



Original article

Second-generation drug-eluting stenting versus coronary artery bypass grafting for treatment of coronary chronic total occlusion



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ARTICLE INFO

Article history:

Received 14 July 2018

Received in revised form 1 October 2018

Accepted 18 October 2018

Available online 2 January 2019

Keywords:

Chronic total occlusion

Second-generation drug-eluting stent

Percutaneous coronary intervention

Coronary artery bypass grafting

ABSTRACT

Background: Limited data are available regarding the long-term clinical outcomes of percutaneous coronary intervention (PCI) using second-generation drug-eluting stents (DESs) versus coronary artery bypass grafting (CABG) for the treatment of coronary artery disease (CAD) with chronic total occlusion (CTO). We compared the clinical outcomes of patients with multivessel CAD including CTO lesions treated with PCI using DESs versus CABG.

Methods: We analyzed data from 423 consecutive patients who underwent successful revascularization for CTO between March 2008 and February 2012. Death or myocardial infarction (MI) and major adverse cardiac and cerebrovascular events (MACCE) were compared between patients treated with PCI using second-generation DESs ($n = 232$, 2nd DES group) versus those treated with CABG ($n = 191$, CABG group). To reduce selection bias according to treatment strategy and other potential confounding factors, inverse probability of treatment weighting (IPTW) was also performed.

Results: During a median follow-up duration of 32 months, there was no significant difference in death or MI [hazard ratio (HR): 0.69; 95% confidence interval (CI): 0.29–1.63; $p = 0.399$] or MACCE (HR: 1.32; 95% CI: 0.74–2.35; $p = 0.341$) between the 2nd DES group and the CABG group based on multivariable analysis. After IPTW adjustment, the incidences of death or MI (HR: 0.72; 95% CI: 0.26–1.95; $p = 0.518$) and MACCE (HR: 1.49; 95% CI: 0.76–2.91; $p = 0.244$) remained similar in the two groups. In subgroup analysis, the effect of second-generation drug-eluting stenting was comparable to that of CABG across various subgroups without a significant p -value for the interaction.

Conclusions: The efficacy of PCI using second-generation DES was comparable to that of CABG in CTO patients with multivessel CAD.

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Introduction

Coronary revascularization achieved by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)

has survival benefits and reduces adverse clinical outcomes in patients with chronic total occlusion (CTO) [1–3]. CABG is widely performed in patients with multiple CTOs, multivessel coronary artery disease (CAD), or diabetes and the surgical outcomes in

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patients with CTOs have improved over time, likely due to better perioperative management and increased surgical experience [3,4]. The success rate of PCI to treat CTO has also increased over time due to an increase in experience and improvements in PCI technology [5]. Drug-eluting stents (DESs) with enhanced durability and lower rates of in-stent neointimal hyperplasia compared with bare metal stents have been developed [6]. In particular, everolimus-eluting or zotarolimus-eluting stents, hereafter referred to as second-generation DESs, have been found to be superior or comparable to first-generation DESs in terms of mid-term outcomes in patients with CTO lesions [7]. However, few studies have compared the long-term clinical outcomes of patients with CTO who underwent PCI using a second-generation DES with those who were treated with CABG. Therefore, we sought to compare the clinical outcomes of PCI using second-generation DESs versus CABG in CTO patients with multivessel CAD.

Methods

Study population

Between March 2008 and February 2012 in South Korea, we investigated 591 consecutive patients who underwent successful coronary revascularization for CTO from a retrospective multi-center registry of four major coronary intervention centers in South Korea: Samsung Medical Center, Samsung Changwon Hospital, Anam Hospital of Korea University Medical Center, and Sejong General Hospital. We included only patients with at least one CTO lesion and multivessel CAD. Ultimately, 423 CTO patients who underwent successful coronary revascularization, excluding patients who underwent balloon-only angioplasty, bare metal stenting, or first-generation drug-eluting stenting, were enrolled in the final analysis. Patients were divided into two groups according to revascularization strategy: patients who underwent PCI using second-generation DESs (2nd DES group) and patients who were treated with CABG (CABG group) (Fig. 1). The local institutional review board of each participating hospital approved this study and waived the requirement for informed consent.

Treatment strategy

Revascularization of CTO was accomplished by PCI with second-generation DESs or CABG. The revascularization strategy in each patient was selected based on the patient's and physician's preferences. PCI was performed using contemporary techniques such as bilateral injections; a specialized stiff, hydrophilic wire with a tapered tip; microcatheters; and a retrograde approach when available. The decision to pursue invasive treatment, the access site, type of DES, use of intravascular ultrasound, and use of glycoprotein IIb/IIIa receptor inhibitor were all left to the operator's discretion. All interventions and procedural anticoagulation were performed according to current standard guidelines. All patients received loading doses of aspirin (300 mg) and clopidogrel (300–600 mg) before PCI unless they had previously received these antiplatelet medications. Aspirin treatment was continued indefinitely, and the duration of clopidogrel treatment was left to the discretion of the physician. Successful revascularization was defined as final residual stenosis less than 20% of the vessel diameter, with thrombolysis in myocardial infarction (TIMI) flow grade ≥ 2 after revascularization, as assessed by visual estimation of angiograms [8]. In the case of CABG for CTOs, arterial grafting with off-pump coronary artery bypass was the preferred technique.

Data collection

Clinical, angiographic, procedural, and outcome data were collected using a web-based reporting system. Additional information was obtained by reviewing medical records or by telephone contact, if necessary. All baseline and procedural cine coronary angiograms were reviewed and analyzed quantitatively at the angiographic core laboratory of each participating hospital with an automated edge-detection system (Centricity CA 1000, GE, Waukesha, WI, USA) using standard definitions [9].

Study outcomes and definitions

Primary outcome was death or myocardial infarction (MI) during follow-up. Secondary outcomes were death, cardiac death, MI, cerebrovascular accident (CVA), repeat revascularization, and major adverse cardiac and cerebrovascular event (MACCE). Repeat revascularization was a composite of target vessel revasculariza-

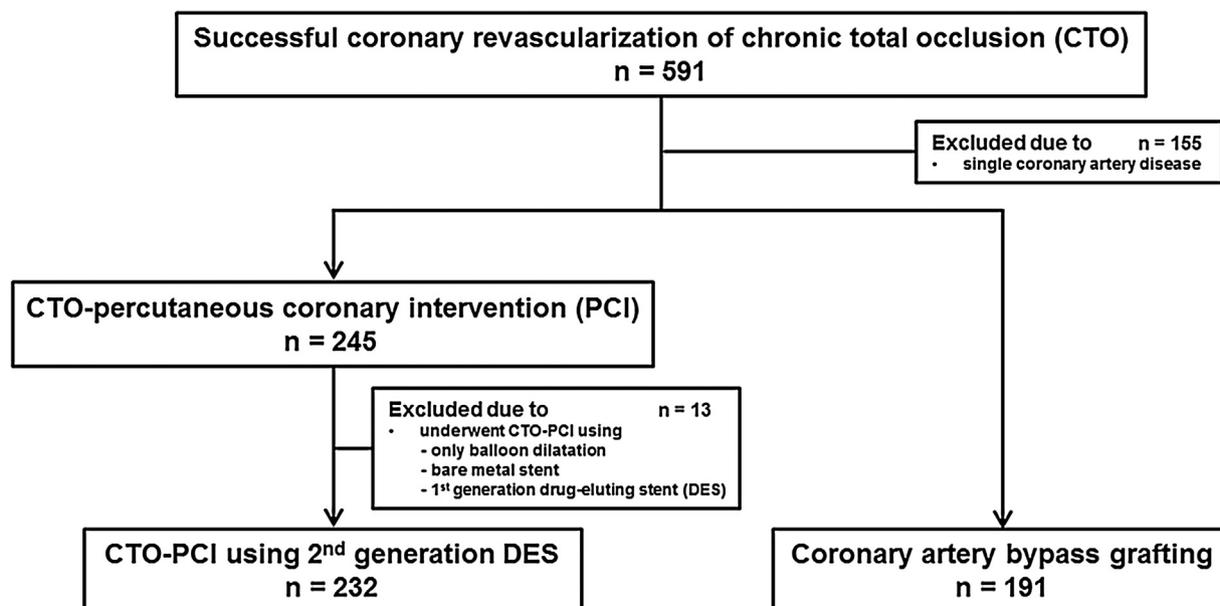


Fig. 1. Schematic illustration of study cohort selection.

tion (TVR) and non-TVR treated with PCI or CABG. MACCE was defined as the composite of death, MI, CVA, or repeat revascularization. All deaths were considered to be of cardiac origin unless a definite non-cardiac cause could be established. MI was defined as elevation of the creatine kinase MB fraction or troponin-T/troponin-I greater than the upper limit of normal with concomitant ischemic symptoms or electrocardiographic findings indicative of ischemia [10]. Perioperative enzyme elevation was not included in this definition of MI. TVR indicates repeated revascularization of the target vessel by PCI or CABG; non-TVR indicates repeated revascularization of any vessel other than the target vessel by PCI or CABG. A CTO lesion was defined as an obstruction of a native coronary artery with TIMI flow grade 0 for an estimated duration >3 months, based on the interval from the last episode of acute coronary syndrome or, in patients with no history of acute coronary syndrome, from the first episode of effort angina consistent with the location of the occlusion or previous coronary angiography [8,11,12]. Multivessel CAD was defined as coronary lesions with $\geq 50\%$ diameter stenosis in at least two of the three major epicardial coronary arteries or their major branches greater than 2.0 mm in diameter.

Statistical analysis

Categorical variables are presented as counts and percentages and were compared by Chi-square or Fisher's exact test. Continuous variables are expressed as mean \pm standard deviation or as median (25th percentile to 75th percentile) for variables lacking a normal distribution. Analysis of continuous variables was performed using Student's *t*-test or Wilcoxon rank-sum test. Survival curves were constructed based on Kaplan–Meier estimates and were compared with the log-rank test. Proportion hazards assumptions of the hazard ratios (HR) associated with PCI using second-generation DESs versus CABG in the Cox proportional hazards models were graphically inspected in the “log minus log” plot and were also confirmed with the Schoenfeld residual test. All Cox proportional hazard models for each clinical outcome presented in the manuscript met the assumption of proportional hazards. Covariates that were statistically significant in univariate analysis ($p < 0.10$) were included in the Cox model, namely diabetes mellitus and a Synergy Between PCI with Taxus and Cardiac Surgery (SYNTAX) score ≥ 24 [13]. To reduce treatment

selection bias according to treatment strategy and other potential confounding factors, we performed inverse probability of treatment weighting (IPTW) adjustment. The IPTW method was performed using generalized boosted models for multiple treatment, and weights were based on the treatment strategy (PCI versus CABG) to evaluate if interactions between the two treatment strategies affected clinical outcomes. All tests were two-tailed, and a p -value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 23 for Windows (IBM, Armonk, New York, USA).

Results

In our multicenter CTO registry, 402 patients underwent PCI and 322 patients (80.1% of CTO-PCI group) were successfully revascularized. In the CTO-PCI group, stent diameter was 3.0 ± 0.4 mm, stent length 32.6 ± 15.5 mm, and number of stents 1.5 ± 0.7 . Another 203 patients were treated with CABG (CTO-CABG group) and complete revascularization was achieved in 187 patients (92.1% of CTO-CABG group) and total arterial graft was performed in 153 patients (75.3%), and 163 patients (80.3%) operated with off-pump technique.

Baseline clinical and angiographic characteristics

Of the 423 patients with at least one CTO lesion and multivessel CAD, 231 patients successfully underwent PCI using second-generation DESs (2nd DES group) while 191 patients successfully underwent CABG (CABG group). Baseline and procedural characteristics of the study populations are shown in Table 1. Compared with the CABG group, patients in the 2nd DES group had a significantly lower prevalence of diabetes mellitus but a higher prevalence of dyslipidemia and acute coronary syndrome. Left ventricular ejection fraction was higher in the 2nd DES group than in the CABG group. After revascularization, the 2nd DES group more frequently took aspirin and angiotensin-converting enzyme inhibitor/angiotensin receptor blockers than the CABG group, but took beta blockers less frequently. Angiographic analysis showed that CTO of the right coronary artery and left circumflex coronary artery, multiple CTOs, abrupt stump, bridge collaterals, and calcified CTO were more frequent in the CABG group than the

Table 1
Baseline clinical characteristics.

	Overall population <i>n</i> = 423	2nd DES group <i>n</i> = 232	CABG group <i>n</i> = 191	<i>p</i> -Value
Age (years)	63.0 \pm 10.6	63.1 \pm 11.1	62.9 \pm 9.9	0.821
Male	346 (81.8)	186 (80.2)	160 (83.8)	0.340
Diabetes mellitus	209 (49.4)	97 (41.8)	112 (58.6)	0.001
Hypertension	273 (64.5)	151 (65.1)	122 (63.9)	0.795
Dyslipidemia	188 (44.4)	118 (50.9)	70 (36.6)	0.003
Current smoker	134 (31.7)	77 (33.2)	57 (29.8)	0.462
Chronic renal failure	33 (7.8)	16 (6.9)	17 (8.9)	0.444
Acute coronary syndrome	116 (27.4)	82 (35.3)	34 (17.8)	<0.001
Previous MI	64 (15.1)	33 (14.2)	31 (16.2)	0.567
Previous CVA	30 (7.1)	15 (6.5)	15 (7.9)	0.580
Previous PCI	73 (17.3)	43 (18.5)	30 (15.7)	0.444
LVEF (%)	54.4 \pm 13.8	56.5 \pm 13.1	52.0 \pm 14.3	0.001
Concomitant medications				
Aspirin	394 (93.1)	222 (95.7)	172 (90.1)	0.022
Statins	334 (79.0)	185 (79.7)	149 (78.0)	0.664
Beta blockers	285 (67.4)	141 (60.8)	14 (7.4)	0.001
ACE inhibitor/ARBs	175 (41.4)	140 (60.3)	35 (18.3)	<0.001

Data are presented as *n* (%) or mean \pm standard deviation.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; DES, drug-eluting stent; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2
Angiographic characteristics.

	Overall population n = 423	2nd DES group n = 232	CABG group n = 191	p-Value
CTO location				
Right coronary artery	214 (50.6)	96 (41.4)	118 (61.8)	<0.001
Left main artery	0 (0)	0 (0)	0 (0)	
Left anterior descending artery	160 (37.8)	92 (39.7)	68 (35.6)	0.392
Left circumflex artery	160 (37.8)	77 (33.2)	83 (43.5)	0.030
Multiple CTOs	120 (28.4)	50 (21.6)	70 (36.6)	0.001
Abrupt stump	155 (36.6)	67 (28.9)	88 (46.1)	<0.001
Bridge collaterals	141 (33.3)	56 (24.1)	85 (44.5)	<0.001
Calcified CTO	83 (19.6)	28 (12.1)	55 (28.8)	<0.001
^a Proximal to mid CTO	308 (72.8)	169 (72.8)	139 (72.8)	0.987
^b Well-developed collateral	157 (44.4)	75 (46.0)	82 (42.9)	0.561
SYNTAX score	26.3 ± 10.8	22.2 ± 9.5	29.8 ± 10.6	<0.001
SYNTAX score ≥24	197 (55.6)	66 (40.5)	131 (68.6)	<0.001

Data are presented as n (%) or mean ± standard deviation.

CTO, chronic total occlusion; CABG, coronary artery bypass grafting; DES, drug-eluting stent; SYNTAX, the Synergy Between percutaneous coronary intervention with Taxus and Cardiac Surgery.

^a We abbreviated “CTO of the proximal to middle portions of the vessel” as “Proximal to mid CTO”.

^b We abbreviated “Rentrop grade 3 collateral flow” as “Well-developed collateral”.

2nd DES group. The SYNTAX score was higher in the CABG group than the 2nd DES group (Table 2).

Clinical outcomes

Complete follow-up data were obtained for the overall study population. During the follow-up (median 32 months, 19 to 44 months), 21 deaths or MIs occurred [8 (3.4%) in the 2nd DES group versus 13 (6.8%) in the CABG group]. In multivariable analysis, the 2nd DES group had a similar risk of death or MI [HR 0.69; 95% confidence interval (CI) 0.29–1.63; $p = 0.399$], death (HR 0.52; 95% CI 0.20–1.31; $p = 0.165$), cardiac death (HR 0.45; 95% CI 0.11–1.81; $p = 0.259$), MI (HR 4.28; 95% CI 0.46–39.74; $p = 0.202$), CVA (HR 0.31; 95% CI 0.08–1.13; $p = 0.077$), and MACCE (HR 1.32; 95% CI 0.74–2.35; $p = 0.341$) to the CABG group (Table 3 and Fig. 2). Repeat revascularization (HR 19.56; 95% CI 2.59–147.82; $p = 0.004$) occurred more frequently in the 2nd DES group than in the CABG group.

Inverse probability of treatment weighting adjustment

After performing IPTW, death or MIs were still not significantly different between the 2nd DES group and the CABG group (HR 0.72; 95% CI 0.26–1.95; $p = 0.518$). Death (HR 0.54, 95% CI 0.18–1.63, $p = 0.278$), cardiac death (HR 0.39, 95% CI 0.07–2.15, $p = 0.281$), MI (HR 2.94, 95% CI 0.22–39.85, $p = 0.418$), CVA (HR 0.60, 95% CI 0.15–

2.44, $p = 0.477$), and MACCE (HR 1.49, 95% CI 0.76–2.91, $p = 0.244$) were similar between the two groups. Repeat revascularization (HR 28.66, 95% CI 3.50–235.06, $p = 0.002$) occurred more frequently in the 2nd DES group than in the CABG group (Table 3).

Subgroup analysis

To assess if there was an association between treatment strategy (second-generation drug-eluting stenting versus CABG) and death or MI in various subgroups, we performed subgroup analyses. The treatment effect of second-generation drug-eluting stenting compared to CABG did not differ significantly across subgroups regardless of age, clinical presentation (stable ischemic heart disease versus acute coronary syndrome), comorbidities (diabetes mellitus as well as heart failure), or angiographic characteristics (multiple CTOs as well as high SYNTAX score ≥24) (Fig. 3).

Discussion

We investigated the long-term clinical outcomes of PCI using second-generation DESs versus CABG in CTO patients with multivessel CAD using a large, dedicated, multicenter registry. The primary finding of our study was that CTO patients with multivessel CAD who underwent successful revascularization using second-generation DESs had a similar risk of death or MI

Table 3
Clinical outcomes for adjusted hazard ratios and inverse-probability-of-treatment weighting method.

	Overall population n = 423	2nd DES group n = 232	CABG group n = 191	^a Adjusted HR (95% CI)	p-Value	HR after IPTW (95% CI)	p-Value
Death or MI	21 (5.0)	8 (3.4)	13 (6.8)	0.69 (0.29–1.63)	0.399	0.72 (0.26–1.95)	0.518
Death	19 (4.5)	6 (2.6)	13 (6.8)	0.52 (0.20–1.31)	0.165	0.54 (0.18–1.63)	0.278
Cardiac death	8 (1.9)	2 (0.9)	6 (3.1)	0.45 (0.11–1.81)	0.259	0.39 (0.07–2.15)	0.281
MI	4 (0.9)	3 (1.3)	1 (0.5)	4.28 (0.46–39.74)	0.202	2.94 (0.22–39.85)	0.418
CVA	13 (3.1)	3 (1.3)	10 (5.2)	0.31 (0.08–1.13)	0.077	0.60 (0.15–2.44)	0.477
Repeat revascularization	21 (5.0)	20 (8.6)	1 (0.5)	19.56 (2.59–147.82)	0.004	28.66 (3.50–235.06)	0.002
^b MACCE	49 (11.6)	28 (12.1)	21 (11.0)	1.32 (0.74–2.35)	0.341	1.49 (0.76–2.91)	0.244

Data are presented as n (%).

CABG, coronary artery bypass graft surgery; CI, confidence interval; CVA, cerebrovascular accident; DES, drug-eluting stent; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; MACCE, major adverse cardiac and cerebrovascular event; SYNTAX, the Synergy Between percutaneous coronary intervention with Taxus and Cardiac Surgery.

^a Adjusted covariates include diabetes mellitus and SYNTAX score ≥24.

^b MACCE was defined as a composite of death, MI, CVA, or repeat revascularization.

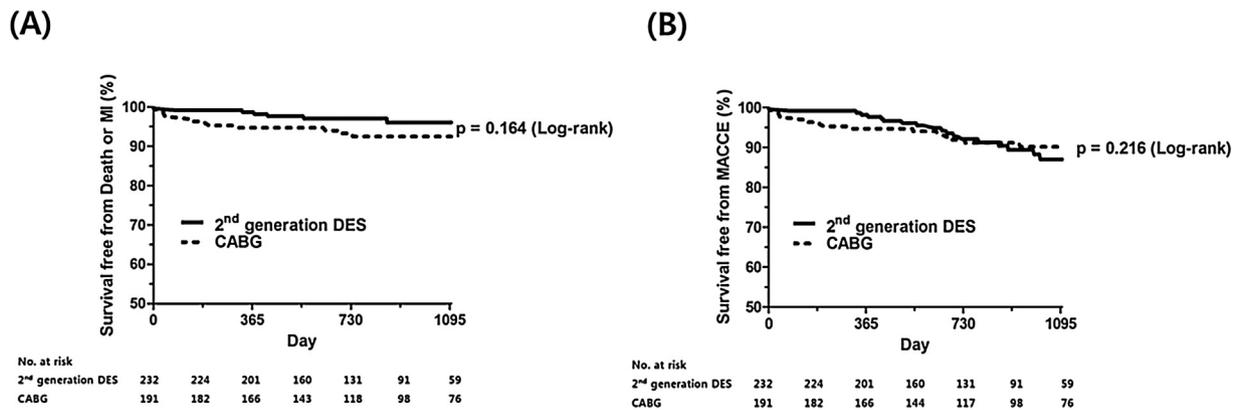


Fig. 2. Survival curves for clinical outcomes. (A) Kaplan–Meier curves for death or MI in patients with CTO who underwent PCI using a 2nd generation DES versus CABG. (B) Kaplan–Meier curves for MACCE in patients with CTO who underwent PCI using a 2nd generation DES versus CABG. CABG, coronary artery bypass grafting; CTO, chronic total occlusion; DES, drug-eluting stent; MACCE, major adverse cardiac and cerebrovascular event; MI, myocardial infarction; PCI, percutaneous coronary intervention.

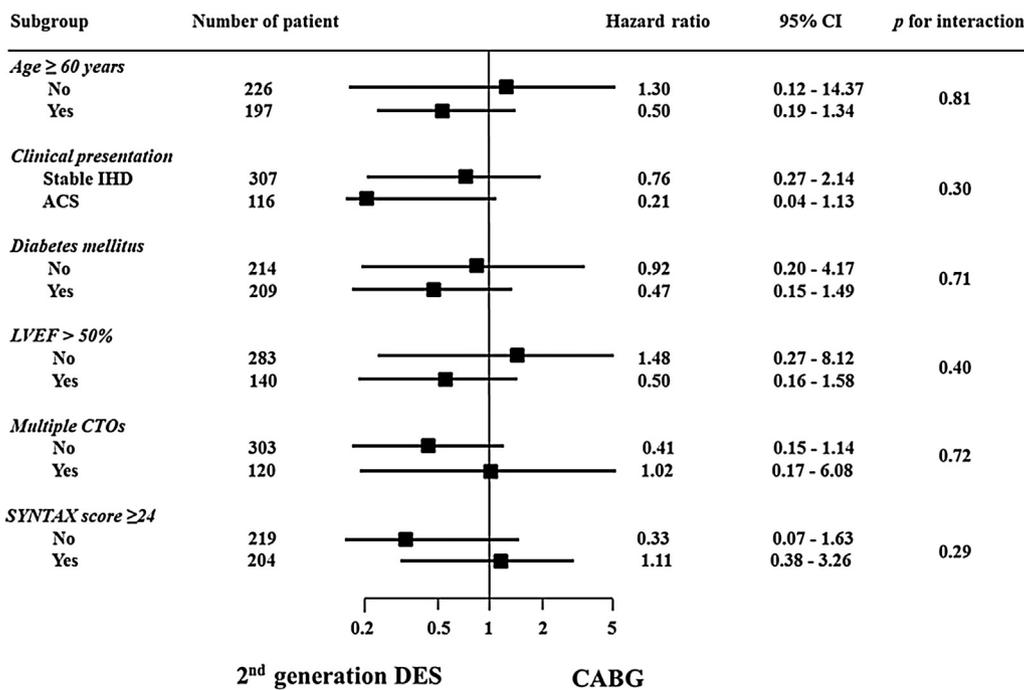


Fig. 3. Comparative unadjusted hazard ratios of death or MI for subgroups of the second-generation DES and CABG groups. ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CI, confidence interval; CTO, chronic total occlusion; DES, drug-eluting stent; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; SYNTAX, the Synergy between Percutaneous coronary intervention with Taxus and Cardiac Surgery.

to those patients treated with CABG. After IPTW, the incidence of death or MI was still comparable between patients who underwent PCI using second-generation DESs and those who were treated with CABG. The efficacy of second-generation drug-eluting stenting was consistent across various subgroups. Although this study was limited by its observational design, this is one of the few reports to specifically address the issue of efficacy and safety of revascularization of second-generation DESs in patients with multivessel CAD including at least one CTO lesion.

Second-generation DESs have thinner struts and more biocompatible polymers than earlier stents. Those features are associated with greater endothelial cell coverage, less thrombogenicity, and less neoatherosclerosis, when compared to previous stents [14,15]. It translated into better outcomes after PCI and the second-generation DESs could become widely adopted to treat patients with CTO lesions [16–19]. Hence, it is crucial to compare CABG outcomes to those of the currently available second-

generation DESs in patients with CTO and multivessel CAD. Previous studies showed that CABG was associated with better outcomes, including lower mortality, than PCI in multivessel CAD [20–22], but those studies compared CABG to bare metal stents or first-generation DESs only, included only a few patients with CTO lesions, and did not focus on the efficacy of successful CTO revascularization. Moreover, the follow-up duration of these previous studies was relatively short and the results were from a heterogeneous population, thus no definite conclusions about CTO patients with multivessel CAD can be drawn from these studies. We used a large dedicated multicenter CTO registry and included more CTO patients with multivessel CAD than most previous studies to address the limitation of a heterogeneous study population. In our study, patients with CTO and multivessel CAD who underwent revascularization with second-generation DESs had similar outcomes to those patients treated with CABG. Because perioperative mortality and potential lethal complications related

to CABG still exist, the result of our study could be helpful in making clinical decisions in real-world settings.

We found that PCI was associated with higher rates of repeat revascularization. Even though second-generation DESs have higher patency rates than first-generation DESs or bare metal stents, CABG continues to be associated with lower rates of repeat revascularization than PCI based on new generation DESs or older generation stents [23,24]. This difference can be partially attributed to the use of left internal mammary grafts, which are known to be associated with high long-term patency [25]. CABG not only bypasses target lesions, but also bypasses adjacent lesions not considered significant at the time of the initial revascularization procedure; those lesions could lead to future events in patients treated with PCI [26].

Study limitations

This study had several limitations. First, its design was non-randomized, retrospective, and observational, which may have significantly affected the results due to confounding factors. Second, due to the retrospective nature of our registry, we could not thoroughly identify the detailed data regarding procedures of CTO revascularization or CABG, clinical variables relating to the SYNTAX II score, and alterations in medical therapy of all study patients during follow-up. Third, we did not routinely evaluate the amount of viable myocardium or ischemia in study patients using functional ischemia testing, nor did we assess graft flow or distal perfusion with follow-up coronary angiography in patients who underwent CABG. Finally, although the vital status of all patients, including patients lost to follow-up, was confirmed with the Korean national database using a citizen registration number that is unique to each individual, we cannot exclude the possibility of under-reporting of clinical outcomes.

Conclusion

In CTO patients with multivessel CAD, successful revascularization using second-generation DESs was associated with a similar incidence of death or MI compared with treatment with CABG. Based on our results, second generation drug-eluting stenting could be an acceptable alternative to CABG in CTO patients with multivessel CAD. A large-scale, randomized trial is needed to confirm these findings.

Funding

None.

Conflict of interest

None.

Acknowledgments

None.

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