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Antiplatelet Therapy for Secondary Prevention After Myocardial Infarction in Antiplatelet-Naive High Cardiovascular Risk Patients with Non-Obstructive Coronary Artery Disease

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ABSTRACT

BACKGROUND.
The growing evidence indicates the importance of non-obstructive coronary artery disease (NOCAD), with a high-risk of MACEs. The relevance of antiplatelet therapy is high and depends on a type of MINOCA. However, the effectiveness of different antiplatelet treatment regimens and secondary prevention strategies for patients with non-obstructive coronary artery disease is still unclear.

OBJECTIVES
In our previous cohort study, we found that secondary prevention with dual antiplatelet therapy with aspirin and P2Y12 receptor antagonist clopidogrel in patients with NOCAD was not significantly effective than aspirin alone in reducing 1-year MACEs. Because the development and validation cohorts of patients with NOCAD were heterogeneous in terms of cardiovascular risk, in the current study we aimed to compare the preventive effect of DAPT with aspirin alone in high cardiovascular-risk patients.

METHODS
Following the aim of our study, we selected 15 of 55 MINOCA patients with a high 10-year risk for ASCVD (≥20%) from the DAPT group and 19 of 60 patients with the same risk from the no-DAPT group.

RESULTS
The results of our previous and present studies corroborate previously published data. DAPT had no secondary preventive effect on one-year MACE in MINOCA patients with different cardiovascular risks.

CONCLUSIONS
The use of DAPT in patients with MINOCA is a topic for discussion and requires further investigations with a long-term follow-up period.

KEYWORDS
Atherosclerotic cardiovascular disease (ASCVD) risk; dual antiplatelet therapy (DAPT); myocardial infarction with non-0bstructive coronary artery (MINOCA) disease; non-obstructive coronary disease (NOCAD).

BACKGROUND

The majority of current therapeutic strategies for coronary artery disease (CAD) are based on the historical paradigm of elimination of coronary artery obstructive plaque.[1] However, the growing evidence indicates the clinical importance of non-obstructive coronary artery disease, which is associated with a high risk of future major adverse cardiovascular events (MACEs).[2-5]

The vulnerability of the non-obstructive plaque with erosion and subsequent thrombosis is a major pathological substrate of NOCAD-associated MACEs.[6-10] Therefore, the relevance of antiplatelet therapy is high in patients with NOCAD. However, the effectiveness of different antiplatelet treatment regimens and secondary prevention strategies for patients with non-obstructive coronary artery disease is still uncertain.[11]

Lindahl B et al. reported a neutral benefit for dual antiplatelet therapy in patients with myocardial infarction with non-obstructive coronary artery (MINOCA) disease.[12]

The ongoing multicenter, prospective, randomized, controlled, and open-label registry-based trial MINOCA-BAT will be answering the question about the usefulness of DAPT in MINOCA patients.[13,14]

In our previous cohort study, we found that secondary prevention with dual antiplatelet therapy with aspirin and P2Y12 receptor antagonist clopidogrel in patients with non-obstructive coronary disease was not significantly effective than aspirin alone for reducing 1-year MACEs.[15] Because the

development and validation cohorts of patients with NOCAD were heterogeneous in terms of cardiovascular risk, in the current study, we aimed to compare the preventive effect of DAPT with aspirin alone in high cardiovascular-risk patients.

METHODS

Patient population

Overall, 115 of 1018 antiplatelet-naïve patients admitted to the Coronary Care Unit of Tsinamdzgvrishvili Center of Cardiology LTD (Tbilisi, Georgia) and classified as MINOCA were included in the study between March 2018 and Aug 2019. The study population was initially divided into two groups: 55 patients with MINOCA were distributed into the cohort of DAPT (aspirin + clopidogrel), and 60 patients with MIINOCA - into the cohort of No-DAPT (aspirin alone). The control group consisted of 50 patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) with obstructive coronary disease. Following the aim of our study, we selected 15 MINOCA patients with a high 10-year risk for ASCVD (≥20%) from the DAPT group and 19 patients with the same risk from the no-DAPT group. The study protocol was reviewed and approved by the Ethic Committees of Tbilisi State Medical University and Tsinamdzgvrishvili Center of Cardiology LTD, and written informed consent was provided by each study participant.

Table 1 depicts the baseline characteristics of patients with a high 10-year risk for ASCVD.

Diagnosis of MINOCA

The criteria for MINOCA were a universal definition for MI with non-obstructive coronary arteries on angiography (<50% stenosis) and no specific clinically evident cause for the acute coronary syndrome.[16-19]

Cardiovascular risk estimation

For the prediction over 10 years of risk of myocardial infarction, stroke, or cardiovascular death, atherosclerotic cardiovascular disease (ASCVD) Risk Estimator Plus was used (intended for people between the ages of 40 and 79).[20]

Bleeding risk estimation

For the stratification post-MI major bleeding risk CRUSADE score calculator was used with following interpretation:[21]

- Score ≤20 - very low risk (3.1%) of major bleeding;
- Score 21-30 - low risk (5.5%) of major bleeding;
- Score 31-40 - moderate risk (8.5%) of major bleeding;
- Score 41-50 - high risk (11.9%) of major bleeding;
- Score >50 - very high risk (19.5%) of major bleeding.

Statistical analysis

IBM SPSS version 26.0 (IBM Corp., Armonk, NY, USA) was used for analyzing data. The differences between development and validation cohorts had assessed by the nonparametric Mann-Whitney U test, descriptive statistics, linear and quantile regression analysis, Pearson correlation, ANOVA test, Z-scores, and B coefficients were used for the statistical analysis of variables. A statistical significance was taken as a 2-tailed p<0.05.

TABLE 1. Baseline characteristics of MINOCA patients with a high 10-year risk for ASCVD

	DAPT n=15	***No-DAPT n=19***	***P value***
Mean age, year, M±SD	65.8±0.77	67.58±1.84	**<0.0001**
Female, n (%)	12 (80)	9 (47)	0,111
Mean BMI, kg/m^2, M±SD	28.3±3.20	27.6±2.98	0.391
Current smoking , n (%)	6 (40)	6 (32)	0.681
Hypertension, n (%)	15 (100)	18 (95)	0.811
Mean HbA1c, M±SD	7.59±1.58	8.30±1.99	0.253
Mean EF, %, M±SD	45.4±5.80	44.16±5.46	0.639
History of ASCVD, n (%)	2 (13)	2 (11)	0.891
Previous revascularization, n (%)	0 (0)	0 (0)	0
Mean 10-year ASCVD score, M±SD	30.25±9.64	30.28±8.59	0.846
Previous major bleeding, n (%)	0 (0)	0 (0)	0
Mean CRUSADE score, M±SD	20.87±3.04	20.63±2.83	0.550
History of AF, n (%)	3 (20)	4 (21)	0.973
Hoistory of COPD, n (%)	0 (0)	2 (11)	0.607
Current AF, n (%)	0 (0)	0 (0)	0
1-vessel NOCAD	6 (40)	7 (37)	0.891
2-vessel NOCAD	2 (13)	3 (16)	0.918
3-vessel NOCAD	7 (47)	9 (47)	0.973
Mean TC, mg/dL, M±SD	229±27.46	231±19.84	0.823
Mean HDL-C, m/dl, M±SD	37±5.97	35±5.86	0.786
Mean GFR, mL/min/1.73 m2, M±SD	75.4±14.88	78.7±12.65	0.202
Mean hs-CRP, mg/L, M±SD	2.37±0.66	2.65±0.63	0.938
Previous ACIs/ARBs, n (%)	13 (87)	15 (79)	0.706
Previous BBs, n (%)	3 (20)	6 (32)	0.584
Previous CCBs, n (%)	3 (20)	4 (21)	0.973
Previous Statins, n (%)	11 (73)	15 (79)	0.784

Abbreviations: ACIs: Angiotensin converting enzyme inhibitors; AF: Atrial fibrillation; ARBs: Angiotensin receptor blockers; ASCVD: Atherosclerotic cardiovascular disease; BB: Beta-blockers; BMI: Body mass index; CCB: Calcium channel blockers; EF: Left ventricle ejection fraction; GFR: Glomerular filtration rate; HDL-C: high density lipoprotein cholesterol; hs-CRP: Highly sensitive C-reactive protein; M±SD: mean ± standard deviation; NOCAD: Non-obstructive coronary artery disease; TC: Total cholesterol.

RESULTS

Patient characteristics

The mean age of the non-DAPT group patients was statistically higher compared to DAPT group patients (67.58±1.84 vs. 65.8±0.77, p<0.0001. There were no significant differences in terms of the female gender, body mass index, smoking status, arterial hypertension, type 2 diabetes mellitus, left ventricular ejection fraction (EF), history of atrial fibrillation, comorbidity with COPD, dyslipidemia, glomerular filtration rate, highly sensitive C-reactive protein concentration, the extent of coronary artery disease, 10-year cardiovascular and bleeding risk, and baseline treatment between the development and validation cohorts. Neither previous revascularization nor a history of major bleeding and ongoing atrial fibrillation was in the comparator groups (Tab.1).

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One-year MACEs

The one-year MACEs, such as all-cause death, myocardial infarction (MI), stroke, hospitalization because of heart failure, revascularization, and atrial fibrillation are presented in Table 2.

TABLE 2. Univariate comparison of one-year MACEs and minor bleeding by groups

	DAPT n=15	*No-DAPT n=19*	*P value*
Death, n(%)	0 (0.00)	2 (10.5)	0.607
Miocardial infarction, n(%)	4 (26.7)	3 (15.8)	0.607
Stroke, n (%)	1 (6.67)	2 (10.5)	0.864
Heart failure hospitalization (HF), n(%)	3 (20.0)	2 (10.5)	0.656
Revascularization, n(%)	2 (13.3)	3 (15.8)	0.918
Atrial fibrillation (AF), n(%)	1 (6.67)	1 (5.26)	0.945
All major adverse cardiac events (MACEs)	11	13	0.811
Minor bleeding, n(%)	1 (6.67)	1 (5.26)	0.945

The association of baseline predictors with separate components of major cardiovascular events

The unique contribution of the baseline indices in the predictions of each constituent of MACEs was assessed by the multivariate regression analysis. Table 3 presents all statistically significant associations.

TABLE 3. Multiple linear regression analysis coefficients of significant correlation between baseine indices and separate components of MACEs

Model	*Coefficient Beta ± SE*	*95% CI*	*p-value*
Predictor: COPD; **Depentednt variable**: all-cause death	1.093±0.335	0.363, 1.823	**0.007**
Predictor: BB; **Depentednt variable**: myocardial infarction	-0.475±0.203	-0.917, -0.034	**0.037**
Predictor: ASCVD; **Depentednt variable**: myocardial infarction	0.789±0.235	0.278, 1.301	**0.006**
Predictor: BMI; **Depentednt variable**: HF hospitalization	0.905±0.193	0.169, 1.012	**0.01**
Predictor: age; **Depentednt variable**: Revascularization	0.449±0.191	0.032, 0,865	**0.037**

Abbreviations: ASCVD: Atherosclerotic cardiovascular disease; BB: beta-blockers; BMI: body mass index; CI: confidential interval; COPD: chronic obstructive pulmonary disease.

By the multivariate linear regression analysis, a positive predictive correlation was seen between all-cause mortality and the history of chronic obstructive pulmonary disease (COPD). A statistically significant association also was revealed between myocardial infarction (MI) and two predictors: a positive correlation in the case of a 10-year atherosclerotic cardiovascular disease (ASCVD) score and a negative in the case of previous use of beta-blockers. The predictor for revascularization was the age of patients.

DISCUSSION

The underlying etiology of MINOCA is heterogenous and the effectiveness of DAPT is unclear.[22] Dual anti-aggregation might be appropriate in case of plaque disruption, coronary embolism, coronary dissection, or hypercoagulability because of thrombophilia,[23,24] and ineffective in such cases as Takotsubo cardiomyopathy, myocarditis, epicardial coronary spasm, etc.[23,25]

In the observational study of the SWEDEHEART registry 66.4% of patients with MINOCA were treated with DAPT with the null effect on 1-year MACE.[12]

In the study conducted by Paolisso et al. treatment with DAPT was not associated with a reduction in MACE or all-cause death in patients with MINOCA.[26]

Cilberti et al. investigated 621 patients with MINOCA with DAPT in 58.8% of cases. The treatment was not associated with a reduction of all-cause mortality, stroke, or heart failure hospitalization.[27]

Treatment with DAPT was not associated with a reduction of MACE in the study conducted by Abdu et al.[28]

The results of our previous[15] and present studies corroborate previously published data. DAPT had no secondary preventive effect on one-year MACE in MINOCA patients with different cardiovascular risk.

It is logical, that high ASCVD risk and previous beta-blocker use are independent predictors of myocardial infarction on multivariable analysis. The same can be said of the correlation between the age of patients with late revascularization procedures. However, it is interesting, that the predictor of all-cause mortality was the comorbidity with COPD rather than traditional cardiovascular risk factors.

The main limitation of the present study is that it was single-center observational research with limited sample size. In addition, we did not differentiate patients with MINOCA type, and only clopidogrel was used in combination with aspirin.

CONCLUSIONS

The use of DAPT in patients with MINOCA is a topic for discussion and requires further investigations with a long-term follow-up period.

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