Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial

*Thomas Engstrøm, Henning Kelbæk, Steffen Helqvist, Dan Eik Høfsten, Lene Kløvgaard, Lene Holmvang, Erik Jørgensen, Frants Pedersen, Kari Saunamäki, Peter Clemmensen, Ole De Backer, Jan Ravkilde, Hans-Henrik Tilsted, Anton Boel Villadsen, Jens Aarøe, Svend Eggert Jensen, Bent Raungaard, Lars Køber, for the DANAMI-3—PRIMULTI Investigators**

Summary

Background **Patients with acute ST-segment elevation myocardial infarction (STEMI) and multivessel coronary disease have a worse prognosis compared with individuals with single-vessel disease. We aimed to study the clinical outcome of patients with STEMI treated with fractional flow reserve (FFR)-guided complete revascularisation versus treatment of the infarct-related artery only.**

Methods **We undertook an open-label, randomised controlled trial at two university hospitals in Denmark. Patients presenting with STEMI who had one or more clinically significant coronary stenosis in addition to the lesion in the infarct-related artery were included. After successful percutaneous coronary intervention (PCI) of the infarct-related artery, patients were randomly allocated (in a 1:1 ratio) either no further invasive treatment or complete FFR-guided revascularisation before discharge. Randomisation was done electronically via a web-based system in permuted blocks of varying size by the clinician who did the primary PCI. All patients received best medical treatment. The primary endpoint was a composite of all-cause mortality, non-fatal reinfarction, and ischaemia-driven revascularisation of lesions in non-infarct-related arteries and was assessed when the last enrolled patient had been followed up for 1 year. Analysis was on an intention-to-treat basis. This trial is registered with ClinicalTrials.gov, number NCT01960933.**

Findings **From March, 2011, to February, 2014, we enrolled 627 patients to the trial; 313 were allocated no further invasive treatment after primary PCI of the infarct-related artery only and 314 were assigned complete revascularisation guided by FFR values. Median follow-up was 27 months (range 12–44 months). Events comprising the primary endpoint were recorded in 68 (22%) patients who had PCI of the infarct-related artery only and in 40 (13%) patients who had complete revascularisation (hazard ratio 0·56, 95% CI 0·38–0·83; p=0·004).**

Interpretation **In patients with STEMI and multivessel disease, complete revascularisation guided by FFR measurements significantly reduces the risk of future events compared with no further invasive intervention after primary PCI. This effect is driven by significantly fewer repeat revascularisations, because all-cause mortality and non-fatal reinfarction did not differ between groups. Thus, to avoid repeat revascularisation, patients can safely have all their lesions treated during the index admission. Future studies should clarify whether complete revascularisation should be done acutely during the index procedure or at later time and whether it has an effect on hard endpoints.**

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Department of Cardiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark (T Engstrøm MD, H Kelbæk MD, S Helqvist MD, D E Høfsten MD, L Kløvgaard RN, L Holmvang MD, E Jørgensen MD, F Pedersen MD, K Saunamäki MD, Prof P Clemmensen MD, O De Backer MD, Prof L Køber MD); **and Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark** (J Ravkilde MD, H-H Tilsted MD, A B Villadsen MD, J Aarøe MD, S Eggert Jensen MD, B Raungaard MD)

Correspondence to:
Dr Henning Kelbæk, Department of Cardiology, Roskilde Hospital, DK-4000 Roskilde, Denmark
hkelbaek@dadlnet.dk

See Online for appendix

Introduction

In patients with acute ST-elevation myocardial infarction (STEMI), the recommended treatment is primary percutaneous coronary intervention (PCI), provided this procedure can be accomplished within a reasonable time from first medical contact.[1,2] About 40–50% of people presenting with STEMI have multivessel disease,[3,4] although most individuals are asymptomatic until the acute presentation.[5] Compared with patients with single-vessel disease, individuals with STEMI and multivessel disease have higher mortality rates and a greater incidence of non-fatal reinfarction.[6–8] It is, however, unclear whether this poorer prognosis is attributable to an increased disease burden or because relevant lesions in other areas are left untreated

Any benefits of revascularisation of lesions in non-infarct-related arteries should be counterbalanced by potential disadvantages connected with additional PCI. Meta-analyses of registry studies in the acute setting of primary PCI[9–11] have not demonstrated any clear benefit when PCI was done in arteries other than the infarct-related artery. In two large meta-analyses, including more than 40 000 patients in each,[12,13] acute multivessel PCI (done during the index procedure) was associated with the highest mortality whereas staged multivessel PCI (done at a later stage during the index admission or within 1 month) was associated with the lowest mortality. However, small

Research in context

Evidence before this study

We searched PubMed and Medline for any studies published in English, and ClinicalTrials.gov for studies ongoing or completed, in which revascularisation of the culprit vessel alone was compared with complete revascularisation in a primary percutaneous coronary intervention (PCI) setting. Our search terms were: "infarct related artery", "complete revascularisation", "culprit vessel", "primary PCI", "primary percutaneous coronary intervention", "primary angioplasty", and "ST-segment elevation myocardial infarction" or "STEMI". We identified five randomised trials. In a trial in a small cohort (di Mario), complete revascularisation at the time of primary angioplasty was compared with PCI of the infarct-related artery only, and reduced need for subsequent repeat revascularisation was noted. In the second trial, Politi compared culprit revascularisation, staged treatment of non-infarct-related arteries, and concomitant treatment of non-infarct-related arteries and showed that rates of all-cause mortality, reinfarction, readmission for acute coronary syndrome, and repeat coronary revascularisation were halved in the complete revascularisation groups, driven by readmission and the need for repeat revascularisation. In a small study (Dambrink), measurement of fractional flow reserve (FFR) to guide PCI of lesions in non-infarct-related arteries did not alter clinical outcome. In the largest study to date (PRAMI), a surprising 65% reduction in the composite endpoint of death, myocardial infarction, and refractory angina was recorded in favour of full revascularisation at the time of treatment of the index artery. Finally, in the CVLPRIT trial (Kelly), immediate or delayed complete revascularisation reduced the composite endpoint of all-cause mortality, recurrent myocardial infarction, heart failure, and repeat revascularisation, although individual components of the primary endpoint were indifferent when compared with index-vessel PCI alone.

Added value of this study

The results of the PRIMULTI trial showed that complete revascularisation guided by FFR measurement of lesions in non-culprit lesions and done 2 days after primary PCI is safe and reduces the primary endpoint. However, the effect of this staged strategy is driven by the need for repeat revascularisation.

Implications of all the available evidence

Although findings of most previous randomised trials suggest a complete revascularisation strategy is beneficial, these studies raise three questions. Does angiographic assessment of stenoses in non-infarct-related arteries offer sufficient information to select lesions for additional treatment? What is the best timing for a complete revascularisation strategy? Are reductions in endpoints sufficiently robust to mandate complete revascularisation in all patients? The findings of our trial shed light on the efficacy and safety of doing revascularisation of additional coronary lesions in a substantial population of patients. Although complete revascularisation should probably be recommended, reinterventions are mainly done on the basis of stable angina.

randomised trials show either no difference in clinical outcome or an improved prognosis in patients treated with acute complete revascularisation.[14–16] Furthermore, in the somewhat larger PRAMI and CVLPRIT trials,[17,18] a benefit in clinical outcome was reported when patients with STEMI and multivessel disease had complete revascularisation guided by angiography, rather than treatment of the infarct-related artery only.

PCI guided by measurement of the fractional flow reserve (FFR) has proven superior to PCI guided by angiography alone in patients with stable coronary disease.[19] Therefore, in a population of patients with multivessel disease who had already had primary PCI of the infarct-related artery, we aimed to investigate the effect of complete revascularisation guided by FFR measurements before discharge compared with no further invasive treatment.

Methods

Study design

The DANAMI-3–PRIMULTI trial is a part of the DANAMI-3 trial programme,[20] done at four large primary PCI centres in Denmark. The programme encompasses three randomised trials investigating the effect of deferred stenting (DANAMI-3–DEFER), ischaemic post-conditioning (DANAMI-3–POSTCON), and complete revascularisation (DANAMI-3–PRIMULTI). The study protocol, approved in Copenhagen by a central ethics committee, has been described in detail elsewhere.[20] The DANAMI-3 trial programme was undertaken in accordance with the Declaration of Helsinki. Ethics committee approval was received, according to local regulations. Data were gathered electronically and stored at the Clinical Trial Unit of Rigshospitalet.

Participants

Individuals presenting with chest pain of less than 12 h duration and ST-segment elevation greater than 0·1 mV in at least two contiguous leads were initially randomised to primary PCI done with a deferred strategy of stent implantation or mechanical postconditioning versus conventional treatment consisting of conventional primary PCI (appendix p 4). After successful treatment of the culprit lesion in the infarct-related artery (defined as a thrombolysis in myocardial infarction [TIMI] flow of 2–3 and residual stenosis <30%), members of the invasive PCI team (TE, HK, SH, LH, EJ, FP, KS, PC, ODB, JR, H-HT, ABV, JA, SEJ, and BR) asked patients with an angiographic diameter stenosis of greater than 50% in one or more non-infarct-related arteries to participate in our trial. Major exclusion criteria included intolerance of contrast media or of relevant anticoagulant or antithrombotic drugs, unconsciousness or cardiogenic

shock, stent thrombosis, indication for coronary-artery bypass grafting, or increased bleeding risk. Because of logistical limitations, two of the four study centres had to transfer patients immediately after the initial PCI procedure; thus, patients at these centres could not be included in the PRIMULTI trial. All patients provided written informed consent.

Randomisation

Immediately after the initial primary PCI procedure, we randomly assigned patients in an open-label manner to either FFR-guided complete revascularisation or no further invasive treatment (ie, PCI of the infarct-related artery only). Randomisation was done with an electronic web-based system in permuted blocks of varying size at each participating centre. The invasive PCI team had no further involvement in subsequent treatment or assessment of patients.

Procedures

For patients randomly allocated FFR-guided complete revascularisation, we did additional PCI procedures—preferably with everolimus-eluting stents because they are proven safe and efficient—2 days after the initial PCI procedure before discharge, according to local routines. We defined complete revascularisation as revascularisation of all coronary lesions not related to the initial infarct-related artery with a greater than 50% diameter stenosis in coronary artery branches of 2 mm or larger in diameter. We calculated FFR values across the lesions by intravenous adenosine infusion; we judged FFR values of 0·80 or lower significant and treated those lesions, in addition to visually estimated stenoses greater than 90%. In patients with lesions we deemed unsuitable for treatment with PCI (eg, chronic total occlusions of long duration, heavy calcification, or extreme tortuosity), we considered coronary-artery bypass surgery.

We followed up all patients at their local hospitals with a general policy of encouraging them to participate in rehabilitation programmes. All additional patients' management during admission and follow-up, including anticoagulant and antithrombotic regimens, were in accordance with contemporary guidelines and at the discretion of the treating clinicians, who were not part of the study staff and, thus, unbiased in their judgments about further examinations and medical treatment.

Study outcomes

The primary endpoint was a composite of all-cause mortality, reinfarction, or ischaemia-driven (subjective or objective) revascularisation of lesions in non-infarct-related arteries. Key secondary endpoints were components of the primary endpoint, occurrence of cardiac death, and urgent and non-urgent PCI of lesions in non-infarct-related arteries. An independent data safety monitoring board supervised safety measurements and an independent clinical events committee adjudicated all events.

We judged all deaths cardiac-related unless they could be clearly attributed to another cause, as determined by the clinical events committee. We defined reinfarction when typical chest pain was accompanied by a substantial rise in troponins, development of new Q-waves on the electrocardiograph, or both.[21]

Statistical analysis

We estimated that the primary endpoint would occur with an annual rate of 18% in patients treated for the infarct-related artery only.[22,23] With an inclusion period of 2·5 years and a minimum follow-up of 1 year, we calculated we would be able to detect a relative reduction of 30% in the primary endpoint, with a two-sided α of 0·05 and a power of 80%, by enrolling 618 patients.

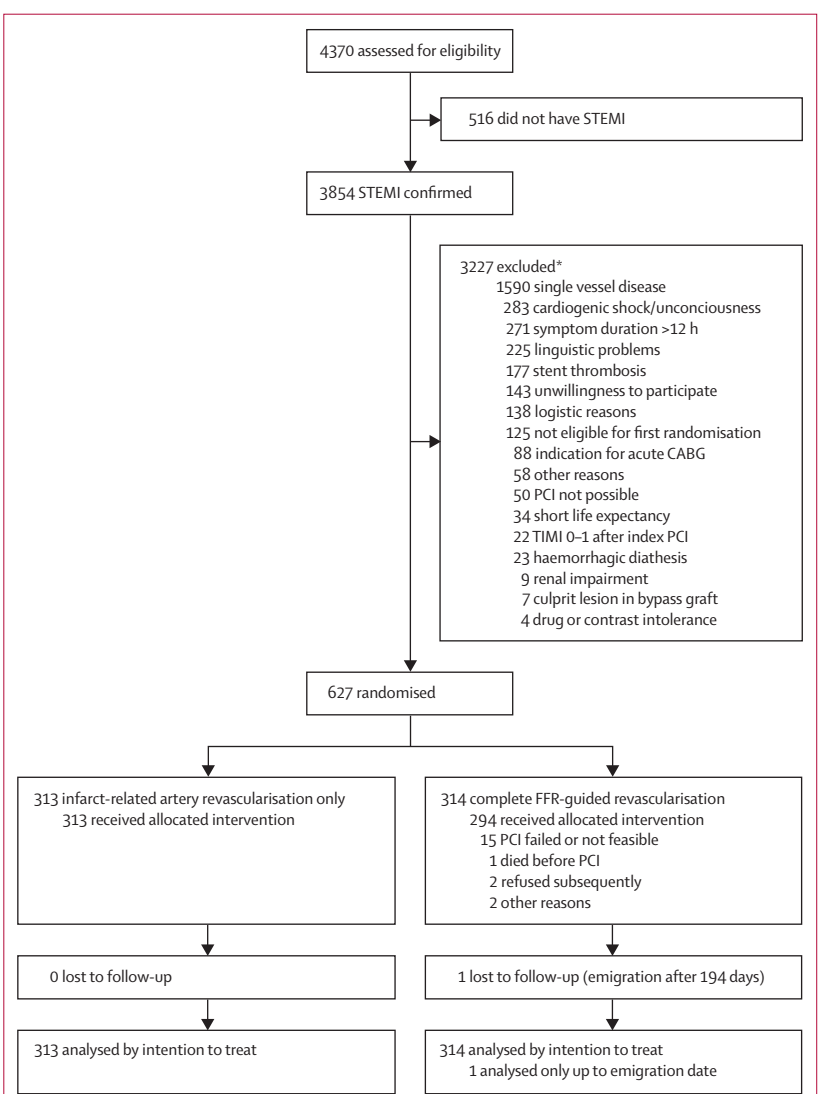

Figure 1: **Trial profile**
CABG=coronary-artery bypass graft operation. FFR=fractional flow reserve. PCI=percutaneous coronary intervention. STEMI=ST-segment elevation myocardial infarction. TIMI=thrombolysis in myocardial infarction. *20 patients met two or more criteria for exclusion.

We did analyses on by intention to treat. We assessed differences between groups in time-to-event endpoints with the log-rank test and used the Kaplan-Meier method to present survival probabilities. We calculated hazard ratios between groups with the Cox proportional-hazards model. We deemed the strength of the proportional-hazard assumption, linearity of continuous variables, and absence of interaction valid unless otherwise indicated. We assessed differences between group means and medians with Student's *t* test for unpaired samples and calculated differences between proportions with the χ^2 test or Fisher's exact test. We judged p values less than 0·05 significant.

This trial is registered with ClinicalTrials.gov, number NCT01960933.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between March, 2011, and February, 2014, 627 patients met inclusion criteria and were enrolled in the PRIMULTI trial (figure 1). 314 patients were randomly allocated complete revascularisation and 313 individuals were assigned no further invasive treatment. Baseline characteristics were well balanced between groups (table 1; appendix p 2).

Complete revascularisation guided by FFR measurements was done a median of 2 days after the initial PCI procedure (IQR 2–4). Median follow-up of all participants was 27 months (range 12–44 months), with the exception of one patient allocated complete revascularisation, who emigrated after 194 days. All patients received best medical treatment, clinical assessments (including echocardiographic control), implantation of intracardiac defibrillator (whenever indicated), and rehabilitation according to national guidelines. Procedural characteristics and management of patients at discharge did not differ between groups (table 2; appendix p 3).

Of 314 patients allocated complete revascularisation, 97 (31%) had FFR values for lesions in non-infarct-related arteries that were greater than the discrimination value of 0·80, and these individuals did not have any further invasive treatment. Moreover, six (2%) patients were judged unsuitable for PCI and had coronary-artery bypass grafting (decision made by treating clinicians). Another 18 (6%) patients did not have complete revascularisation, mainly because of failed or unfeasible PCI.

Of 313 patients assigned no further invasive treatment after primary PCI of the culprit lesion only, nine (3%) had PCI of two culprit lesions and two patients crossed

	Infarct-related artery only (n=313)	Complete revascularisation (n=314)
Median age (range, years)	63 (34–92)	64 (37–94)
Men	255 (81%)	251 (80%)
Women	58 (19%)	63 (20%)
Medical history		
Diabetes	42 (13%)	29 (9%)
Hypertension	146 (47%)	130 (41%)
Current smoking	151 (48%)	160 (51%)
Previous myocardial infarction	27 (9%)	17 (5%)
Infarct location		
Anterior	112 (36%)	105 (33%)
Inferior	179 (57%)	195 (62%)
Posterior	20 (6%)	10 (3%)
Left bundle branch block	2 (1%)	4 (1%)
Three-vessel disease	100 (32%)	97 (31%)
Stenosis on proximal portion of left anterior descending artery	86 (27%)	80 (25%)

Data are number of patients (%), unless otherwise stated.

Table 1: **Baseline characteristics**

	Infarct-related artery only (n=313)	Complete revascularisation (n=314)
Percutaneous coronary intervention		
Arteries treated per patient (n)	1 (1–1)	2 (1–2)
Implanted stents (n)	1 (1–1)	2 (1–3)
Stent diameter (mm)	3·50 (2·75–3·50)	3·00 (2·75–3·50)
Total stent length (mm)	18 (15–28)	33 (18–51)
Stent type		
No stenting	18 (6%)	12 (4%)
Bare metal	5 (2%)	4 (1%)
Drug-eluting	290 (93%)	298 (95%)
Use of glycoprotein IIb/IIIa inhibitor	72 (23%)	64 (20%)
Use of bivalirudin	234 (75%)	237 (75%)
Clinical status at discharge		
Left-ventricular ejection fraction (%)	50 (40–55)	50 (40–55)
Killip class II–IV	20 (6%)	22 (7%)
Medical treatment at discharge		
Antiplatelet drug		
Aspirin	308 (98%)	303 (96%)
Clopidogrel	38 (12%)	43 (14%)
Prasugrel	204 (65%)	194 (62%)
Ticagrelor	67 (21%)	73 (23%)
Statin	308 (98%)	310 (99%)
β blocker	285 (91%)	290 (92%)
ACE inhibitor or ARB	139 (44%)	142 (45%)
Calcium-channel blocker	36 (12%)	29 (9%)

Data are median (IQR) or number of patients (%). ACE=angiotensin converting enzyme. ARB=angiotensin-II-receptor blocker.

Table 2: **Procedural and discharge data**

over to complete revascularisation with coronary-artery bypass grafting (one patient had a left main-stem stenosis and one had three-vessel disease with lesions unsuitable for PCI). Procedure time, contrast volume, fluoroscopy time, and length of stay are reported in the appendix (p 5).

The primary endpoint occurred in 68 (22%) patients allocated no further invasive treatment and in 40 (13%) patients assigned complete revascularisation (hazard ratio 0·56, 95% CI 0·38–0·83; p=0·004; figure 2). The hazard ratios for the individual components of the composite endpoint were 1·40 (0·63–3·00; p=0·43) for all-cause mortality, 0·94 for non-fatal reinfarction (0·47–1·90; p=0·87), and 0·31 for revascularisation of non-infarct-related lesions (0·18–0·53; p<0·0001; table 3; appendix p 7). Thus, the superiority of complete revascularisation compared with revascularisation of the infarct-related artery only was driven by a 69% reduction in the need for repeat revascularisations. The 97 patients with FFR measures greater than 0·80 (who had no further PCI) did not differ from the remainder of the group allocated complete revascularisation (hazard ratio 1·54, 95% CI 0·82–2·90; p=0·18). Subgroup analyses showed a particularly pronounced reduction of the primary endpoint by complete revascularisation in young men with anterior infarction (appendix p 7). However, subgroups were too small to draw firm conclusions.

We observed no significant difference in the occurrence of cardiac-related deaths between the two groups, but 40% of repeat revascularisations were urgent, and the need for both urgent and non-urgent PCI of lesions in non-infarct-related arteries was significantly lower in the group allocated complete revascularisation (table 3). Serious adverse events related to the revascularisation procedure arose in a few patients, with no differences noted between groups (table 4).

Early events did not differ between the two groups (appendix p 8). Because of our trial design, with patients primarily randomised to postconditioning, deferred stenting, or conventional PCI, we tested for interactions with the outcome of our current study. None of the primarily allocated treatments changed the results of our current study (appendix p 9).

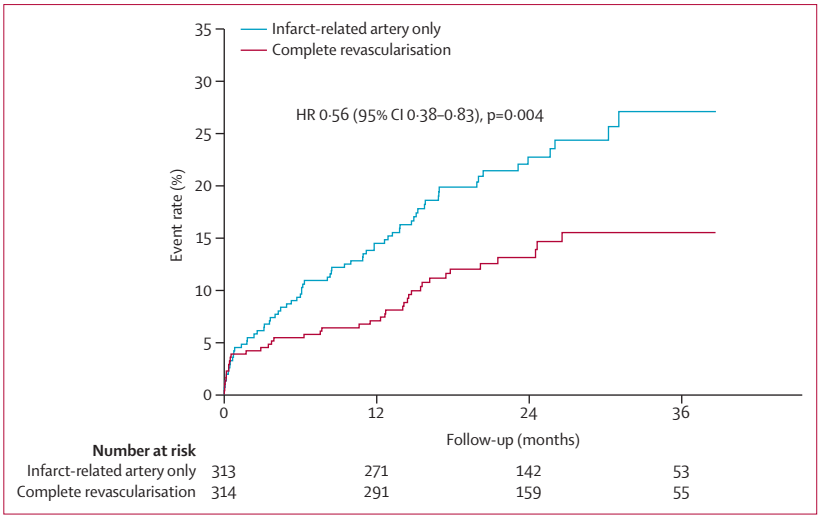

Figure 2: **Event rates of the combined primary endpoint**
Follow-up was for 44 months after primary percutaneous coronary intervention. HR=hazard ratio.

	Infarct-related artery only (n=313)	Complete revascularisation (n=314)	Hazard ratio (95% CI)	p
Primary endpoint*	68 (22%)	40 (13%)	0·56 (0·38–0·83)	0·004
All-cause mortality	11 (4%)	15 (5%)	1·40 (0·63–3·00)	0·43
Non-fatal reinfarction	16 (5%)	15 (5%)	0·94 (0·47–1·90)	0·87
Ischaemia-driven revascularisation	52 (17%)	17 (5%)	0·31 (0·18–0·53)	<0·0001
Secondary endpoints				
Cardiac death	9 (3%)	5 (2%)	0·56 (0·19–1·70)	0·29
Cardiac death or non-fatal myocardial infarction	25 (8%)	20 (6%)	0·80 (0·45–1·45)	0·47
Urgent percutaneous coronary intervention	18 (6%)	7 (2%)†	0·38 (0·16–0·92)	0·03
Non-urgent percutaneous coronary intervention	27 (9%)	8 (3%)	0·29 (0·13–0·63)	0·002
Unplanned coronary-artery bypass graft surgery	7 (2%)	3 (1%)	0·43 (0·11–1·70)	0·22

Data are number of events (%). *The first event per patient is listed. †One patient had both urgent and non-urgent percutaneous coronary intervention.

Table 3: **Clinical outcomes**

	Infarct-related artery only (n=313)	Complete revascularisation (n=314)	p
Periprocedural myocardial infarction	0	2 (1%)	0·2
Bleeding requiring transfusion or surgery	4 (1%)	1 (<1%)	0·2
Contrast-induced nephropathy (>50% rise in plasma creatinine)	7 (2%)	6 (2%)	0·8
Stroke	1 (<1%)	4 (1%)	0·2

Data are number of events (%).

Table 4: **Procedure-related complications**

Discussion

The results of the PRIMULTI trial show that patients with STEMI and multivessel disease, who have timely primary PCI, benefit from supplementary FFR-guided complete revascularisation of lesions in non-infarct-related arteries when the second procedure is done during the index admission. We reported a significant reduction in the combination of all-cause mortality, non-fatal reinfarction, and ischaemia-driven revascularisation of coronary artery lesions located remote from the culprit artery. Further, the effect on the composite primary endpoint was driven by a significant difference in reinterventions, whereas mortality or reinfarction rates did not differ between the two groups. The occurrence of serious adverse events or cardiac mortality did not differ according to treatment. Similar clinical results have been

described in a small study[15] and in the slightly larger CVLPRIT trial, the findings of which have not yet been published.[18]

In a large registry study, the clinical outcome of patients with STEMI was compared between individuals who had PCI of the culprit lesion only during the index procedure, those who had complete revascularisation before discharge, or people who had staged revascularisation of additional lesions in non-infarct-related arteries within 2 months of the index treatment.[24] Lower in-hospital mortality was found in the group treated for the culprit lesion only, whereas long-term mortality was lowest for patients who had complete revascularisation within 2 months. In our study, staged complete revascularisation seems to result in the best clinical outcome for patients with STEMI and multivessel disease, confirming the findings of large—albeit observational—studies.[12,13]

In the PRAMI trial,[17] patients with STEMI were randomly allocated either immediate and complete revascularisation of all stenotic vessels or PCI of the infarct-related artery only. The composite endpoint of cardiac death, non-fatal myocardial infarction, and refractory angina was reduced significantly by 65% in individuals allocated complete revascularisation. The idea of immediate complete revascularisation of patients with STEMI to improve prognosis is at variance with findings of a post-hoc substudy of the HORIZONS-AMI trial,[25] in which multivessel PCI done during the index procedure resulted in higher mortality than when PCI was done as a staged procedure. In the PRAMI trial,[17] most culprit lesions were located in the right coronary artery, particularly in the completely revascularised group, and PCI of lesions in non-infarct-related arteries was done predominantly in the left anterior descending artery, which was similar to our study. However, differences between PRAMI and HORIZONS-AMI with respect to inclusion of patients, the fact that PRAMI was terminated prematurely, and that patients in PRAMI were enrolled with only visually estimated additional lesions could, to some extent, account for the various findings of these trials.

In previous studies, the decision to do PCI in non-infarct-related arteries was based on angiographic judgment of lesion severity, and identification of non-culprit lesions was done in the acute setting of the primary PCI procedure. In our study, a more physiological assessment of stenosis severity was preferred, with FFR measurements of potentially significant non-infarct-related lesions 2 days after the primary PCI procedure. This delay was chosen to avoid the risk of invalid FFR measurements inferred from any acute changes in macrovascular tone or microvascular flow obstruction. Therefore, about a third of patients assigned complete revascularisation based on visual angiographic criteria in our study had lesions with FFR values above the discrimination value of 0·80, and they did not have further PCI. Others have suggested that patients with STEMI and multivessel disease might have a considerable proportion of unstable coronary lesions in addition to the identified culprit artery.[26] Thus, the importance of FFR measurements could be less pronounced, because the burden of ischaemia detected might not accord with the likelihood that vulnerable plaques will rupture and subsequently cause cardiac events. On the other hand, most of our patients did not have cardiac symptoms immediately before admittance with their first STEMI, and in these patients the lesions in non-infarct-related arteries were most likely to be chronic stable lesions. For lesions visually judged to need treatment, in which the FFR value is greater than 0·80, medical treatment seems preferable to intervention.[27]

In our study, we did not note any differences in death and reinfarction between groups; this finding does not accord with those of other trials, but it is not unexpected. These events are rare in patients who achieve more than TIMI 1 flow after successful primary PCI and do not have cardiogenic shock; our trial is not powered for these endpoints. Although the PRAMI and PRIMULTI trials represent two different treatment strategies, the results of these trials, and those of the CVLPRIT study, indicate a clinical reduction in future events by complete revascularisation during index admission. On the other hand, uncertainty remains about whether PCI of non-infarct-related vessels should be done during primary PCI (as was done in the PRAMI trial) or as a staged procedure, either during the index admission or within 2 months of primary PCI, which most large registries indicate.

Our study has some additional limitations. First, FFR measurements done during the early phase of STEMI might be affected by disturbances in microvascular function and oedema in the area. However, FFR assessments have proven reliable in such patients.[28] Second, because of the open-label design of our study, both patients and treating clinicians might have been biased towards subsequent revascularisation in individuals treated with PCI of the infarct-related artery only. Yet, all subsequent revascularisation procedures in both groups were clinically driven without consideration of the treatment group to which patients were originally assigned. Finally, because the number of participants we enrolled was limited, our study was not powered to detect significant differences in mortality or the occurrence of reinfarction. Findings of forthcoming large randomised trials will shed light on these issues, not least the COMPLETE trial (NCT01740479).

In conclusion, taken together with the findings of similar trials, the main implication of our results for daily practice is that complete revascularisation during the index admission of STEMI patients with multivessel disease reduces the risk of future events without increasing the risk of serious adverse events.

Contributors

The DANAMI-3 steering committee designed the trial. The writing committee (HK, TE, SH, LKl, DEH, and LKø) gathered data, did

statistical analyses, and wrote the report. All authors contributed to study implementation and data interpretation and approved the report for publication. Other contributors are named in the appendix (p 1).

Steering committee
H Kelbæk, T Engstrøm, D E Høfsten, S Helqvist, L Kløvgaard, H-H Tilsted, L O Jensen, H E Bøtker, and L Køber.

Clinical events committee
Kristian Thygesen (Chairman; Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark), Jørgen Jeppesen (Department of Medicine, Copenhagen University Hospital Glostrup, Glostrup, Denmark), and Anders Galløe (Department of Cardiology, Roskilde Hospital, Roskilde, Denmark).

Data safety monitoring board
Gorm Boje Jensen (Chairman; Department of Cardiology, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark), Gunnar Gislasson (Department of Cardiology, Copenhagen University Hospital Gentofte, Hellerup, Denmark), and David Erlinge (Department of Cardiology, Lund University, Lund, Sweden).

Declaration of interests
We declare no competing interests.

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References

1 Windecker S, Kolh P, Alfonso F, et al, for the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). 2014 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2014; **35:** 2541–619.

2 O'Gara PT, Kushna FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013; **127:** 529–55.

3 Kelbæk H, Terkelsen CJ, Helqvist S, et al. Randomized comparison of distal protection versus conventional treatment in primary percutaneous coronary intervention: the drug elution and distal protection in ST-elevation myocardial infarction (DEDICATION) trial. *J Am Coll Cardiol* 2008; **51:** 899–905.

4 Rasoul S, Ottervanger JP, de Boer MJ, et al, on behalf of the Zwolle Myocardial Infarction Study Group. Predictors of 30-day and 1-year mortality after primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Coron Artery Dis* 2009; **20:** 415–21.

5 Toma M, Buller CE, Westerhout CM, et al. Non-culprit coronary artery percutaneous coronary intervention during acute ST-segment elevation myocardial infarction: insights from the APEX-AMI trial. *Eur Heart J* 2010; **31:** 1701–07.

6 Halkin A, Singh M, Nikolsky E, et al. Prediction of mortality after primary percutaneous coronary intervention for acute myocardial infarction: the CADILLAC risk score. *J Am Coll Cardiol* 2005; **45:** 1397–405.

7 Sorajja P, Gersh BJ, Cox DA, et al. Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. *Eur Heart J* 2007; **28:** 1709–16.

8 Muller DWM, Topol EJ, Ellis SG, Sigmon KN, Lee K, Califf RM. Multivessel coronary artery disease: a key predictor of short-term prognosis after reperfusion therapy for acute myocardial infarction. *Am Heart J* 1991; **121:** 1042–49.

9 Cavender MA, Milford-Beland S, Roe MT, Peterson ED, Weintraub WS, Rao SV. Prevalence, predictors and in-hospital outcomes of non-infarct artery intervention during primary percutaneous coronary intervention from ST-segment elevation myocardial infarction. *Am J Cardiol* 2009; **104:** 507–13.

10 Bangalore S, Kumar S, Poddar KL, et al. Meta-analysis of multivessel coronary artery revascularization versus culprit-only revascularization in patients with ST-segment elevation myocardial infarction and multivessel disease. *Am J Cardiol* 2011; **107:** 1300–10.

11 Sehti A, Bahekar A, Bhuriya R, Singh S, Ahmed A, Khosla S. Complete versus culprit only revascularization in acute ST elevation myocardial infarction: a meta-analysis. *Cathet Cardiovasc Interv* 2011; **77:** 163–70.

12 Vlaar PJ, Mahmoud KD, Holmes DR, et al. Culprit vessel only versus multivessel and staged percutaneous coronary intervention for multivessel disease in patients presenting with ST-segment elevation myocardial infarction: a pairwise and network meta-analysis. *J Am Coll Cardiol* 2011; **58:** 692–703.

13 Bainey KR, Mehta SR, Lai T, Welsh RC. Complete vs culprit-only revascularization for patients with multivessel disease undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a systematic review and meta-analysis. *Am Heart J* 2014; **167:** 1–14, e2.

14 Di Mario C, Sansa M, Airoldi F, et al. Single vs multivessel treatment during primary angioplasty: results of the multicentre randomised HEpacoat for cuLPrit or multivessel stenting for Acute Myocardial Infarction (HELP AMI) study. *Int J Cardiovasc* 2004; **6:** 128–33.

15 Politi L, Sgura F, Rossi R, et al. A randomised trial of target-vessel versus multi-vessel revascularisation in ST-elevation myocardial infarction: major adverse cardiac events during long-term follow-up. *Heart* 2010; **96:** 662–67.

16 Dambrink J-HE, Debrauwere JP, van't Hof AWJ, et al. Non-culprit lesions detected during primary PCI: treat invasively or follow the guidelines? *EuroIntervention* 2010; **5:** 968–75.

17 Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013; **369:** 1115–23.

18 Kelly DJ, McCann GP, Blackman D, et al. Complete Versus culprit-Lesion only PRimary PCI Trial (CVLPRIT): a multicentre trial testing management strategies when multivessel disease is detected at the time of primary PCI: rationale and design. *EuroIntervention* 2013; **8:** 1190–98.

19 Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009; **360:** 213–24.

20 Høfsten DE, Kelbæk H, Helqvist S, et al, for the DANAMI 3 Investigators. The Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: Ischemic postconditioning or deferred stent implantation versus conventional primary angioplasty and complete revascularization versus treatment of culprit lesion only—rationale and design of the DANAMI 3 trial program. *Am Heart J* 2015; **169:** 613–21.

21 Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012; **60:** 1581–98.

22 Glaser R, Selzer F, Faxon DP, et al. Clinical progression of incidental, asymptomatic lesions discovered during culprit vessel coronary intervention. *Circulation* 2005; **111:** 143–49.

23 Lønborg J, Vejlstrup N, Kelbæk H, et al. Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. *Eur Heart J* 2012; **33:** 1491–99.

24 Hannan EL, Samadashvili Z, Walford G, et al. Culprit vessel percutaneous coronary intervention versus multivessel and staged percutaneous coronary intervention for ST-segment elevation myocardial infarction patients with multivessel disease. *J Am Coll Interv* 2010; **3:** 22–31.

25 Kornowski R, Mehran R, Dangas G, et al. Prognostic impact of staged versus "one-time" multivessel percutaneous intervention in acute myocardial infarction: analysis from the HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial. *J Am Coll Cardiol* 2011; **58:** 704–11.

26 Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med* 2000; **343:** 915–22.

27 De Bruyne B, Fearon WF, Pijls NHJ, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med* 2014; **371:** 1208–17.

28 Ntalianis A, Sels JW, Davidavicius G, et al. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv* 2010; **3:** 1274–81.