TC) >5.0 mmol/l (190.0 mg/dl), low-density lipoprotein (LDL) cholesterol >2.6 mmol/l (100.0 mg/dl), and triglycerides (TG) >1.7 mmol/l (150 mg/dl) or ongoing lipid-lowering treatment. Diabetes mellitus was stated as a history of diabetes, need for antidiabetic agents, or fasting plasma glucose ≥126 mg/dl (7 mmol/l) on two separate occasions. Hypertension was defined as office systolic blood pressure values ≥140 mmHg and/or diastolic blood pressure values ≥90 mmHg or current antihypertensive treatment [26]. Renal failure was diagnosed when creatinine clearance calculated using the Cockcroft-Gault formula was lower than 60 ml/min. A positive family history of MI in first degree relatives (parents, offspring and siblings) without an age cut-off for premature MI was ascertained by interviewing the patients. Prior VTE was recognized in patients with history of symptomatic deep-vein thrombosis and/or pulmonary embolism that were confirmed by colour duplex sonography or computed tomography pulmonary angiography, respectively. Patients who had experienced VTE in the past and stopped therapy, respectively, received vitamin K antagonists (VKA) following MINOCA and CS on the physician's discretion. VKA treatment due to suspected thrombophilia was also allowed.

The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Jagiellonian University. All included patients gave informed consent.

2.1. Sample collection

Patients on VKA discontinued anticoagulation up to 7–14 days and were switched to a low-molecular-weight heparin at therapeutic doses with blood collection >12 h since the last injection (the anti-Xa activity below 0.1 IU/ml). In patients on non-VKA oral anticoagulants (NOACs) blood was taken >24 h since the last dose (drug concentrations below 30 ng/ml when measured using the Hemoclot Thrombin Inhibitor assay for dabigatran and the anti-Xa chromogenic assay, Biophen DiXaI for rivaroxaban; both, Hyphen BioMed, Neuville-sur-Oise, France).

Blood samples were drawn from an antecubital vein into tubes containing citrate anticoagulant (9:1 of 0.106 M sodium citrate), centrifuged at 2.500*g* at a temperature of 18 °C to 22 °C for 20 min and processed immediately or stored in aliquots at −80 °C until analysis. Whole blood samples for DNA isolation were drawn into EDTA-K3 collection tubes and stored in aliquots at −80 °C until processing.

2.2. Thrombophilia testing

Genetic analysis of FVL (dbSNP ID: rs6025) and prothrombin G20210A (dbSNP ID: rs1799963) mutations were determined using TaqMan Genotyping Assays (Assay ID: C_11975250_10 and C_8726802_20, respectively; ThermoFisher Scientific, Waltham, Massachusetts, USA) on QuantStudio Dx Real-Time PCT Instrument (ThermoFisher Scientific). Plasma PC activity was quantified using a chromogenic assay (HemosIL Protein C Instrumentation Laboratory, Milan, Italy or Berichrom Protein C, Siemens Healthcare Diagnostics). Results below 70% were recognized as suggestive of PC deficiency. Free PS levels were measured using an immunoturbidimetric assay (INNOVANCE® Free PS Ag, Siemens Healthcare Diagnostic). PS deficiency was diagnosed at the level of 60% or less. AT activity was assessed using an assay based on FXa inhibition (INNOVANCE™ ATIII, Siemens Healthcare Diagnostics, Marburg, Germany) with AT deficiency diagnosed when the level was below 75%. Two positive results were required to confirm the anticoagulant deficiency [27].

APS was diagnosed according to the current recommendations [28]. The levels of IgG/IgM anticardiolipin and anti-β-2 glycoprotein I

antibodies were determined by enzyme-linked immunosorbent immunoassays (INOVA Diagnostic, San Diego, CA, USA). The anticardiolipin antibodies IgG ≥15 GPL and IgM ≥12.5 MPL were assumed as positive. Positive values for anti-β-2 glycoprotein I antibodies were ≥20 Standard IgG and IgM (SGU and SMU) [29]. Lupus anticoagulant was determined as recommended [30]. The APS was categorized as a single-, double- and triple-positive syndrome based on the number of detected antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and anti-β-2 glycoprotein I antibodies). As was documented, thromboembolic risk increases with each additional antiphospholipid antibody detected. The number of detected antibodies also influences on the decision about appropriate anticoagulant therapy [31].

Plasma FVIII activity was determined by the coagulometric assay using a deficient plasma (Siemens Healthcare Diagnostics) and levels of 150% or more were considered elevated. Fasting total plasma homocysteine (tHcy) was determined in plasma by the enzymatic assay (Roche Diagnostics, Mannheim, Germany). Hyperhomocysteinemia was defined as tHcy ≥15 μmol/l. Lipoprotein (a) was assessed in serum by an immunoenzymatic assay (DRG Diagnostics, Marburg, Germany) with a lower detection limit of 1.2 mg/dl. Elevated lipoprotein (a) was diagnosed >30 mg/dl. Intra-assay and inter-assay coefficients of variation for all commercially available assays were <7%.

2.3. Statistical methods

Statistical analyses were performed with Statistica 13.1 software (StatSoft, Tulsa, OK). Continuous variables are expressed as mean ± standard deviation or median and IQR, whereas categorical variables as number (percentage). Continuous variables were first checked for normal distribution by the Shapiro-Wilk test and then were compared by Student's *t*-test or U-Mann Whitney test if distribution was normal or different than normal, respectively. Categorical variables were analyzed by chi-square test or Fisher exact test. All clinical and laboratory parameters associated (P < 0.2) with APS, hyperhomocysteinemia, factor VIII > 150% and lipoprotein (a) >30 mg/dl and not correlated with another independent variable were identified and then included in the multivariate logistic regression models to identify predictors of above-mentioned disorders. Two-sided P-value of <0.05 was considered statistically significant.

3. Results

As shown in Table 1, the MINOCA and cryptogenic stroke patients were similar in terms of most cardiovascular risk factors, the history of VTE and the medications used at the time of blood collection. However, MINOCA patients were more often males (60.7 vs 33.3%, P < 0.001), obese (34.5 vs 17.9%, P = 0.014), current smokers (51.2 vs 35.7%, P = 0.043) and were more likely to have a family history of MI (27.4 vs 6.0%, P < 0.001). As expected, patients with MINOCA were frequently treated with P2Y12 inhibitors (81.0 vs 0.0%, P < 0.001) and beta-blockers (31.0 vs 8.3%, P < 0.001) as compared with patients with cryptogenic stroke.

Table 1
Patient characteristics.

	MINOCA N = 84	Cryptogenic stroke N = 84	P-value
Age, years	45.5 (37.0–56.5)	46.0 (37.5–55.0)	0.76
Male gender	51 (60.7%)	28 (33.3%)	<0.001
Obesity	29 (34.5%)	15 (17.9%)	0.014
Active smoking	43 (51.2%)	30 (35.7%)	0.043
Hyperlipidemia	36 (42.9%)	31(36.9%)	0.43
Hypertension	41 (48.8%)	45 (53.6%)	0.54
Diabetes mellitus	11 (13.1%)	4 (4.8%)	0.06
Renal failure	6 (7.1%)	6 (7.1%)	1.00
Family MI	23 (27.4%)	5 (6.0%)	<0.001
Prior VTE	11 (13.1%)	19 (22.6%)	0.11
Aspirin	84 (100%)	84 (100%)	1.0
P2Y12 inhibitor	68 (81.0%)	0 (0.0%)	<0.001
VKA	17 (20.2%)	14 (16.7%)	0.55
ACE-I	37 (44.1%)	45 (53.6%)	0.22
Beta-blocker	26 (31.0%)	7 (8.3%)	<0.001
Statin	55 (65.5%)	47 (56.0%)	0.21

Abbreviations: ACE-I: angiotensin-converting-enzyme inhibitor, MI: myocardial infarction, MINOCA: myocardial infarction with non-obstructive coronary arteries, VKA: vitamin K antagonist.

3.1. Thrombophilia

Median time elapsed since the ischemic event to blood sampling was similar (8.0 [6.0–10.0] months for MINOCA vs 9.0 [6.0–11.0] months for cryptogenic stroke, P = 0.56). Thrombophilic factors and additional prothrombotic variables shown in Table 2 indicate their similar distribution in both groups. Inherited thrombophilia occurred in 20 (23.8%) patients with MINOCA and in 13 (15.5%) with cryptogenic stroke (P = 0.17). All patients with FVL and prothrombin G20210A mutation were heterozygous. The most common thrombophilia found in both groups was FVL mutation observed in 12 (14.3%) patients with MINOCA and in 5 (6.0%) patients with cryptogenic stroke. Of note, APS was diagnosed frequently in patients with MINOCA at a similar rate compared with those following stroke (15.5 vs 10.7%, P = 0.36). The distribution of a single- (8.3 vs 4.8%, P = 0.27), double- (6.0 vs 4.8%, P = 0.50) and triple- (1.2 vs 1.2%, P = 1.00) positive APS were similar in both groups with the highest proportion of patients with the former form.

There was no significant difference between groups regarding the prevalence of prothrombin 20210A mutation, deficiencies of all three natural anticoagulants, as well as elevated FVIII and hyperhomocysteinemia. We found a lower proportion of patients with MINOCA who had elevated lipoprotein (a) compared with those following cryptogenic stroke (21.4 vs 39.3%, P = 0.012).

3.2. MINOCA patients with inherited thrombophilia or APS

The patients with MINOCA who had inherited thrombophilia or APS (n = 28 [33.3%]) did not differ from the remaining subjects in terms of age (48.5 [38.0–60.0] vs 43 [36.5–54.0] years, P = 0.13), gender (male: 64.3 vs 58.9%, P = 0.64) and cardiovascular risk factors. The significant difference in the patient characteristics was observed only in terms of clinical presentation, i.e. STEMI was diagnosed less frequently in thrombophilic MINOCA patients (32.1 vs 55.4%, P = 0.04). Of note, prior VTE tended to be more frequently observed in thrombophilic patients with MINOCA (21.4 vs 8.9%, P = 0.11). As expected, patients with inherited thrombophilia or APS were more frequently treated with VKA following MI (42.9 vs 8.9%, P < 0.001).

3.3. MINOCA patients ≤50 years

In the MINOCA group, 53 (63.1%) patients aged ≤50 years did not differ from the remainder in terms of the prevalence of inherited thrombophilia (24.5 vs 22.6%, P = 0.84) as well as in individual thrombophilic disorders. Surprisingly, APS was diagnosed less frequently in patients ≤50 years (5.7 vs 32.3%, P = 0.003), without any differences in the distribution of particular APS types. A similar age-dependent analysis of stroke patients demonstrated no differences in the frequency of inherited thrombophilia (13.2 vs 19.4%, P = 0.54) and particular thrombophilic factors.

3.4. STEMI versus NSTEMI patients

Among MINOCA patients, 40 (47.6%) STEMI patients were diagnosed (Table 3). Median time elapsed since event of MI to blood sampling was similar (8.0 [6.0–10.0] for STEMI vs 8.5 [7.0–10.0] months for NSTEMI, P = 0.47). There were no intergroup differences in the prevalence of

Table 2
Thrombophilic factors.

	MINOCA N = 84	Cryptogenic stroke N = 84	P-value	General population
Inherited thrombophilia	20 (23.8%)[a]	13 (15.5%)[b]	0.17	–
Factor V Leiden	12 (14.3%)	5 (6.0%)	0.07	5.0% [34]
Prothrombin G20210A mutation	4 (4.8%)	3 (3.6%)	0.70	2.0–3.0% [34]
Protein C deficiency	2 (2.4%)	1 (1.2%)	0.56	0.2–0.3% [27]
Protein S deficiency	2 (2.4%)	2 (2.4%)	1.00	0.03–0.1% [34]
Antithrombin deficiency	1 (1.2%)	3 (3.6%)	0.31	0.02–0.2% [27]
Antiphospholipid syndrome	13 (15.5%)	9 (10.7%)	0.36	1.0–5.0% [38]
Single positive	7 (8.3%)	4 (4.8%)	0.27	
Double positive	5 (6.0%)	4 (4.8%)	0.50	
Triple positive	1 (1.2%)	1 (1.2%)	1.00	
Factor VIII >150%	23 (27.4%)	22 (26.2%)	0.86	13.0% [49]
Hyperhomocysteinemia	14 (16.7%)	8 (9.5%)	0.17	5.0–10.0%[c] [50]
Lipoprotein (a) >30 mg/dl	18 (21.4%)	33 (39.3%)	0.012	33.0% [42]

Abbreviations: MINOCA: myocardial infarction with non-obstructive coronary arteries. P-value for differences between groups of MINOCA and cryptogenic stroke.
[a] Coexistence of protein S and antithrombin deficiencies in one patient.
[b] Coexistence of prothrombin G20210A mutation and antithrombin deficiency in one patient.
[c] 12 μM as cut-off point.

inherited thrombophilia (20.0 vs 27.3%, P = 0.43, respectively) as well as in the distribution of individual thrombophilic abnormalities. Unexpectedly, APS was diagnosed less frequently in STEMI patients compared with those with NSTEMI (2.5 vs 27.3%, P = 0.002). When 3 types of APS were analyzed, we found that most NSTEMI patients had a single-positive APS, while this form was absent in the former group (0.0 vs 15.9%, P = 0.008).

3.5. Multivariable models

Age of >50 years, NSTEMI and family history of MI were identified as associated (P < 0.2) with the diagnosis of APS in univariate model (Table 4). In a final multivariate model only age of above 50 years was independently associated with APS (OR 6.5; 95% CI 1.6–27.0; R^2 = 0.13, P = 0.002).

4. Discussion

To our knowledge, the current study is the first to present the results of comprehensive thrombophilia screening in patients with MINOCA. We found that inherited thrombophilia occurred in a substantial proportion of patients, including PC, PS or AT deficiency as well as >10% with APS constituting an indication for life-long anticoagulation which has not been reported so far. We also demonstrated a similar prevalence of inherited thrombophilia and APS in patients with MINOCA and those with cryptogenic stroke. Of practical importance is a higher prevalence of APS among MINOCA patients with NSTEMI compared with STEMI.

Table 3
Comparison of STEMI versus NSTEMI patients.

	STEMI N = 40	NSTEMI N = 44	P-value
Inherited thrombophilia	8 (20.0%)	12 (27.3%)[a]	0.43
Factor V Leiden	4 (10.0%)	8 (18.2%)	0.28
Prothrombin G20210A mutation	2 (5.0%)	2 (4.5%)	0.92
Protein C deficiency	1 (2.5%)	1 (2.3%)	0.95
Protein S deficiency	1 (2.5%)	1 (2.3%)	0.95
Antithrombin deficiency	0 (0.0%)	1 (2.3%)	0.34
Antiphospholipid syndrome	1 (2.5%)	12 (27.3%)	0.002
Single positive	0 (0.0%)	7 (15.9%)	0.008
Double positive	1 (2.5%)	4 (9.1%)	0.20
Triple positive	0 (0.0%)	1 (2.3%)	0.34
Factor VIII >150%	10 (25.0%)	13 (29.5%)	0.64
Hyperhomocysteinemia	6 (15.0%)	8 (18.2%)	0.70
Lipoprotein (a) >30 mg/dl	7 (17.5%)	11 (25.0%)	0.40

Abbreviations: NSTEMI: non-ST-segment elevation myocardial infarction, STEMI: ST-segment elevation myocardial infarction.
[a] Coexistence of protein S and antithrombin deficiencies in one patient.

Our findings provide additional evidence that thrombophilia testing should be routinely performed in MINOCA patients.

The baseline characteristics of the current MINOCA cohort differed from the systematic review of previous observational studies published in 2015 [5]. The sex distributions were similar, however our group was younger (45.5 vs 58.8 years, respectively). In terms of cardiovascular risk factors, we observed similar proportions of patients with hypertension and diabetes mellitus with much higher prevalence of hyperlipidemia (42.9 vs 21%) and a trend towards a higher frequency of active smoking (51.2 vs 42.0%). These differences might be related to a high prevalence of cardiovascular risk factors and adverse health behaviors in the overall Polish population with hyperlipidemia (60%), low physical activity (50%), hypertension (35%), smoking (31%) and obesity (21%) [32,33]. The current data indicate that MINOCA patients should be carefully evaluated for the presence of modifiable risk factors, especially hyperlipidemia and smoking.

Importantly, analysis of inherited thrombophilias and APS in the current MINOCA group showed that their prevalence is higher than in the general European population and patients with MI reported in the literature. The highest heterozygosity rate for FVL of about 5% is found in Caucasians with a positive gradient from Southern to Northern Europe [34]. FVL was associated with an increased risk of premature MI before the age of 45 years in a large Italian cohort [35]. Our data suggest that the prevalence of FVL is substantially greater in MINOCA compared with premature MI patients or in the general population, which is consistent with the 2015 systematic review [5]. The prothrombin G20210A mutation is associated with elevated circulating prothrombin levels, occurs in 2–3% of Caucasians [34] and shows a moderate relationship with MI [36] that is further enhanced among acute coronary syndrome patients who lack the classic cardiovascular risk factors [37]. In our study, this mutation was observed at a similar rate to that in other studies performed in this region of Europe given higher prevalence of this polymorphism in the south of Europe [10,11]. Moreover, the prevalence of PC, PS and AT deficiencies in the general European population ranges

Table 4
Independent determinants of antiphospholipid syndrome in MINOCA group.

	Univariate model			Multivariate model		
	OR	95% CI	P-value	OR	95% CI	P-value
Age > 50 years [yes/no]	7.9	2.0–31.8	0.003	6.5	1.6–27.0	0.010
NSTEMI [yes/no]	14.6	1.8–118.6	0.012	NA	NA	NA
Family MI [yes/no]	4.0	1.2–13.6	0.026	2.8	0.7–10.3	0.13

Abbreviations: CI: confidence interval, MI: myocardial infarction, MINOCA: myocardial infarction with non-obstructive coronary arteries, NA: not applicable, NSTEMI: non-ST-segment elevation myocardial infarction, OR: odds ratio.

from 0.2–0.3%, 0.03–0.1% and 0.02–0.2%, respectively [27,34], which indicates that the 3 thrombophilias were observed more frequently in our MINOCA cohort like in the 2015 systematic review [5]. Taken together, the present study supports the view that inherited thrombophilia is overrepresented among patients with MINOCA (Table 2).

Of vital importance is the present observation indicating high prevalence of APS among MINOCA patients. It is known that antiphospholipid antibodies can be found in 1–5% of healthy subjects with an increased prevalence in older subjects, while the incidence of APS in MI was determined at 11% [38]. Noteworthy, the dominant forms in our MINOCA cohort were single and double positive APS associated with low and medium thromboembolic risk [31]. To our knowledge, this study is the first to show the prevalence of APS based on the criteria recommended since 2006 [28] in the MINOCA patients.

Additional factors measured in the present study included FVIII. Elevated FVIII above 150% was documented in more than a quarter of the current MINOCA patients. High FVIII has been shown as a risk factor for the first and recurrent VTE [39]. There have been reports suggesting its association with the increased risk of premature MI [40] and cryptogenic stroke [41]. This study is the first to indicate that persistently increased FVIII might characterize patients with MINOCA contributing to a prothrombotic state, however given association of FVIII with inflammatory state, its impact on clinical outcomes in MINOCA patients remains to be established.

We also measured lipoprotein (a), a well-known cardiovascular risk factor related to premature atherosclerosis and VTE though data on this latter issue are inconsistent. The prevalence of hyperlipoproteinemia (a) has not been analyzed in overall Polish population. Surprisingly high prevalence of lipoprotein (a) >30 mg/dl was demonstrated in the Copenhagen City Heart Study [42]. Lipoprotein (a) levels were elevated in young and middle-aged white adults with cryptogenic stroke [43]. As was established previously, MINOCA patients represent more favourable lipid profile than obstructive MI patients with simultaneous similar concentration of lipoprotein (a) [44]. The present study is one of the first to assess a prevalence of this factor in the MINOCA patients, although the rate is much lower compared with subjects with cryptogenic stroke and available data on general population (Table 2).

Regarding hyperhomocysteinemia, a highly controversial risk factor for cardiovascular disease due to the known associated increased thrombogenicity, oxidative stress status and endothelial dysfunction [45], we observed its high prevalence in MINOCA patients. Higher levels of homocysteine and significant prevalence of methylenetetrahydrofolate reductase (MTHFR) mutation were previously reported once in young MINOCA patients [12]. It remains to be established whether folic acid supplementation of hyperhomocysteinemic patients with MINOCA can be beneficial since the data available for typical MI patients yielded negative results providing evidence against routine assessment of this marker [46].

From a practical point of view, most of patients with inherited thrombophilia do not need life-long anticoagulation, however those with previous VTE or severe deficiencies of natural anticoagulants or those homozygous for FVL or prothrombin G20210A are treated with anticoagulant agents. This also applies to APS detected in 15.5% of the current MINOCA patients. The latest Cochrane Library review suggested that contemporary knowledge is not sufficient to determine the proper method of arterial thrombosis treatment in patients with APS [47]. The task force of the 13th International Congress on Antiphospholipid Antibodies recommended high-intensity warfarin or combined moderate-intensity warfarin therapy and an antiplatelet agent for secondary thromboprophylaxis in patients with APS with arterial thrombotic events. However, this recommendation did not reach panel consensus [48]. Based on the current evidence there is a subset of MINOCA patients that following thrombophilia screening should receive anticoagulant therapy and undergo close surveillance to reduce the risk of other thromboembolic manifestations of these abnormalities as well as consider family counseling in selected cases.

Our study has several limitations. First, cardiac magnetic resonance, which is recommended [1], was not performed in MINOCA patients. Second, we did not measure FIX, FX, FXI and FXII since their clinical relevance in thrombophilia screening is uncertain, though they are increasingly tested in many centers [45]. Third, we did not perform comparative measurements in cohorts with obstructive MI or ischemic stroke with determined source. Fourth, follow-up to establish clinical significance of detected thrombophilia was beyond the scope of this study.

5. Conclusions

In patients with MINOCA and cryptogenic stroke, the incidence of inherited thrombophilia and most of hypercoagulable states is similar and is higher than in general population. Therefore, we recommend thrombophilia screening in these two groups of patients. In case of a positive result, chronic antithrombotic treatment should be considered in accordance with current recommendations.

Declaration of Competing Interest

A.U. received lecture honoraria from Bayer, Boehringer Ingelheim, Pfizer and Sanofi-Aventis. The remaining authors have nothing to disclose in relation to this study.

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