Kardiologia Polska 2018; 76, 10: 1474–1481; DOI: 10.5603/KP.a2018.0151

ORIGINAL ARTICLE

Comparison of multivessel percutaneous coronary intervention and coronary artery bypass grafting in patients with severe coronary artery disease presenting with non-ST-segment elevation acute coronary syndromes

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Abstract

Background: There are no clinical trials comparing multivessel percutaneous coronary intervention (MV PCI) with coronary artery bypass grafting (CABG) in the non-ST-segment elevation acute coronary syndrome (NSTE-ACS) population.

Aim: We sought to compare long-term outcomes of MV PCI and CABG in patients with severe coronary artery disease (CAD) presenting with NSTE-ACS.

Methods: A total of 3166 consecutive patients with NSTE-ACS hospitalised between 2006 and 2014 were analysed. Patients with left main, proximal left anterior descending artery, or triple-vessel CAD were included in further analysis. Finally, 455 patients were enrolled and divided into two groups (MV PCI or CABG group). The Cox proportional hazards model and propensity score analysis were used to assess the effects of the treatment on 36-month outcomes.

Results: MV PCI was performed in 335 patients, the remaining 120 patients underwent CABG. After propensity score analysis, 99 well-matched pairs were chosen. At 36 months MV PCI was associated with similar incidence of the composite endpoint (all-cause death, non-fatal myocardial infarction [MI], ACS-driven, revascularisation, or stroke) in both Cox proportional hazards model (hazard ratio [HR] 1.26; 95% confidence interval [CI] 0.75–2.11; p = 0.39) and propensity matched analysis (HR 1.28; 95% CI 0.75–2.21; p = 0.36). Rates of 36-month mortality were also comparable before (HR 0.90; 95% CI 0.46–1.75; p = 0.76) and after matching (HR 0.94; 95% CI 0.47–1.89; p = 0.87). Rates of MI and ACS-driven revascularisation were independently higher in MV PCI than in CABG groups (17.8% vs. 5.5%, p = 0.01, and 20.6% vs. 4.4%, p = 0.003, respectively).

Conclusions: It seems that MV PCI is comparable to CABG in terms of long-term combined endpoint and mortality in patients with severe CAD and NSTE-ACS. However, higher rates of MI and ACS-driven revascularisation were observed in the MV PCI group.

Key words: non-ST-segment elevation acute coronary syndrome, multivessel percutaneous coronary intervention, coronary artery bypass grafting

Kardiol Pol 2018; 76, 10: 1474–1481

INTRODUCTION

Previous studies comparing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in the treatment of severe coronary artery disease (CAD) demonstrated the advantage of cardiac surgery, or similar survival rates with a significantly higher incidence of repeat revascularisation in the PCI group [1–17]. Due to paucity of data, there are no clear recommendations regarding the treatment of multivessel

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Received: 8.04.2018 **Accepted:** 18.07.2018 **Available as AoP:** 24.07.2018

CAD in the course of non-ST-segment elevation acute coronary syndromes (NSTE-ACS) [18]. Even though these patients were partly represented in the majority of large multicentre randomised clinical trials (RCTs) comparing PCI and CABG [1, 4–7, 9, 10, 12–17], there are no RCTs directly dedicated to the NSTE-ACS population. The results from retrospective studies in NSTE-ACS patients demonstrated that PCI could be a comparable [19–21] or even better [22] treatment strategy than CABG in terms of long-term survival. However, the large variability of methodology applied in these studies makes it difficult to draw direct conclusions. Contemporary studies suggest that multivessel PCI (MV PCI) may improve long-term outcomes mainly by reducing the need for ischaemia-driven revascularisation in comparison to coronary angioplasty limited to culprit vessel [23].

Therefore, we sought to compare long-term outcomes in patients with severe multivessel CAD presenting with NSTE-ACS undergoing MV PCI or CABG.

METHODS

Study design

Data from an ongoing, single-centre registry of consecutive patients hospitalised due to NSTE-ACS from 2006 to 2014 were analysed. Patients with significant stenosis of the left main coronary artery (LM), double-vessel CAD with significant stenosis of proximal left anterior descending artery (LAD) or triple-vessel CAD were included. Exclusion criteria comprised prior CABG, coexistence of significant valvular disease, single-vessel/epicardial territory PCI, or hybrid revascularisation. The study population was divided depending on the applied revascularisation strategy after coronary angiography: Group I — MV PCI and Group II — CABG. The study was designed and conducted based on per-protocol analysis.

NSTE-ACS was managed in accordance with recommendations that were current at that time [18]. After coronary angiography, all therapeutic decisions regarding revascularisation strategy were made by the Heart Team. Interventional and cardiac surgery techniques were left to the operator's discretion.

Information about the long-term outcomes, including causes of death, exact dates of death, and cardiovascular events, was obtained from the official registry of the National Health Fund. Follow-up was available for all patients enrolled in the study.

Endpoints and definitions

The primary outcome measure encompassed a combined endpoint (all-cause death, non-fatal myocardial infarction [MI], ACS-driven revascularisation, or stroke) and all-cause death at 36 months. A 36-month non-fatal MI, ACS-driven revascularisation, stroke, and 12-month combined endpoint and its components were considered as secondary outcome measures. Non-fatal MI was defined as an ischaemic event that met the criteria of the Third Universal Definition of MI [18]. ACS-driven revascularisation was defined as unplanned angioplasty or CABG performed as an urgent procedure due to acute ischaemic symptoms. Stroke was defined as an ischaemic event that was in accordance with the European Stroke Organisation guidelines [24].

LM CAD was diagnosed in the case of haemodynamically significant (≥ 50%) diameter stenosis in visual assessment with quantitative coronary analysis (QCA) and/or < 6 mm^2 in intravascular ultrasound. Proximal LAD CAD was also determined in the presence of haemodynamically significant (≥ 50%) diameter stenosis in visual assessment with QCA. In other segments ≥ 70% diameter stenosis was considered haemodynamically significant.

The study population was chosen based on the applied treatment. MV PCI includes single- or multistage intervention in significant lesions in at least two major epicardial territories or in their major branches (LAD, LCx, or RCA system).

Statistical analysis

Combined endpoint and all-cause mortality in 36-month follow-up were analysed using the Kaplan-Meier method with log-rank comparison of curves. To minimise the impact of confounding risk factors affecting 36-month outcomes, we used two separate methods of analysis to estimate the treatment effect: the Cox proportional hazards model and propensity score analysis. Factors were analysed using the Cox proportional hazards model by stepwise elimination ($p < 0.3$ for inclusion into the model, $p < 0.05$ to remain in the model). A logistic regression model was used to generate a propensity score for individuals who had undergone MV PCI and CABG. Then, each subject from the MV PCI group was matched to an individual who had undergone CABG, using the derived propensity scoring. The calculation was performed with the nearest neighbour algorithm.

Results of multivariable analyses were presented as hazard ratio (HR) or odds ratio (OR) with 95% confidence interval (CI). A two-sided p-value < 0.05 was considered significant. STATISTICA 10 software (StatSoft Inc., Tulsa, OK, USA) was used for all calculations.

RESULTS

The study flowchart is summarised in Figure 1. Among 513 patients with severe CAD who were scheduled for MV PCI or CABG procedure, 455 patients who underwent the treatment were enrolled in the study. Baseline and angiographic characteristics, short- and long-term results of the intention-to-treat and unperformed treatment cohorts are summarised in **Supplementary materials** (**see journal website**).

In the study population, MV PCI was performed in 335 patients, whereas CABG was carried out in 120 cases. Baseline and angiographic characteristics of the analysed groups are presented in Table 1. Overall, patients treated invasively more often presented with non-ST-segment elevation MI (NSTEMI) chronic obstructive pulmonary disease, had worse left ventricular systolic function and higher risk

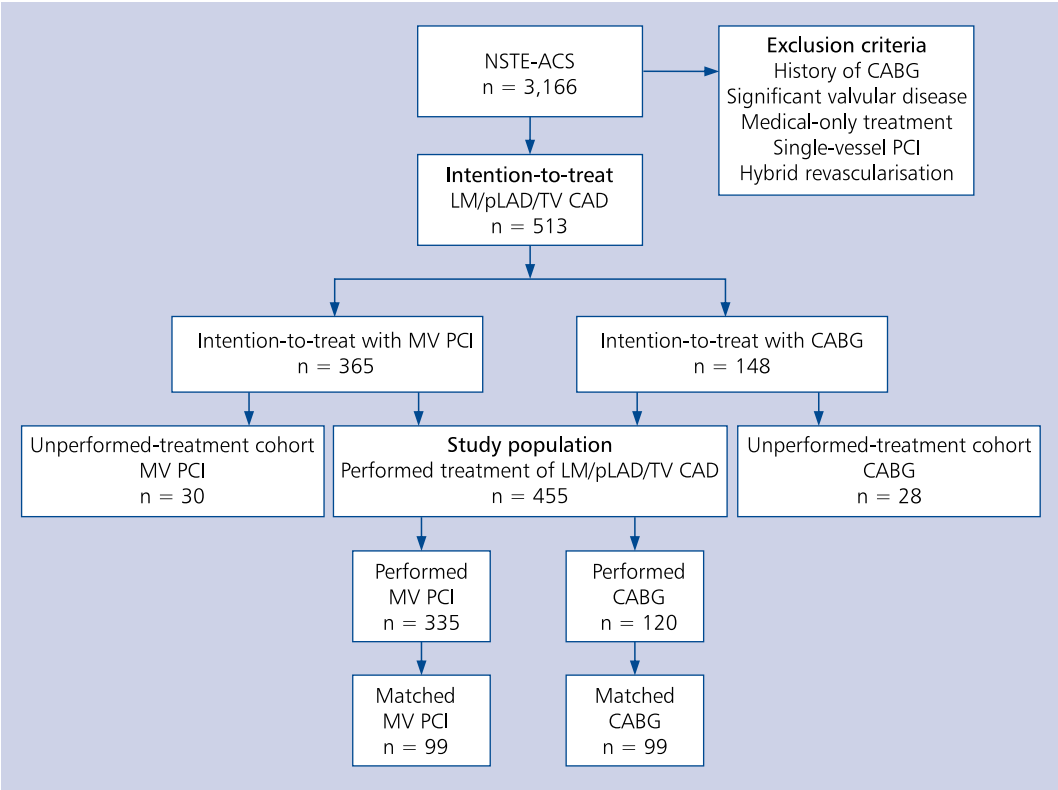

Figure 1. Study design; pLAD — proximal left anterior descending artery; TV — triple-vessel; other abbreviations — see Tables 1 and 2

Table 1. Baseline characteristics of the study population and the matched cohort

Factor	Study population (n = 455)		p	Matched cohort (n = 198)		p
	MV PCI (n = 335)	CABG (n = 120)		MV PCI (n = 99)	CABG (n = 99)	
Age [years]	66.9 ± 10.7	65.6 ± 8.7	0.2	66.9 ± 11.1	66.0 ± 8.9	0.5
Male sex	65.7	75.8	0.04	68.7	75.8	0.3
Diagnosis of NSTEMI	71.0	39.2	< 0.001	48.5	39.4	0.2
Arterial hypertension	76.8	83.3	0.1	78.8	84.9	0.3
Prior MI	32.5	42.0	0.06	39.4	40.4	0.9
Atrial fibrillation	9.3	7.6	0.6	8.1	8.1	0.9
Prior stroke	8.2	8.4	0.9	9.1	9.1	0.9
Diabetes mellitus	38.6	41.2	0.6	29.3	37.4	0.2
History of smoking	43.2	41.2	0.7	50.5	43.4	0.3
Elevated cardiac troponin T*	82.2	68.5	0.0057	76.3	69.3	0.33
ST-segment deviations*	40.1	42.5	0.7	38.7	42.2	0.7
Serum creatinine* [μmol/L]	83.5 (69.7–100.4)	84.7 (72.3–97.5)	0.3	84.1 (69.4–103.1)	83.1 (72.0–94.5)	0.8
LVEF* [%]	43.3 ± 10.8	47.2 ± 8.6	< 0.001	45.6 ± 11.5	47.0 ± 8.6	0.3
GRACE [points]	124 ± 31	117 ± 24	0.01	117 ± 26	117 ± 25	0.9
EuroSCORE II [%]	1.70 (1.20–2.95)	1.39 (0.92–2.99)	0.03	1.66 (1.20–3.14)	1.31 (0.88–3.22)	0.3
Triple-vessel CAD	57.6	53.6	0.5	64.6	55.6	0.1
LM CAD	10.2	35.7	< 0.001	25.2	37.4	0.07

Data are shown as percentage, mean ± standard deviation, or median (interquartile range); *On admission; CABG — coronary artery bypass grafting; CAD — coronary artery disease; LM CAD — left main coronary artery disease; LVEF — left ventricular ejection fraction; MI — myocardial infarction; MV PCI — multivessel percutaneous coronary intervention; NSTEMI — non-ST-segment elevation myocardial infarction

Table 2. Procedural characteristics and short-term outcomes of the study population and the matched cohort

Factor	Study population (n = 455)		p	Matched cohort (n = 198)		p
	MV PCI (n = 335)	CABG (n = 120)		MV PCI (n = 99)	CABG (n = 99)	
MV PCI/CABG during hospitalisation	54.0	36.7	< 0.001	55.6	36.4	0.01
MV PCI/CABG after discharge	36.0	63.3	< 0.001	44.4	63.6	0.01
Time from admission to first procedure [days]	1 (1–1)	31 (11–51)	< 0.001	1 (1–1)	31 (11–51)	< 0.001
Complete revascularisation	49.0	68.3	< 0.001	37.9	68.5	< 0.001
In-hospital outcomes:*						
All-cause death	2.4	4.2	0.3	1.0	5.1	0.1
Non-fatal MI	1.2	0.8	0.8	0.0	1.0	0.3
TVR	2.4	0.0	0.09	3.0	0.0	0.08
Stroke	0.3	2.5	0.03	0.0	2.0	0.2
30-day composite endpoint:	7.5	8.3	0.8	6.1	9.1	0.4
All-cause death	3.3	4.2	0.7	2.0	5.1	0.2
Non-fatal MI	1.8	1.7	0.9	1.0	2.0	0.5
ACS-driven revascularisation	3.0	0.0	0.06	4.0	0.0	0.04
Stroke	0.3	2.5	0.03	0.0	2.0	0.2

Data are shown as percentage or median (interquartile range); *During index hospitalisation; ACS — acute coronary syndrome; TVR — target vessel revascularisation; other abbreviations — see Table 1

measured in GRACE and EuroSCORE II scores than patients treated surgically. Patients who underwent CABG had more advanced CAD with higher frequency of LM CAD and chronic total occlusion (CTO) in comparison to the MV PCI group. Final diagnosis of NSTEMI was an independent factor enforcing the choice of MV PCI, whereas CTO and LM CAD were associated with CABG as the treatment modality.

After propensity score matching of the study population, 99 pairs were selected. The differences in baseline clinical characteristics and angiography were reduced, with non-significant p-values in all the analysed factors. Generally, characteristics of the matched patients were similar to those of the overall population. However, in the matched MV PCI group, in contrast to the baseline MV PCI group, lower frequency of NSTEMI diagnosis (48.5% vs. 71.0%) and higher rate of LM CAD (25.2% vs. 10.2%) were observed.

Table 2 contains procedural characteristics and short-term outcomes. Overall, the procedure was conducted during index hospital stay in 54.0% of the MV PCI patients and in 36.7% of patients in the CABG group. Drug-eluting stents were implanted in 39% of patients before, and in 47% after propensity score matching. Apart from a higher incidence of in-hospital and 30-day stroke in the surgery arm, there were no differences in baseline short-term outcomes. After propensity score matching, early ACS-driven revascularisation was performed more often in the MV PCI patients, with similar occurrence of other adverse events in both groups.

Unadjusted and adjusted HRs for long-term outcomes at 12 and 36 months in both groups are shown in Table 3. Kaplan-Meier survival curves for the percentage of combined endpoint and all-cause mortality at 36 months are presented in Figure 2. The total incidence of 12-month combined endpoint was 19.3%, whereas the rate at 36 months was 25.5%. Cox proportional hazards model and propensity score matching analyses showed that the primary 36-month combined endpoint was similar in the MV PCI and CABG groups, with comparable occurrence of 36-month all-cause death. The rates of non-fatal MI and ACS-driven revascularisation were independently higher in the MV PCI than in the CABG group at 12 and 36 months. Other long-term outcomes before and after adjustment were similar in both groups.

DISCUSSION

The principal findings of the present comparison between MV PCI and CABG in treatment of severe CAD and NSTE-ACS are as follows: 1) clinical status and anatomical criteria were crucial factors determining the modality of revascularisation; 2) rates of combined endpoint and all-cause death at 36 months were similar in both groups; and 3) MV PCI was independently associated with an increased incidence of non-fatal MI and the need for ACS-driven revascularisation at 12 and at 36 months. It should be emphasised that, to the best of our knowledge, this is the first contemporary retrospective cohort study comparing MV PCI and CABG, limited to a population of NSTE-ACS patients who completed the treatment.

Table 3. Unadjusted and adjusted hazard ratios for the occurrence of 12-month and 36-month outcomes in the study groups before and after propensity score matching

	Study population (n = 445)		Unadjusted HR	95% CI	p	Adjusted HR[a]	95% CI	p
	MV PCI [%] (n = 335)	CABG [%] (n = 120)						
12-month composite endpoint:	22.7	16.7	1.39	0.85–2.27	0.2	1.34	0.77–2.35	0.3
All-cause death	10.4	10.8	0.97	0.51–1.83	0.9	0.69	0.33–1.46	0.3
Non-fatal MI	9.2	4.2	2.26	0.88–5.82	0.09	2.38	0.85–6.69	0.1
ACS-driven revascularisation	10.7	1.7	6.75	1.63–28.04	0.009	13.3	2.89–60.88	< 0.001
Stroke	2.1	4.2	0.49	0.16–1.56	0.2	0.48	0.14–1.65	0.2
36-month composite endpoint:	28.0	26.1	1.07	0.70–1.65	0.8	1.26	0.75–2.11	0.4
All-cause death	16.5	18.0	0.89	0.52–1.50	0.7	0.90	0.46–1.75	0.8
Non-fatal MI	10.7	4.5	2.43	0.94–6.28	0.07	3.59	1.19–10.85	0.02
ACS-driven revascularisation	11.9	3.6	3.47	1.23–9.84	0.02	7.60	2.21–26.08	0.001
Stroke	2.7	6.4	0.42	0.15–1.19	0.1	0.41	0.14–1.23	0.1
	Matched cohort (n = 198)		Adjusted HR[b]	95% CI	p			
	MV PCI [%] (n = 99)	CABG [%] (n = 99)						
12-month composite endpoint:	29.3	17.2	1.76	0.96–3.20	0.07			
All-cause death	11.1	11.1	0.99	0.43–2.29	0.9			
Non-fatal MI	14.1	5.0	2.88	1.04–7.99	0.04			
ACS-driven revascularisation	19.2	2.0	10.38	2.41–44.58	0.002			
Stroke	3.0	4.0	0.74	0.17–3.31	0.7			
36-month composite endpoint:	35.6	28.6	1.28	0.75–2.21	0.4			
All-cause death	19.2	19.8	0.94	0.47–1.89	0.9			
Non-fatal MI	17.8	5.5	3.34	1.19–9.36	0.02			
ACS-driven revascularisation	20.6	4.4	5.18	1.72–15.60	0.003			
Stroke	4.1	6.6	0.62	0.15–2.47	0.5			

[a]Cox proportional hazards model; [b]Propensity score matching analysis; CI — confidence interval; HR — hazard ratio; other abbreviations — see Table 1

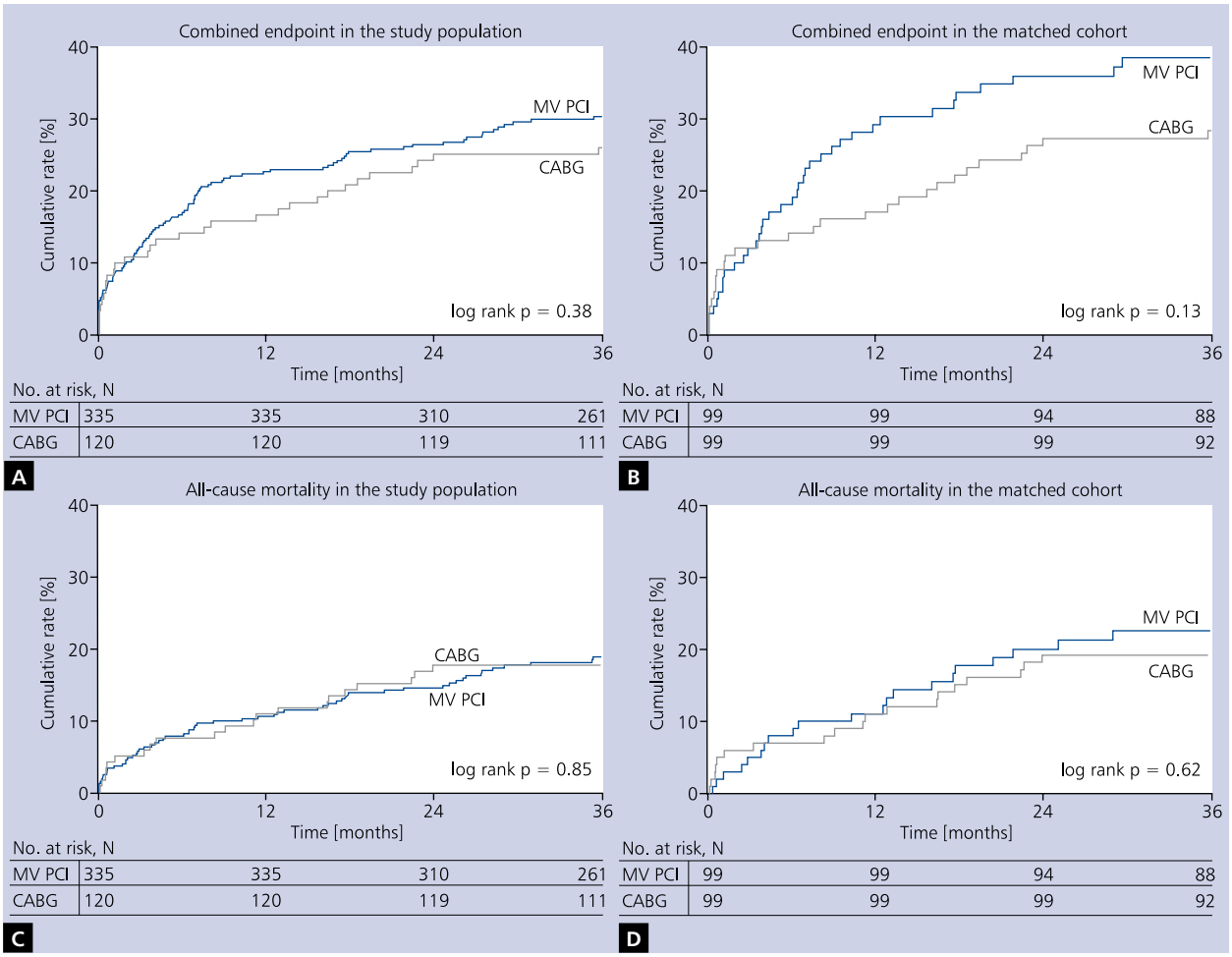

Figure 2. Kaplan-Meier survival curves for 36-month rates of combined endpoint and all-cause death in the study population (**A**, **C**) and the matched cohort (**B**, **D**), depending on the procedure type (multivessel percutaneous coronary intervention vs. coronary artery bypass grafting); abbreviations — see Tables 1 and 2

Baseline characteristics

Current guidelines for the management of NSTE-ACS recommend that the mode of revascularisation should be chosen on the basis of the patient's clinical condition and comorbidities, coronary lesion morphology, extent of myocardial damage, patient preference, and operator and hospital experience [18]. In the present analysis, patients undergoing PCI MV were characterised by a higher GRACE risk score and a lower left ventricular ejection fraction. Additionally, final diagnosis of NSTEMI was more frequently associated with the choice of MV PCI as a treatment method. On the other hand, advanced anatomy of coronary arteries, in particular the presence of the LM CAD and CTO, was independently associated with the performance of CABG. We may conclude that a higher risk of ischaemia is related with more frequent PCI, while a more advanced CAD is associated with CABG [25].

Timing of revascularisation

The adopted inclusion criteria, especially the timing of CABG, may seem controversial because some of the CABG procedures were performed after the acute phase of NSTE-ACS. Only some of the high-risk patients were eligible for urgent CABG, while those who were stabilised were scheduled for a planned CABG. It is noteworthy that in the CABG arm almost 40% of patients were operated on during index hospitalisation, whereas more than 82% of the procedures were performed during the first two months after NSTE-ACS. This is consistent with clinical practice because, on the basis of retrospective registries, many patients were operated on a relatively long time after the acute phase of NSTE-ACS. Zembala et al. [26] showed that only 60% of patients initially referred for cardiac surgery underwent CABG, of which more than two-thirds were operated on in the first three months after ACS. In other studies, the implementation of deferred CABG was associated with comparable [27, 28] or even more favourable short-term results [29] than early CABG. In registers comparing PCI and CABG in NSTE-ACS there was no time delay from admission to implementation of CABG [19–22].

Short-term outcomes

In most studies comparing these two methods of revascularisation, rates of early adverse cardiovascular events were

similar [19, 21, 22] or higher [20] in the CABG arm. In the present study the rates of in-hospital complications and short-term outcomes were comparable, except for higher frequency of ACS-driven revascularisation in the PCI arm. Similar in-hospital outcomes in our study could be explained by 1) a higher GRACE score in the MV PCI compared to the CABG group and/or 2) time from admission due to NSTE-ACS to implementation of the procedure (median one day for MV PCI and 31 days for CABG). Nevertheless, at three months after NSTE-ACS the incidence of adverse cardiovascular events was also comparable in both groups.

Long-term outcomes

In the present study, the long-term composite endpoint and mortality were similar in both groups; however, PCI was associated with a higher frequency of non-fatal MI and ACS-driven revascularisation. The occurrence of adverse cardiovascular events seems to be relatively high in relation to randomised trials of patients with unstable angina or recent MI, but comparable to other large ACS registries [30]. This is caused by a high-risk profile and advancement of CAD in the study population. Previous retrospective studies in NSTE-ACS and severe CAD demonstrated comparable [20, 21] or ever better outcomes of PCI and CABG [22]. In the prospective, intention-to-treat MILESTONE registry, lower rates of death in patients who were referred for PCI rather than CABG were reported, especially in high-risk clinical subgroups [22]. However, the rates of CTO and complete revascularisation, the number of patients who in fact underwent CABG, and the number of cross-over cases were not presented in that study.

Perspectives for the future

All the presented results should be interpreted with caution. High heterogeneity of the NSTE-ACS population associated with different baseline clinical and angiographic characteristics may cause difficulties in designing an objective study comparing PCI and CABG. Another controversial issue is the timing of PCI/CABG implementation after NSTE-ACS. It appears that in further studies the analysis should be limited to individual subpopulations of NSTE-ACS patients. Indeed, all available data should be included in clinical assessment, but the final choice of the revascularisation modality should be made on the basis of the Heart Team's individual approach towards every patient.

The results of multivariable analysis and propensity score matching may be biased because of the potential confounding effect of inacessible predictors. Coronary angiographic analysis was based on visual estimation with QCA, without available data on the SYNTAX score. The choice of the type as well as optimal timing of the procedure differed between the patients and depended on the decision of the operator or the Heart Team. Small sizes of the analysed groups may not be sufficient for precise assessment of the treatment modality. We did not have complete data on haemorrhagic complications, re-thoracotomy, or the impact of periprocedural MI on the operation in the CABG group.

In conclusion, the study depicts real-life clinical management of NSTE-ACS, where the method of treatment is determined by the Heart Team's assessment of the anatomical possibilities of revascularisation and the risk associated with each method. MV PCI is comparable to CABG in terms of long-term combined endpoint and mortality in patients with severe CAD and NSTE-ACS. However, MV PCI was associated with a higher incidence of non-fatal MI and ACS-driven revascularisation in comparison with CABG. These results highlight the effects of good clinical practice, wherein the outcomes of individually-chosen surgical and endovascular treatment are balanced in terms of risk of death in short- and long-term observation.

Conflict of interest: *Michał O. Zembala — consultant for Abbott, Articure Inc., Boston Scientific. Other authors declare no conflict of interest.*

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Cite this article as: Desperak P, Hawranek M, Hrapkowicz T, et al. Comparison of multivessel percutaneous coronary intervention and coronary artery bypass grafting in patients with severe coronary artery disease presenting with non-ST-segment elevation acute coronary syndromes. Kardiol Pol. 2018; 76(10): 1474–1481, doi: 10.5603/KP.a2018.0151.

WHAT IS NEW?

To the best of our knowledge, this is the first contemporary clinical study comparing multivessel percutaneous coronary intervention (MV PCI) and coronary artery bypass grafting (CABG) in a population of patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) who completed the treatment. The present study showed that MV PCI is comparable to CABG in terms of long-term combined endpoint and mortality in patients with severe coronary artery disease and NSTE-ACS. However, MV PCI was associated with higher incidence of non-fatal myocardial infarction and ACS-driven revascularisation in comparison with CABG. These findings come from a limited population; however, they reflect the high-risk profile of real-world patients.