

Comparison of Invasive and Medical Treatment in Patients With Isolated Non-Ostial Side-Branch Stable Coronary Artery Disease

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Abstract: Objectives. Invasive treatment strategies have been extensively investigated in stable coronary artery disease, but their impact on clinical outcomes remains controversial. It is unknown if simple percutaneous intervention is more beneficial than medical therapy in patients with isolated side-branch (SB) disease. Therefore, we aimed to compare the effect of invasive and medical treatment strategies on long-term adverse outcomes in patients with isolated non-ostial SB stable coronary artery disease (CAD). **Methods.** A total of 176 patients diagnosed with isolated non-ostial SB stable CAD by coronary angiography were included in this study. The study population was categorized into 2 groups according to treatment strategy: 97 patients with invasive therapy and 79 patients with medical therapy. Isolated SB stable CAD was defined as $\geq 50\%$ stenosis in any SB without significant stenosis in the main coronary artery. Major adverse cardiac and cerebrovascular events (MACCE) were defined as all-cause death, myocardial infarction, and cerebrovascular events (CVE). **Results.** The median follow-up time for the groups was 50 (2-110) months. According to the American College of Cardiology lesion classification, the frequency of diagonal artery disease and B2- and C-type lesions was similar between the groups ($P=.346$ and $P=.481$, respectively). Total MACCE rate was 22.2%; there was no significant difference between the groups (22.8% vs 21.6%, respectively; $P=.857$). Prior CVE were defined as independent predictors of MACCE (hazard ratio, 4.086; confidence interval, 95% [1.281-13.052], $P=.017$). **Conclusion.** No significant difference was seen between invasive and medical treatment strategies in terms of adverse clinical events in patients with isolated non-ostial SB stable CAD.

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Key words: invasive treatment, isolated non-ostial side branch, medical therapy, stable coronary artery disease

Introduction

Globally, atherosclerotic coronary artery disease (CAD) is one of the leading causes of morbidity and mortality.^{1,2} Atherosclerotic CAD may present with different clinical conditions, such as acute coronary syndrome (ACS) or stable CAD. The beneficial effect of invasive treatment strategies on mortality is well documented for ACS.^{3,4} However, it is still unclear if invasive treatment strategies have a positive effect on clinical outcomes in stable CAD. In many clinical studies and a meta-analysis, it has been reported that an invasive approach provides a significant decrease in mortality for patients with stable CAD with evidence of ischemia.⁵⁻⁹ In contrast, some large studies have reported that invasive treatment is not superior to a medical therapy approach in reducing mortality in patients with stable CAD.¹⁰⁻¹³ Stable CAD with side-branch (SB) involvement constitutes a relatively small group for which data on both its frequency and treatment are insufficient in the literature. Most of the studies

in the literature involve SB disease accompanied by main vessel disease. Due to the lack of data regarding the effectiveness of invasive and medical treatment strategies on long-term clinical outcomes in patients with isolated non-ostial SB stable CAD, we aimed to compare them in this study.

Methods

Study Population

Patients who underwent coronary angiography (CAG) with a diagnosis of stable angina pectoris (SAP) between December 2012 and March 2019 were included in this retrospective cohort study. Patients with 50% or more stenosis in at least one SB of the coronary arteries, a SB lesion at least 3 mm away from the ostium (non-ostial SB lesion), and a SB diameter of 2.25 mm or greater were included. Left ventricular ejection fraction under 50%, acute renal failure or end-stage renal disease

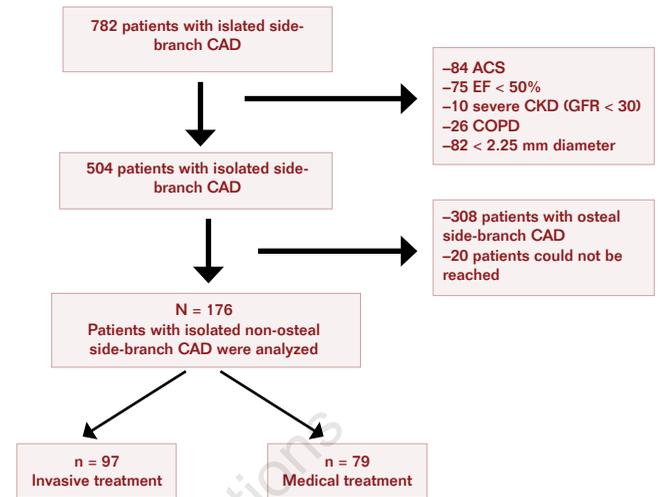
Table 1. Baseline demographic characteristics of study groups.

| | All population (N = 176) | Invasive (n = 97) | Medical (n = 9) | P value |
|---|--------------------------|-------------------|-----------------|---------|
| Age (years) | 61.2 ± 11 | 57.6 ± 11 | 65.7 ± 10 | <.001 |
| Male (%) | 133 (75.6) | 79 (81.4) | 54 (68.4) | .053 |
| Hypertension (%) | 103 (58.5) | 55 (56.7%) | 48 (60.8) | .646 |
| Diabetes mellitus (%) | 60 (34.1) | 34 (35.1) | 26 (32.9) | .873 |
| Hyperlipidemia (%) | 53 (30.1) | 33 (34.0) | 20 (25.3) | .249 |
| Active smoking (%) | 79 (44.9) | 43 (44.3) | 36 (45.6) | .880 |
| Prior CVA (%) | 4 (2.3) | 1 (1.0) | 3 (3.8) | .327 |
| Prior AF (%) | 22 (12.5) | 10 (10.3) | 12 (15.2) | .366 |
| Family history (%) | 33 (18.8) | 18 (18.6) | 15 (19.0) | .999 |
| Treadmill test (%) | 132 (75.0) | 71(73.2) | 61(77.2) | .542 |
| Medications | | | | |
| ASA (%) | 166 (9.3) | 97 (100.0) | 69 (87.3) | <.001 |
| Clopidogrel (%) | 90 (51.1) | 69 (71.1) | 21 (26.6) | <.001 |
| Beta-blocker (%) | 153 (86.9) | 89 (91.8) | 64 (81.0) | .045 |
| CCB (%) | 19 (10.8) | 10 (10.3) | 9 (11.4) | .813 |
| Nitrate (%) | 98 (55.7) | 65 (67.0) | 33 (41.8) | .001 |
| Ranolazine (%) | 8 (4.5) | 2 (2.1) | 6 (7.6) | .142 |
| Statin (%) | 162 (92.0) | 96 (99.0) | 66 (83.5) | <.0001 |
| Diagonal artery (%) | 64 (36.4) | 32 (33.0) | 32 (40.5) | .346 |
| ACC classification | | | | |
| A + B1 (%) | 125 (71.1) | 71 (73.2) | 54 (68.4) | .481 |
| B2 + C (%) | 51 (28.9) | 26 (26.8) | 25 (31.6) | |
| Follow-up period (month)* | 50 (2-110) | 44 (6-110) | 56 (2-96) | .093 |
| *median (min-max) | | | | |
| ACC = American College of Cardiology; AF = atrial fibrillation; ASA = acetylsalicylic acid; CCB = calcium channel blockers; CVA = cerebrovascular accident. | | | | |

requiring hemodialysis, history of coronary artery bypass grafting or percutaneous coronary intervention (PCI), a significant lesion in the main branch, SB diameter under 2.25 mm, SB lesions less than 3 mm from the ostium, and being under age 18 were the exclusion criteria. Approximately 15,842 patients were screened, and 176 met the final analysis criteria after exclusion criteria. Of these, 97 patients who underwent PCI and 79 patients who were on medical therapy constituted the invasive and medical treatment groups, respectively. A flow chart of the study group is seen in **Figure 1**. The study was approved by the local ethics committee.

Study Protocol

Isolated SB CAD was defined as the presence of 50% or more stenosis in any SB of the coronary arteries, with no significant stenosis in the main vessel. Lesions beginning more than 3 mm beyond the SB ostium were defined as non-ostial lesions.^{14,15}



ACS = acute coronary syndrome; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; EF = ejection fraction.

Figure 1. Trial flow diagram.

CAG images were evaluated and recorded by 2 independent, experienced invasive cardiologists. In case of a controversial image, an experienced third invasive cardiologist performed the evaluation. The diameter of the SB, and whether the SB lesion was ostial or not, was decided and recorded by the invasive cardiologists mentioned above. All lesions were morphologically classified as A, B1, B2, and C classes using the American College of Cardiology (ACC) lesion classification.⁹ Initial demographic and lab data of the patients were obtained from the hospital database. Clinical adverse events were determined by electronic records of patients or hospital visits. In addition, mortality data were obtained from the national death registry system.

Clinical Outcomes

The entire study population was evaluated for major adverse cardiac and cerebrovascular events (MACCE) during the follow-up period. MACCE was defined as all-cause death, myocardial infarction (MI), and cerebrovascular events (CVE). In addition to MACCE, all patients were evaluated for cardiac hospitalization, need for recurrent CAG, and new-onset atrial fibrillation (AF).

Statistical Analysis

Continuous variables are presented as the mean ± standard deviation. Categorical variables are presented as frequency (percentages). Normal distribution analysis of the data was performed using the Kolmogorov-Smirnov test. Student's t-test was performed in cases where the data were normally distributed, and the Mann-Whitney U test was used in cases where the data were abnormally distributed. Categorical parameters were evaluated by Pearson's chi-square test. Predictors for MACCE were calculated by a multivariate analysis using parameters with $P < .1$ in the univariate analysis. Long-term follow-up of patients according to treatment strategy was evaluated using the Kaplan-Meier survival analysis. Statistical

Table 2. Baseline biochemical characteristics of study groups.

| | All population (N = 176) | Invasive (n = 97) | Medical (n = 9) | P value |
|---|-----------------------------|----------------------|--------------------|---------|
| Glucose (mg/dL) | 122.3 ± 42 | 122.8 ± 39 | 121.5 ± 46 | .222 |
| HbA1c (%) | 6.3 ± 1 | 6.3 ± 1 | 6.3 ± 1 | .591 |
| Creatinine (mg/dL) | 0.92 ± 0.2 | 0.92 ± 0.2 | 0.91 ± 0.3 | .132 |
| Total cholesterol (mg/dL) | 176.1 ± 41 | 172.5 ± 44 | 180.7 ± 48 | .253 |
| LDL cholesterol (mg/dL) | 119.4 ± 42 | 113.4 ± 40 | 126.7 ± 44 | .035 |
| HDL cholesterol (mg/dL) | 44.7 ± 11 | 44.2 ± 11 | 45.4 ± 11 | .437 |
| Triglyceride (mg/dL) | 151.0 ± 81 | 161.6 ± 64 | 137.9 ± 92 | .124 |
| Hemoglobin (mg/dL) | 13.5 ± 2 | 13.6 ± 2 | 13.4 ± 2 | .373 |
| Leukocytes (/mm ³) | 8567 ± 2574 | 8816 ± 2584 | 8260 ± 2545 | .155 |
| Lymphocytes (/mm ³) | 2314 ± 920 | 2405 ± 853 | 2201 ± 991 | .145 |
| Monocytes (/mm ³) | 686 ± 230 | 707 ± 233 | 661 ± 225 | .186 |
| Neutrophils (/mm ³) | 5153 ± 1987 | 5374 ± 2104 | 4881 ± 1810 | .101 |
| Platelets (x10 ³ /mm ³) | 234.6 ± 62 | 241.4 ± 66 | 226.1 ± 55 | .074 |
| HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LD = low-density lipoprotein. | | | | |

significance criterion in the analysis was $P \leq .05$. The SPSS version 21 packet program was used for analysis.

Results

Clinical and Demographic Features and Laboratory Parameters

The median follow-up period was 50 (2-110) months. The mean age of the patients included in the study was 61.2 ± 11 years. The mean age of the medical treatment group was higher than the invasive treatment group (65.7 ± 10 vs 57.6 ± 11 ; $P < .001$). Of the entire study population, 75.6% was male. The frequency of male gender was significantly lower in the medical treatment group (68.4% vs 81.4%; $P = .053$). The number of patients with positive ischemia by the treadmill test was 132 (75.0%), and there was no significant difference between the groups (77.2% vs 73.2%; $P = .542$).

The use of acetylsalicylic acid, clopidogrel, beta-blockers, nitrates, and statins was significantly higher in the invasive treatment group ($P < .001$, $P < .001$, $P = .045$, $P = .001$, and $P < .001$, respectively). According to ACC lesion classification, the frequency of diagonal artery involvement and B2 + C lesions was similar between the groups ($P = .346$ and $P = .481$, respectively). Follow-up times were similar in both groups ($P = .093$). Demographic characteristics of the study group are shown in **Table 1**. Low-density lipoprotein (LDL) cholesterol levels were significantly higher in the medical treatment group (126.7 ± 44 vs 113.4 ± 40 ; $P = .035$); other biochemical parameters are shown in **Table 2**.

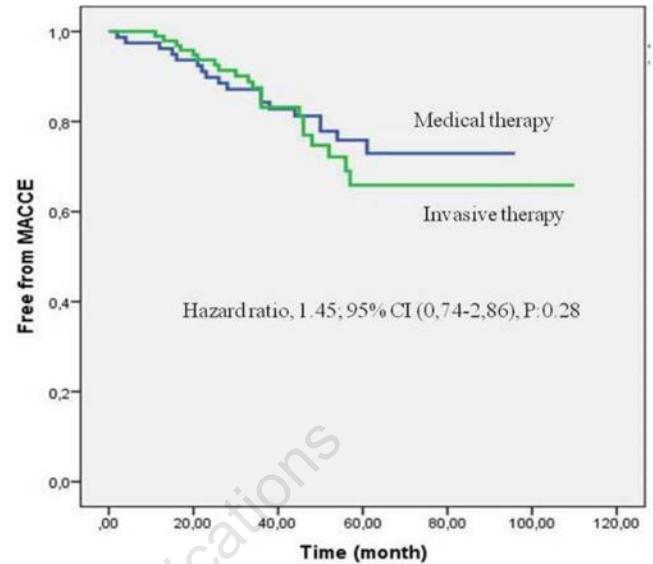


Figure 2. Kaplan-Meier curve for major adverse cardiac and cerebrovascular events according to presence of invasive therapy and medical therapy at long-term follow-up.

Clinical Outcomes

The rates of MACCE, recurrent hospitalization, need for recurrent CAG, and newly diagnosed AF of the invasive and medical treatment groups during long-term follow-up are shown in **Table 3**. The overall MACCE rate was 22.2%, with no significant difference between the invasive and medical treatment groups (22.8% vs 21.6%; $P = .857$). In addition, there was no statistically significant difference between the groups in terms of death, MI, and CVE ($P = .712$, $P = .796$, and $P = .885$, respectively). Also, there was no significant difference between the groups in terms of the frequency of cardiac hospitalization, the need for recurrent coronary angiography, and new-onset AF ($P = .910$, $P = .462$, and $P = .733$; respectively). The Kaplan-Meier curve generated from the long-term follow-up MACCE rates of the groups is shown in **Figure 2**.

Multivariable Analysis

The results of the Cox multivariable analysis are shown in **Table 4**. During the long-term follow-up period, a multivariate analysis was performed for MACCE based on the following variables: diabetes mellitus, prior CVE, baseline creatinine levels, total cholesterol levels, and invasive treatment. Prior CVE (hazard ratio, 4.086; confidence interval, 95% [1.281-13.052]; $P = .017$) was identified as an independent predictor of MACCE.

Discussion

This study demonstrated no statistically significant difference between the groups in terms of death, MI, CVE, and MACCE. It also showed that the frequency of cardiac hospitalization, need for recurrent CAG, or new-onset AF did not differ between groups during the follow-up period. Prior CVE was found to be an independent predictor of adverse outcomes. Our results

Table 3. Clinical endpoints at long-term follow-up.

| Long-Term Follow-Up | All Population | Invasive (n = 97) | Medical (n = 9) | P value |
|--------------------------|----------------|-------------------|-----------------|---------|
| Death (%) | 12 (6.8) | 6 (6.2) | 6 (7.6) | .712 |
| MI (%) | 19 (10.8) | 11 (11.3) | 8 (10.1) | .796 |
| CVA (%) | 15 (8.5) | 8 (8.2) | 7 (8.9) | .885 |
| MACCE (Death/MI/CVA) (%) | 39 (22.2) | 21 (21.6) | 18 (22.8) | .857 |
| Hospitalization (%) | 52 (29.5) | 29 (29.9) | 23 (29.1) | .910 |
| Recurrent CAG (%) | 54 (30.7) | 32 (33.0) | 22 (27.8) | .462 |
| AF (%) | 24 (13.6%) | 14 (14.4%) | 10 (12.7%) | .733 |

AF = atrial fibrillation; CVA = cerebrovascular accident; CAG = coronary angiography; MACCE = major adverse cardiac and cerebrovascular event; MI = myocardial infarction.

showed that the mean age and frequency of female gender were significantly higher in the medical treatment group than the invasive group. In addition, the frequency of ASA and statin use was lower in the medical group. On the other hand, there was no difference between the groups in terms of lesion complexity, frequency of diagonal artery disease, and follow-up.

Although treatment strategies are an important clinical issue that has been studied for many years in stable CAD, the effect of invasive or medical treatment approaches on clinical outcomes remains unclear. According to the RITA-2 study conducted by Henderson et al, no significant difference was found between invasive and noninvasive treatment strategies, in terms of death and MI, in patients with stable CAD involving the main coronary vessels, in a 7-year follow-up. However, improvement was observed in both anginal symptoms and exercise tolerance in the invasive treatment group.¹² Likewise, in 2007, Boden et al reported no significant difference in clinical outcomes between invasive and noninvasive treatment strategies in an average 7 years of follow-up.¹¹ These 2 studies were conducted during the bare metal stent (BMS) era. In the FAME-2 studies, patients with a responsible lesion fractional flow reserve value under 80% were divided into invasive and noninvasive groups and followed up after approximately 12 months. While there was no significant difference between the groups in terms of death and MI, the need for urgent revascularization was higher in the noninvasive treatment group.^{7,16} The most comprehensive and actual data on this subject belongs to the ISCHEMIA study; Maron and colleagues announced its results in 2020. The study included 5100 patients with evidence of moderate-to-severe ischemia and were followed up for an average of 3.2 years. There was no significant difference between the groups in terms of death, MI, and MACE. The number of procedural MI was higher in the invasive group.¹⁰ In a meta-analysis published by Gada et al in 2015, it was reported that invasive treatments reduced the mortality rate in patients with evidence of ischemia documented by invasive or noninvasive examinations.⁸ Based on the results of 42 bifurcation studies including SB, a meta-analysis was published by Peyman et al. They reported that deployment of a drug-eluting stent (DES) to the SB in bifurcation lesions made

Table 4. Independent predictors of major adverse cardiac and cerebrovascular events.

| | HR | % 95 CI | P value |
|--------------------|-------|--------------|-------------|
| Diabetes mellitus | 1.379 | 0.713-2.678 | .337 |
| CVE | 4.086 | 1.281-13.052 | .017 |
| Creatinine | 1.701 | 0.557-5.122 | .353 |
| Total cholesterol | 1.007 | 0.994-1.016 | .132 |
| Invasive treatment | 1.448 | 0.741-2.863 | .281 |

CI = confidence interval; CVE = cerebrovascular events; HR = hazard ratio.

no difference in MACE, death, and stent thrombosis, but it caused a 3% increase in MI.¹⁷ It was also reported that the lowest MACE rate was observed in cases with DES implantation to the main branch and provisional protection of the side branch; the highest MACE rate was observed with BMS implantation in both main and SBs.

Song et al determined that balloon dilatation of the SB prior to main vessel stent implantation did not cause an increase in death and MI in bifurcation lesions but resulted in an increased need for recurrent revascularization compared with a provisional approach.¹⁸ As summarized above, studies have mostly been done with main vessel stable CAD in the literature. Data regarding isolated SB stable CAD are not sufficient. Our study has a retrospective design that represents current life data. Patients who underwent CAG and were diagnosed with SAP as a result of noninvasive tests were analyzed. The most important advantage of our study is that all patients had documented coronary angiography images. In addition, the inclusion of patients with a minimum SB vessel diameter of 2.25 mm provided a more homogeneous distribution of the study group in terms of angiographic features. Another advantage of our study was the use of a DES in patients undergoing stent implantation. Exclusion of ostial lesions is consistent with the objectives of our study in terms of excluding a group whose treatment strategy may be complicated and whose benefits are controversial from the beginning. We believe that our study will create some of the information needed to fill the gap in the literature on this issue.

Study Limitations

Our study has some limitations. First, it was a retrospectively designed, single-center study with a relatively small number of patients from different age groups. In addition, target LDL cholesterol levels might differ, and some anti-anginal agents such as ranolazine were not available during some patient-inclusion periods. Another limitation is that changing treatment trends and invasive approaches between 2012 and 2019 may have affected the results.

Conclusion

This study demonstrated that there was no significant difference between invasive and medical treatment strategies in terms

of clinical adverse events in patients with isolated non-ostial SB stable CAD. Therefore, medical treatment should always be an option for this patient group before invasive treatment is considered. Our study highlights this gray area of the literature. Based on this, additional multicenter and prospective studies in a larger cohort of patients are needed to confirm our findings. ■

Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors report no conflicts of interest regarding the content herein.

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