Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data†

Stuart J. Heada, Michael J. Mackb, David R. Holmes Jr, Friedrich W. Mohrc, Marie-Claude Moric, Patrick W. Serruysd and A. Pieter Kappeteina,*

a Department of Cardio-thoracic Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands
b The Heart Hospital, Baylor Health Care System, Plano, TX, USA
c Department of Cardiovascular Disease, Mayo Clinic Rochester, Rochester, MN, USA
d Department of Cardiac Surgery, Heart Center, University Leipzig, Leipzig, Germany
e Department of Cardiology, Institut Hospitalier Jacques Cartier, Massy, France
f Department of Cardiology, Erasmus University Medical Center, Rotterdam, The Netherlands

* Corresponding author. Department of Cardio-thoracic Surgery, Erasmus University Medical Center, PO Box 2040, 3000 CA, Rotterdam, The Netherlands.
Tel: +31-10-7034476; fax: +31-10-7039933; e-mail: a.kappetein@erasmusmc.nl (A.P. Kappetein).

Received 3 October 2011; accepted 25 October 2011

Abstract

OBJECTIVE: To assess whether incomplete revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) has an effect on long-term outcomes.

METHODS: During a heart team discussion to evaluate whether patients were eligible for randomization in the SYNTAX trial, both the cardiologist and surgeon agreed on which vessels needed revascularization. This statement was compared with the actual revascularization after treatment. Incomplete revascularization was defined as when a preoperatively identified vessel with a lesion was not revascularized. Outcomes were major adverse cardiac or cerebrovascular events (MACCE), the composite safety endpoint of death/stroke/myocardial infarction (MI), and individual MACCE components death, MI and repeat revascularization at 3 years. Predictors of incomplete revascularization were explored.

RESULTS: Incomplete revascularization was found in 43.3% (388/896) PCI and 36.8% (320/870) CABG patients. Patients with complete revascularization by PCI had lower rates of MACCE (66.5 versus 76.2%, P < 0.001), the composite safety endpoint (83.4 versus 87.9%, P = 0.05) and repeat revascularization (75.5 versus 83.9%, P < 0.001), but not death and MI. In the CABG group, no difference in outcomes was seen between incomplete and complete revascularization groups. Incomplete revascularization was identified as independent predictor of MACCE in PCI (HR = 1.55, 95% CI 1.15–2.08, P = 0.004) but not CABG patients. Independent predictors of incomplete revascularization by PCI were hyperlipidaemia (OR = 1.59, 95% CI 1.04–2.42, P = 0.031) and the number of vessels (OR = 1.58, 95% CI 1.41–1.77, P < 0.001) and the number of vessels (OR = 1.58, 95% CI 1.41–1.77, P < 0.001). Independent predictors of incomplete revascularization by CABG were unstable angina (OR = 1.42, 95% CI 1.02–1.98, P = 0.038), diffuse disease or narrowed ( < 2 mm) segment distal to the lesion (OR = 1.87, 95% CI 1.31–2.69, P = 0.001) and the number of vessels (OR = 1.70, 95% CI 1.53–1.89, P < 0.001).

CONCLUSIONS: Despite the hypothesis-generating nature of this data, this study demonstrates that incomplete revascularization is associated with adverse events during follow-up after PCI but not CABG.

Keywords: Myocardial revascularization • Completeness • Percutaneous coronary intervention • Coronary artery bypass grafting • Outcomes • SYNTAX

BACKGROUND

Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are both options for the treatment of coronary disease. Whether PCI or CABG is preferred for a particular patient often depends on the number of diseased vessels, lesion complexity and co-morbidities. Complete revascularization cannot always be achieved due to procedural difficulties [1, 2].

Previous studies have tried to address whether incomplete revascularization is associated with reduced survival and increased revascularization [3–6]. However, these have been methodologically restricted by a retrospective design and most often relied on post-procedural classification of completeness of revascularization by the treating physician. The Synergy between
PCI with TAXUS and Cardiac Surgery (SYNTAX) trial [7] had a more accurate method to determine the completeness of revascularization. Preoperatively, both the interventional cardiologist and surgeon had to agree which vessels needed revascularization on a basis of any lesion with more than 50% diameter stenosis in coronary vessels ≥1.5 mm. Patients were categorized as incompletely revascularized when the number of diseased segments that were treated did not match the Heart Team decision. The objective of this study was to assess whether incomplete revascularization according to the SYNTAX definition had an effect on the 3-year outcome of the SYNTAX trial.

METHODS

Study design

The SYNTAX trial design and methods have been described previously [7, 8]. It was a prospective, multicentre randomized trial in which patients with de novo left main and/or three-vessel disease were randomly assigned to undergo PCI with the TAXUS drug-eluting stent or CABG. The institutional review board of each of the 85 participating sites approved the protocol. The trial is registered on the National Institute of Health website with identifier NCT00114972.

Definitions

During the Heart Team meeting when patients were assessed for randomization [9], both the interventional cardiologist and surgeon documented which vessels with a ≥1.5 mm diameter and a 50% stenosis needed revascularization. Incomplete revascularization was assessed by correlating this preoperative status as follows: (i) after allocation but before treatment: Q-wave [new pathological Q-waves in ≥2 leads lasting ≥0.04 s with creatine kinase-MB (CK-MB) levels elevated above normal] and non-Q-wave MI [elevation of CK levels ≥2× the upper limit of normal (ULN) with positive CK-MB or elevation of CK levels to >2× ULN without new Q-waves if no baseline CK-MB was available]; (ii) <7 days after intervention: new Q-waves and either peak CK-MB/total CK >10% or plasma level of CK-MB 5× ULN; and (iii) ≥7 days after intervention: new Q-waves or peak CK-MB/total CK >10% or plasma level of CK-MB 5× ULN or plasma level of CK 5× ULN. The CK/CK-MB enzyme levels were normal (ULN) with positive CK-MB or elevation of CK levels to ≥1.5 mm. Patients were categorized as incompletely revascularized when the number of diseased segments that were treated did not match the Heart Team decision. The objective of this study was to assess whether incomplete revascularization according to the SYNTAX definition had an effect on the 3-year outcome of the SYNTAX trial.

RESULTS

Patient characteristics

In the SYNTAX trial, 1800 patients were randomized to PCI (n = 903) or CABG (n = 897). Revascularization was not performed or informed consent was withdrawn in 34 patients. A total of 1766 patients were analysed. In the PCI cohort, 43.3% (388/896) had incomplete revascularization, compared with 36.8% (320/870) in the CABG cohort. Table 1 shows the baseline characteristics of complete and incomplete revascularized patients.

Incomplete revascularization was especially present in patients with three-vessel disease (Fig. 1). Within SYNTAX score terciles, an increasing score is associated with an increased rate of incomplete revascularization (Fig. 2).

In the PCI group, patients with incomplete revascularization had a higher prevalence of diabetes and hyperlipidaemia. Patients with complete and incomplete revascularization had a comparable logistic EuroSCORE (3.7 ± 5.0 versus 3.9 ± 3.8, respectively, in the complete and incomplete revascularization groups) and Parsonnet score (8.2 ± 6.8 versus 9.0 ± 7.1, respectively). The coronary disease complexity, however, was significantly worse in patient with incomplete revascularization. The SYNTAX score was 31.4 ± 11.8 compared with 26.2 ± 10.6 in the complete revascularization group. More often, a total occlusion (34.3 versus 16.9%, P < 0.001) or bifurcation (67.3 versus 58.9%, P = 0.010) lesion was present. Patients with incomplete revascularization had more frequently diffuse disease or narrowed (<2 mm) segments distal to the lesion (26.5 versus 19.1%, P = 0.008). A higher mean number of lesions were seen in incompletely revascularized patients (4.6 ± 1.5 versus 3.5 ± 1.6, P < 0.001).

In the CABG cohort, patients with incomplete revascularization had a higher logistic EuroSCORE (4.3 ± 4.9 compared with 3.6 ± 4.0 in the complete revascularization group, P = 0.014) (Table 1). Similar to the PCI cohort, CABG patients with incomplete revascularization had more complex coronary disease according to the SYNTAX score (31.3 ± 11.4 versus 27.9 ± 11.1), and higher incidences of diffuse disease or narrowed vessels.
In the PCI cohort, incomplete and complete revascularization groups had similar number of stents implanted (respectively, 4.6 ± 1.6 versus 4.3 ± 1.5 in the complete revascularization group, P < 0.001).

The number of lesions was significantly higher in the incomplete revascularization group (4.8 ± 1.6 versus 3.5 ± 1.5 in the complete revascularization group, P < 0.001).

In the PCI cohort, incomplete and complete revascularization groups had similar number of stents implanted (respectively, 4.6 ± 2.0 versus 4.7 ± 2.4, P = 0.55) and a comparable total stent length in mm (respectively, 83.6 ± 42.3 versus 88.0 ± 51.7, P = 0.18). CABG patients in the incomplete revascularization group had similar procedure time as those with complete revascularization (respectively, 3.4 ± 1.0 versus 3.5 ± 1.5, P = 0.13).

### Predictors of incomplete revascularization

Predictors of incomplete revascularization are displayed in Table 2. For stent patients, hyperlipidaemia (OR = 1.59, 95% CI 1.04–2.42), a total occlusion (OR = 2.46, 95% CI 1.66–3.64) and the number of lesions (OR = 1.58, 95% CI 1.41–1.77) were independent predictors of incomplete revascularization in the multivariate model (Table 2).

In CABG patients, multivariate analysis identified only unstable angina (OR = 1.42, 95% CI 1.02–1.98), the diffuse disease or small vessels (OR = 1.87, 95% CI 1.31–2.69) and the number of lesions (OR = 1.70, 95% CI 1.53–1.89) as independent predictors.
Outcomes

Incomplete revascularization was associated with a higher MACCE rate at 3 years follow-up in patients who underwent PCI (33.5 versus 23.8% in patients with complete revascularization, \( P < 0.001 \)) (Fig. 3) but not in patients that underwent CABG (21.9 versus 18.9% in patients with complete revascularization, \( P = 0.29 \)).

The composite safety endpoint (16.6 versus 12.1%, \( P = 0.05 \)) was higher with incomplete revascularization in the PCI cohort, but within the CABG cohort there was no difference (12.5 versus 11.4%, respectively, in incomplete and complete revascularization groups, \( P = 0.62 \)).

Mortality was not significantly different between incomplete and complete revascularization groups in patients that underwent PCI (respectively, 10.1 versus 7.4%, \( P = 0.13 \)) or CABG (respectively, 7.1 versus 6.2%, \( P = 0.60 \)). Rates of MI were also not significantly different in PCI (8.2 versus 6.2% in incomplete and complete revascularization, \( P = 0.25 \)) and CABG (respectively, 4.5 versus 2.9%, \( P = 0.26 \)). However, in the incomplete revascularization group, there was a significantly higher rate of repeat revascularization in PCI (24.5 versus 16.1%, \( P < 0.001 \)), but not CABG (13.0 versus 9.4%, \( P = 0.11 \)).

Predictors of MACCE

Univariate Cox regression analysis identified incomplete revascularization as one of the predictors of MACCE, among others (Table 3). In the PCI arm, significant multivariate predictors for increased MACCE at 3 years were incomplete revascularization (HR = 1.55, 95% CI 1.15–2.08, \( P = 0.004 \)), insulin requiring diabetes (HR = 1.94, 95% CI 1.33–2.84, \( P = 0.001 \)), previous MI (HR = 1.42, 95% CI 1.04–1.92, \( P = 0.026 \)) and carotid artery disease (HR = 1.96, 95% CI 1.24–3.11, \( P = 0.004 \)). In the CABG cohort, only PVD (HR = 1.82, 95% CI 1.21–2.74, \( P = 0.004 \)) and the Parsonnet score (HR = 1.03, 95% CI 1.01–1.05, \( P = 0.006 \)) remained associated with MACCE in the multivariate model.

DISCUSSION

This study shows that in the SYNTAX population of patients with left main and/or multi-vessel coronary disease, PCI with
complete revascularization is associated with improved outcome compared with incomplete revascularization. In CABG patients, there was no additional risk of adverse events with incomplete revascularization.

The increased rate of MACCE in incomplete revascularized PCI patients is mainly attributed to a higher rate of repeat revascularization. The composite endpoint of death, MI and stroke was also higher with incomplete PCI, but for the individual components of MACCE no significant difference between complete and incomplete revascularization could be demonstrated.

The impact of incomplete revascularization on adverse events after CABG has been studied extensively since the early 1980s [11-13]. These studies uniformly concluded that survival and symptom relief after complete revascularization is favourable compared with incomplete revascularization. After the introduction of stents, many studies have also focused on the impact of completeness of revascularization in PCI patients. Several studies found that incomplete revascularization was associated with higher risk of long-term mortality or repeat revascularization [14]. There are, however, only a handful of studies that compared the influence of complete revascularization on MACCE in CABG and PCI patients simultaneously and there is only one report from a randomized study [6, 15, 16]. The evaluation of incomplete revascularization in non-randomized CABG and PCI cohorts is therefore limited because of differences in patient characteristics. Studies can also not be compared due to differences in definitions of complete revascularization.

Rates of complete revascularization vary significantly between studies. The ARTS trial showed an 82.1 and 70.5% rate of complete revascularization after CABG and PCI for multivessel disease [17]. These rates are much higher compared to this study, which rates were 63.2 and 56.7%, respectively. The rate of revascularization in the ARTS trial was probably higher due to less complex coronary lesions, but also due to the fact that the significant...
coronary lesions that needed treatment were not defined by the heart team prior to randomization. The surgical procedure was scored as complete revascularization if the diseased segments had been treated according to the surgical report. The ARTS trial showed a significant higher MACCE rate after PCI in the incomplete revascularization group compared with complete revascularized patients (30.6 versus 23.4% respectively, <0.001), which was driven by a higher rate of repeat CABG (10.0 versus 2.0%, <0.001) [6]. Similar as in ARTS (12.2 versus 10.1%), however, we found no differences between incomplete and complete revascularization groups within CABG patients [6, 16]. The 43% incompletely revascularized rate with PCI in SYNTAX is lower than 69% that was reported from 39 centres in a study with 11 294 PCI patients [18]. ARTS-II performed PCI with a drug-eluting stent and had a 49% incomplete revascularization rate, quite similar to other studies that reported rates above 50% [15, 16]. In other studies, the rate of incomplete revascularization in CABG patients is ~10–19%, which is much lower than in the SYNTAX trial [5, 6, 19, 20], although Kim et al. [15], who also used the SYNTAX score to classify lesions, found a rate of 33% which is close to the 37% in SYNTAX. The reason for such a high incomplete revascularization rate in the SYNTAX CABG cohort is due to the used definition. Previous studies have often based incomplete revascularization on the surgeons report without a pre-operative statement which vessels contained a significant lesion that needed treatment. In the SYNTAX trial, the heart team was obliged to state before the randomization process took place which vessels needed revascularization. Linking this statement to the actual revascularization concludes whether revascularization was complete.

The number of lesions and total occlusion were predictive of incomplete revascularization in the multivariate model, while the SYNTAX score terciles were significant in the univariate analysis. Therefore, incomplete revascularization with PCI is more likely in patients with extensive coronary disease and technically more challenging lesions. In CABG patients, incomplete revascularization was higher in patients with diffusely diseased or narrowed (<2 mm) segments distal to the lesion.

### Study limitations

We are aware that this subgroup analysis has limited power due to the methodological limitations of such analyses. The complete and incomplete revascularization subgroups were not predefined in the study protocol. We have performed and reported 10 subgroup analyses and this will produce one significant result by chance only. These results should be interpreted with caution and be considered hypothesis generating.

### CONCLUSION

At 3 years, incomplete versus complete revascularization with PCI is associated with increased rates of MACCE and repeat revascularization. In patients treated with CABG, adverse events are similar in incomplete and complete revascularization groups.

### Funding

This research was supported by Boston Scientific Corp.

### Conflicts of interest

P.W.S. and F.W.M. were the SYNTAX study principal investigators, and A.P.K. and M.-C.M were co-principal investigators. A.P.K. reports receiving consulting and lecture fees from Boston Scientific.

### REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr M. Mack (Dallas, TX, USA): My discussion is going to be limited to three questions about this study.

First of all, we were surprised at such a high rate of incomplete revascularization, at least in the CABG arm of this study. I remember sitting there with the heart team and deciding what we were intending to revascularize ahead of time. And surely this incomplete revascularisation rate is much higher than any of us thought, or that we’ve ever seen in the literature before. Is it because the intent for revascularization was decided ahead of time, rather than post hoc, that you think that it was so high in CABG?

Dr Head: I think you were spot-on there at the end, that previous studies actually had the definition of incomplete revascularization defined postoperatively, so whenever the surgeons left the OR, they would say, ‘well, I revascularized everything that I had to revascularize.’

But in SYNTAX, they had to define that preoperatively. And if, during the OR, they were revascularizing the vessel because it was, for instance, too small distally, which has also been a predictor of incomplete vascularization, they had an incomplete revascularization. So instead of doing whatever they could have done, they already missed a few vessels, so that’s why the percentage is probably higher than in other studies.

Dr Mack: The second question is that every study of both CABG and PCI has shown that the less complete the revascularization, the less good the results. But it only mattered for PCI here rather than CABG. Why do you think that is? Do you think that, for instance, incomplete revascularization with PCI was inability to open a chronic total occlusion, and in CABG it was not bypassing a small diagonal that had diffuse disease? Are there different types of incomplete revascularization that may have led to those outcomes?

Dr Head: Yes, I think so. And especially the small vessels at the end with the lesions, if they could not be revascularized, it has been said it would impact more on angina instead of survival or adverse events.

And with PCI, exactly as you say, chronic total occlusions are associated with adverse events and that’s the difference, I guess, between PCI and CABG.

Dr Mack: The third question is that now with the results of the FAME trial, looking at functional flow reserve, the concept of functionally complete revascularization rather than anatomically complete revascularization is an area of interest right now, and, at least from an interventional PCI standpoint, I think they have gone back and said that there would probably be 35 percent fewer stents placed in the PCI arm of this. What are your thoughts about this in the CABG arm? Do you think it would influence the number of grafts we place? Would the number of grafts that we end up placing be less in the future if we use FFR, and would that, perhaps, lead to less graft occlusion because of competitive flow? Any thoughts on that?

Dr Head: Well, what I understand currently is that when the trial was designed, the 50% stenosis of FFR was 0.8, which was defined as haemodynamically significant for stenosis. And I guess in the CABG, the percentage would be lower if you set the threshold maybe higher, the percentage of incomplete revascularization, but I don’t think that it would eventually have an impact on the outcomes because, as you already see now, there is no difference between incomplete and complete revascularization.

Dr D. Pagano (Birmingham, UK): Just a thought on the second question, Dr. Mack, you asked us. The literature of incomplete revascularization in coronary artery bypass grafting is actually very thin and what I do think is that show that incomplete revascularization is associated with worse outcomes. This is just a thought and I’m curious to have your counter thoughts and possibly Dr. Mack’s. It is entirely possible that the effects of incomplete revascularization by PCI are manifest earlier in the longitudinal follow-up than for coronary artery bypass grafting and you may see a difference a bit later on with the coronary artery bypass grafting, too. What do you think?

Dr Head: Well, what I understand currently is that, of course, with PCI and CABG, that PCI needs revascularization earlier than CABG. And I guess the follow-up with CABG tends to be with fewer events than PCI, especially in this trial, so we think that you are right, yes.

Dr D.P. Taggart (Oxford, UK): I think what you’ve illustrated very clearly is that when you look through the literature in cardiac surgery about incomplete revascularization, you find very conflicting answers as to what it actually is. You get papers that say it makes no difference to outcome. You get other papers that say it has a profound influence on outcome. And I think what it does illustrate is that there are two types of incomplete revascularization: there is inappropriate incomplete revascularization and there is appropriate incomplete revascularization.

So, for example, putting a fourth graft to a second small obtuse marginal will have absolutely no adverse impact on outcome, although technically it may lead to temporarily inferior results. Whereas if you leave a big vessel, which may be occluded or whatever, and you don’t graft it, that will adversely affect outcome. So I think we should try and be more accurate and define these as appropriate and inappropriate incomplete revascularization.