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LONG-TERM OUTCOMES OF MYOCARDIAL REVASCULARIZATION IN DIABETIC PATIENTS WITH MULTIVESSEL CORONARY ARTERY DISEASE

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Abstract

Background: The optimal strategy of revascularization in patients with diabetes mellitus (DM) and multivessel coronary artery disease (CAD) is not clearly defined.

Aim: To compare the long-term results of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in patients with multivessel CAD with and without DM.

Methods: 406 patients with low and intermediate Syntax scores (SS) underwent PCI with drug-eluting stents (n=200, 100 with SS ≤22 and 100 with SS 23-32), and CABG (n=206, 100 with SS≤22 and 106 with SS 23-32). Patients were also stratified by diabetes status: 134 patients with DM and 272 patients without diabetes. The mean follow-up period was 9±1.9 years. The endpoints of the study were as follows: major adverse cardiac and cerebrovascular events (MACCE), a repeat revascularization, diminished left ventricular ejection fraction (LVEF), and high SS (≥33) in dynamics.

Results: For patients with DM, neither PCI nor CABG showed advantages in terms of the main indicators of MACCE (76% vs. 63%; HR: 1.1; CI: 0.8 - 1.7; p = 0.55). For patients with insulin-requiring DM, PCI showed an advantage over CABG in terms of overall mortality (14% vs. 52%; HR 0.3; CI 0.1- 1; p=0.048, respectively). DM significantly influenced the progression of coronary atherosclerosis in both general cohort and PCI and CABG groups.

Conclusions: For patients with DM and multivessel CAD, neither PCI nor CABG showed advantages in terms of the main indicators of MACCE. For patients with insulin-requiring DM, PCI showed superiority over CABG in terms of all-cause mortality.

Keywords: *Diabetes mellitus; Coronary Artery Disease; Coronary Artery Bypass Grafting; Percutaneous Coronary Intervention; SYNTAX Score.*

Резюме

ОТДАЛЕННЫЕ ИСХОДЫ РЕВАСКУЛЯРИЗАЦИИ МИОКАРДА У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ С МНОГОСОСУДИСТЫМ ПОРАЖЕНИЕМ КОРОНАРНОГО РУСЛА

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Введение: Оптимальная стратегия реваскуляризации у больных сахарным диабетом (СД) и многососудистым поражением коронарного русла четко не определена

Цель. Сравнить отдаленные результаты чрескожного коронарного вмешательства (ЧКВ) и аортокоронарного шунтирования (АКШ) у больных с многососудистым поражением коронарного русла с СД и без него.

Методы: 406 пациентам с низкими и средними баллами шкалы Syntax (SS) было выполнено ЧКВ со стентами с лекарственным покрытием (n=200, 100 с SS ≤22 и 100 с SS 23-32), и АКШ (n=206, 100 с SS≤22 и 106 с SS 23-32). Также пациенты были стратифицированы по статусу диабета: 134 больных СД и 272 пациента без диабета. Период наблюдения составил в среднем 9±1,9 лет. Конечными точками исследования были определены: основные неблагоприятные кардиальные и цереброваскулярные события (MACCE), повторная реваскуляризация, снижение фракции выброса левого желудочка, высокая градация SS (≥33) в динамике.

Результаты. Для больных СД ни ЧКВ, ни АКШ не показало преимуществ по основным показателям MACCE (76% vs. 63%; HR: 1.1; CI: 0.8 - 1.7; p = 0.55). Для пациентов с инсулин-потребной формой СД ЧКВ показало преимущество над АКШ по показателю общей смертности (14% vs. 52%; HR 0.28; CI 0.08- 0,99; p=0.048, соответственно). СД достоверно влиял на прогрессирование коронарного атеросклероза, как в общей когорте, так и в группах ЧКВ и АКШ.

Выводы. Для пациентов с СД и многососудистым поражением коронарного русла ни ЧКВ, ни АКШ не показало преимуществ по основным показателям MACCE. Для больных с ИПФ СД ЧКВ показало превосходство над АКШ по показателю общей смертности.

Ключевые слова: *Сахарный диабет, ишемическая болезнь сердца, аортокоронарное шунтирование, чрескожное коронарное вмешательство, SYNTAX Score.*

Түйіндеме

КОРОНАРЛЫҚ АРНАНЫҢ КӨП ТАМЫРЛЫ ЗАҚЫМДАНУЫ БАР ҚАНТ ДИАБЕТІМЕН АУЫРАТЫН НАУҚАСТАРДА МИОКАРД РЕВАСКУЛЯРИЗАЦИЯСЫНЫҢ ҰЗАҚ МЕРЗІМДІ НӘТИЖЕЛЕРІ

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Кіріспе*:* Қант диабеті (ҚД) және коронарлық арнаның көп тамырлы зақымдануы бар науқастарда реваскуляризацияның оңтайлы стратегиясы нақты анықталмаған.

Мақсаты: ҚД бар және онсыз көп тамырлы коронарлық ауруы бар науқастарда тері асты коронарлық интервенция (ТАКИ) және аорта-коронарлық шунттауының (АКШ) ұзақ мерзімді нәтижелерін салыстыру.

Әдістері: Төмен және орташа Syntax ұпайлары (SS) бар 406 пациентке дәрі-дәрмекпен қапталған стенттерімен ТАКИ (n=200, 100 с SS ≤22 и 100 с SS 23-32), және АКШ (n=206, 100 с SS≤22 и 106 с SS 23-32) жасалды. Сондай-ақ, пациенттер қант диабеті мәртебесі бойынша стратификацияланды: 134 ҚД бар және 272 қант диабеті жоқ науқастар. Бақылау кезеңі орта есеппен 9±1,9 жылды құрады. Зерттеудің соңғы нүктелері анықталды: үлкен қолайсыз жүрек-қан тамырлары және цереброваскулярлық оқиғалар (MACCE), қайталанатын реваскуляризация, сол жақ қарыншаның лактырыс фракциясының төмендеуі, динамикадағы жоғары SS градациясы (≥33).

Нәтижелері: ҚД-мен ауыратын науқастар үшін ТАКИ араласулар да, АКШ да MACCE негізгі көрсеткіштері бойынша артықшылықтар көрсеткен жоқ (76% vs. 63%; HR 1.1; CI: 0.8 - 1.7; p = 0.55). Инсулинді қажет ететін ҚД бар пациенттер үшін жалпы өлім жітім көрсеткіші бойынша ТАКИ АКШ-дан артықшылық көрсетті (14% vs. 52%; HR 0.3; CI 0.1- 1; p=0.048, тиісінше). Қант диабеті жоқ науқастар үшін АКШ жалпы MACCE комбинациясы бойынша ТАКИ-дан артықшылық көрсетті (48.3% vs. 73.6%, HR 1.53, CI 1.1 – 2.1; p= 0.008, тиісінше). ҚД жалпы когортта да, және ТАКИ мен АКШ топтарында да коронарлық атеросклероздың дамуына сенімді әсер етті.

Қорытынды: ҚД және коронарлық арнаның көп тамырлы зақымдануы бар емделушілер үшін ТАКИ да, АКШ да MACCE негізгі көрсеткіштері бойынша артықшылықтар көрсеткен жоқ. Инсулинді қажет ететін ҚД бар науқастар үшін ТАКИ жалпы өлім-жітім көрсеткіші бойынша АҚШ-тан артықшылық көрсетті.

Негізгі сөздер; Қант диабеті, жүректің ишемиялық ауруы, аорта-коронарлық шунттау, тері асты коронарлық интервенция, SYNTAX Score.

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Introduction

Cardiovascular diseases (CVDs) are the leading causes of mortality worldwide [12, 23], and type 2 diabetes mellitus (DM), in turn, is an independent risk factor for coronary heart disease (CHD), stroke and death from other vascular causes [1, 2, 19]. Modern literature indicates that there is a strong correlation between CHD and type 2 diabetes, so atherosclerotic progression occurs earlier and largely in DM patients than in non-diabetic patients [18]. Myocardial revascularization is undoubtedly the primary method of CHD treatment, and percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) have become standard revascularization strategies in real clinical practice over the past decades. DM is a predictor of adverse cardiovascular events after both CABG and PCI in patients with CHD [17]. According to the latest published meta-analyses and systematic reviews, CABG demonstrates an advantage over PCI in patients with DM and multivessel coronary artery disease (CAD) [3, 6-8, 24]. However, it should be noted that the number of published randomized controlled trials (RCTs) involving patients with diabetes is currently small, most of the studies were not long-term (follow-up period up to 5 years), were of limited size, and were conducted with early stent constructions. The introduction of advanced drug-eluting stents (DES) casts doubts on the relevance of past research to modern realities. Most long-term and large-scale studies do not find a significant difference in the outcomes of PCI and CABG in diabetic patients [9, 21]. It should be noted that despite the improvement of surgical techniques, CABG remains a highly invasive method of revascularization, unlike PCI, and it is obvious that performing surgical intervention in all patients with DM with multivessel coronary artery disease (MCAD) is impractical. In this regard, it is worth noting that patients with high surgical risk were likely more to initially undergo stenting, which worsened the general outcomes of PCI. In our study, patients with severe coronary lesions with clear indications for surgical revascularization were excluded, who, for a number of reasons, underwent PCI. Thus, the extent to which diabetes affects the results of modern revascularization strategies in patients with CHD is not clearly defined. In this regard, this study aimed at comparing the long-term results of PCI with DES and CABG in patients with DM and MCAD is relevant.

Methods

Study design and patients

The process of selecting patients for the study was described earlier [15]. Briefly, our study was a retrospective, two-center, clinical cohort study. According to the archives of medical histories of the National Research Cardiac Surgery Center in Astana and at the Pavlodar Regional Cardiology Center, we selected 406 patients with MCAD with low and intermediate degrees of coronary atherosclerotic damage by Syntax score (SS) (<33 points) [11, 20], who had undergone primary PCI with DES (n=200, 100 with SS ≤22 and 100 with SS 23-32 points) and primary CABG (n=206, 100 with SS≤22 and 106 with SS 23-32) in the period 2010-2013. The SS was not used, initially, but it was performed retrospectively based on archival angiograms. Patients with prior cardiac surgery or stenting were excluded from the study. The following indicators were also exceptions from the study: acute coronary syndrome with an ST-segment elevation; left main coronary artery disease; an SS ≥ 33; age over 65; single vessel coronary disease; an aneurysm of the left heart ventricle; severe valvular dysfunction in combination with CHD; rheumatic and congenital heart disease; a left ventricular ejection fraction (LVEF) of less than 40%; severe chronic renal failure (i.e., glomerular filtration rate [GFR] using the Cockcroft-Gault equation of less than 30 ml/min/1.73m2).

Patients were followed up according to the clinical electronic databases of the centers, the clinical medical information system (CMIS) (https://pvd.dmed.kz), the electronic register of inpatient (ERIP) (www.eisz.kz), and via personal contacts with the patients. The average follow–up period was 9±1.9 years, the maximum period was 12 years. In this study, 134 patients were diagnosed with diabetes mellitus. The observation was carried out in accordance with the principles of the Helsinki Declaration, and it was approved by the Local Ethical Commission of the Non-profit JSC "Semey Medical University" and committees of the participating centers. No funding was received for this study.

Endpoints and definitions

The clinical endpoints of the study were a combination of major adverse cardiac and cerebrovascular events (MACCE) and their individual components: all-cause death, cerebrovascular accident (transient ischemic attack [TIA]/stroke), myocardial infarction (MI); repeated revascularization; development of chronic heart failure (CHF) (according to clinical status, decreased LVEF, dilation of the heart chambers with valvular dysfunction); and a high degree of atherosclerotic coronary artery lesion as characterized by an SS≥ 33 in dynamics. It should be noted that if it was not possible to establish an unambiguous non-cardiovascular cause of death, then death was regarded as a definite cardiovascular one.

In the present study, the following subgroups with DM were identified and analyzed: 1) insulin-treated patients with

or without oral hypoglycemic agents; and 2) non–insulin-treated patients (using hypoglycemic agents and non-pharmacological therapy only).

Statistical analysis

The outcomes of patients randomized for PCI and CABG were evaluated and stratified by the presence of DM as well as by the status of insulin use.

Continuous variables were compared using the Student's t- test or the Mann-Whitney U-test. Categorical variables were presented as percentages and numbers and compared using the χ2 criterion or Fisher's exact probability test. The assessment of long-term events was carried out using the Kaplan-Meyer method with a log-rank test in diabetic and non-diabetic patients in the PCI and CABG groups. The Hazard ratio (HR) with a 95% confidence interval (CI) was estimated based on Cox proportional regression. All of the statistical analyses were conducted using IBM SPSS Statistics 23.0 (IBM Corporation, Armonk, NY, USA), and the p value <0.05 was considered to be an indication of statistical significance.

Results

Baseline characteristics

The Baseline diabetes status was known in all patients included in the study. Diabetes was present in 134 of 406 patients (33%); 42 patients were treated with insulin and 92 were treated with oral hypoglycemic agents without insulin and with non-pharmacological measures.

Baseline clinical and angiographic characteristics of the patients included in the study are shown in Table 1.

Table 1.

Baseline Characteristics of Patients According to Diabetes Status in the Overall Cohort.

	No Diabetes (n=272)	Diabetes (n = 134)	p Value
Age, years	55,6(±6,2)	55,5(±6,3)	0,86
Women	32 (11,8%)	38(28,4%)	<0,001
Men	240(88,2%)	96(71,6%)	<0,001
Heredity	65 (23,9%)	42(31,3%)	0,12
Current smoker	100(36,8%)	33(24,6%)	0,02
Body-mass index (BMI), kg/m²	28,4(25-31,5)	31(28-34,6)	<0,001
Weight categories			
Normal weight, BMI 18-24,9.	40(14,7%)	8(6%)	0,011
Overweight, BMI 25-29,9 kg/m²	123(45,2%)	46(34,3%)	0,037
Obesity 1 dg., BMI 30-34,9 kg/m²	75(27,6%)	47(35,1%)	0,12
Obesity 2 dg., BMI 35-39,9 kg/m²	22(8,1%)	29(21,6%)	<0,001
Obesity 3dg., BMI ≥40 kg/m²	12(4,4%)	4(3%)	0,67
Waist circumference, male	102,6(±12)	105,8(±9,4)	0,096
Waist circumference, female	102,5(±15,5)	107,9(11,4)	0,24
Dyslipidemia	212(77,9%)	112(83,6%)	0,18
Atherogenic index	3,5(2,7-4,5)	4,1(2,8-5,3)	0,003
GFR, ml/min/1.73m2	89,9(±17,7)	91,9(±21,7)	0,32
Hypertension	267(98,2%)	132(98,2%)	>0,05
Degrees of hypertension			
Mild hypertension	18(6,6%)	2(1,5%)	0,046
Moderate hypertension	95(34,9%)	34(25,4%)	0,052
Severe hypertension	154(56,6%)	96(71,6%)	0,004
Previous myocardial infarction	166(61%)	88(65,7%)	0,36
Previous stroke or transient ischaemic attack	19(7%)	11(8,2%)	0,8
Arrhythmia, atrial fibrillation	54(19,9%)	26(19,4%)	0,9
Peripheral arterial disease	37(13,6%)	30(22,4%)	0,025
Chronic lung disease	35(12,9%)	15(11,2%)	0,63
Previous pulmonary embolism	0	1	>0,05
Charlson Comorbidity Index [4,5]	4(3-5)	6(4,8-7)	<0,001
Left ventricular ejection fraction (%)	55,2(±6,4)	54,2(±6,8)	0,14
SYNTAX Score	20,7(±6,9)	20,9(±6,5)	0,68
Two-vessel disease	138(50,7%)	68 (50,7%)	0,99
Three-vessel disease	134(49,3%)	66(49,3%)	0,99
PCI	125(46%)	75(56%)	0,058
CABG	147(54%)	59(44%)	0,058

Values are shown as mean ± SD (n), Me(Q1-Q3) or % (n/N).

CABG = coronary artery bypass grafting; MI = myocardial infarction; PCI = percutaneous coronary intervention; Atherogenic index (AI) was calculated using the formula AI = (total cholesterol -density lipoproteins)/high-density lipoproteins; GFR = glomerular filtration rate according to the Cockcroft-Gault formula; LAD – left anterior descending artery, CF – left circumflex artery, RCA– right coronary artery.

According to the ratio of surgical and percutaneous intervention, patients with and without diabetes did not differ significantly. By gender, men predominated among patients with and without diabetes, but there were more women diagnosed with diabetes than without diabetes (28.4% and 11.8%, respectively, p < 0.001). Patients without DM were more likely to smoke compared to diabetic patients (36.8% and 24.6%, respectively, p = 0.02). Patients diagnosed with diabetes compared with patients without DM had a higher body mass index (31 [28-34,6] and 28.4 [25-31.5], respectively, p<0.001), a higher atherogenic index (4.1 [2.8-5.3] and 3.5[2.7-4.5], respectively, p=0.003), more often suffered from a high degree of arterial hypertension (71.6% and 56.6%, respectively, p=0.004), peripheral atherosclerosis (22.4% and 13.6%, respectively, p= 0.025), and overall, had more comorbidities (Charlson Comorbidity index [4, 5] 6 [4.8-7] and 4 [3-5], p<0.001) (Table 1). At the same time, within the group of patients with DM, patients with insulin-requiring diabetes had more comorbidities than non–insulin-treated patients (Charlson Comorbidity index 6 [5-8] and 5 [4-6], p=0.003) According to the Syntax score among diabetic patients, operated patients had 2 points more than stented patients (22.3 [±6.8] and 19.9 [±6.1], p=0.03) (Table 1).

Outcomes

Clinical outcomes depending on the status of diabetes are presented in Table 2.

Table 2.

Clinical Outcomes According to DM Status and Revascularization Treatment.

	No Diabetes (n=272)	Diabetes (n = 134)	Hazard ratio (95% CI)	P value
MACCE	163(59,9%)	94(70,1%)	1,25(0,98-1,6)	0,078
Repeat revascularisation	116(42,6%)	66(49,3%)	0,8(0,6-1,1)	0,15
All-cause-Death /MI/Stroke/TIA	90(33,1%)	59(44%)	1,4(1,02-1,96)	0,04
Cardiac Death/ MI/ Stroke /TIA	78(28,7%)	52(38,8%)	0,7(0,49-0,99)	0,04
Death, all-cause	37(13,6%)	35(26,1%)	2(1,26-3,2)	0,003
Cardiac death	23(8,5%)	23(17,2%)	2,1(1,2-3,8)	0,012
Non-cardiac death	14(5,1%)	12(9%)	0,55(0,25-1,2)	0,125
Average age of death*	62,7(±5,9)	62,7(±6,6)		0,96
Mean number of years after intervention until death*	6,2(±2,3)	6,4(±3,1)		0,7
Myocardial infarction	35(12,9%)	23(17,2%)	0,7(0,4-1,2)	0,19
Stroke/TIA	37(13,6%)	17(12,7%)	0,99(0,56-1,77)	0,99
Pulmonary embolism during follow-up	2(0,7%)	1(0,7%)	0,94(0,09-10,3)	0,96
Mean number of years after intervention until recurrent angina*	4,1(±2,9)	4,1(±2,7)		0,8
LVEF during follow-up (%)*	51,9(±10,2)	50,2(±11,1)		0,15
Decrease in LVEF	72(34,1%)	40(35,7%)	0,88(0,6-1,3)	0,5
Heart chambers dilatation + valvular insufficiency	32(15,2%)	20(17,9%)	0,8(0,46-1,4)	0,44
SYNTAX Score during follow-up*	21,5(11-30,3)	27,5(17,5-35,5)		0,001
SYNTAX Score =0	6(3,9%)	0	40,7(0,038-43271)	0,3
SYNTAX Score, ≤22	81(52,9%)	30(36,1%)	1,46(0,96-2,2)	0,075
SYNTAX Score, 23-32	33(21,6%)	25(30,1%)	0,7(0,42-1,2)	0,19
SYNTAX Score, ≥33	33(21,6%)	28(33,7%)	0,63(0,38-1,04)	0,07
Left main disease during follow-up	9(5,9%)	5(6%)	0,93(0,3-2,8)	0,9
Stent restenosis	49(38,6%)	33(47,8%)	0,8(0,52-1,25)	0,3
bypass graft occlusion	46(48,4%)	19(35,8%)	1,3(0,77-2,2)	0,3

Values are number of events (%), unless otherwise indicated

**- Values are shown as mean ± SD (n), Me (Q1-Q3) or % (n/N). CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; MACCE-major adverse cardiac and cerebrovascular events = All-cause-death +MI+Stroke/TIA+ Repeat revascularisation; MI = myocardial infarction; TIA = transient ischemic attack; LVEF = Left ventricular ejection fraction*

The combination of all-cause death + MI + cerebrovascular events (Stroke/TIA) was significantly more common in patients with diabetes compared with non-diabetic ones (44% and 33.1%, respectively, hazard ratio [HR] 1.4; confidence interval [CI] 1.02-1.96; p=0.04). All-cause and cardiac mortality rates in the diabetes group significantly prevailed in comparison with the non-diabetic group (26.1% vs. 13.6%; HR 2; CI 1.26-3.2; p=0.003 and 17.2% vs. 8.5%; HR 2.1; CI 1.2-3.8, respectively; p=0.012). According to the SS, on average, diabetic patients developed a more marked atherosclerotic lesions of the coronary arteries over time than patients without diabetes (27.5 [17.5-35.5] vs. 21.5 [11 - 30.3], respectively; p = 0.001).

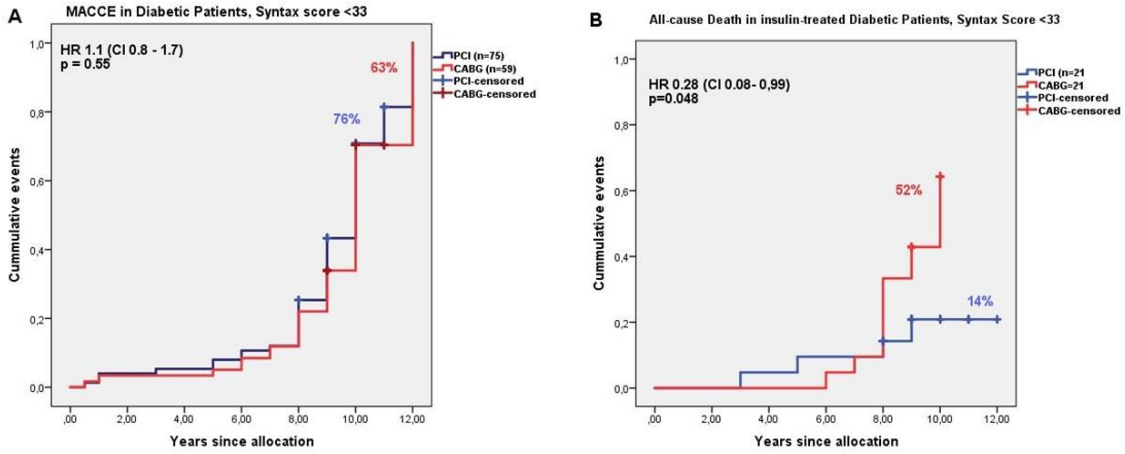
Clinical Outcomes According to DM Status and Revascularization Assignment are shown in Table 3. In diabetic patients, PCI and CABG showed no advantages in terms of the main components of MACCE (Figure 1). Within the non-diabetic group, CABG showed superiority over PCI in total combination of MACCE (48.3% vs. 73.6%, HR 1.53, CI 1.1 – 2.1, respectively; p= 0.008). This superiority was due to the need for repeated revascularization and registration of more cases of MI in the PCI group compared to CABG (63.2% vs. 25.2%; HR 2.5, CI 1.8-3.8; p<0.0001 and 18.4% vs. 8.2%; HR 2.34, CI 1.2-4.7; p=0.028, respectively) (Figure 2).

Table 3.

Clinical Outcomes According to DM Status and Revascularization Assignment.

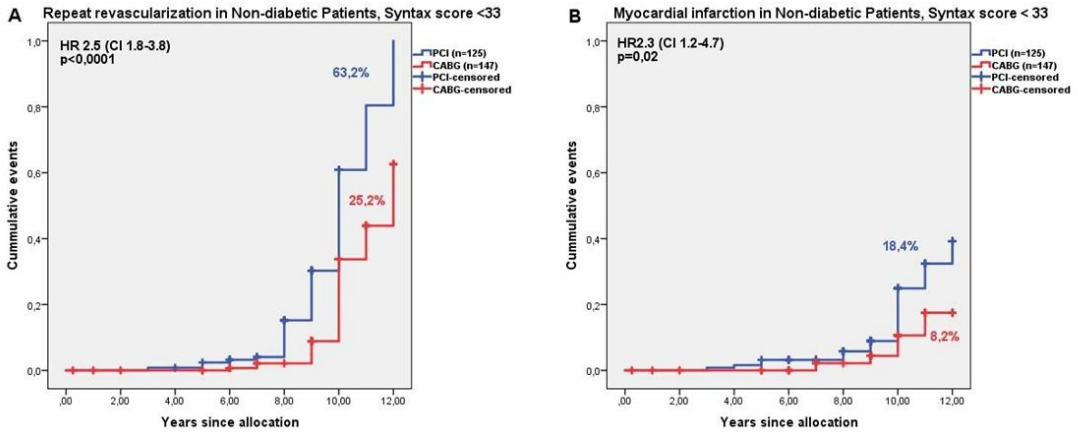
	Patients With DM (n=134)				Patients Without DM (n=272)			
	PCI (n=75)	CABG (n=59)	Hazard ratio (95% CI)	P value	PCI (n=125)	CABG (n=147)	Hazard ratio (95% CI)	P value
MACCE	57 (76%)	37 (62,7%)	1,14 (0,75-1,72)	0,55	92 (73,6%)	71 (48,3%)	1,53 (1,12-2,1)	0,008
Repeat revascularisation	45 (60%)	21 (35,6%)	1,53 (0,91-2,59)	0,11	79 (63,2%)	37 (25,2%)	2,49 (1,68-3,69)	<0,000
All-cause-Death /MI/Stroke/TIA	30 (40%)	29 (49,2%)	0,79 (0,47-1,32)	0,37	43 (34,4%)	47 (32%)	1,13 (0,74-1,71)	0,57
Cardiac Death/ MI/ Stroke /TIA	27 (36%)	25 (42,4%)	0,82 (0,47-1,42)	0,48	37 (29,6%)	41 (27,9%)	1,1 (0,7-1,72)	0,68
Death, all-cause	16 (21,3%)	19 (32,2%)	0,65 (0,34-1,28)	0,2	16 (12,8%)	21 (14,3%)	0,95 (0,49-1,81)	0,87
Cardiac death	9 (12%)	14 (23,7%)	0,49 (0,21-1,13)	0,09	9 (7,2%)	14 (9,5%)	0,77 (0,33-1,77)	0,53
Non-cardiac death	7 (9,3%)	5 (8,5%)	1,13 (0,36-3,57)	0,83	7 (5,6%)	7 (4,8%)	1,33 (0,47-3,8)	0,59
Average age of death*	62,75±6,6	62,74±6,7		0,99	61,4±7	63,7±4,9		0,25
Mean number of years after intervention until death*	5,47±2,9	7,2±3,1		0,09	6,6±2,2	5,9±2,4		0,33
Myocardial infarction	13 (17,3%)	10 (16,9%)	0,96 (0,42-2,22)	0,96	23 (18,4%)	12 (8,2%)	2,34 (1,16-4,72)	0,018
Stroke/TIA	10 (13,3%)	7 (11,9%)	1,02 (0,38-2,74)	0,96	15 (12%)	22 (15%)	0,82 (0,42-1,59)	0,56
Mean number of years after intervention until recurrent angina*	3,6±2,6	4,8±2,8		0,14	4±2,75	4±3,1		0,79
LVEF during follow-up (%)*	52,2±9,3	47,9±12,5		0,044	52,6±10,8	51,3±9,55		0,37
Decrease in LVEF	19 (31,7%)	21 (40,4%)	0,69 (0,37-1,3)	0,26	27 (26,5%)	45 (41,3%)	0,65 (0,4-1,04)	0,07
Heart chambers dilatation + valvular insufficiency	9 (15%)	11 (21,2%)	0,66 (0,27-1,6)	0,36	11 (10,8%)	21 (19,3%)	0,6 (0,29-1,24)	0,17
SYNTAX Score during follow-up*	19 (10,1-29,6)	33 (27,8-42)		<0,0001	15 (7,8-23)	26,5 (20,5-35,5)		<0,0001
SYNTAX Score =0					6 (7,3%)	0	63(0,09-45090)	0,22
SYNTAX Score, ≤22	28 (60,9%)	2 (5,4%)	10,8 (2,57-45,4)	0,001	55 (67,1%)	26 (36,6%)	2,18(1,36-3,48)	0,001
SYNTAX Score, 23-32	10 (21,7%)	15 (40,5%)	0,47 (0,21-1,1)	0,066	15 (18,3%)	18 (25,4%)	0,8 (0,41-1,62)	0,55
SYNTAX Score, ≥33	8 (17,4%)	20 (54,1%)	0,27 (0,12-0,6)	0,002	6 (7,3%)	27 (38%)	0,22 (0,09-0,53)	0,001
Left main disease during follow-up	1 (2,2%)	4 (10,5%)	0,13 (0,01-1,22)	0,07	5 (6,1%)	4 (5,6%)	1,13 (0,3 -4,23)	0,86

Values are number of events (%), unless otherwise indicated
**- Values are shown as mean ± SD (n), Me(Q1-Q3) or % (n/N).*
CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention;
MACCE-major adverse cardiac and cerebrovascular events = All-cause-death +MI+Stroke/TIA+ Repeat revascularisation; MI = myocardial infarction; TIA = transient ischemic attack; LVEF = Left ventricular ejection fraction.



CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention; MACCE-major adverse cardiac and cerebrovascular events = All-cause-death + Myocardial infarction +Stroke/ Transient ischemic attack + Repeat revascularisation; HR = Hazard Ratio; CI = Confidence interval

Figure 1. 12-Year Outcomes of PCI Versus CABG on MACCE (A) and all-cause death (B) in Diabetic (A) and insulin-treated Diabetic Patients (B).



CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention; MACCE-major adverse cardiac and cerebrovascular events = All-cause-death + Myocardial infarction +Stroke/ Transient ischemic attack + Repeat revascularisation; HR = Hazard Ratio; CI = Confidence interval

Figure 2. 12-Year Outcomes of PCI Versus CABG on Repeat revascularization (A) and Myocardial infarction (B) in non-diabetic patients.

For other components and combinations of MACCE, the PCI and CABG groups did not differ among non-diabetic patients. Considering the issue, depending on the revascularization strategy in the CABG group, patients with DM compared with operated patients without diabetes were significantly more likely to have a combination of all-cause mortality + MI + cerebrovascular events (49.2% vs. 32%, HR 1.7, CI 1.1-2.7, respectively; p = 0.025), all-cause death (32.2% vs. 14.3%, HR 2.4, CI 1.3-4.5, respectively; p=0.006), cardiac death (23.7% vs. 9.5%, HR 2.6, CI 1.3-5.6, respectively; p=0.01) and IM (16.9% vs. 8.2%, HR 2.4, CI 1-5.5, respectively; p = 0.047). There were no significant differences in outcomes in stented patients depending on the status of diabetes.

Regardless of the diabetes status, CABG was associated with a greater degree of progression of coronary atherosclerosis than after PCI (Table 3). In both PCI and CABG groups, the subgroups with DM showed, on average, higher SS over time compared to patients without diabetes (21.8±15.5 vs. 16.2±11.8, p=0.023 and 33 [27.8-42] vs. 26.5 [20.5-35.5], p=0.002; respectively).

Within the diabetes group, patients with insulin-requiring DM were more likely to experience CHF with a decrease in LVEF than patients with non- insulin-requiring diabetes (45.9% vs. 30.7%; HR 2, CI 1.1-3.8, p = 0.03). While dividing the diabetes group depending on the revascularization strategy in the PCI and CABG subgroups, the need for insulin therapy did not affect the development of CHF. In the subgroup of operated patients with insulin-treated DM was significantly associated with the development of all-cause death (52.4% and 21.1%, HR 2.97, CI 1.15-7.67, p=0.025), however, when events were divided into cardiac and non-cardiac death, the differences lost their validity. Among diabetic patients in the PCI group, the need for insulin therapy was significantly associated with the development of cerebrovascular events (HR 4.5, CI 1.3-15.9, p = 0.02). It should also be noted that in the PCI group, patients with insulin-requiring diabetes developed angina symptoms 3 years earlier than the patients with non-insulin-requiring diabetes. For patients with insulin-requiring DM, PCI showed superiority over CABG in terms of all-cause mortality (14.3% vs. 52.4%, HR 0.28, CI 0.08-0.99, p= 0.048) (Figure 1), however, when the causes of death were divided into cardiac and non-cardiac, the significance was lost.

Discussion

In our study, we analyzed the outcomes of myocardial revascularization in patients with multivessel CAD of low and intermediate SS gradation 9±1.9 years after PCI with DES compared with CABG, depending on the status of diabetes, both with and without insulin therapy. The following results were obtained:

1. For the general cohort of patients:

1.1 Diabetes mellitus significantly influenced the development of cardiac mortality.

1.2 In diabetic patients, PCI and CABG showed no advantages in terms of the main components of MACCE.

1.3 Among non-diabetic patients, CABG showed an advantage over PCI in terms of MACCE, mainly due to the greater need for repeated revascularization and registration of a greater number of MI cases after PCI in dynamics.

1.4 In the group of stented patients, DM did not show a significant association with the development of MACCE

1.5 In the CABG group, DM was significantly associated with cardiac mortality and MI.

2. Within the diabetes group:

2.1. The need for insulin therapy was significantly associated with the registration of a greater number of CHF cases with a decrease in LVEF, in comparison with diabetic patients with non-insulin hypoglycemic therapy.

2.2. In patients with insulin-requiring DM, CABG was associated with a large number of all-cause death in comparison with stented insulin-requiring diabetic patients.

2.3. In the group of patients with insulin-treated diabetes, recurrent angina developed after PCI 4 years earlier than after CABG

2.4. In non-insulin-treated diabetic patients PCI and CABG did not show benefits in terms of MACCE.

2.5. In operated diabetic patients, insulin treatment was significantly associated with an increased all-cause mortality rate in comparison with patients with non-insulin-treated diabetes after CABG.

2.6. In stented diabetic patients, the need for insulin therapy was significantly associated with the development of cerebrovascular events and earlier (by 3 years) registration of recurrent angina, compared with stented non-insulin-requiring diabetic patients.

3. In both diabetic and non-diabetic patients, CABG in comparison with PCI was associated with greater atherosclerotic coronary lesson as measured by the SS.

4. DM significantly influenced the progression of coronary atherosclerosis in both general cohort and groups of PCI and CABG.

Previous studies examining the efficacy of PCI and CABG in patients with DM and multivessel disease have come to different conclusions. The first randomized one-year study of the results of multivessel revascularization in patients with CARDia (Coronary Artery Revascularization in Diabetes) did not show a significant difference in outcomes between PCI with DES and CABG [14]. The first randomized study with sufficient power for direct comparison of PCI and CABG in patients with FREEDOM diabetes showed that CABG leads to lower all-cause mortality than PCI with DES over a follow-up period of 3.8 years [10]. However, in the future, with the continuation of FREEDOM Follow-On with an average follow-up period of 7.5 years, despite the numerical advantage of CABG over PCI with DES, the statistical significance of the obtained difference was lost [9]. In the large-scale study, SYNTAXES, assessing the 10-year survival of 1800 patients with three-vessel and/or left main disease, depending on the method of revascularization, no significant benefits of PCI or CABG for diabetic patients were found, regardless of the use of insulin [21]. Our data partially agree with the conclusions of the above studies. Thus, according to our observation, PCI and CABG showed no benefits for patients with DM. However, this study for insulin-requiring diabetic patients showed superiority of PCI over CABG in terms of all-cause mortality.

According to the latest published meta-analyses and systematic reviews, CABG demonstrates an advantage over PCI in patients with DM [3, 6-8, 24]. At the same time, the authors note that modern advances in PCI technology

are beginning to challenge this version. The development of 1st and 2nd generation DES has narrowed the gap between CABG and PCI, and new stent modifications, image-guided stent deployments, and usage of modern antiplatelet and lipid-lowering agents continue to improve PCI outcomes [3, 6-8, 24]. Also in this regard, it should be noted that in most of the above-mentioned observations, in contrast to our study, patients with different degrees of coronary atherosclerotic lesions were included, involving those with more complex and left main diseases, incomplete revascularization, and patients with acute forms of CAD , different age categories, which undoubtedly influenced the results.

It should also be taken into consideration that most of the studies comparing the outcomes of PCI and CABG in diabetic patients are an analysis of subgroups of the diabetic cohort of the main study population, which reduces their power. Therefore, further research using large randomized studies, including long-term follow-up comparing CABG and PCI with 2-nd generation DES, is needed to determine the optimal intervention in patients with diabetes.

Study limitations

Several limitations should be taken into account in our study.

Firstly, due to the modest sample size, this analysis may not have sufficient statistical power.

Secondly, despite the taken measures and corrections, due to the retrospective observational type of the study, there was a possibility of a systematic selection bias.

Thirdly, our study included stable patients with MCAD without left main disease with low and intermediate Syntax scores, who underwent primary PCI or CABG at the age of 65 years. Therefore, these results cannot be extrapolated to other patients with CAD.

Fourthly, we did not collect detailed information on the pharmacological therapy of CAD after PCI and CABG during the follow-up period. Although the extent to which pharmacological therapy influences outcomes is unclear, unmeasured mixed effects cannot be excluded.

Fifthly, the main focus in the treatment of diabetes is on optimal glycemic control. Unfortunately, the present study did not collect data on the use of specific oral hypoglycemic agents and data on long-term glycemic control. In concurrence with this, it is obvious that patients did not receive or received short-term hypoglycemic agents of a new generation, which have been shown to reduce the risk of cardiovascular mortality in patients with type 2 diabetes [13, 16, 22].

Sixthly, the number of patients receiving insulin was small, so statistical significance was lost when the group with insulin-requiring diabetes was divided by many indicators.

Seventhly, it should be noted that our patients underwent PCI with DES and CABG in 2010-2013, so our results cannot be absolutely applicable to modern treatment technologies. In this situation, we must recognize that, despite the importance of long-term observations, they are inevitably based to a certain extent on outdated technologies.

Conclusions

For patients with DM, neither PCI nor CABG showed advantages in terms of the main indicators of MACCE. For patients with insulin-requiring diabetes, PCI showed an advantage over CABG in terms of all-cause mortality. For non-diabetic patients, CABG showed an advantage over PCI in terms of the combination of MACCE, mainly due to the greater need for repeated revascularization and registration of a greater number of MI cases in dynamics after PCI. DM significantly influenced the progression of coronary atherosclerosis in both general cohort and groups of PCI and CABG.

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Abbreviations:

CAD - coronary artery disease
CHD - coronary heart disease
CABG - coronary artery bypass grafting
CHF - chronic heart failure
CI - confidence interval
CVD - cardiovascular diseases
DES - drug-eluting stent
GFR - glomerular filtration rate
HR - hazard ratio
LVEF - left ventricular ejection fraction
MACCE - major adverse cardiac and cerebrovascular events
MI - myocardial infarction
MCAD - Multivessel coronary artery disease
PCI - percutaneous coronary intervention
RR - repeat revascularization
RCT - randomized clinical trials
SS - SYNTAX score
TIA - transient ischemic attack

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