Comparison of Long-term Preventive Effects of Dual Antiplatelet Therapy vs. Monotherapy in High Cardiovascular Risk Patients After Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA)

Ioseb Sikharulidze,1 Kakhaber Chelidze,2 Levan Chelidze,3 Tamar Kajaia,4 Irma Bakhlishvili1

ABSTRACT

BACKGROUND
Myocardial infarction with nonobstructive coronary arteries (MINOCA) has similar outcomes to patients with acute MI with obstructive coronary disease for up to 1 year. According to existing evidence, dual antiplatelet therapy (DAPT) was not significantly better than aspirin alone in lowering 1-year MACCEs in different cardiovascular risk patients with non-obstructive coronary artery disease.

OBJECTIVES
In the present study, we aimed to compare the long-term preventive effect of DAPT to aspirin alone in high cardiovascular-risk patients over 5 years.

METHODS
For the long-term observation, 34 MINOCA patients with a high 10-year risk of atherosclerotic cardiovascular disease (ASCVD ≥20%) were randomly distributed among the DAPT group (15 patients on aspirin plus clopidogrel therapy) and the MAPT group (19 patients on aspirin alone). The decision about prolonged DAPT was made through the case-by-case evaluation of the bleeding and ischemic risks via the DAPT score calculator.

RESULTS
By Kaplan-Meier survival analysis, the mean survival time for the DAPT group (4.7±0.048 years 95% CI [4.60 to 4.79]) was significantly longer than the mean survival time for the APMT group (4.5±0.049 years 95% CI [4.41 to 4.61]), with p-value less than 0.0001.

CONCLUSIONS
Long-term dual antiplatelet therapy effectively and safely reduces major adverse cardiovascular and cerebrovascular events (MACCEs) in patients after myocardial infarction with nonobstructive coronary arteries (MINOCA).

KEYWORDS
Atherosclerotic cardiovascular disease (ASCVD) risk; dual antiplatelet therapy (DAPT); major adverse cardiovascular and cerebrovascular events (MACCEs); myocardial infarction with nonobstructive coronary artery (MINOCA) disease.

BACKGROUND
Myocardial infarction with nonobstructive coronary arteries (MINOCA), a disorder with heterogeneous pathophysiology, has similar outcomes to patients with acute MI with obstructive coronary disease for up to 1 year.1-4 The prevalence of MINOCA varies between 5 to 15% depending on the observed population and is associated with younger age (<55 years), female gender, genetic predispositions, and mental stress.5-9

Growing evidence indicates that nonobstructive coronary artery disease (NOCAD) is linked with a significant risk of future major adverse cardiovascular and cerebrovascular events (MACCEs), primarily due to nonobstructive plaque erosion and subsequent thrombosis.10-13 Therefore, antiplatelet therapy becomes especially important in patients with NOCAD. However, the efficacy of various antiplatelet therapy regimens for preventing MACCEs in individuals with nonobstructive coronary artery disease remains unclear.14

According to existing evidence, dual antiplatelet therapy (DAPT) was not significantly better than aspirin alone in lowering 1-year MACCEs in different cardiovascular risk patients with NOCAD.15-18

The same results were found in our recent cohort study of secondary prevention DAPT (aspirin plus the P2Y12 receptor antagonist clopidogrel) was not significantly better than aspirin alone in lowering 1-year MACCEs.19
In the present observational cohort study, we aimed to compare the long-term preventive effect of DAPT to aspirin alone in high cardiovascular-risk patients over 5 years.

Methods

Patient population

Overall, 115 of 1018 antiplatelet-naïve patients without previous revascularization admitted to the Coronary Care Unit of Tsinamdzgvrishvili Center of Cardiology LTD (Tbilisi, Georgia) and categorized as MINOCA were included in the research between March 2018 and August 2019. For the long-term observation, 34 MINOCA patients with a high 10-year risk of atherosclerotic cardiovascular disease (ASCVD ≥20%) were randomly distributed among the DAPT group (15 patients on aspirin plus clopidogrel therapy) and the MAPT group (19 patients on aspirin alone). The decision about prolonged DAPT was made through the case-by-case evaluation of the bleeding and ischemic risks via the DAPT score calculator.25

Periprocedural full blood count, renal and liver function, electrolytes, glycated hemoglobin (HbA1c), high-sensitive C-reactive protein, coagulation screen and D-dimer, lipid profile, serial cardiac troponin, N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) and infection screening were performed in all study patients. In addition, echocardiography was performed in all patients. The CRUSADE score calculator was used to assess post-MI major bleeding risk.

Diagnosis of MINOCA

All study patients meet the criteria for a diagnosis of MINOCA criteria, such as acute myocardial infarction with nonobstructive (≤50%) infarct-related epicardial stenosis during angiography and absence of overt alternative systemic cause (Tab.1).5,22

Cardiovascular risk estimation

The 10-year Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator Plus (designed for persons aged 40 to 79) was used to predict the risk of myocardial infarction, stroke, or cardiovascular mortality.23

Follow-up

A five-year follow-up period was used in both groups to determine a six-point MACCE, including all-cause mortality, myocardial infarction, stroke, hospitalization for heart failure, coronary revascularization, and atrial fibrillation (AF). In addition, the registration of bleeding associated with antiplatelet therapy was performed using the bleeding severity classification developed through the Thrombolysis in Myocardial Infarction (TIMI) study group.24 Spontaneous gross hematuria, spontaneous hematemesis, or observed bleeding with a decrease in hemoglobin ≥3 g/dl but ≤15% was classified as minor bleeding, and intracranial bleeding or overt bleeding with a decreased in hemoglobin ≥5 g/dl or decrease in hematocrit ≥15% was classified as major bleeding.24 The DAPT risk score calculation results were used to decide whether to keep or stop DAPT.25

Results

Baseline characteristics of study patients

Table 1 represents the baseline characteristics of study patients.

Table 1. Baseline characteristics of MINOCA patients with a high 10-year risk for ASCVD randomly distributed by the regimen of antiplatelet therapy

![Table 1](image-url)
There was no statistically significant difference between the groups by baseline characteristics, except for mean age, which was higher in the APMT group patients compared to DAPT group patients (67.58±1.84 vs. 65.8±0.78, p<0.0001).

Follow-up

Table 2 represents the annual cumulative incidence of MACCEs in DAPT and APMT groups during the five-year follow-up period.

<table>
<thead>
<tr>
<th>TABLE 2. Annual cumulative incidence of MACCEs in DAPT and APMT groups during the five-year follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
</tr>
<tr>
<td>1st year cumulative MACCEs</td>
</tr>
<tr>
<td>2nd year cumulative MACCEs</td>
</tr>
<tr>
<td>3rd year cumulative MACCEs</td>
</tr>
<tr>
<td>4th year cumulative MACCEs</td>
</tr>
<tr>
<td>5th year cumulative MACCEs</td>
</tr>
<tr>
<td>5-year cumulative MACCEs</td>
</tr>
</tbody>
</table>

Abbreviations: APMT, antiplatelet monotherapy; DAPT, dual antiplatelet therapy; MACCEs, major adverse cardiovascular and cerebrovascular events.

Our previous study showed that DAPT had no secondary preventive effect on one-year cumulative MACCEs in MINOCA patients with high cardiovascular risks. The neutral effect of dual antiplatelet therapy was observed during the second follow-up year; however, from the third year until the end of the follow-up, the preventive effect of DAPT on cumulative MACCEs significantly exceeded the effect of antiplatelet monotherapy with aspirin.

By Kaplan-Meier survival analysis, the mean survival time for the DAPT group (4.7±0.048 years 95% CI [4.60 to 4.79]) was significantly longer than the mean survival time for the APMT group (4.5±0.049 years 95% CI [4.41 to 4.61]), with p-value less than 0.0001 (Fig. 1).

FIGURE 1. Kaplan-Meier survival functions for 5-year MACCEs in study groups

| Log Rank (Mantel-Cox) | 18.365 | 1 | .000 |

Abbreviations: APMT, antiplatelet monotherapy; DAPT, dual antiplatelet therapy; MACCEs, major adverse cardiovascular and cerebrovascular events.

When the effect of different antiplatelet regimens on individual components of MACCEs was evaluated, DAPT was found to have a more substantial preventative effect on all of them; however, only a decrease in the incidence of myocardial infarction (RR=0.45, 95% CI [0.23 to 0.87], z statistic=2.372, p=0.02, NNT[Benefit]=6.196 95% CI [3.51 to 26.58]) and revascularization (RR=0.32, 95% CI [0.14 to 0.73], z statistic=2.677, p=0.007, NNT[Benefit]=5.793, 95% CI [3.51 to 16.62]) was statistically significant (Tab. 3).

<table>
<thead>
<tr>
<th>TABLE 3. Survival analysis of 5-year all-cause mortality, myocardial infarction, stroke, heart failure hospitalization, revascularization, and atrial fibrillation in comparator groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACCEs components</td>
</tr>
<tr>
<td>All-cause mortality</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
</tr>
<tr>
<td>Revascularization</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
</tbody>
</table>

Abbreviations: APMT, antiplatelet monotherapy; DAPT, dual antiplatelet therapy; MACCEs, major adverse cardiovascular and cerebrovascular events.

The predictive correlation between age, female gender, 10-year atherosclerotic cardiovascular disease (ASCVD) score, and 5-year cumulative MACCEs was evaluated by the multivariate linear regression analysis. The only correlation between a 10-year ASCVD score and the cumulative MACCEs was statistically significant (unstandardized/standardized coefficients B=0.749; zero order correlation=0.738; partial correlation=0.736; p<0.0001).

There were no cases of major bleeding in comparator groups during the 5-year follow-up. However, four and five cases of minor bleeding were observed in the DAPT and APMT groups, respectively (OR=1.014, 95% CI [0.26 to 3.02], z statistic=0.02, p=0.98).

DISCUSSION

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is not benign pathology with comparable outcomes with acute myocardial infarction due to obstructive coronary artery disease. The existing scanty evidence shows that treatment with statins and angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs) has a long-term
beneficial effect, and with beta-blockers has a positive effect on outcomes in patients with MINOCA.\textsuperscript{15,26}

Despite the neutral effect on 1-year outcomes, dual antiplatelet treatment (12 months followed by a lifetime single agent) is advised since plaque disruption is considered one of the primary substrates for MINOCA.\textsuperscript{15-18,27}

Our prior research results support previously published data on the lack of a secondary preventative effect of DAPT on one-year MACE in MINOCA patients with different cardiovascular risks.\textsuperscript{19,28}

Pending trial evidence about the usefulness of DAPT in MINOCA patients from ongoing MINOCA-BAT trial,\textsuperscript{29} we decided to compare the long-term preventive effect of dual antiplatelet therapy with a monotherapy regimen in high cardiovascular risk (10-year ASCVD $\geq$20%) MINOCA patients.

Thirty-four high cardiovascular-risk MINOCA patients were distributed among two groups with different antiplatelet therapy regimens: 15 patients in dual antiplatelet therapy with aspirin and clopidogrel (DAPT group) and 19 patients in antiplatelet monotherapy with aspirin (APMT group). All study patients were initially evaluated regarding post-MI major bleeding risk using a CRUSADE score calculator. After the first follow-up year, the DAPT risk score calculation was used to decide whether to keep or stop DAPT. Even though the DAPT Risk Calculator was designed for post-PCI procedure patients without having a major bleeding or ischemic event on DAPT and who were not on chronic oral anticoagulation,\textsuperscript{25} we had to use this application for our study patients, due to the lack of an alternative.

The neutral impact of dual antiplatelet treatment was found during the first two years of follow-up; however, from the third year to the end of the study, the preventative effect of DAPT on cumulative MACCEs considerably outperformed the effect of antiplatelet monotherapy with aspirin. The relative risk for 5-year cumulative MACCEs was 0.49, 95% CI [0.36 to 0.68] and NNT(Benefit)=9.7 95 CI [6.75(Benefit) to 0.67(Benefit)].

Analyzing each component of 5-year MACCEs, we found a decrease in cumulative cases in the DAPT group compared to the APMT group. However, only a reduction in myocardial infarction and revascularization incidence was statistically significant ($p=0.02$ and $p=0.006$, respectively). For a 5-year myocardial infarction, the relative risk was equal to 0.45, 95% CI [0.23 to 0.87], and NNT=6.2(Benefit), 95% CI [3.5(Benefit) to 26.5(Benefit)]. For 5-year revascularization, the relative risk was 0.32, 95% CI [0.14 to 0.73], and NNT=5.8(Benefit), 95% CI [3.5(Benefit) to 16.6(Benefit)].

Considering the observed efficacy and the favorable safety profile of long-term dual antiplatelet therapy, it may be safe to assume that the primary cause of most MINOCA cases is atherosclerotic plaque erosion/rupture and thrombosis, coronary embolism, or coronary artery dissection.

Finally, we emphasize the primary limitation of the present study, which is the single-center observational design with a small sample size. Furthermore, we did not use intravascular ultrasound (IVUS), optical coherence tomography, or cardiac MRI to distinguish underlying causes of MINOCA. Additionally, only clopidogrel combined with aspirin was used for dual antiplatelet therapy.

CONCLUSIONS

Long-term dual antiplatelet therapy effectively and safely reduces major adverse cardiovascular and cerebrovascular events (MACCEs) in patients after myocardial infarction with nonobstructive coronary arteries (MINOCA). Therefore, long-term DAPT should be considered case-by-case after carefully evaluating the benefits and risks of dual antiplatelet therapy. Further investigations are required to confirm the efficacy of long-term anti-aggregation therapy after myocardial infarction with nonobstructive coronary arteries.

AUTHOR AFFILIATION

\textsuperscript{1}Batumi Center for Cardiovascular Diseases and Interventional Medicine, Ckubuc "MedCenter" LTD, Batumi, Georgia;

\textsuperscript{2}Department of Internal Medicine, Tbilisi State Medical University (TSMU), Tbilisi, Georgia;

\textsuperscript{3}Angio-cardiology Clinic “Adapti” LTD, Tbilisi, Georgia;

\textsuperscript{4}Department of Interventional Cardiology & Cardio Surgery, LTD Tbilisi Heart Center, Tbilisi, Georgia.

ACKNOWLEDGEMENTS

Special thanks to Prof. Bezhan Tsinamdzgrishvili M.D., Ph.D. head of Tsinamdzgrishvili Center of Cardiology LTD for his support during the present study.

REFERENCES


10. Carl J, Pepine M, Dunning A, Ferdinand MD, Leslee J. Shaw P, PHD; Kelly Ann Light-McGroary, MD; Rashmee U. Shah, MD, MS; Martha Gulati, MD, MS; Claire Duvernoy, MD; Mary Nonine Walsh, MD, C. Noel Barrey Merz, MD. Emergence of Nonobstructive Coronary Artery Disease. A Women’s Problem and Need for Change in Definition on Angiography. J Am Coll Cardiol. 2015;66(17):1918-1933.


