Long-term Outcomes of Contemporary Coronary Revascularization by Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting in Young Adults

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ABSTRACT: **Background:** Current guidelines for choosing between revascularization modalities may not be appropriate for young patients.

Objectives: To compare outcomes and guide treatment options for patients < 40 years of age, who underwent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) between 2008 and 2018.

Methods: Outcomes were compared for 183 consecutive patients aged < 40 years who underwent PCI or CABG between 2008 and 2018. Outcomes were compared as time to first event and as cumulative events for non-fatal outcomes.

Results: Mean patient age was 36.3 years and 96% were male. Risk factors were similar for both groups. Drug eluting stents were implemented in 71% of PCI patients and total arterial revascularization in 74% of CABG patients. During a median follow-up of 6.5 years, 16 patients (8.6%) died. First cardiovascular events occurred in 35 (38.8%) of the PCI group vs. 29 (31.1%) of the CABG group (log rank $P = 0.022$), repeat events occurred in 96 vs. 51 ($P < 0.01$), respectively. After multivariate adjustment, CABG was associated with a significantly reduced risk for first adverse event (hazard ratio [HR] 0.305, $P < 0.01$) caused by a reduction in repeat revascularization. CABG was also associated with a reduction in overall repeat events (HR 0.293, $P < 0.01$). There was no difference in overall mortality between CABG and PCI.

Conclusions: Young patients with coronary disease treated by CABG showed a reduction in the risk for non-fatal cardiac events. Mortality was similar with CABG and PCI.

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KEY WORDS: coronary artery bypass grafting (CABG), coronary artery disease (CAD), percutaneous coronary intervention (PCI), young adults

The average age at presentation of coronary artery disease (CAD) is approximately 55 years for men and 65 years for women [1]. However, subclinical coronary atherosclerosis develops decades prior to clinical manifestations. Post-mortem studies showed that up to 19% of men and 9% of women aged 30–34 have significant coronary stenosis [2]. Likewise, a number of studies have reported varying rates of myocardial infarction (MI) in young patients, depending on the cutoff age used [3,4]. There is no clear age cutoff for defining premature CAD, although the cutoff used in research is generally in the range of 40–45 years.

Regardless of the definition, these patients have different risk factor profiles [5,6], clinical presentations [2,3,7], and prognosis [8,9] compared to the overall CAD population. Although premature CAD is an uncommon entity, it constitutes a significant challenge for physicians and patients because of its devastating effect on the relatively active lifestyle of young patients and the substantial economical toll on society due to the cumulative loss of quality-adjusted life-years. With the increasing prevalence of obesity and its related metabolic abnormalities in young adults [10,11], the prevalence of premature CAD is expected to increase.

Data on long-term outcomes of patients with premature CAD who underwent coronary revascularization are limited. Overall, young patients have better prognosis following either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery [5,12,13] compared to older patients. However, most of the relevant data are derived from studies that were conducted during a time with very different medical standards from current practice (e.g., in relation to the use of drug eluting stents [DES] and total arterial revascularization).

Similarly, the optimal revascularization strategy for young patients with CAD is not well established, since current revascularization guidelines are based on data from trials that include very few patients with premature CAD and therefore may not be applicable to this unique patient subgroup [14]. In this study, we describe the characteristics, clinical presenta-

*The first and second authors contributed equally to this study tion, angiographic findings, and long-term clinical outcomes of patients with premature CAD who underwent PCI or CABG at our medical center.

PATIENTS AND METHODS

STUDY DESIGN AND POPULATION

This single center retrospective study comprised all patients < 40 years of age who underwent their first ever revascularization procedure (PCI or CABG) at Rabin Medical Center between 2008 and 2018. Exclusion criteria included unusual etiologies for coronary disease (e.g., vasculitis, end-stage renal disease, s/p chest radiation, allograft vasculopathy, penetrating chest trauma), performance of a procedure other than isolated CABG (valvular or structural surgical intervention) during the index procedure, or known CAD with a previous revascularization (PCI or CABG).

Patients were included in the cohort if they had been referred, either as urgent or elective patients, for angiography due to symptoms suspected to be related to CAD (e.g., stable angina, unstable angina, or MI). After assessment of the coronary anatomy, the attending cardiologist decided whether to proceed to PCI or refer the patient for CABG.

The index hospitalization was defined as the admission during which the patients underwent the revascularization procedure. The equipment used during PCI (balloon angioplasty, bare metal stent, or DES) and the surgical technique for CABG (arterial/venous grafts, on/off pump surgery) was chosen by the attending operator, considering both the availability of equipment throughout the study period and the patient characteristics.

FOLLOW-UP AND OUTCOMES

The primary outcomes were a composite of all-cause mortality, MI, cerebrovascular accident, and repeat revascularization (RR) between the index procedure and December 31, 2018. The secondary outcomes were the individual components of the composite primary outcome. For PCI patients, data were collected from the Rabin Medical Center PCI database, which is a prospective registry that follows all patients who undergo PCI at the interventional cardiology unit [15]. The database is managed by the research unit of the interventional cardiology institute. The database includes detailed demographic, clinical and angiographic data on each patient, as well as long-term clinical follow-up after discharge. It is updated at 6-month intervals, by review of data from electronic medical records. These records included admission and discharge diagnoses from all 23 medical centers in Israel. Full discharge summaries, laboratory data, and in-hospital procedure reports from 16/23 centers, as well as medical diagnoses and clinical follow-up in outpatient community clinics for the two largest health maintenance organizations in Israel, were also collected.

For CABG patients, we compiled a list of all isolated CABG procedures performed in patients < 40 years of age at the time of surgery during the study period. We then reviewed the electronic medical records of these patients to check for previous revascularization procedures or other exclusion criteria. After compiling the final CABG cohort, we retrieved demographic, clinical, and angiographic data for the index procedure from the discharge letter and collected follow-up and outcome data from electronic medical records of the same way data were collected for PCI-treated patients.

Mortality was ascertained by cross reference with the national mortality registry. For all other outcomes, the diagnosis was extracted from patient electronic medical records. All outcomes found in medical records were reviewed by two physicians (DBL, AS). If they did not reach an agreement regarding the event, a third physician (GW) reviewed the case and adjudicated the event. MI was defined per the third universal definition of MI [16].

The study was approved by the Rabin Medical Center institutional review board.

STATISTICAL ANALYSIS

Baseline characteristics were described for the entire cohort using Student's *t*-test or Mann–Whitney U test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables as appropriate. Outcomes were compared between PCI and CABG using the same methods. We performed two sets of survival outcome analyses. For time-to-first-event analysis, occurrences of the primary outcome and its individual components were compared by plotting Kaplan–Meier curves and using the log-rank test. We then calculated hazard ratios (HR) for the primary and secondary outcomes according to the type of revascularization using a Cox proportional hazard model adjusted for age, major cardiovascular risk factors (e.g., diabetes mellitus, hypertension, dyslipidemia, history of smoking, or family history), presentation (e.g., stable CAD, unstable angina pectoris, or MI), ejection fraction, and year of the procedure.

For repeat events analysis, we compared the cumulative occurrence of all non-fatal outcomes during the follow-up period and calculated HR for all these outcomes. For this analysis, we used a negative binomial general linear model that was adjusted for the same variables included in the Cox model described above. A P value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

PATIENTS AND PROCEDURAL CHARACTERISTICS

The study cohort comprised 183 patients, 172 male (94%); 93 patients underwent CABG and 90 PCI. Table 1 presents the demographic, clinical, angiographic, and procedural characteristics of the cohort according to revascularization mode. For the entire cohort, the median number of risk factors for atherosclerotic disease was 2 (interquartile range 1–3). The most prevalent risk factor was active smoking, followed by dyslipidemia, family history of CAD, hypertension, and diabetes. The prevalence of major risk factors for CAD did not differ significantly between the groups. Patients in the CABG group were slightly older (37.5 years old ± 3.3 vs. 34.8 ± 9.5 years, $P = 0.01$) and the ejection fraction was similar (50.4 ± 1.5% vs. 53 ± 1.2%, $P = 0.41$). There were, however, significant differences in clinical presentation and angiography findings between the groups. Patients in the CABG group were more likely to present with stable or unstable angina, and much less likely to present with MI (30.8% vs. 6.7%, 50.3% vs. 26.7%, and 14.9% vs. 62.2%, respectively, $P < 0.01$). CABG patients were more likely to be diagnosed with left main disease, multi-vessel disease, and triple vessel disease (20% vs. 0%, 79.8% vs. 30%, and 44.7% vs. 11.1%, respectively, $P < 0.01$ for all comparisons). Regarding stent and graft characteristics, 64/90 PCI patients (71.1%) were treated exclusively with DES and 92/93 of CABG patients (98.9%) received at least one arterial graft.

In this young cohort, most CABG patients (69/93, 74.2%) received total arterial revascularization, 15/93 (16.1%) received more than one arterial graft, and 9/93 (9.6%) received a single arterial graft (left internal mammary artery to the left anterior descending [LAD]) and saphenous veins utilized for all other grafts. One patient (1.1%), who had non-LAD disease, received only vein grafts.

Table 1. Demographic and clinical characteristics according to revascularization mode

	All patients (N=183)	CABG (N=93)	PCI (N=90)	*P* value
Age, years	36.3 ± 6.4	37.5 ± 3.3	34.8 ± 9.5	0.01
Male	172 (93.9%)	86 (91.5%)	86 (95.6%)	0.37
Diabetes mellitus	34 (18.5%)	22 (23.4%)	12 (13.3%)	0.13
Hypertension	53 (28.9%)	32 (34%)	21 (23.3%)	0.19
Dyslipidemia	101 (55.1%)	56 (59.6%)	45 (50%)	0.29
History of smoking	124 (67.7%)	59 (62.8%)	65 (72.2%)	0.23
Family history of CAD	89 (48.6%)	42 (44.7%)	47 (52.2%)	0.26
Presentation				< 0.01
Stable CAD	35 (19.1%)	29 (30.8%)	6 (6.7%)	–
Unstable angina pectoris	74 (40.4%)	50 (50.3%)	24 (26.7%)	–
Myocardial infarction	70 (38.2%)	14 (14.9%)	56 (62.2%)	–
Ejection fraction (%)	51.6% ± 2.1	50.4% ± 1.5	53% ± 1.2	0.41
Left main disease	19 (10.3%)	19 (20%)	0 (0%)	< 0.01
Multi-vessel disease	102 (55.7%)	75 (79.8%)	27 (30%)	< 0.01
Triple vessel disease	52 (28.4%)	42 (44.7%)	10 (11.1%)	< 0.01
Drug eluting stent	NA	NA	64 (71.1%)	NA
Left internal mammary artery used	NA	92 (98.9%)	NA	NA
Total arterial revascularization	NA	69 (74.2%)	NA	NA
Average number of grafts	NA	2.96	NA	NA

CABG = coronary artery bypass grafting, CAD = coronary artery disease, PCI = percutaneous coronary intervention

CLINICAL FOLLOW-UP AND OUTCOMES

Over a median follow-up of 6.5 years, 64 major adverse cardiovascular and cerebrovascular events (MACCE) occurred overall, considering first events only and including 16 (8.6%) mortality events. When including repeat events of non-fatal outcomes (MI, CVA, or RR), 147 MACCE events occurred. During the follow-up period, 17/90 (18.8%) of the PCI treated patients underwent CABG. The mean follow-up was 1.6 years from the index PCI.

TIME TO FIRST EVENT ANALYSIS

Figure 1 shows Kaplan–Meier curves for the cumulative incidence of the clinical outcomes. The overall incidence of MACCE was significantly higher in the PCI group (38.8% vs. 31.1%, log rank $P = 0.022$ [Figure 1A]). This difference was driven solely by an increase in the incidence of RR procedures (36.6% vs. 20.2%, log rank $P = 0.003$ [Figure 1B]). Incidences of MI and all-cause mortality were not statistically different between PCI and CABG treated patients [Figures 1C, 1D].

MULTIVARIATE ADJUSTED ANALYSIS

Table 2 shows hazard ratios for MACCE, MI, and RR for patients treated with CABG or PCI after adjustment for age, diabetes, hypertension, dyslipidemia, history of smoking, family history, presentation, and year of the index procedure. CABG was associated with a statistically significant decrease of almost 70% for any MACCE event (HR 0.305, 95% confidence interval [95%CI] 0.146–0.637, $P < 0.01$), driven by an almost 80% reduction in the risk for RR (HR 0.205, 95%CI 0.090–0.464, $P < 0.01$). The hazard ratios for MI and mortality were not statistically different between the two groups.

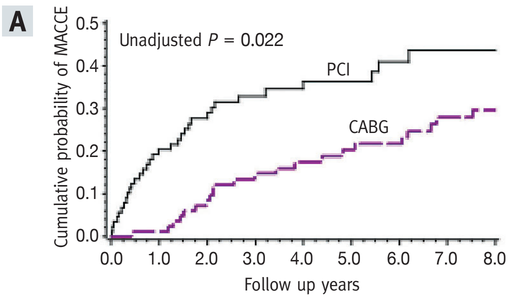
SUBGROUP ANALYSIS PER CORONARY ANATOMY

No interaction was found between the benefit gained from CABG in terms of MACCE in the subgroups of patients with single and multi-vessel coronary disease or 1–2 and triple vessel coronary disease or non-LAD and LAD disease ($P = 0.78$, 0.53, and 0.57, respectively).

OUTCOME ANALYSIS INCLUDING REPEAT EVENTS

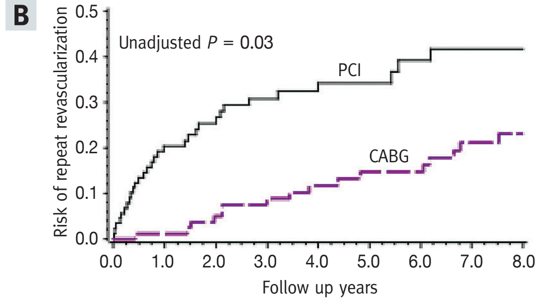
Table 3 shows the hazard ratios for MACCE, MI, and RR, calculated by using a negative binomial general linear model adjusted for age, diabetes, hypertension, dyslipidemia, history of smoking, family history, presentation, and year of the index procedure. The results regarding MACCE and RR were consistent with those of the Cox model in the first event analysis. There was a reduction of just over 70% in the risk of cumula-

Figure 1. Kaplan–Meier curves for clinical outcomes Kaplan–Meier curves for MACCE **[A]**, RR **[B]**, MI **[C]**, and mortality **[D]**



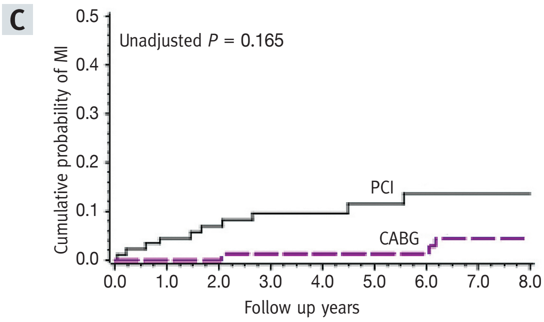
Patients at Risk

Follow-up years	2	4	6	8
PCI 89	55 (0.29)	37 (0.35)	23 (0.41)	18 (0.44)
CABG 86	73 (0.08)	58 (0.17)	53 (0.22)	38 (0.3)



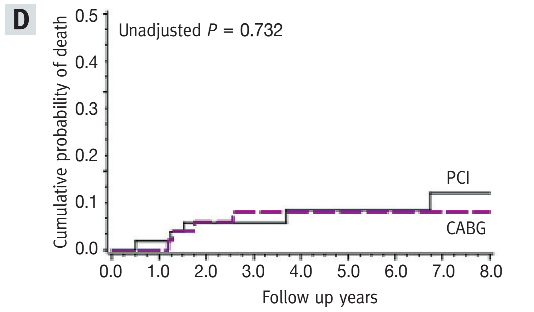
Patients at Risk

Follow-up years	2	4	6	8
PCI 89	55 (0.27)	37 (0.32)	23 (0.39)	18 (0.42)
CABG 86	73 (0.05)	58 (0.12)	53 (0.15)	38 (0.23)



Patients at Risk

Follow-up years	2	4	6	8
PCI 90	72 (0.27)	54 (0.32)	37 (0.39)	31 (0.42)
CABG 86	77 (0)	67 (0.01)	63 (0.01)	50 (0.04)



Patients at Risk

Follow-up years	2	4	6	8
PCI 90	77 (0.03)	59 (0.05)	44 (0.05)	37 (0.07)
CABG 86	77 (0.04)	68 (0.05)	64 (0.05)	53 (0.05)

MACCW = major adverse cardiovascular and cerebrovascular events, MI = myocardial infarction, RR = repeat revascularization

Table 2. Hazard ratios for clinical outcomes, comparing coronary artery bypass grafting to percutaneous coronary intervention*

Outcome	Hazard ratio	95%CI	*P* value
Death	1.168	0.256–5.338	0.84
MACCE	0.305	0.146–0.637	‹ 0.01
Myocardial infarction	0.236	0.047–1.638	0.24
Repeat revascularization	0.205	0.090–0.464	‹ 0.01

*Adjusted for age, diabetes, hypertension, dyslipidemia, history of smoking, family history, presentation, ejection fraction, and year of procedure

95%CI = 95% confidence interval, MACCE = major adverse cardiovascular and cerebrovascular events

Table 3. Hazard ratios for adverse outcomes following coronary artery bypass grafting compared to percutaneous coronary intervention including repeat events of non-fatal outcomes*

Outcome	Hazard ratio	95% CI	*P* value
MACCE	0.293	0.151–0.569	‹ 0.01
Myocardial Infarction	0.311	0.099–0.981	0.046
Repeat revascularization	0.225	0.106–0.480	‹ 0.01

*Adjusted for age, diabetes, hypertension, dyslipidemia, history of smoking, family history, presentation, ejection fraction and year of procedure

95%CI = 95% confidence interval, MACCE = major adverse cardiovascular and cerebrovascular events

tive MACCE events (HR 0.293, 95%CI 0.151–0.569, $P < 0.01$), and 78% in the risk for RR (HR 0.225, 95%CI 0.106–0.480, $P < 0.01$) with CABG. Contrary to the previous analyses (the Kaplan–Meier unadjusted analysis and the Cox model adjusted analysis), when considering all MI events that occurred during follow-up, CABG was associated with a statistically significant reduction of almost 70% in the risk for subsequent MI events (HR 0.311, 95%CI 0.099–0.981, $P = 0.046$).

DISCUSSION

This retrospective study followed a cohort of consecutive patients with premature CAD who underwent revascularization at a tertiary academic referral center. Patients with premature CAD have a high prevalence of traditional atherosclerotic risk factors, with history of smoking being the leading risk factor, followed by family history of coronary disease. The mortality rate was much higher than expected for this age group, and similar to that of age appropriate CAD patients (8.6% at a median follow-up of 6.5 years). The overall cardiovascular morbidity burden was significant and comparable to patients with age appropriate CAD (MACCE rate of 34% at a median follow-up of 6.5 years). CABG was associated with a significant reduction in long-term MACCE compared to PCI, driven mainly by a reduction in the need for RR procedures but also from lower risk for MI. The mortality rate was similar following the two procedures. Of the patients who were treated with PCI, 19% subsequently underwent CABG during a median follow-up period of 6.5 years.

Our results show that in patients with premature CAD, CABG is associated with increased benefits over PCI in two aspects: avoidance of a repeat procedure and reduced risk of MI. The fact that with CABG there were less repeat procedures is not surprising, since in the overall CAD population, CABG has been shown to be superior to PCI in terms of RR [17]. The HR for RR following PCI compared to CABG was higher in the current study than in the overall CAD population, as reported by one of the largest observational trials to date (4.87 vs. 2.35) [18]. This may be explained in part by the low use of second-generation DES in our study (29%). Another possible explanation for the greater benefit of CABG in our cohort is the high probability of genetic factors (as evident from the very high rate of family history of CAD) in addition to traditional atherosclerotic risk factors. Genetic factors are probably less amenable to the secondary prevention measures that are implemented in the overall CAD population for combating traditional risk factors, and therefore, the superior revascularization completeness offered by CABG is especially beneficial compared to PCI. An additional factor that may explain the benefit of CABG over PCI in premature CAD is non-compliance to medical treatment, which has been reported to be higher in young patients with hypertension [19].

While non-compliance for medical therapy post-PCI may lead to stent thrombosis and acceleration in the rate of restenosis, bypass grafts are probably less affected by noncompliance [20]. Notably, the use of arterial grafts, which are less prone to de novo stenosis, was very high in our cohort (74% of patients treated with total arterial revascularization and 99% treated with at least one arterial graft). Our cohort was mainly composed of patients with multi-vessel CAD (60%), with a considerable portion of triple vessel CAD (28%). Nonetheless, no interaction was found between the benefits from CABG with either multi-vessel or triple vessel disease. Our results are in line with two reports that examined revascularization in premature CAD. Saraiva and colleagues [21] compared 163 patients younger than 40 years who underwent CABG in their institution to their complete cohort of CABG patients above the age of 40 and found excellent results both in the short- and long-term. In their young cohort, like ours, history of smoking and family history were very common. Li et al. [22] compared the results of 406 propensity score matched pairs of Chinese patients with diabetes, aged 45 years or younger who underwent PCI or CABG and found that CABG was superior to PCI in terms of survival and reduced risk of MI and RR, but the risk of stroke was higher. These results are similar to comparisons between CABG and PCI in the older population. Given the established advantage of CABG over PCI in patients with diabetes and with multi-vessel disease, the benefit of less mortality in CABG reported by Li et al. compared to our results is probably related to the difference between the studies in the prevalence of diabetes (100% compared to 18% in our cohort). Of interest, the benefits of CABG were achieved in the Li study even though total arterial revascularization was very uncommon, at 5.4% (compared to 74% in our cohort), while in the PCI group, DES were used in 95% of patients (compared to only 71% in our cohort).

STUDY STRENGTHS

Our study has several strengths, especially when compared to previous observational trials of premature CAD. The data are derived from a period of relatively contemporary practice, as evident from the high use of DES and extremely high use of arterial grafts. The follow-up period is long, as appropriate for a trial focusing on a patient population in their fourth decade of life at inclusion. We used novel statistical methods that are especially relevant and suitable for evaluating a young population with a low expected mortality rate and long life expectancy. In such a population, non-fatal outcomes such as MI and RR have a greater relative significance and importance. Therefore, the use of statistical analysis methods that focus on time to first event, which is suitable when fatal outcomes are the primary interest and constitute a significant share of the overall morbidity burden, have the risk of not properly reflecting differences between treatments in terms of cumulative overall non-fatal events. In clinical settings of low mortality and an emphasis on non-fatal outcomes, different results and conclusions are reached by repeat event analysis rather than time to first event analysis [23]. In our results when time to first event analysis was used, the only advantage of CABG over PCI was a reduction in the risk for RR; whereas in the repeat events analysis, a significant advantage in reduction in the risk for MI with prognostic significance was shown as well.

LIMITATIONS

The sample size is moderate; however, the fact that we used repeat events analysis enabled accruing clinical outcomes comparable to a trial with a larger sample size. The number of MACCE events over 5 years follow-up among the patients with diabetes in the SYNTAX trial (n=452) is similar to our study

(147 compared to 164 in that cohort) [24]. Since the decision to refer patients to CABG or PCI was not randomized, resulting in significant differences between the CABG and PCI groups, most notably regarding coronary anatomy, our results cannot show causation, only association between the use of CABG in young patients and clinical benefit. As an observational trial, our results are susceptible to confounding facts that cannot be completely accounted for by multivariate adjustment. Moreover, an observational study has two main types of bias. Selection bias, since we do not have data regarding the reasons for deciding between PCI and CABG by the attending physician during the index hospitalization, and information bias, since the collection of follow-up data relied on reviewing electronic medical records.

Another limitation is that we could not distinguish between familial hyperlipidemia and other forms of dyslipidemia, which again may be responsible for some degree of confounding. In our cohort, even though DES was used in most PCI patients, its use was still lower than in current practice, especially in young patients. Although this can account for some of the advantage of CABG, it would not account for the difference in recurrent MI, which is the most important finding in our study [25]. This is because the use of DES has only been shown to reduce MACCE due to a reduction in RR and has not been shown to be associated with a reduction in MI. As a single center trial, our results may reflect factors that are unique to our patients and therefore may not be applicable to the overall premature CAD population.

CONCLUSIONS

Patients with premature CAD are a unique subgroup within the CAD population. Our results suggest that these patients may fare better when treated with CABG compared to PCI, but this requires corroboration from prospective studies. These results should draw attention to the need for more high-quality clinical data on revascularization in patients with premature CAD and may eventually lead to a tailored approach and recommendations for revascularization procedures in this unique patient population.

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