

Comparison of Long-term Outcomes in Patients with Premature Triple-vessel Coronary Disease Undergoing Three Different Treatment Strategies: A Prospective Cohort Study

Jing-Jing Xu¹, Yin Zhang¹, Lin Jiang¹, Jian Tian¹, Lei Song¹, Zhan Gao¹, Xin-Xing Feng², Xue-Yan Zhao¹, Yan-Yan Zhao³, Dong Wang¹, Kai Sun⁴, Lian-Jun Xu¹, Ru Liu¹, Run-Lin Gao¹, Bo Xu¹, Lei Song^{4,5}, Jin-Qing Yuan¹

¹Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100037, China

²Department of Endocrinology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100037, China

³Medical Research and Biometrics Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100037, China

⁴Department of State Key Laboratory of Cardiovascular Disease, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100037, China

⁵Department of Hypertension, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100037, China

Abstract

Background: Patients with premature triple-vessel disease (PTVD) have a higher risk of recurrent coronary events and repeat revascularization; however, the long-term outcome of coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), and medical therapy (MT) alone for PTVD patients is controversial. The aim of this study is to evaluate the long-term outcome of PTVD patients among these three treatment strategies, to find out the most appropriate treatment methods for these patients.

Methods: One thousand seven hundred and ninety-two patients with PTVD (age: men ≤ 50 years and women ≤ 60 years) were enrolled between 2004 and 2011. The primary end point was all-cause death. The secondary end points were cardiac death, myocardial infarction, stroke, or repeat revascularization.

Results: PCI, CABG, and MT alone were performed in 933 (52.1%), 459 (25.6%), and 400 (22.3%) patients. Both PCI and CABG were associated with lower all-cause death (4.6% vs. 4.1% vs. 15.5%, respectively, $P < 0.01$) and cardiac death (2.8% vs. 2.0% vs. 9.8%, respectively, $P < 0.01$) versus MT alone. The rate of repeat revascularization in the CABG group was significantly lower than those in the PCI and MT groups. After adjusting for baseline factors, PCI and CABG were still associated with similar lower risk of all-cause death and cardiac death versus MT alone (all-cause death: hazard ratio [HR]: 0.35, 95% confidence interval [CI]: 0.23–0.53, $P < 0.01$ and HR: 0.35, 95% CI: 0.18–0.70, $P = 0.003$, respectively, and cardiac death: HR: 0.32, 95% CI: 0.19–0.54, $P < 0.01$ and HR: 0.36, 95% CI: 0.14–0.93, $P = 0.03$, respectively).

Conclusions: PCI and CABG provided equal long-term benefits for all-cause death and cardiac death for PTVD patients. Patients undergoing MT alone had the worst long-term clinical outcomes.

Trial Registration: ClinicalTrials.gov; Identifier: NCT02634086. <https://www.clinicaltrials.gov/ct2/show/record/NCT02634086?term=NCT02634086&rank=1>

Key words: Coronary Artery Bypass Grafting; Medical Therapy; Percutaneous Coronary Intervention; Premature Coronary Heart Disease; Triple-vessel Coronary Disease

Address for correspondence: Dr. Jin-Qing Yuan,

Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100037, China
E-Mail: dr_jinqingyuan@sina.com

INTRODUCTION

Due to the potentially aggressive progression of coronary atherosclerosis, patients with premature coronary heart

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

© 2017 Chinese Medical Journal | Produced by Wolters Kluwer - Medknow

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.221273

Received: 08-09-2017 **Edited by:** Li-Min Chen

How to cite this article: Xu JJ, Zhang Y, Jiang L, Tian J, Song L, Gao Z, Feng XX, Zhao XY, Zhao YY, Wang D, Sun K, Xu LJ, Liu R, Gao RL, Xu B, Song L, Yuan JQ. Comparison of Long-term Outcomes in Patients with Premature Triple-vessel Coronary Disease Undergoing Three Different Treatment Strategies: A Prospective Cohort Study. Chin Med J 2018;131:1-9.

disease may have a higher risk of recurrent coronary events and repeat revascularization, especially patients with premature triple-vessel disease (PTVD).^[1,2] Previous studies of premature coronary heart disease including small sample-size case reports of PTVD patients did not compare the three primary treatment strategies (percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG], and medical therapy [MT]) for prognosis.^[3] Therefore, the optimal treatment for PTVD patients remains controversial. Our study is to assess the long-term clinical outcomes following CABG, PCI, or MT alone in a large-scale clinical study of PTVD patients.

METHODS

Ethical approval

The study complied with the guidelines of the *Declaration of Helsinki*. The Ethics Committee of Fuwai Hospital approved the research protocol (Ethics application number: IRB2012-BG-006 and approval number: 2013-449), and all patients signed informed consent.

Patient selection

All data were collected from the “Long-term Outcome of Triple-vessel Coronary Artery Disease Undergoing Three Different Strategies (LOTUS)” study (ClinicalTrials.gov ID: NCT02634086), a prospective cohort study that enrolled consecutive triple-vessel disease (TVD) patients in Fuwai Hospital (Beijing, China) from April 2004 to February 2011. PTVD patients were defined as men ≤ 50 years and women ≤ 60 years.^[4] TVD was defined as angiographic stenosis of $\geq 50\%$ in all three main coronary arteries, left anterior descending (LAD), left circumflex, and right coronary artery. There were no predetermined exclusion criteria. For all patients accepting clinical follow-up and providing written informed consent, we recorded baseline demographics, procedural or operative characteristics, and outcome data in a dedicated independent research database. The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score was calculated using the calculator: <http://www.syntaxscore.com> by a dedicated group of researchers blinded to the clinical data.^[5]

Procedures

The selection of CABG or PCI was based on clinical and anatomical factors, contemporary treatment guidelines,^[6,7] and patients’ preferences. For the PCI group, all patients were prescribed acetylsalicylic acid (ASA) plus clopidogrel (loading dose: 300 mg) before the procedure. The techniques, devices, and drugs used during PCI were at the surgeon’s discretion. Following stent implantation, patients received standard dual antiplatelet therapy, consisting of 100 mg/d ASA and 75 mg/d clopidogrel, for at least 12 months. For the CABG group, the internal mammary artery was chosen as the first graft to the LAD with standard bypass techniques. The choice of on-pump or off-pump procedure and whether to perform complete revascularization using arterial grafts was at the surgeon’s discretion.

Patients not undergoing PCI or CABG either because of the risk associated with each revascularization procedure or the patient’s or physician’s preference underwent MT alone. All patients were prescribed an optimal medical regimen at baseline, which continued until the end of follow-up. This MT was tailored to each patient and included but was not limited to nitrates, ASA, clopidogrel, statins, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, or a combination unless contraindicated and as recommended based on current practice, as for the other two groups.^[8,9]

Follow-up and definition of the end points

The primary end point was all-cause death. The secondary end points were cardiac death, major adverse cardiovascular and cerebrovascular events, and a composite consisting of all-cause death, myocardial infarction, stroke, or repeat revascularization, or any one of these components. Causes of death were considered cardiac related unless an unequivocal noncardiac cause could be established. All outcome data were systematically collected since the index angiography. Information on in-hospital outcomes was obtained by medical record review, and long-term clinical outcome data were evaluated by telephone, follow-up letter, or patient visit on 6 and 12 months after the procedure, then annually thereafter. All adverse events were evaluated by a group of independent clinical physicians and carefully checked and confirmed. Investigators were trained, questionnaires blinded, and telephone interviews recorded for quality control, as shown in flow chart [Figure 1].

Statistical analysis

Continuous variables are presented as a mean \pm standard deviation (SD), and categorical variables are presented as number with frequency. Normally distributed continuous variables were compared using the one-way analysis of variance test, and categorical variables were compared using Pearson’s Chi-square test between groups. Survival curves were calculated using Kaplan-Meier estimates and compared with the log-rank test for end points. Cox

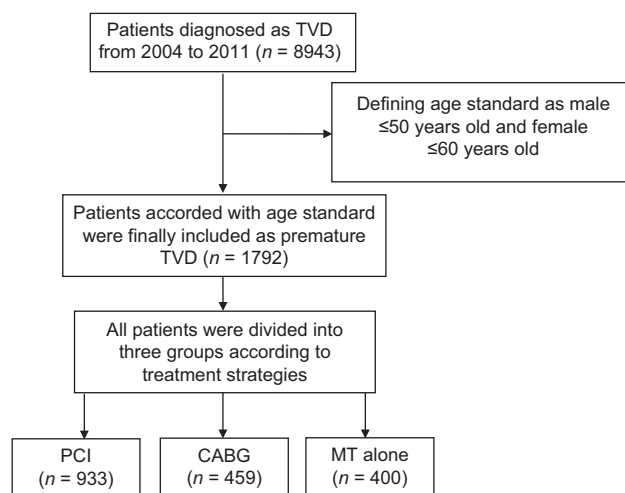


Figure 1: Flow chart of this study. TVD: Triple-vessel disease; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; MT: Medical therapy.

proportional-hazards regression results are expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) and compare long-term outcomes between groups. All clinically and statistically significant covariates were entered into the model with adjustments in the multivariate analysis for age, gender, hypertension, prior myocardial infarction, diabetes mellitus, hyperlipidemia, prior revascularization procedure, stroke, current smoking, family history of cardiovascular disease, and left ventricular ejection fraction (LVEF). The following factors were used in the multivariate cox regression analysis for subgroup analyses of assigned treatments: SYNTAX score (low risk: 0–22, intermediate risk: 22–32, or high risk: >32), LVEF (<40% or ≥40%), left main artery disease, gender, diabetes mellitus, prior myocardial infarction, and current smoking.

All statistical analyses were two sided with $P < 0.05$ considered statistically significant. All statistical analyses were performed using SAS[®] software (SAS Institute Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

A total of 1792 PTVD patients (20.0%) were registered among 8943 patients in the LOTUS registry. There were 933 (52.1%) patients treated with PCI, 459 (25.6%) with CABG, and 400 (22.3%) with MT alone. Patients undergoing PCI were younger, more likely to be male, had a higher incidence of acute myocardial infarction, lower incidence of previous myocardial infarction and diabetes mellitus, lower SYNTAX score, and lower proportion of LVEF <40% compared with patients receiving CABG or MT alone [Table 1]. Compared with the PCI and CABG groups, the MT alone group had higher N-terminal-pro-brain natriuretic peptide levels, higher rates of LVEF <40%, prior myocardial infarction, prior revascularization, and more comorbidities such as diabetes mellitus [Table 1].

In the CABG and MT alone groups, the rate of patients with left main disease was significantly higher compared with the PCI group (31.8% vs. 16.5% vs. 8.2%, respectively, $P < 0.01$).

Table 1: Baseline characteristics of premature TVD patients

Items	PCI group (n = 933)	CABG group (n = 459)	MT group (n = 400)	P
Epidemiology				
Age (years), mean ± SD	46.8 ± 6.0	49.2 ± 6.0	48.0 ± 6.6	<0.01
Female, n (%)	206 (22.1)	162 (35.3)	118 (29.5)	<0.01
BMI (kg/m ²), mean ± SD	26.6 ± 3.1	26.4 ± 3.1	26.4 ± 3.4	0.42
LVEF (%), mean ± SD	60.8 ± 11.9	59.7 ± 12.7	56.0 ± 16.2	<0.01
LVEF <40%, n (%)	49 (5.3)	33 (7.3)	74 (18.8)	<0.01
Risk factor and coronary condition				
Acute myocardial infarction, n (%)	320 (34.3)	53 (11.5)	104 (26.0)	<0.01
Previous myocardial infarction, n (%)	275 (29.5)	154 (33.6)	177 (44.3)	<0.01
Previous revascularization, n (%)	217 (23.3)	79 (17.2)	124 (31.0)	<0.01
Previous PCI, n (%)	117 (12.5)	50 (10.9)	69 (17.3)	0.02
Previous CABG, n (%)	14 (1.5)	2 (0.4)	21 (5.3)	<0.01
Hypertension, n (%)	576 (61.7)	294 (64.1)	246 (61.5)	0.66
Diabetes mellitus, n (%)	302 (32.4)	154 (33.6)	162 (40.5)	0.02
Hyperlipidemia, n (%)	569 (61.0)	262 (57.1)	260 (65.0)	0.06
Stroke history, n (%)	41 (4.4)	27 (5.9)	24 (6.0)	0.33
Smoke, n (%)	569 (61.0)	242 (52.7)	222 (55.5)	<0.01
Family history of CAD, n (%)	358 (38.4)	186 (40.5)	156 (39.0)	0.74
Left main + TVD, n (%)	76 (8.2)	143 (31.8)	65 (16.5)	<0.01
SYNTAX score, mean ± SD	21.7 ± 7.7	29.6 ± 9.0	24.7 ± 10.2	<0.01
Medication on discharge, n (%)				
Aspirin	918 (98.4)	440 (95.9)	371 (92.8)	<0.01
Beta-blocker	844 (90.5)	417 (90.8)	360 (90.0)	0.91
ACEI	446 (47.8)	31 (6.8)	208 (52.0)	<0.01
Statin	843 (90.4)	64 (13.9)	345 (86.3)	<0.01
Laboratory tests, mean ± SD				
Creatinine (μmol/L)	79.0 ± 15.6	77.3 ± 18.9	78.7 ± 17.9	0.20
TC (mmol/L)	4.7 ± 1.1	4.8 ± 1.2	4.8 ± 1.2	0.33
LDL-C (mmol/L)	2.6 ± 0.9	2.8 ± 1.0	2.7 ± 0.9	0.06
HbA1c (%)	6.5 ± 1.7	6.6 ± 1.5	6.8 ± 1.8	0.17
NT-proBNP (pmol/L)	668.7 ± 474.3	700.0 ± 484.2	923.2 ± 886.3	<0.01

ACEI: Angiotensin converting enzyme inhibitor; BMI: Body mass index; CABG: Coronary artery bypass graft; CAD: Coronary artery disease; HbA1c: Hemoglobin A1c; LDL-C: Low density lipoprotein cholesterol; LVEF: Left ventricular ejective fracture; MT: Medical therapy; PCI: Percutaneous coronary intervention; TVD: Triple vascular disease; TC: Total cholesterol; SYNTAX: Synergy Between PCI With Taxus and Cardiac Surgery; NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

The rate of statin use in the CABG group was significantly lower than those of the PCI and MT alone groups (13.9% vs. 90.4% vs. 86.3%, respectively, $P < 0.01$; Table 1).

Outcomes

A total of 1792 patients completed a median 6.8-year follow-up. Patients undergoing revascularization therapy had significantly lower rates for all-cause death and cardiac death compared with MT alone, and there was no difference between the PCI and CABG groups [Table 2 and Figure 2]. The rate of repeat revascularization was significantly lower in the CABG group compared with the PCI and MT groups [Table 2 and Figure 2e]. The incidence of myocardial infarction was lower in the CABG and MT alone groups than that in the PCI group [Figure 2d]. There was no significant

difference for stroke when comparing the three groups [Table 2 and Figure 2f].

After adjusting for baseline clinical characteristics, PCI and CABG groups maintained a lower risk of all-cause death (PCI: $HR: 0.35$, 95% $CI: 0.23-0.53$, $P < 0.01$; CABG: $HR: 0.35$, 95% $CI: 0.18-0.70$; $P < 0.01$) and cardiac death (PCI: $HR: 0.32$, 95% $CI: 0.19-0.54$, $P < 0.01$; CABG: $HR: 0.36$, 95% $CI: 0.14-0.93$, $P = 0.03$, respectively), compared with MT alone group [Table 3]. CABG patients had a lower risk of repeat revascularization than did patients in the PCI and MT alone groups. An increased risk of myocardial infarction remained in the PCI group compared with the MT alone group; however, the difference disappeared when comparing the PCI group

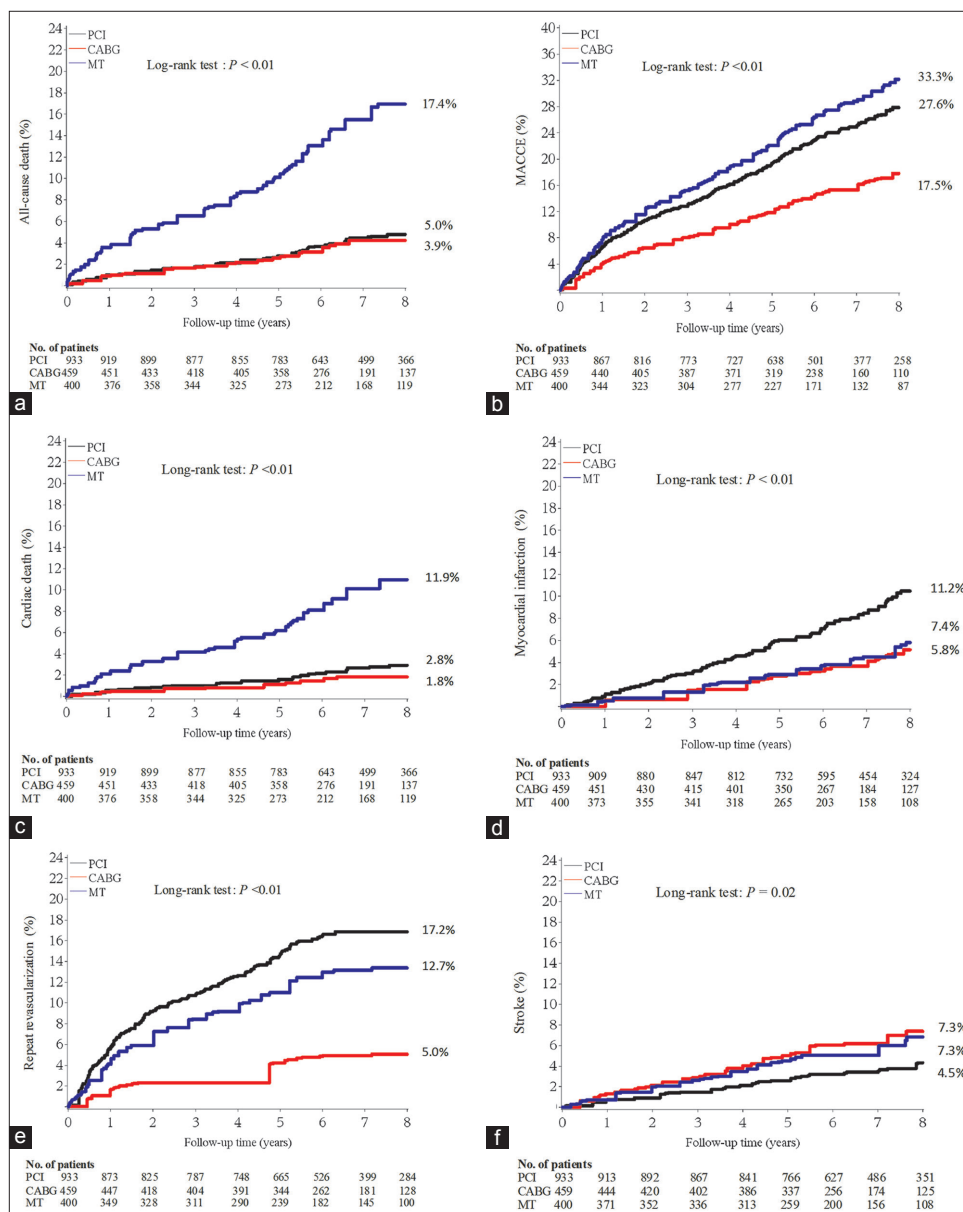


Figure 2: Kaplan-Meier Survival curve among CABG, PCI, and MT alone (a-f). No difference in all-cause death and cardiac death were found between the PCI and CABG groups (a and c). The incidence of myocardial infarction was lower in the CABG and MT alone groups than that in the PCI group (d). The rate of repeat revascularization was significantly lower in the CABG group compared with the PCI and MT groups (e). There was no significant difference for stroke when comparing the three groups (f). CABG: Coronary artery bypass graft; PCI: Percutaneous coronary intervention; MT: Medical therapy.

with the CABG group. The risk of stroke did not differ among three groups.

Subgroup analysis

No significant difference was found between the PCI and CABG groups for the risk of all-cause death [Figure 3a]. However, this risk was lower in both the PCI and CABG groups compared with MT alone except for the subgroups with LVEF <40%, SYNTAX score <22, and SYNTAX score >32 [Figure 3b and 3c].

DISCUSSION

PTVD patients have a relatively long life expectancy and therefore, a longer exposure to potentially aggressive progressive coronary atherosclerosis, which leads to a high risk of recurrent coronary events and repeat

revascularization.^[1] Prognosis evaluation and treatment strategy selection in these patients is an active research focus. In this study, we enrolled all PTVD patients and avoided the limitation of randomized trials of having highly selective populations. To our knowledge, our study is the largest single-center clinical cohort study assessing long-term outcomes of PTVD patients to date. After a median 6.8-year follow-up, patients undergoing PCI and CABG both showed lower all-cause death and cardiac death rates compared with MT alone, and patients receiving MT alone had the worst long-term clinical outcomes. Compared with PCI, CABG patients had a lower incidence of repeat revascularization.

Previous studies evaluated the effects of treatment in patients with premature coronary heart disease, but no studies involved TVD patients and none compared the long-term

Table 2: Outcomes for patients treated with PCI, CABG, and MT

Items	PCI group (n = 933)	CABG group (n = 459)	MT group (n = 400)	P
All-cause death	43 (4.6)	19 (4.1)	62 (15.5)*†	<0.01
MACCE	256 (27.4)	82 (17.9)*	131 (32.8)*†	<0.01
Cardiac death	26 (2.8)	9 (2.0)	39 (9.8)*†	<0.01
Myocardial infarction	91 (9.8)	20 (4.4)‡	18 (4.5)*	<0.01
Repeat revascularization	149 (16.0)	21 (4.6)‡	45 (11.3)†	<0.01
Stroke	37 (4.0)	31 (6.8)‡	23 (5.8)*	0.07

Data are shown as n (%). *P value had significantly difference compared with PCI group; †P value had significantly difference compared with CABG group. CABG: Coronary artery bypass graft; MACCE: Main adverse cardiovascular and cerebrovascular events; MT: Medical therapy; PCI: Percutaneous coronary intervention.

Table 3: Outcomes according to treat strategy

Items	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
All-cause death				
PCI versus MT	0.26 (0.18–0.38)	<0.01	0.35 (0.23–0.53)	<0.01
CABG versus MT	0.25 (0.15–0.41)	<0.01	0.35 (0.18–0.70)	<0.01
CABG versus PCI	0.96 (0.56–1.65)	0.88	1.00 (0.50–2.02)	0.99
MACCE				
PCI versus MT	0.85 (0.68–1.06)	0.15	0.95 (0.75–1.20)	0.64
CABG versus MT	0.51 (0.38–0.69)	<0.01	0.49 (0.34–0.71)	<0.01
CABG versus PCI	0.60 (0.46–0.78)	<0.01	0.52 (0.36–0.73)	<0.01
Cardiac death				
PCI versus MT	0.25 (0.15–0.41)	<0.01	0.32 (0.19–0.54)	<0.01
CABG versus MT	0.19 (0.09–0.38)	<0.01	0.36 (0.14–0.93)	0.03
CABG versus PCI	0.75 (0.35–1.60)	0.46	1.14 (0.43–3.05)	0.79
Myocardial infarction				
PCI versus MT	1.92 (1.16–3.19)	0.01	2.04 (1.22–3.42)	<0.01
CABG versus MT	0.90 (0.48–1.70)	0.74	1.14 (0.53–2.46)	0.73
CABG versus PCI	0.47 (0.29–0.76)	<0.01	0.56 (0.29–1.08)	0.08
Repeat revascularization				
PCI versus MT	1.30 (0.93–1.81)	0.12	1.33 (0.95–1.87)	0.10
CABG versus MT	0.36 (0.22–0.61)	<0.01	0.29 (0.16–0.53)	<0.01
CABG versus PCI	0.28 (0.18–0.44)	<0.01	0.22 (0.13–0.39)	<0.01
Stroke				
PCI versus MT	0.59 (0.35–0.99)	0.05	0.75 (0.44–1.28)	0.29
CABG versus MT	1.11 (0.65–1.91)	0.70	0.82 (0.41–1.64)	0.57
CABG versus PCI	1.89 (1.17–3.04)	<0.01	1.09 (0.56–2.11)	0.80

CABG: Coronary artery bypass graft; CI: Confidence interval; HR: Hazard ratio; MACCE: Main adverse cardiovascular and cerebrovascular events; MT: Medical therapy; PCI: Percutaneous coronary intervention.

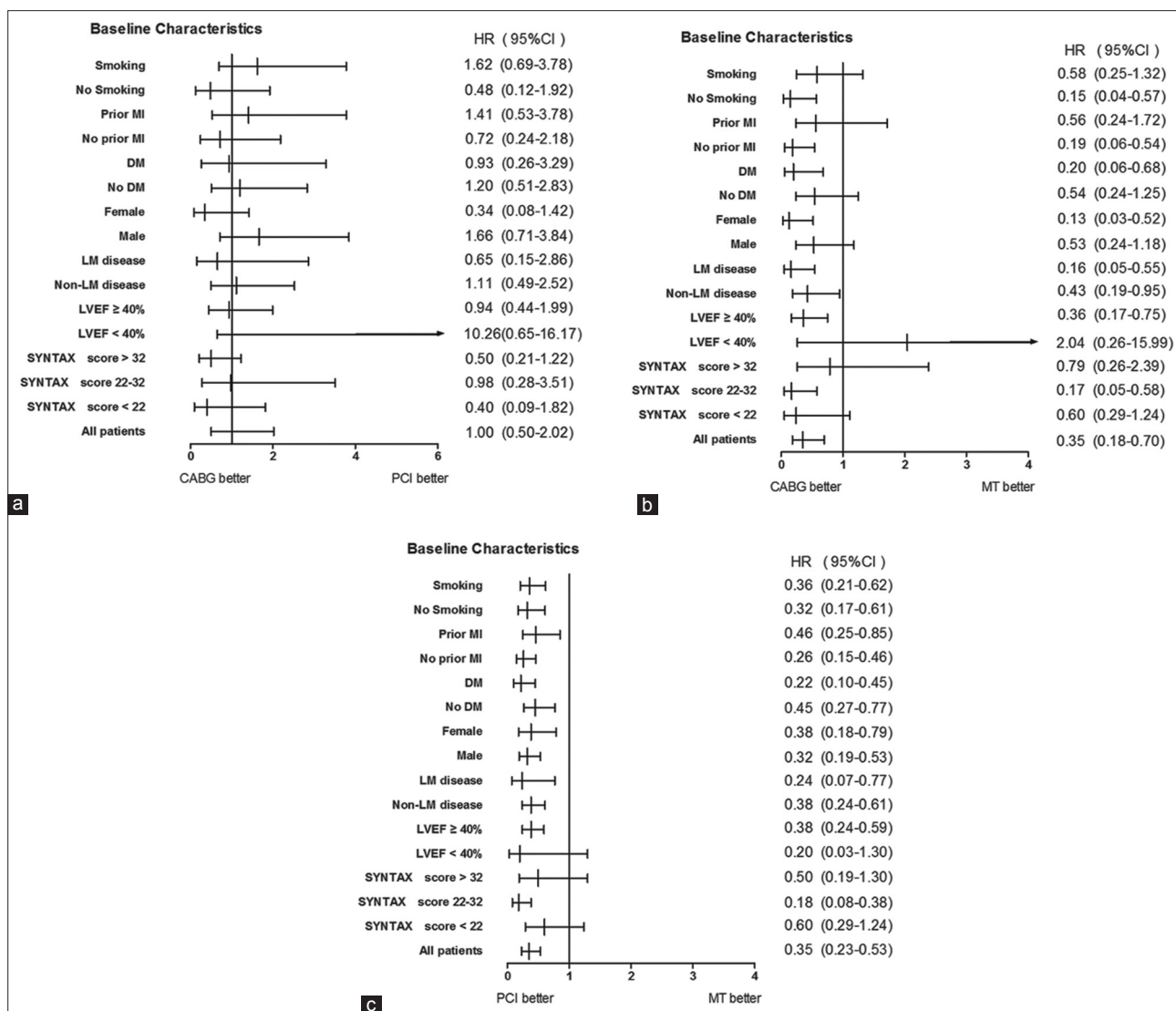


Figure 3: Subgroup analysis of all-cause mortality. No significant difference was found between the PCI and CABG groups for the risk of all-cause mortality (a). This risk was lower in both the PCI and CABG groups compared with MT alone except for the subgroups with LVEF <40%, SYNTAX score <22, and SYNTAX score >32 (b and c). DM: Diabetes mellitus; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; MT: Medical therapy; LVEF: Left ventricular ejection fraction; SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

outcomes of different treatment strategies. The Coronary artery disease in young adults study (CRAGS study) is the only previous study that analyzed PCI or CABG in patients aged ≤50 years.^[10,11] Results showed that PCI and CABG were both associated with lower risk of all-cause death and that CABG was associated with a lower risk of myocardial infarction and repeat revascularization, similar to our results. However, the CRAGS study did not compare different MTs, and the median follow-up time was only 3 years. Furthermore, the outcomes of PCI and CABG in the CRAGS study were analyzed separately in two independent and different patient populations, making the results noncomparable. The PCI patients were also classified only by clinical symptom and not by the number of diseased vessels, and CABG patients were not limited strictly to TVD but instead were defined as having at least double-vessel

disease. In our study, we analyzed the long-term (median: 6.8 years) outcomes of three treatment strategies including PCI, CABG, and MT alone in patients with confirmed PTVD in a unified population who received different treatments almost at the same time interval, which made the results more comparable.

CABG is considered the best treatment for patients with TVD.^[12,13] Most previous studies comparing outcomes of CABG and PCI in patients with multivessel coronary disease suggest that long-term mortality following CABG is better than for PCI.^[14-16] Brener *et al.*^[17] enrolled 6033 consecutive patients undergoing revascularization; PCI was performed in 872 patients, and 5161 patients underwent CABG. The study showed that PCI was associated with an increased risk of death; however, with improved interventional operation skill and technology, especially after the using of new generation

drug-eluting stents,^[18] PCI has been increasingly chosen in patients with more complex disease including TVD. Recent studies have shown that PCI is associated with a similar risk of death compared with CABG in patients with multivessel disease,^[19,20] especially in patients with lower SYNTAX score.^[21,22] However, these studies focused only on TVD patients, not PTVD patients. Our results showed that PCI was associated with equal long-term benefit compared with CABG for all-cause death and cardiac death. Although baseline conditions and coronary anatomical complexity in the PCI group were better than in the CABG group, the better results for all-cause death and cardiac death persisted after adjustment. To our knowledge, our results are the first to show the same therapeutic benefits with PCI and CABG in PTVD patients in a clinical study, indicating that PCI may be an alternative treatment for PTVD patients, with equivalent results to CABG.

The MASS II trial is the only randomized study showing benefits of PCI (with bare metal stents) and CABG over MT alone regarding several primary end points at 10-year follow-up.^[18] However, the study involved patients with multiple-vessel disease, preserved left ventricular function, and did not include PTVD patients. Our study showed that PTVD patients receiving MT alone had the worst outcomes for both all-cause and cardiac death compared with PCI and CABG patients, demonstrating that, at least for PTVD patients, and revascularization therapy with either PCI or CABG is an optimal strategy compared with medication alone.

Randomized controlled trials and meta-analyses including stable multivessel coronary artery disease patients found that CABG was better than PCI when comparing repeat revascularization and myocardial infarction rates.^[18,23-25] This result was confirmed in our study. As a result of the higher rates of complete revascularization provided by CABG, myocardial infarction and revascularization rates also decreased. Furthermore, because of the difficulty of post-CABG surgery, revascularization was more difficult to repeat in the CABG group compared with the PCI group. In our study, the incidence of myocardial infarction in the CABG group was significantly lower than in the PCI group before adjustment. However, after adjusting for baseline characteristics, the risk of myocardial infarction was no different when comparing CABG and PCI, possibly because of the significantly lower rate of statin use in the CABG group. These results also reflect the current clinical use of post-CABG MT and the protective effect of statins for myocardial infarction.^[26]

CABG is generally considered to be associated with an increased incidence of stroke.^[27,28] A meta-analysis by Alam *et al.*^[29] demonstrated that CABG had a higher rate of stroke compared with PCI in patients with a mean age of >70 years. Our results showed that the incidence of stroke was initially higher in the CABG and MT alone groups compared with the PCI group in paired comparisons, but the difference disappeared after adjustment. These findings may be related

to the different baseline characteristics in the CABG and MT alone patients who were older, and who had more complications such as diabetes mellitus and more complex coronary artery anatomy. These results suggest that when deciding on treatment options in younger TVD patients, the risk of stroke caused by CABG may not be a consideration.

As current guidelines recommend, the treatment strategy for patients with TVD should be chosen according to the SYNTAX score.^[30,31] In our study, subgroup analysis showed a similar risk for all-cause mortality for PCI and CABG patients in all subgroups, especially with different SYNTAX scores. This result suggests that the long-term outcome efficacy of PCI in PTVD patients may be comparable to CABG and that PCI should also be a treatment option for these patients.

Randomized clinical trials randomly assign patients to standard and investigational arms and follow patients over a defined period; this approach does not necessarily reflect clinical practice.^[32] In our study, we assessed patients without predesigned exclusion criteria, which avoided the selection restrictions of randomized controlled trials and provided better clinical evidence of effectiveness in actual practice;^[33-36] therefore, our results are more reliable.

There are certain limitations to consider in our study. First, our findings were based on data from a single center, which may limit its generalizability. Second, we performed a baseline patient characteristics adjustment to reduce selection bias to better reflect actual clinical practice; however, because data for certain undefined or unmeasured risk factors related to the treatment choice and to the end points were not collected, bias could be present in our results. Third, patients undergoing complete revascularization or incomplete revascularization cannot be distinguished in this study, which may cause a certain impact on the result of prognosis. Finally, we could not access postdischarge compliance data even though all patients were discharged from the hospital on standard guideline-directed MT.

In conclusion, revascularization therapies, no matter PCI or CABG, both had comparable long-term clinical benefits in PTVD patients. Patients receiving MT alone had the worst long-term clinical outcomes. CABG patients had a reduced risk of repeat revascularization compared with PCI patients.

Acknowledgment

We thank all individuals participating in this study for their contribution to data collection, patient selection, and quality control.

Financial support and sponsorship

This study was supported by grants from the CAMS Innovation Fund for Medical Sciences (No. CAMS-I2M, 2016-I2M-1-002), National Basic Research Program of China (No. 2010CB732601), National High Technology Research and Development Program of

China (No. 2015AA020407), and National Natural Science Foundation of China (No. 81470380).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Meliga E, De Benedictis M, Gagnor A, Belli R, Scrocca I, Lombardi P, *et al.* Long-term outcomes of percutaneous coronary interventions with stent implantation in patients ≤ 40 years old. *Am J Cardiol* 2012;109:1717-21. doi: 10.1016/j.amjcard.2012.01.400.
- Sadeghi R, Adnani N, Erfanifar A, Gachkar L, Maghsoomi Z. Premature coronary heart disease and traditional risk factors-can we do better? *Int Cardiovasc Res J* 2013;7:46-50.
- Reddy SM, Byrapaneni RB, Rangappa C, Gouni UK, Vakati C, Suryavanshi S, *et al.* Surgical revascularization for premature coronary artery disease in second and third decade of life. *Interact Cardiovasc Thorac Surg* 2017;24:99-101. doi: 10.1093/icvts/ivw295.
- Do R, Stitzel NO, Won HH, Jorgensen AB, Duga S, Angelica Merlini P, *et al.* Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. *Nature* 2015;518:102-6. doi: 10.1038/nature13917.
- Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, *et al.* Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360:961-72. doi: 10.1056/NEJMoa0804626.
- Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, *et al.* 2011 ACCF/AHA guideline for coronary artery bypass graft surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2011;58:e123-210. doi: 10.1016/j.jacc.2011.08.009.
- Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, *et al.* 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011;58:e44-122. doi: 10.1016/j.jacc.2011.08.007.
- Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, *et al.* 2013 ESC guidelines on the management of stable coronary artery disease: The task force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;34:2949-3003. doi: 10.1093/eurheartj/ehz296.
- Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE Jr., *et al.* 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2012;60:645-81. doi: 10.1016/j.jacc.2012.06.004.
- Lautamäki A, Airaksinen KE, Kiviniemi T, Vinco G, Ribichini F, Gunn J, *et al.* Prognosis and disease progression in patients under 50 years old undergoing PCI: The CRAGS (Coronary artery disease in young adults) study. *Atherosclerosis* 2014;235:483-7. doi: 10.1016/j.atherosclerosis.2014.05.953.
- Biancari F, Onorati F, Faggian G, Heikkinen J, Anttila V, Jeppsson A, *et al.* Determinants of outcome after isolated coronary artery bypass grafting in patients aged ≤ 50 years (from the coronary artery disease in young adults study). *Am J Cardiol* 2014;113:275-8. doi: 10.1016/j.amjcard.2013.08.038.
- Serruys PW, Ong AT, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJ, *et al.* Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: The final analysis of the arterial revascularization therapies study (ARTS) randomized trial. *J Am Coll Cardiol* 2005;46:575-81. doi: 10.1016/j.jacc.2004.12.082.
- Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, *et al.* Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012;367:2375-84. doi: 10.1056/NEJMoa1211585.
- Serruys PW, Onuma Y, Garg S, Vranckx P, De Bruyne B, Morice MC, *et al.* 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel *de novo* coronary artery lesions. *J Am Coll Cardiol* 2010;55:1093-101. doi: 10.1016/j.jacc.2009.11.049.
- Yan TD, Padang R, Poh C, Cao C, Wilson MK, Bannon PG, *et al.* Drug-eluting stents versus coronary artery bypass grafting for the treatment of coronary artery disease: A meta-analysis of randomized and nonrandomized studies. *J Thorac Cardiovasc Surg* 2011;141:1134-44. doi: 10.1016/j.jtcvs.2010.07.001.
- Rodriguez AE, Grinfeld L, Fernandez-Pereira C, Mieres J, Rodriguez Alemparte M, Berrocal D, *et al.* Revascularization strategies of coronary multiple vessel disease in the Drug Eluting Stent Era: One year follow-up results of the ERACI III trial. *EuroIntervention* 2006;2:53-60.
- Brener SJ, Lytle BW, Casserly IP, Schneider JP, Topol EJ, Lauer MS, *et al.* Propensity analysis of long-term survival after surgical or percutaneous revascularization in patients with multivessel coronary artery disease and high-risk features. *Circulation* 2004;109:2290-5. doi: 10.1161/01.CIR.0000126826.58526.14.
- Vieira RD, Hueb W, Gersh BJ, Lima EG, Pereira AC, Rezende PC, *et al.* Effect of complete revascularization on 10-year survival of patients with stable multivessel coronary artery disease: MASS II trial. *Circulation* 2012;126:S158-63. doi: 10.1161/CIRCULATIONAHA.111.084236.
- Bangalore S, Guo Y, Samadashvili Z, Blecker S, Hannan EL. Revascularization in patients with multivessel coronary artery disease and severe left ventricular systolic dysfunction: Everolimus-eluting stents versus coronary artery bypass graft surgery. *Circulation* 2016;133:2132-40. doi: 10.1161/CIRCULATIONAHA.115.021168.
- Deb S, Wijeyesundera HC, Ko DT, Tsubota H, Hill S, Fremes SE, *et al.* Coronary artery bypass graft surgery vs. percutaneous interventions in coronary revascularization: A systematic review. *JAMA* 2013;310:2086-95. doi: 10.1001/jama.2013.281718.
- Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stähle E, Colombo A, *et al.* Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013;381:629-38. doi: 10.1016/S0140-6736(13)60141-5.
- He JQ, Yu XP, Peng C, Li Q, Luo YW, Gao YC, *et al.* Predictive ability of the SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery score II for long-term mortality in patients with three-vessel coronary artery disease undergoing percutaneous coronary intervention treated with second-generation drug-eluting stents. *Chin Med J* 2015;128:2176-82. doi: 10.4103/0366-6999.162510.
- Fanari Z, Weiss SA, Zhang W, Sonnad SS, Weintraub WS. Comparison of percutaneous coronary intervention with drug eluting stents versus coronary artery bypass grafting in patients with multivessel coronary artery disease: Meta-analysis of six randomized controlled trials. *Cardiovasc Revasc Med* 2015;16:70-7. doi: 10.1016/j.carrev.2015.01.002.
- Habib RH, Dimitrova KR, Badour SA, Yammine MB, El-Hage-Sleiman AK, Hoffman DM, *et al.* CABG versus PCI: Greater benefit in long-term outcomes with multiple arterial bypass grafting. *J Am Coll Cardiol* 2015;66:1417-27. doi: 10.1016/j.jacc.2015.07.060.
- Park SJ, Ahn JM, Kim YH, Park DW, Yun SC, Lee JY, *et al.* Trial of everolimus-eluting stents or bypass surgery for coronary disease. *N Engl J Med* 2015;372:1204-12. doi: 10.1056/NEJMoa1415447.
- Norris DM, Anderson JR. Statin loading before percutaneous coronary intervention to reduce periprocedural myocardial infarction. *Cardiol Rev* 2012;20:319-24. doi: 10.1097/CRD.0b013e31826db7ff.

27. Athappan G, Chacko P, Patvardhan E, Gajulapalli RD, Tuzcu EM, Kapadia SR, *et al.* Late stroke: Comparison of percutaneous coronary intervention versus coronary artery bypass grafting in patients with multivessel disease and unprotected left main disease: A meta-analysis and review of literature. *Stroke* 2014;45:185-93. doi: 10.1161/STROKEAHA.113.003323.
28. Palmerini T, Biondi-Zoccai G, Reggiani LB, Sangiorgi D, Alessi L, De Servi S, *et al.* Risk of stroke with coronary artery bypass graft surgery compared with percutaneous coronary intervention. *J Am Coll Cardiol* 2012;60:798-805. doi: 10.1016/j.jacc.2011.10.912.
29. Alam M, Virani SS, Shahzad SA, Siddiqui S, Siddiqui KH, Mumtaz SA, *et al.* Comparison by meta-analysis of percutaneous coronary intervention versus coronary artery bypass grafting in patients with a mean age of ≥ 70 years. *Am J Cardiol* 2013;112:615-22. doi: 10.1016/j.amjcard.2013.04.034.
30. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, *et al.* 2014 ESC/EACTS guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the Special Contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;35:2541-619. doi: 10.1093/eurheartj/ehu278.
31. He JQ, Gao YC, Yu XP, Zhang XL, Luo YW, Wu CY, *et al.* Syntax score predicts clinical outcome in patients with three-vessel coronary artery disease undergoing percutaneous coronary intervention. *Chin Med J* 2011;124:704-9.
32. Grapow MT, von Wattenwyl R, Guller U, Beyersdorf F, Zerkowski HR. Randomized controlled trials do not reflect reality: Real-world analyses are critical for treatment guidelines! *J Thorac Cardiovasc Surg* 2006;132:5-7. doi: 10.1016/j.jtcvs.2006.03.035.
33. Kunz R. Randomized trials and observational studies: Still mostly similar results, still crucial differences. *J Clin Epidemiol* 2008;61:207-8. doi: 10.1016/j.jclinepi.2007.05.021.
34. Guller U. Surgical outcomes research based on administrative data: inferior or complementary to prospective randomized clinical trials?. *World J Surg* 2006; 30: 255-66. doi: 10.1007/s00268-005-0156-0.
35. Hoffman SN, TenBrook JA, Wolf MP, Pauker SG, Salem DN, Wong JB. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one- to eight-year outcomes. *J Am Coll Cardiol* 2003; 41:1293-304. doi: S0735109703001578.
36. Brener SJ, Lytle BW, Casserly IP, Schneider JP, Topol EJ, Lauer MS. Propensity analysis of long-term survival after surgical or percutaneous revascularization in patients with multivessel coronary artery disease and high-risk features. *Circulation* 2004; 109: 2290-5. doi: 10.1161/01.CIR.0000126826.58526.14.