Outcomes of coronary artery bypass grafting versus percutaneous coronary intervention with second-generation drug-eluting stents for patients with multivessel and unprotected left main coronary artery disease

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Abstract
Objectives: To compare the efficacy and safety of percutaneous coronary intervention using second-generation drug-eluting stents with those of coronary artery bypass grafting among patients with multivessel disease and/or unprotected left main coronary artery disease in terms of mortality, myocardial infarction, repeat revascularization, and angina.

Background: Although coronary artery disease is a leading cause of death in the Western world and in many developing countries, its optimal treatment is still a matter of controversy. Several studies have examined the clinical safety and efficacy of percutaneous coronary intervention using first-generation drug-eluting stents over coronary artery bypass grafting in patients with multivessel disease and/or unprotected left main coronary artery disease. However, this study compared the efficacy of percutaneous coronary intervention using second-generation drug-eluting stents to that of coronary artery bypass grafting for multivessel disease and/or unprotected left main coronary artery disease.

Methods: This was a prospective single-center cohort study conducted from September 2012 to November 2014 at the Nicosia General Hospital. In total, 140 patients (94% men and 6% women) with chronic coronary artery disease undergoing revascularization with either percutaneous coronary intervention using second-generation drug-eluting stents or coronary artery bypass grafting were evaluated. We examined the differences in clinical outcomes between coronary artery bypass grafting and percutaneous coronary intervention at 1-year follow-up.

Results: Percutaneous coronary intervention with second-generation drug-eluting stents as opposed to coronary artery bypass grafting resulted in similar rates of mortality (5.7% vs 11.4%, respectively; p = 0.135), myocardial infarction (0% vs 4.3%, respectively), repeat revascularization (4.3% vs 8.6%, respectively; p = 0.115) and angina (10% vs 18.6%, respectively; p = 0.153).

Conclusion: In this patient population, percutaneous coronary intervention with second-generation drug-eluting stents was not inferior to coronary artery bypass grafting in terms of mortality, myocardial infarction, repeat revascularization, or angina.

Keywords
Coronary artery bypass grafting, percutaneous coronary intervention, drug-eluting stents, coronary artery disease

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Introduction
Globally, coronary artery disease (CAD) is the leading cause of death and is predicted to remain so for the next 20 years.¹ Coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) are both well-established revascularization modalities to treat CAD.

The introduction of drug-eluting stents (DES) has led to their increased use in multivessel disease (MVD). Comparative
studies of PCI with first-generation DES over CABG have shown a higher rate of both major adverse cerebrovascular and cardiac events (MACCE) and repeat revascularization in the PCI group. Second-generation DES are constructed from cobalt-chromium and have thin stent struts (80–90 µm) and more biocompatible polymer with more uniform polymer coating of the strut surface, which decreases neo-intimal response and enables more rapid re-endothelialization.2

This study aimed to compare the efficacy and safety of PCI using second-generation DES with those of CABG among patients with MVD and/or unprotected left main coronary artery disease (ULMCAD) in terms of mortality, myocardial infarction (MI), repeat revascularization, and angina.

**Methods**

**Patient population**

This prospective study was conducted at the Nicosia General Hospital. During the period of September 2012 to November 2014, a sample of 140 patients who were eligible for participating in the study was selected. We selected patients with chronic CAD (MVD and/or ULMCAD) undergoing revascularization with either PCI using second-generation DES or CABG. Chronic CAD was defined as the presence of symptoms of stable angina or a positive result on a myocardial ischemia stress test (exercise tolerance test, stress ECHO, or thallium scintigraphy). The study excluded patients presenting with unstable angina, non-ST-segment elevation MI, or ST-segment elevation MI and those undergoing CABG for valve surgery.

Of the 140 patients (131 men (93.6%) and 9 women (6.4%)), 70 were treated with PCI using second-generation DES and 70 with CABG. The patients’ ages ranged from 43 to 97 years, with a mean of 67.1 years. CABG surgery was performed on-pump. Patients undergoing PCI received either zotarolimus- or everolimus-eluting stent (EES). The decision for revascularization strategy was based on coronary disease complexity, patient comorbidities, and patient preference. The National Ethics Committee of Cyprus approved the study. Written informed consent was obtained from all patients and controls according to committee guidelines. Table 1 shows patient characteristics, including sex, age, and risk factors for CAD.

**SYNTAX score calculation**

An experienced cardiologist calculated the SYNTAX score (SS) using the SS algorithm. The patients were divided into tertiles according to SSs (< 22, 22–32, and >32). Most patients treated with PCI had low SSs (<22). In contrast, patients treated with CABG came from all three tertiles.

**Clinical outcomes**

The primary endpoint (major adverse cardiac events [MACE]) was defined as the composite outcome of death, nonfatal MI, repeat revascularization, and angina. Cardiac death was defined as death due to a demonstrable cardiovascular cause or any unexplained death. Acute MI was diagnosed in the presence of any elevation of troponin or creatine kinase-MB above the upper normal limit. Recurrent angina was defined as the occurrence of chest pain due to myocardial ischemia. Repeat revascularization included repeat PCI or CABG of the target vessel.

**Statistical analysis**

One year after revascularization (PCI or CABG), information was recorded on four outcomes: angina, MI, repeat revascularization, and death. The answers were binary, in the form of Yes or No. SPSS version 22 software was used to statistically analyze the data. For each of the four outcomes, an odds ratio (OR) test was applied because the data were binary, and the cross-tabulations were 2 × 2 tables. The baseline differences were tested if they were statistically significant, thus indicating the differences between the outcomes of the two treatments. Propensity score matching was also used to compare 1-year clinical outcomes in two groups.

**Results**

The first check was performed on the angina results. Of the 70 patients treated with PCI, angina occurred in 7, and of the 70 treated with CABG, angina occurred in 13. No significant difference was detected in the occurrence of angina in patients treated with CABG compared to those treated with PCI (OR: 0.487; 95% confidence interval (CI): 0.182–1.306; p=0.153).

The second check was performed on MI. No patients treated with PCI had MI. In contrast, three of those treated with CABG had MI. Because the sample size was small, statistical analysis showed no indications that MI was more
likely after CABG than after PCI. The OR could not be calculated because there was a 0 cell.

The third check was performed on new revascularization. There were three cases of this in the PCI group and six cases in the CABG group. Statistical analysis showed no indications of differences between the two groups (OR: 0.478; 95% CI: 0.115–1.991; p = 0.115).

The last check was regarding death. There were four deaths among PCI patients and eight deaths among CABG patients. However, in analysis, the OR test clearly showed that this difference between the two groups was not statistically significant, leading to the conclusion that the risk of mortality for the two treatments was similar (OR: 0.470; 95% CI: 0.135–1.638; p = 0.135).

Overall, the results showed that PCI with second-generation DES was not inferior to CABG in terms of mortality, MI, repeat revascularization, or angina. Results are shown in Table 2.

Results were not materially changed when we repeated the analysis with the propensity-matched cohort. At 1-year follow-up, there were no significant differences in mortality (p = 0.565), MI (p = 0.997), angina (p = 0.577), or repeat revascularization (p = 0.781) between the two groups.

### Discussion

Although CAD is a leading cause of death in the Western world and in many developing countries, its optimal treatment is still a matter of controversy. Several studies have examined the clinical safety and efficacy of PCI using first-generation DES over CABG in patients with MVD and/or ULMCAD, as discussed below.

In SYNTAX study, 1800 patients with MVD and/or ULMCAD were randomly assigned to undergo either CABG or PCI (using first-generation DES). Their 1-year and 5-year follow-up results were similar and indicated that patients with SSs from 23 to 32 or higher had higher rates of MACCE when treated with PCI than with CABG.3,4

Arterial Revascularization Therapies Study Part II (ARTS II) trial is a nonrandomized, open-label study of percutaneous coronary intervention with sirolimus-eluting stents (SES) in patients with multivessel de novo coronary artery disease. Outcomes of 607 patients treated with PCI using sirolimus eluting stents in ARTS II were compared with the outcomes of 602-patient CABG surgery group and 600-patient bare-metal-stent (BMS) PCI group in the ARTS I trial. The study reported that PCI using DES had a safety record comparable to that of CABG and superior to that of BMS. In addition, PCI using DES had a rate of MACCE that was higher than in patients treated with CABG but lower than in those treated with BMS.5

The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal management of Multi-Vessel Disease (FREEDOM) study randomized 1900 patients with MVD and diabetes mellitus into treatment with either PCI using first-generation DES or CABG. The rate of the primary composite endpoint, which was a combination of death from any cause, MI, or stroke, was significantly lower in the CABG patients, as were the 5-year mortality rates for death from all causes and from MI.6

Registries and randomized studies have favored the safety and efficacy of PCI using first-generation DES in patients with unprotected left main coronary artery stenosis.7,19 The left main sub-study of the SYNTAX trial compared PCI using paclitaxel-eluting stents (PES) and CABG in patients with ULMCAD, showing similar safety and efficacy for both revascularization strategies.12

The Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using SES in Patients with Left Main Coronary Artery Disease (PRECOMBAT) trial found that CABG was not superior to PCI using SES in terms of the 5-year rate of MACCE.18

All the above randomized trials of PCI versus CABG for MVD and ULMCAD used first-generation DES. Recently, two studies compared the outcomes in patients with MVD who underwent CABG with the outcomes of those who underwent PCI with the use of SES. In the BEST (Bypass Surgery Versus Everolimus Eluting Stent Implantation for Multivessel Coronary Artery Disease) study,20 PCI with EES was associated with increased risk of MI and repeat revascularization, without any mortality difference compared with CABG. Another large cohort by Bangalore et al.21 suggested that PCI with EES was associated with a lower risk of stroke, a similar risk of death, and a higher risk of MI than CABG.

The results of both studies were fairly consistent for individual end points. Mortality rate was not significantly different between PCI and CABG patients and higher rate of MI after PCI occurred in both studies. Nevertheless, in the study of Bangalore et al., there was no difference in MI rate between PCI and CABG in patients who were completely revascularized with PCI. Both studies provide a large amount of data regarding the differences between PCI with second-generation DES and CABG for multivessel CAD. The data suggest only minor differences, except for patients in whom complete revascularization cannot be achieved.

American and European guidelines on revascularization give preference to CABG in patients with multivessel CAD. The data from the recent trials comparing PCI with second-generation

### Table 2. Differences in MACE between CABG and PCI with second-generation DES at 1-year follow-up.

|                | PCI          | CABG         | p-value |
|----------------|--------------|--------------|---------|
| Angina         | 7 (10%)      | 13 (18.6%)   | 0.153   |
| Myocardial infarction | 0 (0%)      | 3 (4.3%)     | –       |
| New revascularization | 3 (4.3%)    | 6 (8.6%)     | 0.115   |
| Death          | 4 (5.7%)     | 8 (11.4%)    | 0.135   |

MACE: major adverse cardiac events; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; DES: drug-eluting stents.
DES versus CABG suggest that new-generation stents might narrow the gap between the two revascularization strategies for patients with MVD.

Two recent randomized trials compared PCI using new-generation DES with CABG in patients with ULMCAD. The EXCEL (Evaluation of XIENCE vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial\(^2\) showed that PCI with EES was non-inferior to CABG regarding the composite endpoint of death, stroke, or MI at 3 years in patients with low or intermediate SSs. In contrast, the NOBLE (Nordic–Baltic–British Left Main Revascularization) trial\(^3\) showed that the 5-year risk of major adverse events was higher after PCI with biolimus DES compared to CABG, despite similar mortality.

This study compared the efficacy of PCI using second-generation DES (zotarolimus-eluting stent and EES) to that of CABG for MVD and/or ULMCAD. In this patient population, PCI using second-generation DES was not inferior to CABG in terms of angina, MI, repeat revascularization or death, 1 year after the treatment.

**Study limitations**

This study had some limitations. First, the population size was small and therefore may not have been suitably powered for the measured outcomes. The follow-up period was limited to 1 year. A longer follow-up period might have found different results. Selection bias in choosing PCI or CABG may also be a limitation of our analysis. The study is also limited by the lack of angiographic follow-up. An additional limitation is that angiographic characteristics (such as lesion length, tortuosity, calcification) were not included in the analysis.

**Conclusion**

In patients with MVD and/or ULMCAD, PCI using second-generation DES may be a reasonable alternative to CABG in the near future.

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**Declaration of conflicting interests**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethics approval**

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**Informed consent**

Written informed consent was obtained from all patients before the study.

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