

Comparing 5-year Outcomes of Aorta-Coronary Bypass Surgery and Percutaneous Coronary Intervention Performed with New-Generation Drug-Eluting Stents in Non-Diabetic Patients with Multivessel Acute Coronary Syndrome Patients and Intermediate Syntax Score

Orta Dereceli Syntax Skoruna Sahip Diabetik Olmayan ve Çoklu Damar Hastalığı Bulunan Akut Koroner Sendromlu Hastalarında Aorta-Koroner By-pass Cerrahisi ile Yeni Kuşak İlaç Kaplı Stent ile Yapılan Perkütan Koroner Girişimin 5 Yıllık Sonuçlarının Karşılaştırılması

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ABSTRACT

Objective: Our main objective is to determine the difference between patients undergoing CABG and PCI with new-generation drug-eluting stents who were non-diabetic during the course of a multivessel acute coronary syndrome (ACS) and intermediate SYNTAX score.

Methods: Between 2012 and 2014, we retrospectively evaluated 1011 non-diabetic patients with ACS in a single center. The patients were followed up up to 5-years. All-cause mortality, cardiac death, myocardial infarction, stroke, revascularization and stent thrombosis were recorded accordingly.

Results: A total of 516 (51%) patients were included in the PCI group and 495 patients (49%) in the CABG group. Stroke occurrence (PCI group: 0.8%, and CABG group: 2.6%, $p=0.022$), requirement for recurrent revascularizations (PCI group: 13.6%, and CABG group: 8.1%, $p=0.005$) and the MACE percentage (PCI group: 20.3%, and CABG group: 14.5%, $p=0.015$) were statistically significant between two groups. However, there was no statistical significance difference between two groups in terms of primary endpoints including death, MI, and stroke (PCI group: 10.9%, and CABG group: 8.3%, $p=0.165$) and all-cause mortality (PCI group 6.2%, and CABG group: 4.7%, $p=0.298$).

Conclusion: There was no difference in all-cause mortality and myocardial infarction between the PCI and the CABG groups during 5-year follow-up. The frequency of repeated revascularizations was lower in the CABG group than the PCI group. In contrast, the stroke rates were higher in the CABG group.

Keywords: PCI; CABG; non-diabetic; stent; mortality; acute coronary syndrome

ÖZ

Amaç: Araştırmadaki temel amacımız, çok damarlı akut koroner sendromu (ACS) ve ara değer SYNTAX puanı bulunan sürece diyabetik olmayan CABG ve (yeni nesil ilaç salınımlı stentli) PCI geçiren hastalar arasındaki farkı saptamaktır.

Yöntem: 2012-2014 arasında tek merkezde, ACS'li 1011 diyabetik olmayan hastayı retrospektif olarak değerlendirdik. Hastaların takibi 5 yıla kadar yapılmıştır. Tüm nedenlere bağlı ölüm, kardiyak ölüm, miyokard enfarktüsü, inme, revaskülarizasyon ve stent trombozu buna göre kaydedilmiştir.

Bulgular: 516 (%51) hasta PCI grubuna, 495 hasta (%49) CABG grubuna alınmıştır. İnme oluşumu (PCI grubunda %0,8 ve CABG grubunda %2,6, $p=0,022$), tekrarlanan revaskülarizasyon gereksinimi (PCI grubunda %13,6 ve CABG grubunda %8,1, $p=0,005$) ve MACE yüzdeleri (PCI grubunda %20,3, CABG grubunda %14,5, $p=0,015$) iki grup arasında istatistiksel olarak anlamlı derecede farklı bulunmuştur. Öte yandan, ölüm, MI ve inme (PCI grubunda %10,9 ve CABG grubunda %8,3, $p=0,165$) ve tüm nedenlere bağlı mortalite (PCI grubunda %6,2, CABG grubunda %4,7, $p=0,298$) dahil olmak üzere birincil sonuçların noktaları arasında iki grup karşılaştırıldığında istatistiksel açıdan anlamlılık fark yoktur.

Sonuç: Beş yıllık takip sırasında tüm nedenlere bağlı mortalite ve miyokard enfarktüsü açısından PCI ile CABG grupları arasında anlamlı fark bulunmamıştır. Tekrarlanan revaskülarizasyon ise CABG grubunda PCI grubundan daha düşüktür. Bunun aksine, inme oranları CABG grubunda daha yüksek çıkmıştır.

Anahtar kelimeler: PCI; CABG; diyabetik olmayan; stent; mortalite; akut koroner sendrom

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INTRODUCTION

Despite advances in therapeutic, surgical and percutaneous invasive interventions, coronary artery disease (CAD) remains the leading cause of death in both Western and developing countries. The optimal approach to revascularization in patients with multi-vessel coronary artery disease has been the main focus of randomized clinical trials performed over the past 30 years. American College of Cardiology Foundation/American Heart Association^{1,2} and the European Cardiology Association/European Cardio-Thoracic Surgery Association³ guidelines provide guidance for decision-making in patients with multi-vessel diseases. In both guidelines, when the surgical risk is acceptable, it is recommended to prefer aorto-coronary shunt rather than percutaneous coronary intervention in individuals with multivessel coronary artery disease accompanied by diabetes. This is especially true in cases when the anastomosis of the left internal mammary artery to the left anterior descending artery is possible.

However, there are disagreements over decision of the optimal revascularization method for patients with multivessel disease without diabetes, the death rate is undoubtedly the key point while choosing a treatment strategy. Furthermore, most of the randomized studies do not have sufficient statistical power to clarify the difference in mortality rates between the coronary artery bypass graft surgery (CABG) and the percutaneous coronary intervention (PCI). The patient information resource in these studies can be proposed to increase statistical power and provide sufficient time to analyze these problems⁴.

Comparisons of CABG with PCI have shown results in favor of surgery in the studies of the first-generation drug-eluting stents. In these studies, this was more evident in diabetic patients.

New generation drug-eluting stents had a lower metal load and more sensitive citrate compounds

compared to the first-generation drug-eluting stents; citrate is a more uniform and bio-degradable polymer in the new generation drug-eluting stents which also have less thrombogenic and inflammatory properties^{5,6}. For this reason, we have decided to investigate the effects of new-generation drug-eluting stents on non-diabetic patients with multi-vessel acute coronary syndromes.

MATERIALS and METHODS

This study evaluated the 1011 consecutive non-diabetic patients with unstable angina pectoris (USAP) and non-ST segment elevation myocardial infarction (NSTEMI) who had undergone coronary revascularization therapy in two parts. The first part was a retrospective evaluation and the second part was a prospective follow-up by the same physician during the study period between the years 2012 and 2014.

Patients were included in the study; if (I) they had been admitted with an ACS (USAP or NSTEMI) and had multi-vessel coronary artery disease (CAD) involving at least two stenotic ($\geq 70\%$) epicardial coronary arteries (II) had Non-DM, (III) had undergone isolated PCI or CABG, and (IV) had an intermediate Syntax score. Patients with left main CAD, history of cardiac surgery, PCI, cardiogenic shock, acute myocardial infarction (MI), new ST-Elevation Myocardial Infarction (STEMI), and elevated creatinine (>2 md/dl) were all excluded. USAP was defined as discomfort on the chest or acceleration of previous angina which occurred during a long-lasting exertion. ST-T changes were the supporting indicators of USAP, in that group of patient's normal troponin levels also supported the diagnosis of USAP and NSTEMI is defined as acute chest pain without persistent ST-segment elevation, and an increase and/or decrease of cardiac troponin, with at least one value above the 99th percentile of the upper reference limit⁷.

The clinical characteristics, laboratory parameters, and medical history were obtained from the pa-

tient charts recorded at the time of index hospitalization. Systemic blood pressure levels exceeding 140/90 mmHg with repeated measurements or treatment with antihypertensive medication were defined as hypertension. Non-DM was diagnosed as fasting blood glucose <126 mg/dL. Baseline total cholesterol level >200 mg/dL or current treatment with statins and/or lipid-lowering agents was defined as hypercholesterolemia. Current smokers were those with regular smoking within the previous 6 months. Syntax score was calculated according to the SYNTAX score algorithm⁸.

Standard techniques were used for PCI and new-generation drug-eluting stents were implanted in the PCI group. All patients used clopidogrel as P2Y12 inhibitor and acetylsalicylic acid (ASA) as dual antiplatelet therapy strategy for a minimum 12 months after stent implantation. Patients were evaluated with echocardiography by experienced echocardiographers according to the European Association of Echocardiography/American Society of Echocardiography guidelines⁹.

Follow-up and outcomes

Patients were followed up for 30 days, 1 year, and 5 years. Follow-up information was collected either via phone contact or by face-to-face hospital visits. All clinical events, such as all-cause mortality, cardiac death, MI, stroke, revascularization, and stent thrombosis were recorded accordingly. Both short-term (within 30 days) and long-term (median 60 months) outcomes were evaluated. Short-term and long-term all-cause mortality was the primary endpoint of the study and major adverse cardiovascular events (MACE) that covered all-cause mortality, MI, stroke, and repeated revascularization were the secondary endpoints.

The definition of MI was made as spontaneous, PCI-related and CABG-related. The indicators of MI were new or pathologic Q wave and/or serum troponin level elevations during the 5-year follow-up. We investigated all causes of death and

divided them into two groups as cardiac and non-cardiac causes. Cancer-related death was defined as a separate group. Cerebrovascular events were defined as acute conditions lasting for at least 24 hours with a permanent loss of function and brain damage. All cerebrovascular events were confirmed by a neurologist and imaging methods.

Statistics

All analyses were performed by SPSS 18.0 package program. Continuous variables were expressed as mean and SD values, and categorical variables as percentages. Chi-square and independent samples t-test were used for statistical analysis. Differences in long-term events were evaluated by the Kaplan-Meier curve with the log-rank test. A p-value below 0.05 was considered statistically significant.

RESULTS

A total of 1011 non-DM patients out of a total 1643 cases with ACS were included in the study. The PCI group included 516 (51%), and CABG group 495 (49%) patients. The characteristics of the groups are shown in Table 1. There were no significant differences between the groups in terms of age, gender, the prevalence of hyper-

Table 1. Demographic, laboratory and clinical characteristics of the study groups.

	CABG n=495 (%49)	PCI n=516 (%49)	p
Age, y (mean±SD)	56,6(±8,3)	55,6 (±9,1)	0.954
Women, n (%)	62 (%12,5)	49 (%9,5)	0.124
Hypercholesterolemia, n (%)	308 (%62,2)	319 (%61,8)	0.896
Current smoker, n (%)	114 (%23)	117 (%22,6)	0.798
Previous stroke, n (%)	10 (%0,8)	6 (%1,2)	0.569
HT, n (%)	184 (%35,7)	329 (%66,5)	0.001
Peripheral vascular disease, n (%)	45 (%9,1)	12 (%2,5)	0.045
CKD (creatinine 150-200 mg/dl), n (%)	11 (%2,1)	18 (%3,6)	0.152
LVEF<%40, n (%)	168 (%32,6)	134 (%27,1)	0.057

PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting surgery, USAP: unstable angina pectoris, HT: hypertension, CKD: chronic kidney disease, LVEF: left ventricle ejection fraction.

cholesterolemia, stroke, chronic kidney disease, left ventricular ejection fraction, current smoking status, and Syntax score. Patients with hypertension were significantly higher in the CABG group than the PCI group.

The left internal mammary artery (LIMA) was used in 95% of patients undergoing CABG. Median follow-up time was 60.7 months (interquartile range: 47-71 months).

All-cause mortality during a 5-year-follow-up period was observed in 32 patients (6.2%) in the PCI group, and in 23 patients (4.7%) in the CABG group ($p=0.298$) without any significant intergroup difference. Furthermore, rates of MI (PCI group 7.4%, and CABG group: 4.6% $p=0.07$) and primary endpoint during 5-years (PCI group: 10.9%, and CABG group 8.3%, $p=0.165$) were not statistically significantly different between two groups.

Kaplan-Meier Survival Analysis also showed that there was no significant difference between PCI

and CABG groups in terms of the use of new-generation drug-eluting stents during 5-years of observation ($p=0.09$) (Figure 1).

The rates of requirement for repeated revascularization, and stroke were statistically significantly different between PCI (13.6% vs 0.8%), and CABG (8.1% vs 2.6%) groups ($p=0.005$; and 0.022, respectively).

The MACE percentage in the PCI group (20.3%) was statistically significantly higher in the CABG group (14.5%) ($p=0.015$) (Table 2).

Table 2. Estimates of major adverse cardiovascular and cerebrovascular events at 5-year follow-up after the procedure.

EVENT	5-year follow-up, n (%)		P value
	PCI	CABG	
MACE	105(20.3%)	72(14.5%)	0.015
Death	31(6.2%)	22(4.7%)	0.298
Cardiac mortality	18(58.1%)	16(66.7%)	0.515
Myocardialinfarction	38(7.4%)	23(4.6%)	0.070
Stroke	4(0.8%)	13(2.6%)	0.022
Repeated revascularization	70 (13.6%)	40(8.1%)	0.005
Primary endpoint	56(10.9%)	41(8.3%)	0.165

PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting surgery, MACE: Major Adverse Cardiac Events.

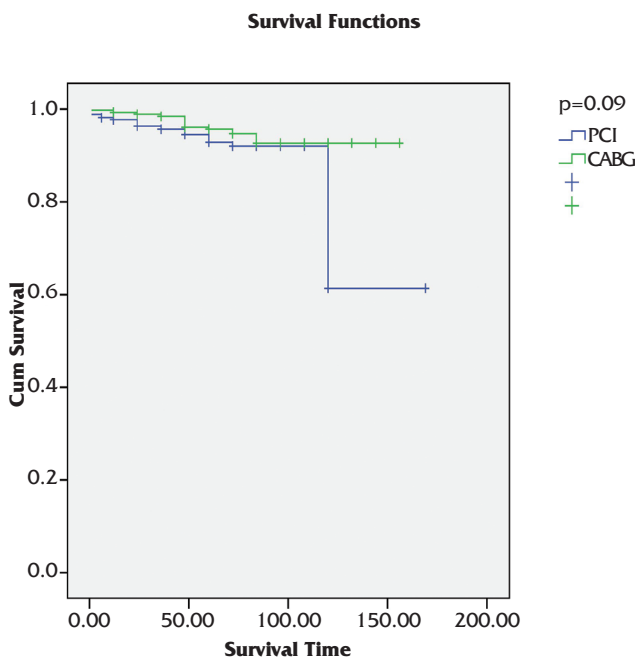


Figure 1. Kaplan-Meier Survival Analysis also shows that there is no difference between PCI (in the use of new-generation drug eluting stents) and CABG during 5-year observation.

When the long-term mortality rates were evaluated, there were only 32 deaths in the PCI group. These deaths were related to cardiac ($n=18$; 58.1%), and extracardiac (41.9%) etiologies (cancer, etc). There were 23 deaths in the CABG group. While 66.7% of these deaths were due to cardiac causes (15 deaths), and 33.3% of them to extra-cardiac causes (cancer, etc.) ($p=0.515$).

DISCUSSION

With this study, we revealed that in non-diabetic patients with ACS and intermediate SYNTAX scores, performing CABG instead of PCI decreases the requirement of repeated PCI and MACE but exposes the patients to an increased risk of a new stroke. On the other hand, a significant difference

was not found between performing PCI or CABG in this group of patients, in terms of all-cause mortality, re-infarction, and primary endpoints.

In a study conducted by Serruys and his colleagues, it was seen that in patients with moderate or advanced SYNTAX scores CABG induced an important decrease in primary endpoints compared with PCI. In the SYNTAX study, 75% of patients were nondiabetic⁸.

The long-term benefits of CABG are due to its reduction in the rates of repeated revascularization. Early results of this study were included in the ACCF/AHA and ESC/EACTS clinical recommendations. However, the biggest disadvantage of the SYNTAX research today is the use of first-generation drug-eluting stents. It is seen that these stents are far inferior when compared to the new generation stents in terms of repeated revascularization, in-stent thrombosis and myocardial infarction¹⁰.

In contrast to the SYNTAX study, in our study, no differences were found in the primary endpoints between the two groups ($p=0.165$) thanks to the use of new-generation drug-eluting stents.

Unlike the first-generation drug-eluting stents, the polymer portion of these stents is very thin and completely absorbable within the 6 months of implantation, which translates into a significant reduction of MI and death both in the short and long-term follow-up after the procedure¹¹.

This advantage gained from the new generation drug-eluting stents has also been revealed in the BEST trial. In that study, which involved 880 patients with multi-vessel coronary artery disease, 60% of patients were nondiabetic. Again in that study, there were no differences between the two groups in terms of the primary endpoints. However, at 4.6 years of follow-up, it was revealed that CABG was superior in terms of reducing the requirement for repeated revascularization¹².

However, neither the SYNTAX nor the BEST research has sufficient statistical power to predict mortality in nondiabetic patients. To address this problem, Chang et al.¹³ examined the meta-analysis of the SYNTAX and the BEST studies in nondiabetic patients. In this meta-analysis, that included 1275 patients, the mean follow-up time was 61 months. In this study, CABG was superior in reducing the rates of all-cause mortality ($p=0.039$), myocardial infarction ($p<0.001$), and repeated revascularization ($p<0.001$). The 5-year stroke rates were similar to the SYNTAX study ($p=0.714$).

However, there were some shortcomings in the study by Chang et al. The most important of these disadvantages was the fact that most patients were transferred from the SYNTAX study, where the first-generation drug-eluting stents were used. It was known that the first-generation drug-eluting stents caused more serious complications than the second or third-generation drug-eluting stents¹⁴⁻¹⁶. In this regard, our study has more profound reflections on the differences imposed by the use of new-generation drug-eluting stents. Unlike other studies, in our study, there were no differences in terms of all-cause mortality ($p=0.298$), myocardial infarction ($p=0.07$), and primary endpoints between the two groups during the 5-year follow-up. In our study, while CABG was superior concerning reduction on repeated revascularization rates ($p=0.005$), it remained inferior to PCI in terms of decreasing stroke incidents ($p=0.022$). The MACE percentage seen in nondiabetic patients favoring CABG was secondary to repeated revascularizations ($p=0.015$). Unlike other studies, the difference we achieved in our study stemmed from the use of new-generation drug-eluting stents.

The ASCERT study demonstrated similar results in a 1-year mortality rate between the two groups (risk ratio: 0.95; 95% CI: 0.90 to 1.00). However, the 4-year mortality rate was lower in the CABG group. This difference was the same in the nondiabetic group¹⁷.

Athappan G et al.¹⁸ found that postoperative stroke was a serious complication increasing the rates of mortality and morbidity. In this study, it was revealed that early stroke was significantly lower in the PTCA group compared to the CABG group. However, in the long-term, the stroke rates between the two groups became similar.

In our study, stroke in non-diabetic patients was more common in the CABG group compared to the PTCA group. This was even more pronounced in the CABG group, particularly in the early post-operative periods¹. The difference in rates of stroke between studies is more likely to result from research design, treatment strategies, and timing¹⁹⁻²¹.

This similar difference was also revealed in the 2.9-year follow-up of another study using everolimus-eluting stents²². Looking at all these discussions, it can be seen that in patients with multi-vessel coronary artery disease with intermediate SYNTAX scores, PCI is not inferior to the CABG. As a result, PTCA can be considered as an alternative in this group of patients.

Study limitations

Our study has several limitations. First it was a single-center study. Besides, if there were many more patients, we could have achieved more comprehensive results, and we might also be able to evaluate subgroups. New p2y12 inhibitors were not used in this study because the only accessible p2y12 inhibitor was clopidogrel in our country. Lack of randomization to either PCI or CABG groups might be accepted as a limitation. However, retrospective enrollment of our patients is a strength of the study as it represents the real-life clinical settings.

CONCLUSION

This real-world setting of nondiabetic patients showed that there was no difference in all-cause mortality and MI between the PCI and the CABG

groups during the 5-year follow-up period. Repeated revascularizations were more frequently performed in the PCI group than in the CABG group. In contrast, the stroke rates were higher in the CABG group.

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