This supplement contains the following items:
1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes
Summary of changes from first version of the DANAMI-3 trial program to the final version of the protocol.

The Danami-3 program started with an application to the Danish Research Council with the name EDITORS. The purpose of this application was to test different clinical strategies for improving prognosis in patients with acute myocardial infarction, both STEMI and non-STEMI. The non-STEMI study is a still ongoing study of acute CT-angiography in the triage of patients with acute coronary syndrome without ST elevation in the ECG. This study is performed in Copenhagen only and has the acronym VERDICT. The STEMI study was originally planned as a study of ischemic postconditioning in addition to primary PCI. Both studies were an EastDanish initiative but during discussions with other primary PCI centres in Denmark there was interest in making the STEMI study national. When it was decided to make the study national it was decided to include additional research questions (a study of deferred stenting and a study of complete vs. culprit only revascularization). Originally, it was discussed to make a 3-arm comparison (standard direct stenting vs. deferred stenting vs. postconditioning), but as not all patients could be randomized into all 3 arms, it was decided to split this into 2 studies. During this process the name first changed to Depher and was given the Brand name DANAMI-3 (as all centres in Denmark accepted to participate). Later we added DANAMI to the name of all STEMI studies.

Enclosed, please find the application for the EDITORS grant, the first protocol from January 2010 in Danish (I apologize for this, but it is in Danish), the first protocol considered final after deciding to test several revascularization strategies, the last version of the protocol, and the statistical analysis plan for the postconditioning study. The original analysis plan is described in the protocol.

Amendments to the ethical committee only included change in wording of the informed consent pages.

Changes to the overall trial program:

- Change in name
- 'One of the 5 centers stopped performing primary PCI and could thus not be part of DANAMI-3 program.
- Cardiac mortality as part of endpoints was changed to all cause mortality.
- Angina at 1 year was only used as secondary endpoint in the complete revascularization vs. culprit only study.

Changes made to the ischemic postconditioning study were:

- 'Realizing that MRI could only be performed in a limited proportion of patients the secondary endpoint of change in LVEF was made by echocardiography using Simpsons method (in stead of wall motion index). The echocardiography was scheduled to be made after 12 months, but it turned out that a window of 12-18 months was needed, and still this analysis is only based on a proportion of patients.

Changes made to the deferred stenting study:

- Only 3 centers accepted to do deferred stenting
• A small increase in sample size. As patients with TIMI flow 2-3 could not be randomized in the ischemic postconditioning trial more patients were available for this trial.

Changes made to the complete revascularization vs. culprit only study:

• Only 2 centers were able to participate in this study for logistic reasons.
**Application Form - Danish Council for Strategic Research (DSF), March 2009**

**NOTE:** This Form is for final applications - NOT for Phase 1 applications (prequalification)

Concerning use of the form, see: DSF’s Application Guide, March 2009

| 0 | File number if applicable | 2142-09-0106 |
| File number if applicable | Applicable only to applications ensuing from an approved Phase 1 application |

*Items 1-11 are identical to the corresponding items on the Form for Phase 1 applications and may be copied from that Form and subsequently adjusted, if necessary.*

| 1 | Call | Individual, disease and Society |
| Call | State the name of the call (one only) the application concerns |

| 2 | Theme(s) | Clinical research |
| Theme(s) | State the name(s) of the theme(s) the application concerns. Only themes under the selected call may be checked. |

| 3 | Instrument (check one option only) | Strategic research centre |
| Instrument (check one option only) | Check only instruments offered under the selected themes, cf. the call (double click the check box and then select “Checked”). |
| | [x] Strategic research alliance |
| | [ ] Strategic research project |
| | [ ] Other: enter designation |

| 4 | Project title (in English) max. 180 characters incl. spaces. | EDITORS (Eastern Denmark Initiative To imprOve Revascularization Strategies) |

<p>| 5 | Project title (in Danish) max. 180 characters incl. spaces. | Østdansk initiativ til at forbedre strategier ved revaskularisering |</p>
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<td>Lars V Køber 030458-0941</td>
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<td>8</td>
<td><strong>Applicant’s position and educational qualifications</strong>&lt;br&gt;<strong>max. 39 characters incl. spaces.</strong></td>
<td>Professor in cardiology, MD, D.Sci</td>
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<td>9</td>
<td><strong>Applicant’s telephone no. and e-mail</strong></td>
<td>T: +45 35 45 22 85 E-mail: <a href="mailto:LK@HEART.DK">LK@HEART.DK</a></td>
</tr>
<tr>
<td>10</td>
<td><strong>Applicant’s workplace incl. address</strong>&lt;br&gt;Please enter the name of a Danish workplace in English as well as in Danish&lt;br&gt;<strong>If the funding applied for is to be administered by another institution/company than the proposer’s workplace, information about this must also be provided here.</strong></td>
<td>Department of Cardiology, Section 2141&lt;br&gt;The Heart Center, Rigshospitalet&lt;br&gt;University of Copenhagen&lt;br&gt;Blegdamsvej 9, DK-2100 Copenhagen&lt;br&gt;Denmark&lt;br&gt;Kardiologisk afdeling B, afsnit 2141&lt;br&gt;Hjertecenteret, Rigshospitalet&lt;br&gt;Københavns Universitet&lt;br&gt;Blegdamsvej 9&lt;br&gt;2100 København Ø&lt;br&gt;Danmark</td>
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<td>11</td>
<td><strong>Scientific keywords</strong>&lt;br&gt;<strong>Max. 5 scientific keywords to describe the research activity.</strong></td>
<td>Ischemic heart disease, acute coronary syndrome, Multi Slice CT-scan, revascularization, randomized clinical trial</td>
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<td>12</td>
<td><strong>Project duration and commencement date</strong>&lt;br&gt;<strong>State the estimated number of years and months and the anticipated commencement date</strong></td>
<td>The project can start Approximately January 1st, 2010 and will last 5 years.</td>
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</table>
**Popular-science project description (max. 1,500 characters incl. spaces)**

*Must always be completed in Danish*

Hjertesygdomme som følge af åreforkalkning er skyld i 20 mio dødsfald årlig på verdensplan, og over halvdelen af disse skyldes akutte koronare syndromer - blodprop i hjertet og ustabil angina pectoris. Aktuelle behandlingsstrategier opdeler patienterne i henhold til ændringer i elektrokardiografiske undersøgelser (EKG) og visse biomarkører. Nogle patienter tilbydes umiddelbar undersøgelse med genåbning af kranspulsåre, og andre tilbydes undersøgelse og eventuel genåbning efter en periode med medicinsk behandling. Gennem de seneste år er der udviklet en avanceret røntgenundersøgelse, som fremstiller meget detaljerede billeder af hjertet og karrene, der forsyner hjertet (Multislice CT-scanning). Denne undersøgelse har som potentielt helt at ændre behandlingsplanerne i hele verden, fordi den kan udføres meget hurtigt overalt.

1. Den første randomiserede undersøgelse vil inkludere 5000 patienter og afgøre om alle patienter med akutte koronare syndromer vil have gavn af umiddelbar undersøgelse og behandling af lukkede/forsnævredte kar.

**14 The funding applied for from the Danish Council for Strategic Research must be broken down by expense type** (as a simple summing of DSF funding across all the project’s partners; see the statements on the forms for the appendices designated “dsf1”):

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<tr>
<td>15</td>
<td>Is project funding being applied for from other sources? If so, state from which body, what amount(s) and which budget items</td>
</tr>
<tr>
<td>16</td>
<td>If the application derives from an approved Phase 1 application (prequalification), a BRIEF explanation should be given here as to the changes made compared to the Phase 1 application if any Budget has been increased by 3.1%, which is the overhead requirement. Existing equipment was included in the previous budget, but has been removed from the final version.</td>
</tr>
<tr>
<td>17</td>
<td>If the application is a renewed submission of one or more previously submitted applications (in revised form, if necessary), a BRIEF explanation should be given here, and file numbers must be stated in the case of applications for schemes under the Danish Agency for Science, Technology and Innovation. Not relevant.</td>
</tr>
<tr>
<td>18</td>
<td>If the application is linked to other grants, a BRIEF statement must be made as to the correlation/synergy, together with key data for the other grants. File numbers must be stated if applications to the Danish Agency for Science, Technology and Innovation are involved. As this study gives us a unique possibility to generate data for phd projects other foundations will be approached in order to increase the number of phd students.</td>
</tr>
<tr>
<td>19</td>
<td>Any supplementary information.</td>
</tr>
</tbody>
</table>
20 List of appendices
(see requirements in the call regarding appendices).

A. A complete budget (dsf2_editors)
B. List of PhD and postdoctoral grants (dsf4_editors)
C. List of other Scientific/Academic and Tech/Admin. staff participants (dsf5_editors)
D. Project description
E. CV
F. Statement concerning budgetary correlations
G. Detailed budgets (dsf1_Rh_editors and dsf1_Gentofte_editors)
H. None enclosed
I. Confirmation of cooperation

The applicant undertakes to notify the Danish Agency for Science, Technology and Innovation in the event of any subsequent material changes affecting the information submitted, including the amount of financing for the project or fraction thereof awarded by other sources.

The applicant hereby confirms that all the information provided herein is accurate.

<table>
<thead>
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<th>August 27, 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applicant’s signature</td>
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Danish privacy law (Danish Act on Processing of Personal Data, *Lov om persondata*, no. 429 of 31 May 2000) accords you certain rights when information concerning you is processed electronically. We therefore ask you to note the following:

1. You have the right at your request to inspect and verify information concerning you if such information is processed electronically.

2. The Programme Commission reserves the right to obtain information about any previous and current expressions of interest and applications you may have submitted to the Scientific Research Councils, The Danish Council for Strategic Research, The Danish Council for Technology and Innovation and/or the Danish Agency for Science, Technology and Innovation, and this information may be included in the processing of your application.

3. In the event that project funding is or will be applied for from elsewhere (see item 15 of the form), the Programme Commission reserves the right to obtain information as to whether the amount has been granted.

4. The Programme Commission sends applications for external assessment in the following instances: If the council/commission/committee lacks expert knowledge in a given application, where a total of more than DKK 10 million is applied for, or if a member of the commission is the principal applicant or
an associate and a total of more than DKK 1 million is being applied for or if the Commission otherwise finds it appropriate.

5. If the application is approved in whole or in part, details of the applicant’s title, name and place of employment, the names of the project partners, the project’s title and duration, key figures for the grant and the size of the grant will be published in the Danish Research Database (http://www.forskningsdatabasen.dk) and on the Danish Agency for Science, Technology and Innovation’s website (http://www.fi.dk) and in The Danish Council for Strategic Research’s publications. The popular science description of the project may be published in the same places.

6. Where relevant, in connection with the awarding of a grant, a requirement may be made for the collected data material to be submitted to Dansk Data Arkiv (DDA) in its documented state.
1. Summary

Atherosclerotic heart disease is the cause of death in 20 million people annually worldwide and over half of these cases are caused by Acute Coronary Syndromes (ACS – includes myocardial infarction and unstable angina pectoris). This study addresses key questions regarding the developing treatment of ACS. 1) Unstable angina and myocardial infarction with signs of partial blockage of coronary arteries (non ST-elevation myocardial infarction) are offered delayed invasive treatment of lesions. This study will address the value of urgent treatment. A total of 5000 patients will be randomised to either urgent treatment within hours or usual delayed treatment within days. The main potential benefit of the project is rapid treatment of patients and improved outcome. A secondary potential benefit is reduced costs of treatment secondary to increased patient flow. Thus even a neutral outcome of the project has positive implications. 2) In spite of rapid and successful invasive treatment of patients with ACS, a considerable proportion of the patients end up with severe chronic heart failure due to widespread and irreversible ischemic damage of the cardiomyocytes, i.e. reperfusion injury. Therefore, search for adjunct treatment regimens before, during, and after the revascularization (so called postconditioning, e.g. by repeated episodes of ischemia or intracoronary drug administration) are needed. A large study in 2500 patients with ACS is planned. 3) A developing radiological scanning technique (Multislice CT coronary angiography) offers rapid and complete imaging of coronary lesions that can be performed on any hospital with the apparatus and does not depend on physical presence of highly trained experts. The technique can therefore be implemented on any hospital receiving acute patients. This project will systematically examine the potential value of this technique as a first line examination of patients with ACS.

2. Objective of the project – scientific and in relation to societal/commercial aspects

The project is composed of 3 linked studies to be performed simultaneously in Eastern Denmark.

Object 1) Will patients with Acute Coronary Syndrome with signs of partial blockage of coronary arteries (non ST-elevation myocardial infarction or unstable angina) benefit from urgent revascularization compared to usual care with invasive treatment after days?

Object 2) Will patients with Acute Coronary Syndrome with signs of complete blockage of coronary arteries ST-elevation myocardial infarction) benefit from mechanical postconditioning (repeated episodes of ischemia applied after revascularization)?
Object 3) Will Multislice CT coronary angiography be able to select patients with Acute Coronary Syndrome with signs of partial blockage of coronary arteries that will benefit from urgent revascularization?

Immediately prior to invasive treatment patients will be subjected to a Multislice CT coronary angiography. The result will be kept for later analysis and not used in the immediate evaluation. Detailed analyses will then be used to determine a) whether detailed vessel analysis can detect which patients need urgent treatment of lesions b) whether detailed vessel analysis can detect which patients do not require invasive treatment. Secondary analyses will be details of atherosclerotic plaque anatomy, importance of regional myocardial damage and health economics.

3. The main results of the project

This project will answer 3 important questions. Neutral, negative as well as positive results will have implications for clinical practise in the western world.

1. Immediate revascularization of patients with acute coronary syndromes may or may not be of benefit to patients. This benefit can be in terms of decreased mortality and/or morbidity as well as shortening of length of hospital stay. If a clinical relevant benefit is demonstrated this will have immediate effects for future clinical practise.

2. Mechanical postconditioning immediately following revascularization for ACS may or may not reduce infarct size and result in a reduction in long term mortality and morbidity. Mechanical postconditioning is without any economical cost, and can be implemented instantaneously in all centers performing revascularization. Thus, a positive result will change future practise in cardiology. A neutral (or even negative) result will prevent future futile trials in the same area, and stimulate search for other tools that can reduce reperfusion injuries.

3. Multislice CT coronary angiography is being performed worldwide without proper documentation of a clinical benefit to patients or evidence based guidance for clinicians. This study will determine is multislice CT coronary angiography can be used for patient selection in the setting of acute coronary syndrome. If multislice CT coronary angiography is able to predict which patients that will benefit from immediate revascularization and who that will not benefit from immediate revascularization the technique will be justified.
for widespread use. This will decrease mortality and morbidity for patients with acute coronary syndrome, and further decrease duration of hospital stay for patients, thereby reduce costs.

4. Background and hypothesis of the project

First major hypothesis: Urgent invasive treatment of acute coronary syndromes without ST-segment elevation leads to a reduction in morbidity and mortality

Rationale

Patients with acute coronary syndromes receive medical as well as interventional treatments, all shown to reduce mortality and morbidity. However, despite this considerable reduction the remaining event rate in subjects with ACS is still many times higher than in the matched background population, leaving much room for improvements in interventional treatment within this field of medicine.

Patients with ST elevation on the ECG are considered to have complete blockage of coronary arteries and currently receive urgent reopening of vessels with balloon catheters supplemented with metal stents to prevent reocclusion. Other patients with ACS are generally evaluated invasively after a few days (average 3-5) of medical therapy. This strategy was developed because it was the only feasible one at the time of its introduction and remains the “gold standard” treatment even though some recent trials have questioned the benefit of an early invasive treatment strategy, while others have found decreasing time to angiographic evaluation to be beneficial with regards to clinical outcome. But the strategy currently used does not necessarily reflect the underlying coronary pathophysiology. Thus, at least 10% of patients with acute coronary syndrome have an occluded coronary artery but are not revascularized immediately since the ECG is without ST-segment elevation. Another 10% have very unstable coronary lesions which also are attractive candidates for immediate revascularization. Finally an unknown proportion of patients have continued damage to the myocardium while waiting for revascularization. It would therefore appear logical to test whether the majority of patients can benefit from urgent treatment. The current strategy is costly because patients wait days for treatment in addition to the direct treatment related costs. Thus, even a neutral outcome of the study with respect to patient benefit could make the new treatment attractive because of reduced costs.
Second major hypothesis: Postconditioning with repetitive ischemia in conjunction with acute revascularization of patients with ST-elevation myocardial infarction will result in reduced morbidity and mortality

Rationale

Patients with complete occlusion of a coronary artery (with ST-elevation on ECG) often develop reduced left ventricular systolic function and heart failure despite initial successful invasive therapy (percutaneous coronary intervention – PCI). This is believed to be due to widespread and irreversible ischemic damage of the cardiomyocytes, i.e. reperfusion injury. A pilot study performed at Rigshospitalet has shown a benefit of applying repeated episodes of ischemia following PCI. This will be tested in a large trial in patients with ST-elevation myocardial infarction. Presently, a pilot study of pharmacological postconditioning is being performed at Rigshospitalet. This pilot study will end in 2009. If this approach appears to be promising a combined pharmacological and mechanical study of postconditioning is planned, which can be incorporated in this project.

Third major hypothesis: Rapid CT coronary angiography will provide the rationale for selection of patients for immediate revascularization

Rationale

Multi-slice CT coronary angiography (MSCT-angio) has in recent years evolved as a non-invasive diagnostic tool for the evaluation of coronary pathology. Three dimensional images of luminal stenosis and vessel wall composition of the coronary vascular tree may be obtained with high spatial resolution. Logistically the method is simple and can be performed within 30 minutes. In contrast the current angiographic techniques the method does not involve highly trained experts for producing images. Evaluation of images requires expertise, but images can be transmitted to specialist centres for immediate evaluation. The technique therefore has the potential to detect which patients do not require further invasive evaluation, which patients require immediate evaluation and which patients who can wait for further evaluation. Currently, up to 10% of patients with ACS do not have significant stenoses. The current study is linked to the randomisation of patients with non-ST elevation Acute Coronary Syndromes and all patients transferred to Rigshospitalet or Gentofte Hospital will be evaluated with MSCT coronary angiography immediately prior to invasive procedures. The results of the MSCT will be kept for later evaluation. This study has the potential to improve patient outcome by early appropriate selection of patients for further revaluation. It also has the potential to spare patients with no or few lesions from further studies and can therefore substantially shorten their hospitalisation. Thus, the project is expected to reduce treatment costs for future patients.
5. Significance of the project for growth, development and welfare in Denmark

These projects will provide data for a rational treatment of patients with acute coronary syndromes, which affects more than 20,000 Danes each year. The average age of patients with ACS is 67 years, so many patients are still working and living an active life. Even a small reduction in mortality and morbidity may have an important influence on the percentage of patients that are able to return to work after a myocardial infarction. Secondly, a reduction in the length of hospital stay may have considerably beneficial effects on the economy of the health care system.

Postconditioning as a mechanical treatment in conjunction with acute revascularization has the potential to further reducing mortality and/or morbidity following ACS. It is inexpensive, easy to perform and can be implemented immediately in all regions in Denmark.

Multislice CT coronary angiography is being implemented in most larger hospitals. Determination of how to use this diagnostic modality will result in more timely transfer of patients to invasive centers as well as avoidance of transfer of patients that will not benefit from an invasive treatment strategy.

The initiation of this scientific alliance between the two hospitals in Eastern Denmark responsible for acute invasive treatment of patients with ACS for a population of more than 2 million Danes will result in a rational, cost-effective organization of patient management.

6. Project’s methodology and anticipated results

Randomized, clinical trials – the basis for evidence based medicine

The scheduled projects will be conducted according to the highest standard for randomized clinical trials in order to obtain conclusive evidence for future patient management. The studies are on purpose overpowered in order to give conclusive data, which will have worldwide influence.
Baseline data for all included patients will be collected in an electronic Case Report Form (eCRF), which already is developed for another study. This eCRF is webbased and does not require specific software except a pdf-reader. It has been tested and has been functioning without any problems during a 2-year period. All data will be linked to the Danish central personnel register (CPR) number for later identification. For the study of patients with ACS without ST-elevation in the ECG randomization will be performed at the local hospital. This system has performed successfully in large studies. For the study of postconditioning randomization will be performed at Rigshospitalet or at Gentofte hospital. Patients will be followed after 6 and 12 months, and thereafter yearly.

**Blood samples**

During the studies blood samples will be collected at Rigshospitalet and at Gentofte Hospital using a computer aided system to manage the samples. Samples will be used for known biomarkers ongoing, whereas samples will be stored for later analyses. These samples will be stored for future DNA analyses as well as analyses for newer biomarkers. DNA extraction is expected to be performed by international collaborators and possibly with the use of commercial organisations. This large biobank with complete clinical follow-up will be used for epidemiological research, and provide the data for some of the phd projects.

**Individual projects**

**Non-ST-segment elevation Acute Coronary Syndrome**

Over 3 years 5000 patients with ACS with signs of partial blockage of coronary arteries (non ST-elevation myocardial infarction and unstable angina) will be randomized to a) urgent treatment within hours and b) usual invasive treatment after a few days (hypothesis 1). The main outcome will be death or myocardial infarction over 5 years. Secondary outcomes will be other morbidity outcomes, quality of life and health economics. With a combined endpoint a power of more than 90% is available for comparison between the 2 arms in order to detect a clinical relevant difference. With an expected median event-free survival of 10 years, 2 years of additional follow-up after the randomization period and a power of 80%, 1344 patients in each arm is needed in order to show a relative benefit of 20% (two-sided test).

Anticipated results and implications: If a reduction in mortality and/or morbidity is obtained by the more aggressive approach this will result in a shift in treatment strategy of patients with ACS. This will lead to a more comprehensive workload acutely, but will be followed by a shorter hospital stay in total, and for this reason a reduction in costs. It is anticipated that this study will result in
one publication in a major international medical journal (i.e. New England Journal of Medicine or Lancet) and at least 3 other publications in peer-reviewed journals of high impact. However, irrespectively of the results the study will result in a clear guidance whether immediate revascularization is beneficial in terms of clinical outcome or a reduction in length of hospital stay.

**Postconditioning in ST-segment elevation Acute Coronary Syndrome**

More than 2000 patients with ACS and suspected complete blockage of a coronary artery (ST-elevation myocardial infarction) will be randomized to a) postconditioning following acute reperfusion with PCI and b) usual care following PCI (hypothesis 2). The main outcome will be death or myocardial infarction over 5 years. Secondary outcomes will be other morbidity outcomes and left ventricular systolic function measured. A median event-free survival of 6 years corresponding to a yearly event rate of 10% is expected. With risks of type 1 and 2 errors on 5% and 20%, respectively, a reduction of a combined end point of 25% during additional 2-year follow up can be detected with 518 patients in each group.

Anticipated results and implications: This study may result in an inexpensive tool for further reduction in mortality or morbidity for patients with ST-elevation myocardial infarction. A positive result favouring postconditioning can be implemented immediately, as the technique does not require additional equipment or training. Secondly, implementation will be without increase in cost per procedure, as the extra time required is approximately 5 minutes. This study is intended to be published in New England Journal of Medicine or Lancet, and 2 or more additional publications in peer-reviewed journals of high impact will be made.

**Accelerated Non-invasive diagnostic testing in patients with ACS – Multislice CT coronary angiography**

Immediately prior to invasive treatment patients will be subjected to a Multislice CT coronary angiography – for urgent patients as well as delayed patients (when transferred a few days after hospital admission). The result will be kept for later analysis and not used in the immediate evaluation. Detailed analyses will then be used to determine a) whether detailed vessel analysis can detect which patients need urgent treatment of lesions b) whether detailed vessel analysis can detect which patients do not require invasive treatment (hypothesis 3). Secondary analyses will be details of atherosclerotic plaque anatomy, importance of regional myocardial damage and health economics. A recent study performed at Rigshospitalet suggests that this technique can be used to determine which plaques in the coronary artery that is unstable.
The study will be performed using the recently developed 320 slice CT-scanner at Rigshospitalet. The unique features of this latest generation of scanners include image acquisition within one heart beat which reduces motion artefacts and allows imaging of patients with irregular heart beats. Furthermore, as helical oversampling is reduced compared to older 64 slice scanners the patients irradiation is substantially reduced to the 4-6 mSv range, which is considerably below a conventional coronary angiography. At Gentofte hospital the study will start on a 64 slice CT-scanner, but a 320 slice CT-scanner will most likely be available during 2010. The image quality is acceptable with this scanner, but irradiation is slightly higher (10-15 mSv).

This study is performed as part of the study on patients with non-ST-elevation myocardial infarction described above. All patients are examined with MSCT coronary angiography after arrival in the invasive centre. A sample of more than 5,000 patients with MSCT can be obtained over 3 years. The power of the outlined study is more than 95% to detect clinical meaningful differences overall, and above 80% in individual studies.

Anticipated results and implications: The outlined studies will reveal whether MSCT coronary angiography set in the first line of examination of patients with coronary artery disease will improve the management and prognosis of patients with acute coronary syndromes. Similarly, this study is intended to be published in New England Journal of Medicine or Lancet, and several publications in peer-reviewed journals of high impact will be made focusing on the findings by MSCT coronary angiography.

7. Project plan

Prior to study start

Ethical approval of the project will be obtained during 2009.

Data Protection Agency approval is obtained.

It is anticipated that results of this application is available in December 2009, making it possible to start from January 2010.
Year 1

The initial 3 months will be used for arrangement of logistic details. This will include employment of technical personnel for CT-scanning, for assistance of study procedures (blood samples etc.) and make the final structure of the electronic database. The first milestone for the project will be inclusion of the first patient after 3 months.

Final agreement with the Advisory Board will be made during the initial 3 months, and first meeting will be scheduled spring 2009.

During the second half of 2009 phd students will be identified and arrangements for employment will be made.

Year 2

As data should be available in order to complete the phd’s the first 2 phd students will start in 2011. Arrangements for additional analyses of biomarkers and potentially DNA extraction will be made. Preparation of a data analyses plan will be made.

Year 3

Additional analyses of blood samples will be started. Data analyses will begin in order to ensure that relevant data are ready for the different populations as inclusion ends.

Year 4

Inclusion period ends, which will an important milestone. Analyses of the baseline populations are available, and manuscripts are produced based on this.

Year 5

Analyses of the primary endpoints performed, and results disseminated in terms of presentations on congresses and publications.
### Abbreviated Gantt diagram.

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TAP=technical/administrative personnel

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8. **Project’s international dimension**

The treatment of patients with acute coronary syndromes offers both great opportunities and considerable challenges for international health care systems. While treatments and diagnostic equipment must be safe, reliable and easy to implement and maintain, they should also offer "good value for money". Danish experiences in such areas would be relevant for other countries. The results of the proposed trials will have international influence on future treatment of patients with acute coronary syndromes.
A pivotal part of this collaboration is the use of multislice CT coronary angiography as part of frontline patient assessment. This will be performed in close collaboration with Professor Jeroen Bax from the CT-unit at Leiden Hospital in The Netherlands. Two PhD students are planned to be working on this project, one in Leiden and one in Denmark. A post Doc from Leiden are encouraged to work on the project in Copenhagen as part of the quality control of the CT-scans.

The research group will present preliminary results at international meetings and conferences.

The invasive treatment strategy is outlined in collaboration with Professor Magnus Ohman from Duke medical center, who is international member of the Advisory Board. Conversely, at least 2 of the other phd students are expected to work 6-12 months at the Duke Medical Center, NC, USA.

9. Legal and ethical aspects

The strategic alliance will perform pivotal trials in acute coronary syndromes. Currently many patients are being treated by invasive procedures based on retrospective analysis, data from registries or even individual operators discretion. We aim to randomize patients to regimens currently being employed without the proper scientific documentation. No patients will be submitted to intervention hitherto know to be of harm. Radiation exposures will be kept to a minimum based on the documented experience of these high volume centers. Radiation will be monitored throughout the study. The steering committee will publish all relevant findings of the program regardless, whether it be positive, neutral or negative for the treatment in question. All patients will provide written informed consent prior to study entry, and can withdraw from the study at any time. The informed consent form will be prepared according to current guidelines from the Danish authorities. The Data Safety and Monitoring Board (DSMB) will have predefined rules for stopping one or more of the treatment arms in the case of unexpected adverse outcomes.

The studies will be conducted according to the World Medical Association Declaration of Helsinki: “Ethical Principals for Medical Research Involving Human Subjects” (Adopted in 1964 (Helsinki) and revised in 1975 (Tokyo), 1983 (Venice), 1989 (Hong Kong), 1996 (Somerset-West) and 2000 (Edinburgh)).

10. Publication and promotional strategy
All results from the study will be published in international peer reviewed scientific journals. It is expected that the 3 main hypothesis will generate separate publications in the papers with the highest impact factor.

Within the budget are 6 phd projects focused on Multislice CT coronary angiography, non-ST segment elevation ACS and ST-segment elevation ACS. Results will be presented at major conferences, and when results have public interest simultaneously in Danish lay press. Within the timeline of the main studies these PhD theses and accompanying papers will be published/submitted and the PhD theses written.

It is the intention that the database created for these studies will be updated for many years and used for additional phd’s not budgeted in this application. Other foundations will be approached in order to get additional funding for this. Similarly, the biobank is intended to be used for future publications as well. Separate funding for later analyses will be necessary, but is expected to be achieved when the clinical database has proven its value.

11. Exploitation of results

Dissimination of results will be through scientific journals and whenever possible also the lay press as described above.

As results from the study emerge the Tech-Trans unites of the hospital region (Region H) will be contacted in order to exploit if patenting of ideas are possible. If unique features of postconditioning can be identified this has a relevant potential for patenting.

12. The participating parties

Department of Cardiology at Rigshospitalet and at Gentofte Hospital are together responsible for all invasive treatment of acute coronary syndromes in Eastern Denmark. Patients are transferred from refferral hospitals by ambulance (or helicopter). Both departments are part of University of Copenhagen, and are used to perform large scale interventional trials according to good clinical
practice. The referring hospitals are used to participate in a similar set-up for clinical trials, and it is very attractive to participate, as a substantial number of patients are transferred earlier than normally. Senior consultants will perform invasive treatments according to the protocol, and trained research staff is available. Together the departments have more than 20 phd students associated.

The applicant and professor Christian Torp-Pedersen both have extensive experience in the conduct of large clinical trials and in clinical epidemiology based on registry data.

Ass. Prof. Henning Kelbæk has extensive expertise in studies of invasive treatment of patients with acute coronary syndrome and postconditioning.

Ass. Prof. Thomas Engstrøm has extensive expertise in studies of invasive treatment of patients with acute coronary syndrome and postconditioning.

Ass. Prof. Jan Skov Jensen has extensive experience in epidemiology, invasive treatment of coronary artery disease and acute coronary syndrome.

Ass. Prof. Peter Clemmensen has extensive expertise in invasive and non-invasive studies of patients with acute coronary syndrome.

Ass. Prof. Jan Kyst Madsen has extensive experience in experimental invasive treatment, invasive treatment of coronary artery disease and acute coronary syndrome.

Ass. Prof. Lene Holmvang has extensive experience in experimental invasive treatment, invasive treatment of coronary artery disease and acute coronary syndrome.

Ass. Prof. Klaus Kofoed has extensive experience in clinical studies of ischemic heart disease and Multislice CT angiography.
Professor Jeroen Bax from Leiden University represents the highest expertise in cardiovascular imaging, including Multislice CT coronary angiography.

13. Project management

Administrative organisation

The scientific collaboration is organized with a Board of Directors, a Steering Committee (SC) for each of the 3 planned main studies, an international Advisory Board, a Data Safety and Monitoring Board (DSMB) and an Events Committee (EC). For each SC there will be a committee for substudies and PhD programmes. All projects based on the data from the project require approval by the steering committee.

For each scientific study to be conducted the steering committee overviews that appropriate approvals from ethical committees are obtained and that data as well as samples are used as approved.

The Board of directors meets with the Steering Committees once yearly. The joint Steering Committee meets every 3 months. All investigators including students and national/international collaborators meet once yearly. The DSMB will establish their own guidelines as their main responsibility is patient safety.

The international advisory board consists of Danish members from the SCs and invited international experts. Professor Jeroen Bax from Leiden University and Professor Magnus Ohman from Duke medical center has accepted participation, and additional experts have been approached for participation.

Primary responsible persons for the individual studies:

Non-ST-elevation myocardial infarction and urgent revascularization: Henning Kelbæk, Lene Holmvang and Peter Clemmensen.
ST-elevation myocardial infarction and postconditioning: Jan Skov Jensen and Thomas Engstrøm.

Multislice CT: Klaus F. Kofoed and Jeroen Bax.

Data management: Christian Torp-Pedersen and Lars Køber.

Data Safety and Monitoring (DSMB): Local experts and international participants

Events Committee (EC): Local experts, experienced from previous committees.

Each SC will include members from participating hospitals and relevant experts.

The administrative core will handle patient logistics, meetings, budget, newsletters and will require a full-time employed person. Data management will employ an established internet based reporting system compliant with good clinical practice. An independent statistician will provide regular reports for the DSMB.

**Database Management**

Collection of data will be performed at Gentofte and at Rigshospitalet. An electronic case report form has been developed for data entry. Patients will be followed yearly for at least 5 years, and a regular search in the Danish central personnel register will be performed in order to identify deceased patients.

**14. Network function**

The scheduled project is an alliance between the 2 departments in Eastern Denmark that treats patients invasively with ACS. The project will coordinate their activity, which will be of considerable logistic benefit.

The cooperation with Professor Jeroen Bax, the director of non-invasive imaging and director of echo-lab in the Department of Cardiology at University of Leiden will be very important. The University of Leiden is leading within the area of multislice CT coronary angiography.

**15. Key references**
Reference List


(9) Thomsen Lonborg J et al. The Cardio Protective Effect of Mechanical Postconditioning in Patients Treated With Primary Percutaneous Coronary Intervention, Evaluated With Magnetic Resonance. 2009. Abstrac ACC.


DEferred stenting, PostHoc conditioning and completE Revascularisation in primary percutaneous coronary intervention

Acronym: DEPHER

A randomised comparison of the clinical outcome after deferred stent implantation or postconditioning versus conventional treatment and complete revascularisation versus treatment of the infarct-related lesion only in patients with ST-elevation myocardial infarction

En undersøgelse af om en ændret metode til indsættelse af stent og behandling af alle forsnævringer i kranspulsårerne har gavnlig effekt sammen-lignet med vanlig behandling hos patienter med akut blodprop i hjertet

PROTOKOL
Januar, 2010
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1. Ved deferred indgreb efter stentimplantation
2. Efter afdelingens rutine
3. 500 patienter
4. 300 patienter
1. BAGGRUND

Perkutan coronar intervention (PCI) med trombektomi og stent implantation er den mest effektive form for behandling af patienter med ST-elevations myokardie infarkt (STEMI), fordi den både reducerer forekomsten af re-infarkt og bedrer prognosen sammenlignet med behandling med fibrinolyse (1-3). Stent implantation per se synes ikke at ændre prognosen, mens indikationen for anvendelse af drug-eluting stents eller bare-metal stents hos denne patientkategori ikke synes fuldt afklaret (4-7). Til trods for tilsyneladende vellykket revaskularisering af den epikardielle del af det okkluderede kar, ses distal embolisering hos 5-10% af patienterne, hvilket ligesom mikrovaskulær dysfunktion er forbundet med forværret prognose (8-11). Det er uvist om forstyrrelserne i mikrocirkulationen udelukkende skyldes distal embolisation fra det infarcerede område, men forsøg på at undgå embolisation ved anlæggelse af distale protektions devices har ikke vist sig effektive (12,13). Trombektomi har i nogle studier vist sig at bedre prognosen, i andre at øge infarktubredelsen (14,15). Hos en vis del af patienter med STEMI, som behandles med primær PCI ses sekundær ST-elevation under forløbet af den primære PCI-procedure. Det er muligt at udskyde af tidspunkt for implantation af stent ("deferred stenting") kan begrænse risikoen for embolisation og dermed bedre prognosen. En væsentlig årsag til at infarktudbredelsen i forbindelse med primær PCI i visse tilfælde forværres, er forekomsten af reperfusionsskade (16). Dette fænomen synes i nogle nyere studier at kunne begrænse hvis det infarcerede område iskæmi-konditionerer umiddelbart i tilslutning til den revaskulariserende procedure (17). Den gunstige effekt af per- og postkonditionering har i nogle studier vist sig kun at kunne påvises i visse dele af myokardiet (18,19). Cirka 40 % af patienterne med STEMI lider af flerkar koronarsygdom, dvs. signifikante stenoser på mere end én af de store epikardiale koronararterier eller deres betydelige sidegrene, hvorforskæn kun ét koronarkar er relateret til det akutte infarkt (20). De flerkarsyge patienter udviser højere sygelighed og dødelighed efter primær PCI (21,22). En tidlig, komplet revaskularisering af disse patienter kunne således tænkes at reducere disse patienters risiko. Ulemperne ved konsekvent behandling af de ikke infarkt-relaterede forsnævringen kan være tidlige og sene komplikationer i forbindelse med PCI og stenting, i form af procedurerelateret infarkt, stent restenose og stenttrombose. Der er ikke gennemført publicerede prospektive, randomiserede undersøgelser til at belyse spørgsmålet, og data fra 3 registeranalyser har vist modstridende effekt af tidlig komplet revaskularisering på såvel død som gentagen revaskularisering (23-25).

2. FORMÅL
Formålet med projektet er at vurdere om det gængse perkutane indgreb ved ST-elevations myokardieinfarkt forbedres dels ved at udsætte tidspunktet for stent implantation i 3 dage, dels at foretage postkonditionering med gentagne ballondilatationer i det infarkt-relaterede karket m.h.p. at mindske risikoen for akutte flowforstyrrelser perifert for index-læsionen og dermed begrænse myokardieskaden. Desuden ønskes belyst om det bedrer prognosen at foretage komplet revaskularisering af patienter som har flere læsioner end den infarkt-relaterede (index-) sammenlignet med kun at behandle index-læsionen.

3. STUDIE-DESIGN

Prospektiv, randomiseret undersøgelse, som udføres på danske interventionskardiologiske centre. I alt 1500 patienter vil blive randomiseret afhængig af TIMI flow ved indledningen af index-proceduren som følger:

Når der er givet udførlig mundtlig og skriftlig information og indhentet samtykke, randomiseres til et projektnummer. Herefter foretages KAG

- ved TIMI flow 0-1 som øges til 2-3 efter wireplacering/trombektomi/ballondilatation randomiseres 1:1:1 til enten a) konventionel behandling, b) mekanisk postkonditio-nering, eller c) deferred stenting.
  
- Ved TIMI flow 2-3 ved ankomst randomiseres 1:1 til a) konventionel behandling eller c) deferred stenting
  
- Ved TIMI flow 0-1 som først øges til 2-3 efter stent implantation kan randomiseres til a) konventionel behandling eller b) mekanisk postkonditionering. Øges TIMI flow ikke fra 0-1 ekskluderer patienten sekundært.
  
  a) Konventionel behandling: evt yderligere ballondilatation m.h.p. stent implantation
  
  b) Mekanisk postkonditionering: der dilateres (proximalt i karret) med okkluderende ballon i 4 perioder á 30 sekunder med 30 sekunders pause efterfulgt af stent implantation
c) Der tilsigtes residualstenose <90% og TIMI flow 3, om nødvendigt ved gentagne dilatationer med ballon, hvis diameter er < karret reference diameter (kan undlades ved ankomst TIMI flow 2-3 og stenose <90%) . Efter 3-4 dage foretages re-KAG og ved residualstenose >50% stent implantation.

- Der foretages sekundær randomisering 1:1 af patienter med flerkarsygdom m.h.t. selektiv versus komplet revaskularisation. Dette fordrer 1) succesfuld revaskula-risering af index-læsion, 2) >50% diameter stenose af andre kar end index-læsionen, 3) læsion i kargebet 1-8 (RCA, PDA og LAD), 11-13 (Cx), eller kardiameter >2.0 mm.
- Randomiseres til fuld revaskularisation foretages ved >90% diameter stenose PCI, ved 50-90% diameter stenose FFR-måling og kun PCI ved værdi <0.80.

4. ENDEPUNKTER

4.1 Primære endepunkt for Depher/Postcon-del:
   o En kombination af kardiel død, myokardieinfarkt, eller indlæggelse på grund af venstresidig hjerteinsufficiens (inden for 3 år)

Primære endepunkt for Komplet / IRA revaskularisering-del:
   o En kombination af kardiel død, myokardieinfarkt, eller TLR (indenfor 1 år)
   o Anginastatus efter 1 år

4.2 Sekundære endepunkter
   o Størrelsen af index-myokardieinfarktet i forhold til det truede område bedømt ved MR-scanning efter 1 måned
   o Kardiel død, myokardieinfarkt, gentagen revaskularisation og forekomst af ”definite” stenttrombose i henhold til ARC definition inden for 1 år (26)
   o TIMI-flow ved procedureslut
   o ST-resolution – komplet ved 90 min
   o Wall motion index (WMI) bedømt ved ekkokardiografi efter 1 år
   o Livskvalitet
5. **STUDIEPOPULATION**

Patienter med 1.gangs ST-elevations myokardieinfarkt

5.1 **Antal patienter**

I alt 1500 patienter vil blive inkluderet på danske interventions kardiologiske centre i løbet af ca et år. Antallet kan øges til 2500, hvis Styringskomitéen skønner det nødvendigt.

5.2 **Inklusionskriterier**

1. Alder ≥18 år
2. Akut indsættende brystsmerter af < 12 timers varighed
3. ST-segment elevation ≥ 0.1 mV i ≥ 2 tilstødende afledninger eller dokumenteret nyopstået venstresidig grenblok.

5.3 **Eksklusionskriterier**

1. Graviditet
2. Kendt intolerance over for acetylsalicylsyre (ASA), clopidogrel, heparin eller kontrastmiddel, som ikke kan modvirkes medicinsk
3. Ude af stand til at forstå informationen/afgive informeret samtykke
4. Hæmorragisk diatese eller kendt koagulopati

Der vil blive ført en screeningslog på hvert enkelt center.

6. **STUDIEPROCEDURER**

6.1 **Patientinformation**

6.2 Randomisering
Patienterne randomiseres afhængig af TIMI flow forløb i den infarkt-relaterede arterie:

- Ved TIMI flow 0-1 før PCI som øges til TIMI 2-3 efter wiring/trombektomi/ballondilatation randomiseres til én af 3 grupper:
  a) Konventionel primær PCI med akut stent implantation.
  b) Primær PCI med mekanisk postkonditionering (se nedenfor)
  c) Primær PCI med deferred stent implantation (se nedenfor)


- Ved TIMI flow 2-3 før PCI randomiseres til én af 2 grupper:
  a) Konventionel primær PCI med akut stent implantation.
  c) Deferred stent implantation

- Der foretages sekundær randomisering 1:1 af alle patienter med flerkarsygdom med henblik på forsøg på komplet perkutan revaskularisering eller kun revaskularisering af den infarkt-relaterede arterie.

  Allokeringsplanen vil blive baseret på computergenererede vilkårlige tal med blokrandomisering centervis.

6.3 Procedure og behandling
Primær PCI udføres efter gældende retningslinier med medicinsk regime som anført nedenfor.

*Initialt TIMI flow 0-1*
Hos patienter med initalt TIMI flow 0-1 udføres rekanalisering med fortrinsvis floppy guidewire, trombeaspiration med sugekateter og ballonangioplastik med compliant ballon med diameter < karrets reference.

Såfremt TIMI flow øges til 2-3 foretages randomisering som anført ovenfor.
Hos patienter, der randomiseres til deferred stenting kan suppleres med ballon angioplastik med underdimensioneret ballon for at sikre TIMI-3 flow. Der arrangeres re-KAG efter 3-4 dage med henblik på vurdering af index-læsionen og behov for stent implantation, som kan undlades, hvis der er < 50% stenose af mindsket trombebyrde i forhold til index-proceduren.

Hos patienter randomiseret til postkonditionering foretages umiddelbart efter at flow er øget til TIMI 2-3, gentagne inflationer med okkluderende ballon (proximalt i karret) i alt 4 gange å ¥½ minut med ¥½ minuts reperfusion, hvorefter der foretages stent implantation. Operatøren afgør hvilken stent type, der vælges. Dog tilstræbes det at der anvendes drug-eluting stent i kar med reference diameter < 3.0 mm, samt hvor læsionen involverer sidegren.

Hos alle patienter randomiseret til konventionel behandling foretages stent implantation. Operatøren afgør hvilken stent type, der vælges. Dog tilstræbes det at der anvendes drug-eluting stent i kar med reference diameter < 3.0 mm, samt hvor læsionen involverer sidegren.

Hos patienter med initialt TIMI flow 0-1, som ikke øges efter wiring, trombeaspiration og ballonangioplastik, kan efter sikring af korrekt wire beliggenhed, overvejes stent implantation, og hvis dette medfører flow-øgning, randomiseres 1:1 til postkonditionering eller konventionel behandling.

Patienter med initialt TIMI flow 0-1, hvor ingen af ovenstående manøvrer øger flow, ekskluderes sekundært.

Initialt TIMI flow 2-3
Hos patienter med initialt TIMI flow 2-3 randomiseres 1:1 til deferred stenting eller konventionel behandling.

Hos patienter, der randomiseres til deferred stenting, kan suppleres med ballon angioplastik med underdimensioneret ballon for at sikre TIMI-3 flow. Der arrangeres re-KAG efter 3-4 dage med henblik på vurdering af index-læsionen og behov for stent implantation, som kan undlades, hvis der er < 50% stenose af mindsket trombebyrde i forhold til index-proceduren.
Hos alle patienter randomiseret til konventionel behandling foretages stent implantation. Operatøren afgør hvilken stent type, der vælges. Dog tilstræbes det at der anvendes drug-eluting stent i kar med reference diameter < 3.0 mm, samt hvor læsionen involverer sidegren.

Inden (endelig) udskrivelse foretages ekkokardiografi med bestemmelse af wall motion index (WMI) (27) samt kardiel MR-scanning (19) for at fastlægge hvor stor en del af myokardiet, der har været truet.

Hos patienter med visuelt bedømt signifikante (>50% diameter) stenoser udover den infarkt-relaterede, foretages sekundær randomisering til 1) ingen yderligere behandling eller 2) yderligere vurdering m.h.p. komplet revaskularisering. Inden (endelig) udskrivelse foretages re-KAG m.h.p. vurdering af alle ikke-okkluderede kar med FFR. Kan patienten komplet revaskulariseres eller bringes til 1 kar sygdom, foretages PCI. Ved øvrig flerkarsygdom overvejes CABG.

### 6.4 Antikoagulerende og antitrombotisk medicin

**Inden indgreb**
10.000 IE ufraktioneret heparin, ASA mindst 300mg (hvis patienten ikke er i ASA behandling i forvejen), 600 mg clopidogrel eller 60 mg prasugrel.

**Under indgreb**

**Efter indgreb**
Clopidogrel vedligeholdelsesdosis 75 mg dagligt eller Prasugrel 10 mg dagligt i mindst 12 måneder. ASA livslangt

Regimerne kan modificeres afhængig af afdelingsinstruks

### 7. OPFØLGNINGSPERIODE

Efter hospitalsudskrivelse vil patienter blive fulgt op til 5 år efter index-proceduren. Det vil inkludere 2 ambulante kontakter, hvor der foretages henholdsvis kardiel MRscanning og ekkokardiografi og indhentes information om, hvad patienten tager af kardiovaskulærmedicin, og om der har været hospitalisindlæggelser interkurrent.
7.1 3 måneder efter indgreb
Hos 500 patienter (uden klaustrofobi og/eller metalimplantat herunder ICD-enhed) foretages MR-scanning for at bestemme den endelige infarktudbredning (herunder shrink).

7.2 1 år efter indgreb
En vurdering af angina status (i henhold til CCS og Braunwald klassifikation), medicinindtag og eventuelle hjerteterelaterede hændelser. Der foretages ekkokardiografi med WMI bestemmelse, og hos 300 patienter foretages spørgeskemaundersøgelse m.h.p. livskvalitet.

7.3 3 og 5-år efter indgreb (± 30 dage):
Mortalitet og udvikling af venstresidig hjerteinsufficiens vurderes via landspatientsregistret og/eller hospitalernes registre over indlæggelser.

8. STATISTISK ANALYSE

På basis af tidligere lignende studier af patienter med STEMI behandlet med primær PCI forventes at patienter behandlet med konventionel primær PCI har en forekomst af det primære endepunkt, kombinationen af kardiel død eller udvikling af hjerteinsufficiens, på 14% indenfor 1 år. For at påvise en 40% reduktion i endepunktet (til 8.4%) kræves inklusion af ca 500 patienter i hver gruppe (styrke 80% og type 1 fejls risiko 5%). Der kalkuleres ikke med frafald i den kliniske opfølgen, så 1500 patienter søges inkluderet. Endepunkter analyseres med log-rank test og Cox regression som sekundær analyse.

9. ØKONOMI

Der er indhentet tilsagn om økonomisk støtte til ansættelse af forsknings personnel fra offentlige fonde og midler fra sygehusene. Ingen støtteyder har interessekonflikt med hensyn til studiets udfald. Der ansøges separat om løn til 1 forskningssygeplejerske per center i projektperioden. Forskningsansvarlige har ingen økonomisk tilknytning til støttegiver.

10. DATATILSYNET
Studiet anmeldes til og udføres i overensstemmelse med regler udarbejdet af Datatilsynet

11. PUBLIKATION

Resultaterne vil blive publiceret uafhængig af projektets udfald.

12. ETISKE ASPEKTER

Der er kun få etiske problemer i forbindelse med behandlingsdelen af projektet eller de opfølgende undersøgelser herunder ekkokardiografi og MR-scanning. Der kan hos patienter, som trækker "defer"-armen være en let øget risiko for blødning fra indstiksstedet i forbindelse med re-interventionen. Dette anses til fulde at blive opvejet af en mulig fordel ved at undgå nedsat flow under index-proceduren. Der er ikke i tidligere studier observeret komplikationer til posthoc konditionering med gentagne ballondilatationer. Patienterne informeres såvel mundtligt som skriftligt i henhold til bekendtgørelse fra Forskningsministeriet og inkluderes kun ved samtykke. De etiske overvejelser gælder derfor udelukkende tilladelse til at anvende patienternes data i projektsammenhæng. Studiets resultater forventes at være til gavn for fremtidige patienter med akut opstået stor blodprop i hjertet.
13. LÆGMANDSBESKRIVELSE

Ballonudvidelse med opsugning af blodpropsmateriale samt indsdættelse af et metalgitter (en stent) i kranspulsårevæggen er en effektiv behandling hos patienter med en akut opstået stor blodprop i hjertet. Selv om behandlingen umiddelbart kan se ud til at være velgennemført, findes hos en del af patienterne en sværere funktionsnedsættelse af hjertemusklen end forventet, og dette fænomen er forbundet med en dårligere prognose. Dette fænomen kan formentlig begrænse ved at det truede område i hjertet "konditioneres" umiddelbart efter at karret er åbnet. Konditionering foregår ved at den ballon, som åbnede karret udvides flere gange efter hinanden. Noget tyder på at funktionsnedsættelsen til en vis grad skyldes at en del af blodproppen forskydes ned i karret, idet fjernelse af hele eller dele af blodproppen med et suge-kateter kan bedre forløbet for nogle men ikke alle patienter. Det er muligt at udskyde af tidspunkt for indsdættelse af en stent i området ("deferred" stenting) kan begrænse risikoen for forskydnning af blodproppen. En del af patienterne med en stor blodprop har forsnævringer i flere kar. Disse patienter har generelt en dårligere prognose, og det er uvist om det gavner at foretage balloonudvidelse på de forsnævringer, som opdages tilfældigt under den akutte behandling ("komplet" behandling).

Formålet med dette projekt er, at undersøge den gavnlige effekt at "konditionering", "deferred" stenting og "komplet" behandling. idet der sammenlignes med gængse behandlingsformer med henblik på at optimere behandlingen for patienter med stor blodprop. Undersøgelsen vurderer det kliniske forløb hos patienterne.

Der skal indgå 1500 patienter fra danske hjertecentre. Patienterne skal forud for behandlingen give skriftlig informeret samtykke. Patienter under 18 år, patienter som i forvejen deltager i en anden videnskabelig undersøgelse, patienter som ikke er bosiddende i DK og patienter som ikke læser og forstår dansk kan ikke indgå. Patienterne fordeles således at en tredjedel af dem, hvor der ved akut behandling opnås normal blodpassage i det syge kar, får den almindelige behandling med indsdættelse af stent, en tredjedel får foretaget indsdættelse af stenten efter 3 dage ("deferred" stenting) og en tredjedel får foretaget "konditionering" i forbindelse med den akutte behandling. Af de patienter, der har normal blodpassage i det syge kar, får halvdelen den almindelige behandling med indsdættelse af stent, og den anden halvdel får foretaget "deferred" stenting.

Af de patienter, som har forsnævringer i flere kar, får halvdelen foretaget balloonudvidelse af forsnævringer i alle kar, og den anden halvdel kun af karret med blodproppen. Behandlingsprocedurerne foregår i øvrigt efter afdelingens vanlige kriterier, og bivirkninger og risici er de samme som fremgår af den udleverede folder: Ballonudvidelse (PCI). Patienterne vil blive kontaktet telefonisk efter 30 dage, 12 måneder samt 3 og 5 år, hvor de vil blive spurt om helbredstilstand, medicin status og hjerteterelaterede hændelser. Samtlige indlæggelseforløb vil
blive registreret. Der er ikke etiske problemer i forbindelse med behandlingsdelen af projektet. Patienterne informeres såvel mundtligt som skriftligt i henhold til bekendtgørelse fra Forskningsministeriet og inkluderes kun ved samtykke. De etiske overvejelser gælder udelukkende tilladelse til at anvende patienternes data i projektsammenhæng samt de telefoniske kontroller i efterforløbet. Projektets resultater vil forøge viden og forbedre behandlingen af patienter med akut opståede store blod propper i hjertet. Der er ansøgt om økonomisk støtte til dækning af løn til 3 Ph D studerende.
14. REFERENCER


DEPHER flow chart

1. randomisering

2. randomisering
Patientinformation til deltagere i projektet DEPHER

En undersøgelse af om en ændret metode til indsættelse af stent og behandling af alle forsnævringer i kranspulsårerne har gavnlig effekt sammenlignet med vanlig behandling hos patienter med akut blodprop i hjertet.

Vi vil spørge om du vil deltage i dette projekt, som er en videnskabelig undersøgelse.

Baggrund for projektet: Du skal have foretaget en ballonudvidelse af en kranspulsåre, som er lukket af en blodprop. Den behandling vi tilbyder dir. i dag tager sigte på at begrense følgerne af blodproppen, og denne behandling forserger vi til stadighed at forbedre. Undersøgelser tyder på at gentagen udvidelse af en ballon i det kar der indeholder blodproppen kan være gavnlig. Det er også muligt, at man skal vente med at indsaette stenten til der er gået nogle dage, så blodfortyndende medicinen kan opløse resterne af blodproppen inden stenten sættes. Endelig er det uvist om det hos patienter der har mere end en forsnævring har gavnlig effekt at behandle andre forsnævringer end den hvor blodproppen sidder.


Hos patienter med mere end 1 forsnævring vil vi ligeledes undersøge effekten af at foretage ballonudvidelse af alle forsnævringer sammenlignet med kun at handle karret med blodproppen. Fordelingen af patienter i de forskellige behandlingsgrupper sker ved computeriseret lodtrækning. Ca. 1500 patienter deltager i projektet på flere centre i Danmark, heraf ca … fra …………… Deltagelsesvarigheden er 5 år for hver patient.

Kontrolundersøgelser: Du skal komme til ambulant kontrol og scanning af hjertet efter 1 og 12 måneder, og derudover vil vi via et centralt landsregister kontrollere om du har haft hjerterelaterede indlæggelser efter 3 og 5 år.

Ulemper og risici: Eventuelle ulemper, risici og bivirkninger i forbindelse med behandlingen er beskrevet i den informationsfolder, der udleveres i afdelingen vedrørende PCI.

Brug af personlige data/fortrolighed: Dine data er indsamlet til videnskabelig brug, til at samle information om de omtalte behandlinger og kan blive brugt til supplerende videnskabeligt formål, uddannelsesformål og publikation. Alle dine data behandles og opbevares fortroligt, og dine personlige data vil allid blive håndteret efter gældende retningslinier for lov om behandling af personoplysninger og sundhedsloven. Du har mulighed for at få aktindsigt i både personlige data og forsøgsprotokol efter offentligheds-lovens regler og for at få rettet evt. misforståelser.

Økonomisk støtte: Projektet modtager støtte fra Forsknings- og Udviklingsstyrelsen.

Alternative behandlingsmetoder: Der findes ikke alternative metoder end de beskevne til at behandle en akut opstået blodprop.

bidrager til et øget erfaringsgrundlag, som kan hjælpe i behandlingen af fremtidige patienter. Ønsker du yderligere information, kan du henvende dig til:

Kontakt person: Overlæge Henning Kelbæk.
Samtykkeerklæring / fuldmagt til deltagere i projekt DEPHER
En undersøgelse af om gentagen ballonudvidelse og senere indsættelse af stent samt om ballonudvidelse af alle forsnævringer i kranspulsårene har gavnlig effekt sammenlignet med vanlig behandling hos patienter med store blodpropper

Undertegnede giver herved samtykke til deltagelse i DEPHER projektet. Jeg deltager i projektet af egen fri vilje, idet jeg er klar over, at jeg kan undlade at deltage eller på et hvilket som helst tidspunkt trække mig ud af undersøgelsen uden at det får indflydelse på min behandling i øvrigt.

Jeg er blevet informeret om at formålet med undersøgelsen er 1) at undersøge effekten af flere ballon udvidelser før stenten indsættes alternativt at vente 3 dage med at indsætte stenten sammenlignet med at sætte stenten med det samme. Derudover for patienter med flere forsnævringer, at undersøge effekten af at lave ballonudvidelse i alle forsnævringer der påvises sammenlignet med kun at behandle karret med blodpropper. Studiet medfører ambulant kontrol og hjertescanning efter 1 og 12 måneder. Derudover vil vi via et centralt landsregister kontrollere om du har haft hjerterelaterede indlæggelser efter 3 og 5 år.

Jeg giver herved tilladelse til lægerne og Rigshospitalet til at frigive de nødvendige personlige data om mig. Jeg forstår og indvilger i, at mine personlige oplysninger bliver taget fra min sygejournal personer eller anden instans involveret i projektet læger, hospital, offentlige myndigheder, etisk komité og bliver brugt og behandlet i forbindelse med projektet. Jeg har ret til adgang til de personlige oplysninger, der er indsamlet om mig, og til at få rettet eventuelle fejl.

Jeg forbereder mig til at projekt indvollerede personer og relevante myndigheder har adgang til de proektelevante data under forsøget og i op til 15 år efter: Alle dokumenter der hører hjemme i min journal er beskyttet af tavshedsplicht.

Du bedes tilkendegive om du ønsker egen læge informeret om din deltagelse i projektet:

☐ Jeg ønsker min egen læge informeret om min deltagelse i dette projekt
☐ Jeg ønsker ikke min egen læge informeret om min deltagelse i dette projekt

Jeg har mulighed for at få information om projektets opnåede resultater, herunder evt. konsekvenser for mig selv. Ligeledes har jeg mulighed for at få væsentlige oplysninger om min helbredstilstand, der måtte fremkomme undergennemførelsen af projektet.

Du bedes tilkendegive om du ønsker dette:

☐ Jeg ønsker yderligere oplysninger om min helbredstilstand
☐ Jeg ønsker ikke yderligere oplysninger om min helbredstilstand

De Videnskabsetiske Komitéer for Region Hovedstaden har gennemlæst projektprotokollen og har godkendt denne (H-B-xxxx-xxx)

Jeg får udleveret en kopi af den underskrevne samtykkeerklæring og kan henvende mig om spørgsmål vedrørende projektet hos forsøgsansvarlige overlæge Henning Kelbæk.

Patientens navn

Dato ______________ Underskrift ________________________________________

Jeg erklærer at have informeret patienten om formål, potentielle risici og konsekvenser ved deltagelse i projektet DEPHER:

Informere læges navn

Dato ______________ Underskrift ________________________________________

Forsøgslederens navn: Henning Kelbæk
Jeg bekræfter at patienten har fået skriftlig og mundtlig information om projekt DEPHER

Dato ___________________ Underskrift
DEPHER

(DEferred stenting, PostHoc conditioning and completE Revascularization in primary PCI)

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### Study synopsis

| **Designation of investigational treatments** | Ischemic postconditioning, deferred stenting, complete revascularisation. |
| **Title of study** | Depher (Deferred stenting, PostHoc conditioning and compleE Revascularization in primary PCI) |
| **Coordinating Principal Investigators** | Thomas Engstrøm MD, PhD, DMSci, Dept. of Cardiology, Rigshospitalet, Copenhagen University Hospital, Denmark (Postconditioning)  
Henning Kelbaek MD, DMSci, Dept. of Cardiology, Rigshospitalet, Copenhagen University Hospital, Denmark (Deferred stenting)  
Steffen Helqvist MD, DMSci, Dept. of Cardiology, Rigshospitalet, Copenhagen University Hospital, Denmark (Complete revascularization vs. culprit only) |
| **Study centers** | Up to 5 Danish centers are planned to participate |
| **Planned study period** | 2010 – 2015 |
| **Objectives** | In a multicenter, prospective, randomized clinical trial the DANAMI 3 trial program will determine whether 1) either of two approaches to reduce reperfusion injury and distal microvascular obstruction with postconditioning or deferred stent implantation will translate into improved clinical outcome, and whether 2) patients with multivessel disease undergoing primary PCI will benefit from a strategy of FFR-guided complete or culprit only revascularisation. |
| **Methodology** | Following informed consent patients with TIMI 2-3 are randomized in a 1:1 fashion to either deferred stenting or conventional primary PCI and patients with TIMI 0-1 are randomized in a 1:1:1 fashion to either ischemic postconditioning, deferred stenting or conventional primary PCI. In patients with multivessel disease a secondary randomisation to either PCI of the infarct related artery only (i.e. no further treatment), or complete FFR-guided revascularisation is done. |
| **Number of subjects** | 2500 |
| **Inclusion criteria** | 1. Age ≥18 years  
2. Acute onset of chest pain with < 12 hours duration  
3. ST-segment elevation ≥ 0.1 mV in ≥ 2 contiguous leads or documented newly developed left |
Exclusion criteria
1. Potential pregnancy
2. Known intolerance of aspirin, P2Y12 receptor antagonists, heparin or contrast medium
3. Inability to understand information or to provide informed consent
4. Unconsciousness or cardiogenic shock
5. PCI not possible
6. Indication for acute coronary artery bypass grafting
7. Patient presenting with stent thrombosis
8. Hemorrhagic diathesis or known coagulopathy

Primary endpoints
Ischemic postconditioning: All-cause mortality or hospitalisation for heart failure (first occurring) up till the last patient has been followed for 2 years.

Deferred stenting: All-cause mortality, hospitalisation for heart failure, myocardial infarction, or unplanned target vessel revascularisation (first occurring) up till the last patient has been followed for 2 years.

Complete revascularisation: All-cause mortality, myocardial infarction, or ischemia (either subjective or objective) driven revascularisation of non-culprit coronary lesions (first occurring) up till the last patient has been followed for 1 year.

Secondary endpoints
Several clinical, angiographic, electrocardiographic, echocardiographic and MRI endpoints.
1. Abbreviations

AE  Adverse Event
AMI  Acute Myocardial Infarction
DSMB  Data and Safety Monitoring Board
eCRF  Electronic Case Report Form
EDITORS  Eastern Denmark Initiative to Improve Revascularisation Strategies
FFR  Fractional Flow Reserve
iPOST  Ischemic Postconditioning
IRA  Infarct Related Artery
PCI  Percutaneous Coronary Intervention
PI  Principal Investigator
SAE  Serious Adverse Event
STEMI  ST-segment Elevation Myocardial Infarction
TIMI  Thrombolysis In Myocardial Infarction

2. Study rationale

2.1 Background

Reperfusion injury and distal embolization

Percutaneous coronary intervention (PCI) with stent implantation is the most efficacious treatment of patients with ST-segment elevation myocardial infarction (STEMI), by reducing the occurrence of re-infarction and improving prognosis in comparison with fibrinolytic therapy [1-3]. However, a post procedural normal epicardial blood flow (Thrombolysis In Myocardial Infarction [TIMI] flow grade 3) may be present despite an impaired microvascular perfusion and hence lead to an adverse outcome[4, 5] Reperfusion therapy with primary PCI can be considered a “double edged sword”, since the ischemic injury may additionally be worsened by what is known as reperfusion injury [6]. Ischemic postconditioning (iPOST), defined as repetitive interruptions of blood flow to the injured region applied after a prolonged period of ischemia and reperfusion, is suggested to limit the extent of reperfusion injury and has been shown to reduce infarct size in patients with STEMI [7-10] The effect of iPOST on the final infarct size has been evaluated with different modalities such as biomarkers [8, 10], echocardiography [9-10], single photon emission computed tomography [9-10] and cardiac magnetic resonance [7]. In addition, iPOST has been shown to increase the coronary flow reserve and improve ST-segment resolution [11]. Whether these improvements in surrogate markers translate into improved clinical outcome for patients undergoing primary PCI has not yet been investigated in a randomized trial.
Disturbances in the microcirculation caused by reperfusion injury covers a complex chain of events within this vascular territory. In addition, distal embolization of thrombotic material from the ruptured plaque may be present, although attempts to improve outcome by avoiding embolization by means of distal protection devices have, in previous trials, been unsuccessful [12, 13]. Despite successful revascularisation of the epicardial part of the occluded vessel, distal embolization occurs in 5-10% of the patients and impairs the prognosis of patients treated with primary PCI [12, 14, 15]. Because the thrombus burden is reduced considerably during the days after restoration of antegrade flow in an infarct-related artery (IRA), it is possible that postponement of the stent implantation (Deferred stenting) may limit the risk of embolization and improve the prognosis of patients with STEMI. Stent implantation per se does not seem to alter the prognosis [16-18] and thus a strategy of deferred stenting may allow leaving the vessel un-stented in the acute phase of the disease. Whether stent implantation can be totally avoided, in case no significant residual stenosis is present after the thrombus is resolved, will probably also be elucidated in this study.

Multivessel disease
Approximately 40% of patients with STEMI have multivessel disease, i.e. a significant stenosis in at least one of the non-culprit epicardial coronary arteries or their major sidebranches in addition to that of the IRA [19]. Patients with multivessel disease have more comorbidity and a higher mortality after primary PCI than those with single vessel disease [20-21]. A complete revascularisation strategy, as compared to revascularisation of the IRA only, could in these patients potentially improve prognosis, but may on the other hand be associated with potential disadvantages both in terms of early and late complications related to the additional PCI and stenting, i.e. side branch closure, peri-procedural infarction, in-stent restenosis and stent thrombosis. Data from 3 registry analyses have given conflicting results of early, complete revascularisation with regard to both mortality and need for repeat revascularisation [22-24].

This protocol describes the rationale and study design for the DANAMI 3 trial program, which tests three clinical questions: 1) does iPOST improve clinical outcome, 2) does a deferred stenting strategy improve clinical outcome and 3) is FFR guided complete revascularisation clinically superior to revascularisation of the IRA only.
2.2 Purpose of the study

The primary objective in the The Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction (DANAMI 3) trial program is to test three different hypothesis and the study is thus comprised of three randomized multi-center trials evaluating whether the clinical outcome of patients with STEMI can be improved and myocardial damage reduced by either 1) iPOST or 2) by deferred stenting. In addition, the study evaluates 3) whether complete FFR guided revascularisation versus IRA-only revascularisation improves clinical outcome in patients with STEMI and multivessel disease.

2.3 Rationale

In this trial program we test the hypotheses that:

1. iPOST is superior to conventional primary PCI in reducing all-cause mortality and hospitalisation for heart failure in STEMI patients.
2. Deferred stenting is superior to conventional primary PCI in reducing all-cause mortality, hospitalisation for heart failure, myocardial infarction, or unplanned target vessel revascularisation in STEMI patients.
3. FFR-guided complete revascularisation is superior to culprit (IRA) only in reducing all-cause mortality, myocardial infarction, or ischemia (either subjective or objective) driven revascularisation of non-culprit coronary artery lesions.

2.4 Clinical relevance

STEMI remains one of the leading causes of death globally. Thrombolysis was a major step forward in the treatment of STEMI [25-27] and further progress was made when primary PCI was established as a golden therapeutic standard [1]. However, reperfusion therapy with primary PCI can be considered a “double edged sword”, since the ischemic injury may additionally be worsened by what is known as reperfusion injury [6] or by distal embolization of thrombus material [12]. Finally, a considerable fraction of patients present with lesions in other coronary artery branches than the IRA. Whether a strategy of complete or partial revascularisation of these patients should be preferred remains uncertain. Thus addressing these three issues may improve clinical outcome of patients with STEMI.
3. Patients and methods

3.1 Patients
A total of 2500 patients will be included in the studies.

3.1.1 Patient inclusion
Individuals for inclusion will be recruited among patients referred to the participating centers for coronary angiography/PCI because of STEMI (Figure 1). Patients will be recruited from late 2010 till 2013 or until the planned number of patients.

3.1.2 Inclusion criteria
The in- and exclusion criteria are listed in Table 1. Briefly, patients > 18 years of age are eligible if they are admitted with a STEMI with symptom duration of < 12 hours and have given their written informed consent.

3.1.3 Exclusion criteria
Exclusion criteria are listed in Table 1.

Table 1: DANAMI 3 inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tbody>
<tr>
<td>• Age ≥18 years</td>
<td></td>
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<tr>
<td>• Acute onset of chest pain with &lt; 12 hours duration</td>
<td></td>
</tr>
<tr>
<td>• ST-segment elevation ≥ 0.1 mV in ≥ 2 contiguous leads or documented newly developed left bundle branch block</td>
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</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Potential pregnancy</td>
<td></td>
</tr>
<tr>
<td>• Known intolerance of aspirin, P2Y₁₂ receptor antagonists, heparin or contrast medium</td>
<td></td>
</tr>
<tr>
<td>• Inability to understand information or to provide informed consent</td>
<td></td>
</tr>
<tr>
<td>• Unconsciousness or cardiogenic shock</td>
<td></td>
</tr>
<tr>
<td>• PCI not possible</td>
<td></td>
</tr>
<tr>
<td>• Indication for acute coronary artery bypass grafting</td>
<td></td>
</tr>
<tr>
<td>• Patient presenting with stent thrombosis</td>
<td></td>
</tr>
</tbody>
</table>
3.2 Consort patient flow chart

Patients will be included from the 5 primary PCI centers in Denmark, comprising a catchment area of approximately 5.5 million citizens. All centers are performing primary PCI at 24 hours seven days a week throughout the entire study period, and each have a minimum volume of 300 primary PCI procedures annually. Centers are obliged to randomize a minimum of 25 patients in order to participate in the study. The steering committee encompasses representatives from all participating centers. Randomisation will be performed electronically using a web based case report form (eCRF), in which central baseline characteristics of patients will be entered, and clinical events registered during the follow-up period of the trial. Additional patient characteristics and procedure related variables are collected from two national PCI registries (Eastern and Western Denmark Heart Registries), into which the results of all coronary angiograms and PCI procedures are entered.
3.3 Follow-up
All patients will be followed for at least 2 years.
3.4 Endpoints

3.4.1 Primary endpoint

*iPOST*

The primary objective of this part is to investigate the effect of *iPOST* to protect the myocardium and reduce subsequent development of congestive heart failure. Therefore a composite of all cause death and development of heart failure is chosen as the primary endpoint (Table 2).

*Deferred stenting*

The primary objective of this part of the trial is to protect the microvasculature against distal embolization and thus to investigate the influence of the treatment on all cause death and the development of heart failure. Since a deferred stenting strategy leaves the culprit vessel un-stented for some time, re-infarction and repeat target vessel revascularisation are included as components of the primary endpoint (Table 2).

*Complete revascularisation*

The primary endpoint of the complete revascularization vs. culprit only part of the trial is a composite of all-cause mortality, myocardial infarction, or ischemia (either subjective or objective) driven revascularisation of non-culprit coronary artery lesions eligible for and randomized to either of the two treatment arms at the time of the index procedure (Table 2).

3.4.2 Secondary endpoints

Secondary endpoints are listed in Table 2.

**Table 2: Endpoints**

<table>
<thead>
<tr>
<th>Dephen</th>
<th>iPOST vs. conventional PCI</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint (composite)</strong></td>
<td>All-cause mortality or hospitalisation for heart failure</td>
<td>2 years</td>
</tr>
</tbody>
</table>
| **Secondary endpoints** | 1. All of the above components  
2. TIMI flow  
3. ST-segment resolution  
4. Wall motion index (echo)  
5. Salvage index (MRI)  
6. Infarct size (MRI)  
7. LVEF (MRI/echo) | 1. 2 years  
2. Postprocedure  
3. 60, 90 min postprocedure  
4. 1 year  
5. 90 days  
6. 90 days  
7. 90 days/1 year |
### Deferred stenting vs. conventional PCI

<table>
<thead>
<tr>
<th>Primary endpoint (composite)</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality, hospitalisation for heart failure, myocardial infarction, or unplanned target vessel revascularisation.</td>
<td>2 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. All of the above components</td>
</tr>
<tr>
<td>2. TIMI flow</td>
</tr>
<tr>
<td>3. ST-segment resolution</td>
</tr>
<tr>
<td>4. Wall motion index (echo)</td>
</tr>
<tr>
<td>5. Salvage index (MRI)</td>
</tr>
<tr>
<td>6. Infarct size (MRI)</td>
</tr>
<tr>
<td>7. LVEF (MRI/echo)</td>
</tr>
<tr>
<td>8. Microvascular obstruction</td>
</tr>
<tr>
<td>9. Quality of life</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 2 years</td>
</tr>
<tr>
<td>2. Postprocedure</td>
</tr>
<tr>
<td>3. 60, 90 min postprocedure</td>
</tr>
<tr>
<td>4. 1 year</td>
</tr>
<tr>
<td>5. 90 days</td>
</tr>
<tr>
<td>6. 90 days</td>
</tr>
<tr>
<td>7. 90 days/1 year</td>
</tr>
<tr>
<td>8. 48 hours</td>
</tr>
<tr>
<td>9. 1 year</td>
</tr>
</tbody>
</table>

### Culprit only vs. complete revascularisation

<table>
<thead>
<tr>
<th>Primary endpoint (composite)</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality, myocardial infarction, or ischemia (either subjective or objective) driven revascularisation of non-culprit coronary lesions.</td>
<td>1 year</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. All of the above components</td>
</tr>
<tr>
<td>2. Cardiac death or myocardial infarction</td>
</tr>
<tr>
<td>3. Hospitalisation for ACS or acute heart failure</td>
</tr>
<tr>
<td>4. Angina status</td>
</tr>
<tr>
<td>5. Quality of life</td>
</tr>
<tr>
<td>6. Myocardial salvage (MRI)</td>
</tr>
<tr>
<td>7. LVEF (echo)</td>
</tr>
<tr>
<td>8. Cardiac death, myocardial infarction, repeat revascularisation or occurrence of definite stent thrombosis (according to ARC definition) of non culprit lesions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 1 year</td>
</tr>
<tr>
<td>2. 1 year</td>
</tr>
<tr>
<td>3. 1 year</td>
</tr>
<tr>
<td>4. 1 year</td>
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<tr>
<td>5. 1 year</td>
</tr>
<tr>
<td>6. 90 days</td>
</tr>
<tr>
<td>7. 1 year</td>
</tr>
<tr>
<td>8. 1 year</td>
</tr>
</tbody>
</table>

### 3.4.3 Endpoint definition

All endpoints related to mortality or hospitalisations will be identified using national registries, in which all deaths and hospital referrals are reported. Events will subsequently be adjudicated by an events committee, who will review all relevant medical records, angiograms and other available material. Patients will be seen in an outpatient clinic at the randomizing center after 12 months to assess their angina status as well as the left ventricular function measured by echocardiography. Quality of life will be determined using validated self-assessment forms (EQ-5D).

### 3.5 Treatment strategies

#### 3.5.1 Randomisation and invasive procedures

Patients are included in the trial after informed consent as described below. As soon as the assumed culprit lesion is identified, the physician reports the TIMI-flow in the IRA to an...
assistant, who perform the electronic randomisation. Patients with TIMI flow grade 2 or 3 are randomized 1:1 to either deferred stenting or conventional primary PCI (not to iPOST). Patients with TIMI flow grade 0 or 1 are randomized 1:1:1 to iPOST, deferred stenting or conventional PCI. If the physician consider the patient unsuitable for deferred stenting (due to patient characteristics or treatment logistics), this is reported in the eCRF prior to randomisation. In these cases, patients with TIMI flow grade 0 or 1 are randomized 1:1 to conventional treatment or iPOST using a separate stratum, whereas patients with TIMI flow grade 2 to 3 are excluded. This ensures that the deferred stenting part only includes patients from the control group who are considered eligible for deferred stenting, while keeping the ratio of controls 1:1 in both the deferred stenting and iPOST trials.

Primary PCI is performed preferably with floppy guidewires, predilatation using compliant balloons, and everolimus-eluting stents as described below. Thrombectomy is performed at the discretion of the physician. In case a TIMI flow grade >1 cannot be obtained after randomisation, patients are excluded from further analyses. Randomisation is performed using permuted-block with block sizes varying from 2 to 6 patients (in cases of 1:1 randomisation) or 3 to 9 patients (in cases of 1:1:1 randomisation) and stratified by center.

Ischemic Postconditioning

In patients randomised to iPOST, this is performed before stent implantation, within 60 seconds after opening of the artery. After TIMI 2-3 flow in the IRA is secured either by wire insertion alone, thrombectomy, dilatation with an undersized balloon, or a combination of these procedures, a compliant balloon with sufficient diameter to obstruct blood flow to the peripheral vascular bed is inflated at low pressure (4 – 8 atmosphere), and subsequently deflated after 30 seconds. The deflated balloon is left in-situ for another 30 seconds before re-inflation. IPOST is repeated for 4 cycles (30 sec obstruction followed by 30 sec perfusion each) and followed by stent implantation with an everolimus eluting stent with a 1.1/1.0 ratio of stent diameter/reference vessel diameter and a stent length sufficient to cover the entire lesion from healthy to healthy area of the vessel [7].

Deferred stenting

In patients randomised to deferred stenting, the physicians are encouraged to secure stable TIMI 2 or 3 flow exercising as little manipulation of the lesion as possible, ie. thrombectomy and/or dilatation using an undersized balloon during the initial procedure. In cases of
unstable flow and imminent vessel closure despite repeat balloon dilatations, implantation of a stent is considered necessary. These patients are considered 'cross-overs' to conventional treatment, but analyzed with affinity to their allocated treatment group according to the intent-to-treat principle in addition to 'per protocol'. In case a stable TIMI flow grade 2 or 3 is achieved during the initial procedure, a repeat coronary angiography with intended stent implantation in the IRA-lesion is scheduled to be performed preferably >48 hours after the index procedure within the index admission. Stent implantation can be waived, in case the lesion in the IRA at the time of the secondary procedure is considered angiographically insignificant. In these cases, a 3-month follow-up angiogram is planned.

**Multivessel revascularisation**

In patients with one or more additional significant (>50% diameter) stenoses not related to the IRA-lesion, in arteries > 2.0 mm in diameter considered suitable for PCI, a secondary randomisation is performed to either PCI of the IRA only (i.e. no further treatment), or complete revascularisation. In patients randomized to complete revascularisation, this is performed before discharge according to local routines. All multivessel PCI procedures are performed guided by an FFR value < 0.80 or a visually estimated diameter stenosis > 90%. In patients randomized to complete revascularisation with lesions deemed unsuitable for treatment with PCI (chronic total occlusions of long duration, heavy calcification or extreme tortuosity) coronary artery bypass surgery is considered.

**3.5.2 Post-procedure treatment**

All additional patient management during hospitalisation and follow-up, including anticoagulant- and antithrombotic regimens are in accordance with contemporary guidelines at the discretion of the treating physicians.

**4. Statistics and data management**

The data management work up and statistical analyses will be performed at Rigshospitalet, University of Copenhagen, Denmark.

**4.1 Statistical analysis**

Differences between groups in time-to-event endpoints will be assessed with the log-rank test (for the primary endpoint, patients will be censored in case they reach an event or until the
last patient has been followed for 1 year (complete revascularisation) or 2 years (iPOST and deferred stenting); analyses at other time points will be handled in a similar way. Survival probabilities will be displayed using Kaplan-Meier methodology. Hazard ratios between groups will be calculated using a Cox proportional hazard model. Differences between group means/medians will be assessed with parametric or non-parametric statistics. The Chi-square analysis or Fisher's exact test will be used to test differences between proportions. A two-tailed P-value <0.05 is considered statistically significant.

An additional follow-up after 4 years is planned in all studies, focusing on the combined endpoint of all-cause mortality and hospitalisation for heart failure. While patients who do not achieve TIMI 2 or 3 flow during the index procedure are excluded from primary analyses, additional sensitivity analyses including these patients will be performed.

4.2 Safety monitoring

An independent data safety monitoring board (DSMB) will on a regular basis monitor interim analyses for both safety and efficacy study endpoints. The DSMB encompasses one invasive and two non-invasive cardiologists. Premature termination of the study will be mandated in the event that one of the treatment strategies shows statistically significant inferiority with regard to safety to a higher than expected degree. No members of the DSMB participate in recruitment or data collection or have access to any information regarding treatment allocations. A list of all DSMB members will be given in appendix.

4.3 Event recording

The results will be analysed according to the intention-to-treat principle, i.e. patients randomised to a certain group will be followed and assessed irrespectively of the actual treatment. Per protocol analyses will also be performed. Protocol violations will be monitored continuously and the responsible centers notified. The events committee is responsible for adjudicating all primary and major secondary endpoints. No members of the events committee participate in recruitment or data collection or have access to any information regarding treatment allocations. A list of all events committee members is given in appendix.

4.4 Sample size calculations

For the iPOST study, we estimate that the annual rate of the primary end point will be 11% in the control group. With an inclusion period of 2½ years and a minimum follow-up of 2 years,
we will be able to detect a relative reduction in the primary endpoint of 25%, with a two-sided alpha level of 0.05 and a power of 80% by enrolling 1,100 patients.

In the deferred stenting study we expect event rates to differ substantially between patients with TIMI flow grade 0-1 and TIMI flow grade 2-3 at randomisation. For this reason, analyses in two strata depending on pre-randomisation TIMI flow grade will be performed, and the results reported separately as pre-specified hypothesis generating analyses. A combined analysis of both strata is planned as the primary analysis. For the primary endpoint, we estimate an annual event rate of 13% in the two strata combined, by including repeat urgent and non-urgent target vessel revascularisation and non-fatal myocardial infarction in the combined endpoint. With an inclusion period of 2½ years and a minimum follow-up of 2 years, we will be able to detect a relative reduction of 25% in the primary endpoint, with a two-sided alpha level of 0.05 and a power of 80% by enrolling 920 patients.

For the complete revascularization vs, culprit only study we estimate the primary endpoint to occur with an annual rate of 18% in the group treated for the IRA only. With an inclusion period of 2½ years and a minimum follow-up of 1 year, we are able to detect a relative reduction of 30% in the primary endpoint, with a two-sided alpha level of 0.05 and a power of 80% by enrolling 618 patients.

4.5 Database and Case Report Form

The eCRF will be generated automatically based on the ordinary registration form and stored at Rigshospitalet for each patient included. The patient’s identity will always be confidential. Study data will be entered directly in the registry and stored at Rigshospitalet. The investigators are responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs.

5. Administration

5.1 Organization

Danish PCI centers with the possibility to perform primary PCI with interest in the trial program and willingness to include eligible consenting STEMI patients during the study period can participate.
The steering committee will consist of cardiologists from Rigshospitalet and from each of the other participating centers. A list of all steering committee members will be given in appendix.

5.2 Insurance
The patients in the study are covered by the Danish patient insurance.

5.3 Economy
The DANAMI trial program is an academic study program conceived and conducted by cardiovascular interventionalists from the respective centers. The study is independent of commercial interests. Study logistics, handling of data and statistical assessments will be financed by Rigshospitalet, University of Copenhagen, Denmark. The steering committee will apply for grants from public funds. Possible external sponsors will have no influence on the conduct of the study.

6. Ethical considerations
The protocol of the trial will be approved by our regional ethics committee, and the collection of data complies with the regulatory rules of the Danish Data Protection Agency (2007-41-1667), and the study is being conducted in compliance with the Helsinki II Declaration as adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964 and subsequent versions. Particular care is taken to ensure that the primary PCI procedure is not delayed due to the information procedure. Only patients who consent to participate are included in the trial.

6.1 Timing of informed consent
It is secured that patients are allowed sufficient time to read and consider the patient information and decide whether to participate in the trial or not but without delaying reperfusion.

6.2 Risks, side-effects, advantages and disadvantages in participation
Based on previous experiences, iPOST can be performed without additional procedure related risk [7-11]. The postponement of stent implantation and need for an additional procedure in patients randomized to deferred stenting may be associated with an increased risk of re-occlusion of the IRA and procedure related complications, such as bleeding. Given
the potential benefit induced by a reduction in microvascular injury, we consider this risk counterbalanced. In the complete revascularization vs. culprit only part of the trial we also find the potential clinical benefit from treatment of all coronary lesions (versus IRA-only) to outweigh the risk associated with the repeat procedure performed in patients with multivessel disease randomised to complete revascularisation.

6.3 Biological material

Blood samples including whole blood will be collected and stored at -80°C.

6.4 Guidelines for obtaining informed consent

Patients will enter the study after signing the informed consent form. Eligible participants will receive written information of the study, and oral information by the medical doctor performing the primary PCI.

6.5 Withdrawal

A patient can be withdrawn from the study at any time, if it is the wish of the patient, or if it is medically indicated, as judged by the investigator. A patient’s participation in the study will be discontinued, if any of the following criteria applies: a) the patient’s general condition contraindicates continuing the study or b) the patient turns out to be non-eligible patient.

7. Safety assessments

7.1 Safety parameters

The following listed safety parameters will be monitored during the study treatment: Vital signs, bleeding, arrhythmia, ischemia indicating arterial re-occlusion and consciousness. If indicated, basic blood chemistry analyses and blood gases will be examined.

7.2 Adverse Events (AE)

An adverse event is any unexpected medical occurrence in a patient, treated otherwise than with standard primary PCI, and which does not necessarily have a causal relationship with this treatment. Medical occurrences that are symptoms of existing disease, and that do represent an exacerbation of that disease, or the conventional PCI procedure are not defined as adverse events in this clinical trial. Also elective hospitalisations for pre-treatment conditions are not adverse events. Registration of adverse events will start after informed
consent and continue until the patient will leave the hospital after the coronary angiography/PCI procedure in all treatment groups.

7.3 Serious Adverse Event (SAE)
A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires hospitalisation or prolongation of existing inpatients’ hospitalisation,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly or birth effect,
- Other important medical event

Hospitalisation or prolongation for existing inpatient hospitalisation disease which represent an exacerbation of that disease or the standard primary PCI procedure as well as other events non-related to iPOST, deferred stenting or complete revascularisation strategy will not be reported as an SAE, but will be reported as described. Any AE fulfilling the criteria to be an SAE will be reported according to clinical practice outside this clinical trial.

8. Publication
Results, positive as well as negative, will be published in international cardiovascular journals. Publication and author issues will be decided by the steering committee on the basis of involvement in the study (drafting of protocol, core laboratory function, endpoint committee membership, and ability to include patients.)

9. Sub-studies
Initiation of sub-studies are encouraged, but should be accepted by the steering committee. No sub-studies are part of the primary application for ethical approval.
10. References


Appendix A

DANAMI 3 Committee members and investigators

**DANAMI 3 steering committee:**
Henning Kelbæk, Thomas Engstrøm, Lars Køber, Steffen Helqvist, Lene Holmvang, Peter Clemmensen, Dan Eik Høfsten and Lene Kløvgaard, The Heart Center, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Hans Henrik Tilsted, Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark.

Hans Erik Bøtker, Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark.

Lisette Okkels Jensen, Department of Cardiology, Odense University Hospital, Odense, Denmark

**Data safety monitoring board (DSMB):**
To be determined.

**Events committee:**
To be determined.
DANAMI3-trial program

Rationale and Design of the DANMI3-Trial program

Clinical Trials.gov identifiers: NCT01435408, NCT01960933

Protocol no: DANAMI3 H-4-2010-076
## Study synopsis

<table>
<thead>
<tr>
<th>Designation of investigational treatments</th>
<th>Ischemic postconditioning, deferred stenting, complete revascularisation.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title of study</strong></td>
<td>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 revascularisation versus treatment of culprit lesion only</td>
</tr>
</tbody>
</table>
| **Coordinating Principal Investigators** | Thomas Engstrem MD, PhD, DMSci, Dept. of Cardiology, Rigshospitalet, Copenhagen University Hospital, Denmark (DANAMI3-iPOST)  
Henning Kelbaek MD, DMSci, Dept. of Cardiology, Rigshospitalet, Copenhagen University Hospital, Denmark (DANAMI3-DEFER)  
Steffen Helqvist MD, DMSci, Dept. of Cardiology, Rigshospitalet, Copenhagen University Hospital, Denmark (DANAMI3-PRIMULTI) |
| **Study centers**                        | Up to 5 Danish centers are planned to participate |
| **Planned study period**                 | 2011 – 2016 |
| **Objectives**                           | In a multicenter, prospective, randomized clinical trial the DANAMI 3 trial program will determine whether 1) either of two approaches to reduce reperfusion injury and distal microvascular obstruction with postconditioning (D3-iPOST) or deferred stent implantation (D3-DEFER) will translate into improved clinical outcome, and whether 2) patients with multivessel disease undergoing primary PCI will benefit from a strategy of FFR-guided complete or culprit only revascularisation (D3-PRIMULTI). |
| **Methodology**                          | Following informed consent patients with TIMI 2-3 are randomized in a 1:1 fashion to either DEFER or conventional primary PCI and patients with TIMI 0-1 are randomized in a 1:1:1 fashion to either iPOST, DEFER or conventional primary PCI. In patients with multivessel disease a secondary randomisation to either PCI of the infarct related artery only (i.e. no further treatment), or complete FFR-guided revascularisation is done. |
| **Number of subjects**                   | 2650 |
| **Inclusion criteria**                   | 4. Age ≥18 years |
5. Acute onset of chest pain with < 12 hours duration
6. ST-segment elevation ≥ 0.1 mV in ≥ 2 contiguous leads or documented newly developed left bundle branch block

**Exclusion criteria**

9. Potential pregnancy
10. Known intolerance of aspirin, P2Y12 receptor antagonists, heparin or contrast medium
11. Inability to understand information or to provide informed consent
12. Unconsciousness or cardiogenic shock
13. PCI not possible
14. Indication for acute coronary artery bypass grafting
15. Patient presenting with stent thrombosis
16. Hemorrhagic diathesis or known coagulopathy

**Primary endpoints**

D3-iPOST: All-cause mortality or hospitalisation for heart failure (**first occurring**) up till the last patient has been followed for 2 years.

D3-DEFER: All-cause mortality, hospitalisation for heart failure, myocardial infarction, or unplanned target vessel revascularisation (**first occurring**) up till the last patient has been followed for 2 years.

D3-PRIMULTI: All-cause mortality, myocardial infarction, or ischemia (either subjective or objective) driven revascularisation of non-culprit coronary lesions (**first occurring**) up till the last patient has been followed for 1 year.

**Secondary endpoints**

Several clinical, angiographic, electrocardiographic, echocardiographic and MRI endpoints.
1. Abbreviations

AE  Adverse Event
AMI  Acute Myocardial Infarction
CEC  Clinical Event Committee
DEFER  Deferred Stenting
DSMB  Data and Safety Monitoring Board
eCRF  Electronic Case Report Form
EDITORS  Eastern Denmark Initiative to Improve Revascularisation Strategies
FFR  Fractional Flow Reserve
iPOST  Ischemic Postconditioning
IRA  Infarct Related Artery
PCI  Percutaneous Coronary Intervention
PI  Principal Investigator
SAE  Serious Adverse Event
STEMI  ST-segment Elevation Myocardial Infarction
TIMI  Thrombolysis In Myocardial Infarction

2. Study rationale

2.1 Background

Reperfusion injury and distal embolization

Percutaneous coronary intervention (PCI) with stent implantation is the most efficacious treatment of patients with ST-segment elevation myocardial infarction (STEMI), by reducing the occurrence of re-infarction and improving prognosis in comparison with fibrinolytic therapy [1-3]. However, a post procedural normal epicardial blood flow (Thrombolysis In Myocardial Infarction [TIMI] flow grade 3) may be present despite an impaired microvascular perfusion and hence lead to an adverse outcome[4, 5] Reperfusion therapy with primary PCI can be considered a “double edged sword”, since the ischemic injury may additionally be worsened by what is known as reperfusion injury [6]. Ischemic postconditioning (iPOST), defined as repetitive interruptions of blood flow to the injured region applied after a prolonged period of ischemia and reperfusion, is suggested to limit the extent of reperfusion injury and has been shown to reduce infarct size in patients with STEMI [7-11] The effect of iPOST on the final infarct size has been evaluated with different modalities such as biomarkers [8, 10, 11], echocardiography [9-11], single photon emission computed tomography [9-11] and cardiac magnetic resonance [7, 12]. In addition, iPOST has been shown to increase the coronary flow reserve and improve ST-segment resolution [13]. Whether these improvements
in surrogate markers translate into improved clinical outcome for patients undergoing primary PCI has not yet been investigated in a randomized trial.

Disturbances in the microcirculation caused by reperfusion injury covers a complex chain of events within this vascular territory. In addition, distal embolization of thrombotic material from the ruptured plaque may be present, although attempts to improve outcome by avoiding embolization by means of distal protection devices have, in previous trials, been unsuccessful [14, 15].

Despite successful revascularisation of the epicardial part of the occluded vessel, distal embolization occurs in 5-10% of the patients and impairs the prognosis of patients treated with primary PCI [14, 16, 17]. Because the thrombus burden is reduced considerably during the days after restoration of antegrade flow in an infarct-related artery (IRA), it is possible that postponement of the stent implantation (DEFER) may limit the risk of embolization and improve the prognosis of patients with STEMI [18]. Stent implantation per se does not seem to alter the prognosis [19-21] and thus a strategy of DEFER may allow leaving the vessel unstented in the acute phase of the disease. Whether stent implantation can be totally avoided, in case no significant residual stenosis is present after the thrombus is resolved, will probably also be elucidated in this study.

Multivessel disease

Approximately 40% of patients with STEMI have multivessel disease, i.e. a significant stenosis in at least one of the non-culprit epicardial coronary arteries or their major sidebranches in addition to that of the IRA [22]. Patients with multivessel disease have more comorbidity and a higher mortality after primary PCI than those with single vessel disease [23-25]. A complete revascularisation strategy, as compared to revascularisation of the IRA only, could in these patients potentially improve prognosis, but may on the other hand be associated with potential disadvantages both in terms of early and late complications related to the additional PCI and stenting, i.e. side branch closure, peri-procedural infarction, in-stent restenosis and stent thrombosis. Data from 3 registry analyses have given conflicting results of early, complete revascularisation with regard to both mortality and need for repeat revascularisation [26-28].

This protocol describes the rationale and study design for the DANAMI 3 trial program, which tests three clinical questions: 1) does iPOST improve clinical outcome, 2) does a DEFER
strategy improve clinical outcome and 3) is FFR guided complete revascularisation clinically superior to revascularisation of the IRA only.

2.2 Purpose of the study
The primary objective in the The Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction (DANAMI 3) trial program is to test three different hypothesis and the study is thus comprised of three randomized multi-center trials evaluating whether the clinical outcome of patients with STEMI can be improved and myocardial damage reduced by either 1) iPOST (DANAMI 3-iPOST) or 2) by deferred stenting (DANAMI 3-DEFER). In addition, the study evaluates 3) whether complete FFR guided revascularisation versus IRA-only revascularisation improves clinical outcome in patients with STEMI and multivessel disease (DANAMI 3-PRIMULTI).

2.3 Rationale
In this trial program we test the hypotheses that:
1. iPOST is superior to conventional primary PCI in reducing all-cause mortality and hospitalisation for heart failure in STEMI patients.
2. DEFER is superior to conventional primary PCI in reducing all-cause mortality, hospitalisation for heart failure, myocardial infarction, or unplanned target vessel revascularisation in STEMI patients.
3. FFR-guided complete revascularisation is superior to culprit (IRA) only in reducing all-cause mortality, myocardial infarction, or ischemia (either subjective or objective) driven revascularisation of non-culprit coronary artery lesions.

2.4 Clinical relevance
STEMI remains one of the leading causes of death globally. Thrombolysis was a major step forward in the treatment of STEMI [29-31] and further progress was made when primary PCI was established as a golden therapeutic standard [1]. However, reperfusion therapy with primary PCI can be considered a “double edged sword”, since the ischemic injury may additionally be worsened by what is known as reperfusion injury [6] or by distal embolization of thrombus material [14]. Finally, a considerable fraction of patients present with lesions in other coronary artery branches than the IRA. Whether a strategy of complete or partial
revascularisation of these patients should be preferred remains uncertain. Thus addressing these three issues may improve clinical outcome of patients with STEMI.

3. Patients and methods

3.1 Patients
A total of 2650 patients will be included in the study.

3.1.1 Patient inclusion
Individuals for inclusion will be recruited among patients referred to the participating centers for coronary angiography/PCI because of STEMI (Figure 1). Patients will be recruited from March 2011 till November 2013 or until the planned number of patients. The patients will not receive any honorarium for participation.

3.1.2 Inclusion criteria
The in- and exclusion criteria are listed in Table 1. Briefly, patients > 18 years of age are eligible if they are admitted with a first STEMI with symptom duration of < 12 hours and have given their written informed consent.

3.1.3 Exclusion criteria
Exclusion criteria are listed in Table 1.

Table 3: DANAMI 3 inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age ≥18 years</td>
</tr>
<tr>
<td>• Acute onset of chest pain with &lt; 12 hours duration</td>
</tr>
<tr>
<td>• ST-segment elevation ≥ 0.1 mV in ≥ 2 contiguous leads or documented newly developed left bundle branch block</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Potential pregnancy</td>
</tr>
<tr>
<td>• Known intolerance of aspirin, P2Y₁₂ receptor antagonists, heparin or contrast medium</td>
</tr>
<tr>
<td>• Inability to understand information or to provide informed consent</td>
</tr>
</tbody>
</table>
- Unconsciousness or cardiogenic shock
- PCI not possible
- Indication for acute coronary artery bypass grafting
- Patient presenting with stent thrombosis
- Hemorrhagic diathesis or known coagulopathy

3.2 Consort patient flow chart

Patients will be included from the 5 primary PCI centers in Denmark, comprising a catchment area of approximately 5.6 million citizens. All centers are performing primary PCI at 24 hours seven days a week throughout the entire study period, and each have a minimum volume of 300 primary PCI procedures annually. Centers are obliged to randomize a minimum of 25 patients in order to participate in the study. The steering committee encompasses representatives from all participating centers.

Randomisation will be performed electronically using a web based case report form (eCRF), in which central baseline characteristics of patients will be entered, and clinical events registered during the follow-up period of the trial. Additional patient characteristics and procedure related variables are collected from two national PCI registries (Eastern and Western Denmark Heart Registries), into which the results of all coronary angiograms and PCI procedures are entered.

Figure 2: Randomisation flow chart
Reasons for not including particular patients will be documented on an electronic consort patient flow chart (eLog).

3.3 Follow-up
All patients will be followed for at least 2 years.

3.4 Endpoints
3.4.1 Primary endpoint

DANAMI 3-iPOST
The primary objective of this part is to investigate the effect of iPOST to protect the myocardium and reduce subsequent development of congestive heart failure. Therefore a composite of all cause death and development of heart failure is chosen as the primary endpoint (Table 2).

DANAMI 3-DEFER
The primary objective of this part of the trial is to protect the microvasculature against distal embolization and thus to investigate the influence of the treatment on all cause death and the development of heart failure. Since a DEFER strategy leaves the culprit vessel un-stented for some time, re-infarction and repeat target vessel revascularisation are included as components of the primary endpoint (Table 2).

DANAMI 3-PRIMULTI
The primary endpoint of the PRIMULTI part of the trial is a composite of all-cause mortality, myocardial infarction, or ischemia (either subjective or objective) driven revascularisation of non-culprit coronary artery lesions eligible for and randomized to either of the two treatment arms at the time of the index procedure (Table 2).

3.4.2 Secondary endpoints
Secondary endpoints are listed in Table 2.
### Table 4: DANAMI 3 endpoints

<table>
<thead>
<tr>
<th>DANAMI 3-iPOST</th>
<th>iPOST vs. conventional PCI</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong> (composite)</td>
<td>All-cause mortality or hospitalisation for heart failure</td>
<td>2 years</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. All of the above components</td>
<td>10. 2 years</td>
<td></td>
</tr>
<tr>
<td>11. TIMI flow</td>
<td>11. Postprocedure</td>
<td></td>
</tr>
<tr>
<td>12. ST-segment resolution</td>
<td>12. 60, 90 min postprocedure</td>
<td></td>
</tr>
<tr>
<td>13. Left ventricular ejection fraction (echo)</td>
<td>13. 1-1½ year</td>
<td></td>
</tr>
<tr>
<td>14. Salvage index (MRI)</td>
<td>14. 90 days</td>
<td></td>
</tr>
<tr>
<td>15. Infarct size (MRI)</td>
<td>15. 90 days</td>
<td></td>
</tr>
<tr>
<td>16. Left ventricular ejection fraction (MRI)</td>
<td>16. 90 days</td>
<td></td>
</tr>
<tr>
<td>17. Microvascular obstruction (MRI)</td>
<td>17. 48 hours</td>
<td></td>
</tr>
<tr>
<td>18. Quality of life</td>
<td>18. 1-1½ year</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DANAMI 3-DEFER</th>
<th>DEFER vs. conventional PCI</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong> (composite)</td>
<td>All-cause mortality, hospitalisation for heart failure, myocardial infarction, or unplanned target vessel revascularisation.</td>
<td>2 years</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. All of the above components</td>
<td>10. 2 years</td>
<td></td>
</tr>
<tr>
<td>11. TIMI flow</td>
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</tr>
<tr>
<td>13. Left ventricular ejection fraction (echo)</td>
<td>13. 1-1½ year</td>
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<tr>
<td>14. Salvage index (MRI)</td>
<td>14. 90 days</td>
<td></td>
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<tr>
<td>15. Infarct size (MRI)</td>
<td>15. 90 days</td>
<td></td>
</tr>
<tr>
<td>16. Left ventricular ejection fraction (MRI)</td>
<td>16. 90 days</td>
<td></td>
</tr>
<tr>
<td>17. Microvascular obstruction (MRI)</td>
<td>17. 48 hours</td>
<td></td>
</tr>
<tr>
<td>18. Quality of life</td>
<td>18. 1-1½ year</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DANAMI 3-PRIMULTI</th>
<th>Culprit only vs.complete revascularisation</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong> (composite)</td>
<td>All-cause mortality, myocardial infarction, or ischemia (either subjective or objective) driven revascularisation of non-culprit coronary lesions.</td>
<td>1 year</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. All of the above components</td>
<td>9. 1 year</td>
<td></td>
</tr>
<tr>
<td>10. Cardiac death or myocardial infarction</td>
<td>10. 1 year</td>
<td></td>
</tr>
<tr>
<td>11. Hospitalisation for ACS or acute heart failure</td>
<td>11. 1 year</td>
<td></td>
</tr>
<tr>
<td>12. Angina status</td>
<td>12. 1 year</td>
<td></td>
</tr>
<tr>
<td>13. Quality of life</td>
<td>13. 1 year</td>
<td></td>
</tr>
<tr>
<td>14. Myocardial salvage (MRI)</td>
<td>14. 90 days</td>
<td></td>
</tr>
<tr>
<td>15. Left ventricular ejection fraction (echo)</td>
<td>15. 1 year</td>
<td></td>
</tr>
<tr>
<td>16. Cardiac death, myocardial infarction, repeat revascularisation or occurrence of definite stent thrombosis (according to ARC definition) of non-culprit lesions</td>
<td>16. 1 year</td>
<td></td>
</tr>
</tbody>
</table>

### 3.4.3 Endpoint definition

All endpoints related to mortality or hospitalisations will be identified using national registries, in which all deaths and hospital referrals are reported. Events will subsequently be adjudicated by members of our clinical events committee (CEC), who will review all relevant medical records, angiograms and other available material. Patients will be seen in an
outpatient clinic at the randomizing center after 12 to 18 months to assess their angina status as well as the left ventricular function measured by echocardiography. Quality of life will be determined using validated self-assessment forms (EQ-5D).

3.5 Treatment strategies

3.5.1 Randomisation and invasive procedures

Patients are included in the trial after informed consent as described below. As soon as the assumed culprit lesion is identified, the physician reports the TIMI-flow in the IRA to an assistant, who perform the electronic randomisation. Patients with TIMI flow grade 2 or 3 are randomized 1:1 to either DEFER or conventional primary PCI (not to iPOST). Patients with TIMI flow grade 0 or 1 are randomized 1:1:1 to iPOST, DEFER or conventional PCI. If the physician consider the patient unsuitable for DEFER (due to patient characteristics or treatment logistics), this is reported in the eCRF prior to randomisation. In these cases, patients with TIMI flow grade 0 or 1 are randomized 1:1 to conventional treatment or iPOST using a separate stratum, whereas patients with TIMI flow grade 2 to 3 are excluded. This ensures that the DANAMI 3-DEFER trial only includes patients from the control group who are considered eligible for DEFER, while keeping the ratio of controls 1:1 in both the DANAMI 3-DEFER and DANAMI 3-iPOST trials.

Primary PCI is performed preferably with floppy guidewires, predilatation using compliant balloons, and everolimus-eluting stents as described below. Thrombectomy is performed at the discretion of the physician. In case a TIMI flow grade >1 cannot be obtained after randomisation, patients are excluded from further analyses. Randomisation is performed using permuted-block with block sizes varying from 2 to 6 patients (in cases of 1:1 randomisation) or 3 to 9 patients (in cases of 1:1:1 randomisation) and stratified by center. The randomisation procedure is summarized in Figure 1.

Ischemic Postconditioning

In patients randomized to iPOST, this is performed before stent implantation, within 60 seconds after opening of the artery. After TIMI 2-3 flow in the IRA is secured either by wire insertion alone, thrombectomy, dilatation with an undersized balloon, or a combination of these procedures, a compliant balloon with sufficient diameter to obstruct blood flow to the peripheral vascular bed is inflated at low pressure (4 – 8 atmosphere), and subsequently deflated after 30 seconds. The deflated balloon is left in-situ for another 30 seconds before
re-inflation. IPOST is repeated for 4 cycles (30 sec obstruction followed by 30 sec perfusion each) and followed by stent implantation with an everolimus eluting stent with a 1.1/1.0 ratio of stent diameter/reference vessel diameter and a stent length sufficient to cover the entire lesion from healthy to healthy area of the vessel [7].

Deferred stenting

In patients randomized to DEFER, the physicians are encouraged to secure stable TIMI 2 or 3 flow exercising as little manipulation of the lesion as possible, ie. thrombectomy and/or dilatation using an undersized balloon during the initial procedure. In cases of unstable flow and imminent vessel closure despite repeat balloon dilatations, implantation of a stent is considered necessary. These patients are considered ‘cross-overs’ to conventional treatment, but analyzed with affinity to their allocated treatment group according to the intent-to-treat principle in addition to ‘per protocol’. In case a stable TIMI flow grade 2 or 3 is achieved during the initial procedure, a repeat coronary angiography with intended stent implantation in the IRA-lesion is scheduled to be performed preferably >48 hours after the index procedure within the index admission. Stent implantation can be waived, in case the lesion in the IRA at the time of the secondary procedure is considered angiographically insignificant. In these cases, a 3-month follow-up angiogram is planned.

Multivessel revascularisation

In patients with one or more additional significant (>50% diameter) stenoses not related to the IRA-lesion, in arteries > 2.0 mm in diameter considered suitable for PCI, a secondary randomisation is performed to either PCI of the IRA only (i.e. no further treatment), or complete revascularisation. In patients randomized to complete revascularisation, this is performed before discharge according to local routines. All multivessel PCI procedures are performed guided by an FFR value < 0.80 or a visually estimated diameter stenosis > 90%. In patients randomized to complete revascularisation with lesions deemed unsuitable for treatment with PCI (chronic total occlusions of long duration, heavy calcification or extreme tortuosity) coronary artery bypass surgery is considered.
3.5.2 Post-procedure treatment
All additional patient management during hospitalisation and follow-up, including anticoagulant- and antithrombotic regimens are in accordance with contemporary guidelines at the discretion of the treating physicians.

4. Statistics and data management
The data management work up and statistical analyses will be performed at Rigshospitalet, University of Copenhagen, Denmark.

4.1 Statistical analysis
Differences between groups in time-to-event endpoints will be assessed with the log-rank test (for the primary endpoint, patients will be censored in case they reach an event or until the last patient has been followed for 1 year (PRIMULTI) or 2 years (iPOST and DEFER); analyses at other time points will be handled in a similar way). Survival probabilities will be displayed using Kaplan-Meier methodology. Hazard ratios between groups will be calculated using a Cox proportional hazard model. Differences between group means/medians will be assessed with parametric or non-parametric statistics. The Chi-square analysis or Fisher's exact test will be used to test differences between proportions. A two-tailed P-value <0.05 is considered statistically significant.

An additional follow-up after 4 years is planned in all studies, focusing on the combined endpoint of all-cause mortality and hospitalisation for heart failure. While patients who do not achieve TIMI 2 or 3 flow during the index procedure are excluded from primary analyses, additional sensitivity analyses including these patients will be performed.

4.2 Safety monitoring
An independent data safety monitoring board (DSMB) will on a regular basis monitor interim analyses for both safety and efficacy study endpoints. The DSMB encompasses one invasive and two non-invasive cardiologists. Premature termination of the study will be mandated in the event that one of the treatment strategies shows statistically significant inferiority with regard to safety to a higher than expected degree. No members of the DSMB participate in recruitment or data collection or have access to any information regarding treatment allocations. A list of all DSMB members is given in appendix A.
4.3 Event recording
The results will be analyzed according to the intention-to-treat principle, i.e. patients randomized to a certain group will be followed and assessed irrespectively of the actual treatment. Per protocol analyses will also be performed. Protocol violations will be monitored continuously and the responsible centers notified. The CEC is responsible for adjudicating all primary and major secondary endpoints, and consists of 3 experienced cardiologists, one invasive and two non-invasive. No members of the CEC participate in recruitment or data collection or have access to any information regarding treatment allocations. A list of all CEC members is given in Appendix A.

4.4 Sample size calculations
For the DANAMI 3-iPOST study, we estimate that the annual rate of the primary end point will be 11% in the control group. With an inclusion period of 2½ years and a minimum follow-up of 2 years, we will be able to detect a relative reduction in the primary endpoint of 25%, with a two-sided alpha level of 0.05 and a power of 80% by enrolling 1,100 patients.

In the DANAMI 3-DEFER study we expect event rates to differ substantially between patients with TIMI flow grade 0-1 and TIMI flow grade 2-3 at randomisation. For this reason, analyses in two strata depending on pre-randomisation TIMI flow grade will be performed, and the results reported separately as pre-specified hypothesis generating analyses. A combined analysis of both strata is planned as the primary analysis. For the primary endpoint, we estimate an annual event rate of 13% in the two strata combined, by including repeat urgent and non-urgent target vessel revascularisation and non-fatal myocardial infarction in the combined endpoint. With an inclusion period of 2½ years and a minimum follow-up of 2 years, we will be able to detect a relative reduction of 25% in the primary endpoint, with a two-sided alpha level of 0.05 and a power of 80% by enrolling 920 patients.

For the DANAMI 3-PRIMULTI study we estimate the primary endpoint to occur with an annual rate of 18% in the group treated for the IRA only. With an inclusion period of 2½ years and a minimum follow-up of 1 year, we are able to detect a relative reduction of 30% in the primary endpoint, with a two-sided alpha level of 0.05 and a power of 80% by enrolling 618 patients.
4.5 Database and Case Report Form
The eCRF will be generated automatically based on the ordinary registration form and stored at Rigshospitalet for each patient included. The patient’s identity will always be confidential. Study data will be entered directly in the registry and stored at Rigshospitalet. The investigators are responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs.

5. Administration

5.1 Organization
Danish PCI centers with the possibility to perform primary PCI with interest in the trial program and willingness to include eligible consenting STEMI patients during the study period can participate.
The steering committee will consist of cardiologists from Rigshospitalet and from each of the other participating centers. A list of all steering committee members is given in Appendix A.

5.2 Insurance
The patients in the study are covered by the Danish patient insurance.

5.3 Economy
The DANAMI trial program is an academic study program conceived and conducted by cardiovascular interventionalists from the respective centers. The study is independent of commercial interests. Study logistics, handling of data and statistical assessments will be financed by Rigshospitalet, University of Copenhagen, Denmark. The steering committee will apply for grants from public funds. Possible external sponsors will have no influence on the conduct of the study.

6. Ethical considerations
The protocol of the trial has been approved by our regional ethics committee, the collection of data complies with the regulatory rules of the Danish Data Protection Agency (2007-41-1667), and the study is being conducted in compliance with the Helsinki II Declaration as adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964 and subsequent versions. Particular care is taken to ensure that the primary PCI procedure is not delayed due
to the information procedure. Only patients who consent to participate are included in the trial.

6.1 Timing of informed consent

It is secured that patients are allowed sufficient time to read and consider the patient information and decide whether to participate in the trial or not but without delaying reperfusion.

6.2 Risks, side-effects, advantages and disadvantages in participation

Based on previous experiences, iPOST can be performed without additional procedure related risk [7-9, 11]. In addition, we have previously published data from a series of STEMI patients treated with DEFER, suggesting that this can be performed with little or no additional risk to the patient [18]. The postponement of stent implantation and need for an additional procedure in patients randomized to DEFER may be associated with an increased risk of re-occlusion of the IRA and procedure related complications, such as bleeding. Given the potential benefit induced by a reduction in microvascular injury, we consider this risk counterbalanced. In the PRIMULTI part of the trial we also find the potential clinical benefit from treatment of all coronary lesions (versus IRA-only) to outweigh the risk associated with the repeat procedure performed in patients with multivessel disease randomized to complete revascularisation.

6.3 Biological material

Blood samples including whole blood will be collected and stored at -80°C.

6.4 Guidelines for obtaining informed consent

Patients will enter the study after signing the informed consent form. Eligible participants will receive written information of the study, and oral information by the medical doctor performing the primary PCI.

6.5 Withdrawal

A patient can be withdrawn from the study at any time, if it is the wish of the patient, or if it is medically indicated, as judged by the investigator. A patient’s participation in the study will be discontinued, if any of the following criteria applies: a) the patient’s general condition contraindicates continuing the study or b) the patient turns out to be non-eligible patient.
7. Safety assessments

7.1 Safety parameters
The following listed safety parameters will be monitored during the study treatment: Vital signs, bleeding, arrhythmia, ischemia indicating arterial re-occlusion and consciousness. If indicated, basic blood chemistry analyses and blood gases will be examined.

7.2 Adverse Events (AE)
An adverse event is any unexpected medical occurrence in a patient, treated otherwise than with standard primary PCI, and which does not necessarily have a causal relationship with this treatment. Medical occurrences that are symptoms of existing disease, and that do represent an exacerbation of that disease, or the conventional PCI procedure are not defined as adverse events in this clinical trial. Also elective hospitalisations for pre-treatment conditions are not adverse events. Registration of adverse events will start after informed consent and continue until the patient will leave the hospital after the coronary angiography/PCI procedure in all treatment groups.

7.3 Serious Adverse Event (SAE)
A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires hospitalisation or prolongation of existing inpatients' hospitalisation,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly or birth effect,
- Other important medical event

Hospitalisation or prolongation for existing inpatient hospitalisation disease which represent an exacerbation of that disease or the standard primary PCI procedure as well as other events non-related to iPOST, DEFER or PRIMULTI strategy will not be reported as an SAE, but will be reported as described. Any AE fulfilling the criteria to be an SAE will be reported according to clinical practice outside this clinical trial.
8. Publication
Results, positive as well as negative, will be published in international cardiovascular journals. Publication and author issues will be decided by the steering committee on the basis of involvement in the study (drafting of protocol, core laboratory function, endpoint committee membership, and ability to include patients.)

9. Sub-studies
Initiation of sub-studies are encouraged, but should be accepted by the steering committee. No sub-studies are part of the primary application for ethical approval.
10. References


Appendix A

DANAMI 3 Committee members and investigators

**DANAMI 3 steering committee:**
Henning Kelbæk, Thomas Engstrøm, Lars Køber, Steffen Helqvist, Lene Holmvang, Peter Clemmensen, Dan Eik Hofsten and Lene Kløvgaard, The Heart Center, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
Hans Henrik Tilsted, Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark.
Hans Erik Bøtker, Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark.
Lisette Okkels Jensen, Department of Cardiology, Odense University Hospital, Odense, Denmark

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

**Clinical event committee (CEC):**
Kristian Thygesen, Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark (Chairman), Jørgen Jeppesen, Department of Medicine, Copenhagen University Hospital Glostrup, Glostrup, Denmark. Anders Galløe, Department of Cardiology, Roskilde Hospital.
DANAMI-3-iPOST trial statistical analysis plan
August 2013

Overview of Analyses

This document contains the statistical analysis plan for the DANAMI-3-iPOST trial (Ischemic Postconditioning during ST-segment Elevation Myocardial Infarction (STEMI)). The aim is to clarify analyses and to avoid misleading inference from post-hoc analyses. Therefore the statistical analysis plan has been completed prior to the availability of any outcome data. This document describes the analyses to be performed — split primarily by the primary initial analysis on outcomes on the longer terms. Separate manuscripts will be prepared to the outcomes with descriptive statistics and analyses following the structure set out in this document.

Regarding time-lines for analyses the main time points are:

Recruitment of patients started in 2011 and is expected to continue to early 2014
The primary analysis of the study will be conducted when the last patient enrolled has been followed for 2 years, expected early 2016
The principal long term analysis will be performed when the last patient has been followed for at least 4 years or when at least 300 patients have died.

Background of the DANAMI-3-iPOST trial

The principal research question is the following: **Can a policy of routine ischemic postconditioning during revascularization for ST-segment Elevation Myocardial Infarction save lives or reduce incidence of heart failure in patients with STEMI.**

The study is a multi-centre randomized controlled trial conducted by centres capable of doing primary percutaneous coronary angioplasty (PCI) acutely and 24 hours a day.

Inclusion/Exclusion criteria

**Inclusion Criteria.** To be eligible for the study, subjects must fulfill the following criteria:

1. Age ≥18 y
2. Acute onset of chest pain within 12 h duration
3. ST-segment elevation ≥0.1 mV in ≥2 contiguous leads or documented newly developed left bundle-branch block.
4. TIMI flow 0-1
5. **Exclusion Criteria.** To be eligible for this study, subjects must not meet any of the following criteria:
   1. Potential pregnancy
   2. Known intolerance of aspirin, P2Y12 receptor antagonists, heparin, or contrast medium
   3. Inability to understand information or to provide informed consent
4. Unconsciousness or cardiogenic shock
5. PCI not possible
6. Indication for acute coronary artery bypass grafting
7. Patient presenting with stent thrombosis
8. Hemorrhagic diathesis or known coagulopathy.

Consent
Written and signed informed consent is taken from all participants prior to inclusion in the study.

Randomisation
Randomisation is either to standard primary PCI with stent implantation or to re-opening of the infarcted artery followed by repetitive brief interruptions of blood flow before the standard primary PCI with stent implantation.
Patients are individually randomized using an electronic case report system with a randomization module and stratification by center.
There is no blinding in this study.
Accumulating data on the primary outcome (mortality and hospitalization for heart failure) and secondary outcomes by treatment group is only viewed by the independent Data Monitoring Committee during the course of the study.

Study variables and endpoints
Screening/presentation with STEMI
Each centre provides information on patients not randomized into the trial (overall number, reasons for exclusion).

For randomised patients baseline data are collected for a variety of characteristics, including:

- Obtaining or verifying informed consent
- Medical history, including previous surgical procedures
- Physical examination, including height, body weight
- Concomitant medical therapy
- Blood samples for s-creatinine, haemoglobin.

Demographic and admission data:
- Age, sex, diabetes, hypertension, smoking status, hyperlipidemia, previous MI, previous heart
failure, previous PCI, previous CABG, Infarct location, time from onset of symptoms, TIMI-flow at procedure start, culprit lesion

End- PCI data:
TIMI-flow at end of procedure, no. of stents and details of stents, no. of diseased vessels, antithrombotic treatment,

During Follow-up the following data are collected:
Medication at discharge after index hospitalization, left ventricular ejection fraction (LVEF) by echocardiography after 12-18 months*, MRI during index hospitalization and after 3 months*, development or hospitalization for heart failure, survival time, in case of death documentation for circumstances, recurrent MI, stroke, repeated revascularization separated by vessel, Quality of Life by a brief questionnaire

Footnote: * these investigations only performed in patients willing, and in centers able to perform these.

Sample size
For the DANAMI 3-iPOST study, we estimate that the annual rate of the primary end point will be 11% in the control group. With an inclusion period of 2½ years and a minimum follow-up of 2 years, we will be able to detect a relative reduction in the primary endpoint of 25%, with a two-sided alpha level of 0.05 and a power of 80% by enrolling at least 1100 patients.

Study end
This study is continued until the last patients has been followed for 2 years.
The steering committee makes a decision for a final date of study closure. This date will be used as a censoring time for the main analysis. In case the study is stopped early by recommendation of the Data Safety committee or for any other reason, the steering committee will provide the final stopping date.

Statistical Plan for main outcome paper
Statistical analyses will be performed using STATA, SAS and R

Consort diagram
A detailed CONSORT diagram describing patient flow with exclusions and total numbers randomized to each treatment. This diagram will include all patients randomized. At the necessary number of levels patients not included in analysis will be explained. It is expected that a few patients will be randomized erroneously as this is done acutely during a procedure (randomization pressed by mistake), and these will be removed prior to final analysis. The final step in the CONSORT diagram will describe number of patients in the two treatment arms. The intention to
treat population of this study comprises all patients randomised minus those randomised by mistake.

Baseline descriptions of randomized groups
Tables of summary statistics will be produced by randomised group for a number of baseline variables as described above.

Continuous variables will be summarised using the following statistics; n (non-missing sample size), mean, standard deviation, median, IQR, minimum, and maximum. The number of missing observations will also be reported.

The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. The number of missing observations will also be reported.

Primary Outcome Analyses
Primary Analysis of efficacy
The primary analysis will be an analysis of all cause mortality and hospitalization for heart failure between the two treatment groups based on the intention-to-treat population. Patients enter the analysis on the day of randomization and are followed until the defined time of trial closure as indicated by the steering committee. Any patient lost to follow-up (not expected) will be censored at the last time known to be alive. The presentation will be a Kaplan-Meier curve of 1-Survival. Evaluation of difference between the two treatment arms will be performed with a log-rank test. The primary comparison of the study will be the p-value of this log-rank test and a significant difference is considered found if p<0.05

Also presented along with this analysis will be a hazard ratio (including 95% confidence limits) using a Cox proportional hazard model. If the assumption for a Cox model do not hold a poisson regression model with presentation of rate ratios will be used instead.

Multivariable analysis of primary endpoint (Cox or Poisson pending assumptions)
Several multivariable models will be examined also. The first model also includes age, sex and center. The second model will further include all variables that in descriptive statistics differ significantly between the two groups. A final model will include all variables used in the descriptive statistics. Use of these models are subject to tests of model assumptions. Only models where assumptions are not violated in a statistical significant manner will be presented. The proportional hazard assumption will be tested using cumulative residuals, interaction by examining importance of interaction variables and linearity by examining importance of also including quartiles. If the proportional hazard assuption is not met the Cox proportional hazard model will be replaced with Poisson Regression Models. In these models time since randomization will be split in half year intervals for the main analysis. Further splitting will be performed to ensure constant rate in intervals. All variables will enter as discrete variables. Age will be split in 5 year interval, calendar year by each year. As the DANAMI-3 program consists of 3 trials running simultaneously, and a small group of patients can be part of more than one trial test for interaction with the other trials will be performed, and reported in main manuscripts as supplement.

The following interactions are considered important and will be tested: Treatment by sex, age (above/below median), diabetes, infarct location, single vs. multivessel disease, time from onset of symptons (3 hrs).
Sensitivity analyses of the primary endpoint

A sensitivity analysis will include only patients that were treated according to the scheduled treatment.

Secondary endpoint including all patients

The predefined secondary endpoint of the study is the individual components of the primary endpoint (time from randomisation to all cause mortality, or time from randomization to hospitalization for heart failure). The presence of the last endpoint follow evaluation by the endpoint committee. The analysis of this endpoint is performed as described for the primary endpoint in a Cox proportional hazard model, and illustrated as cumulative incidence curves.

Other secondary endpoints

Some of the following endpoints include only patients were data are available will be analyzed as for the primary endpoint, but without sensitivity analyses

1. MRI measurement of final infarct size and Salvage index
2. LVEF by echocardiography
3. Cardiovascular mortality (as evaluated by the critical endpoint committee)
4. Quality of Life
5. Recurrent MI
6. Repeated target vessel revascularization
7. TIMI flow at end-procedure
8. Stroke

Analysis of secondary endpoint: Analysis of MRI data and LVEF will use statistical analyses as for the descriptive statistics. Cardiovascular mortality, repeated target vessel revascularization, stroke and recurrent AMI will be examined as for the primary endpoint, but taking into account competing risk. Cumulative incidence will be reported and comparison will be Gray's test).

Subgroup analyses

A limited number of predefined subgroups will be compared for all endpoints. Tests for interaction will be presented.

Age (cut by median age)

Sex

Diabetes

Anterior vs. non-anterior MI

Single vs. multivessel disease

Symptom duration < 3 hours vs. ≥ 3 hours

Since several interaction tests will be performed, a p-value of <0.01 will be used as a guide before claiming strong evidence of differences between subgroups.
Handling of missing data

The primary outcome analysis should be subject to little or no missing data.

Missing data that occurs in other outcomes, covariates or subgroup variables will be subject to multiple imputations by chained equations in sensitivity analyses to increase precision of the estimates and to avoid potential biases from a complete case analysis. Additional sensitivity analyses may be conducted to assess the impact of the multiple imputation and a complete case analysis will also be conducted. All imputations will be examined to ensure sensible values are being generated. Imputation models will contain baseline variables, outcome variables, and variables used to define subgroups.

Adverse events

Adverse events are reported throughout the trial and tabulations of all reported adverse events will be provided, subdivided by treatment group.

Special focus will be on the following adverse events as evaluated by the critical events committee

- Serious bleeding events during index hospitalization
- Urgent CABG in connection with the primary PCI
- Primary PCI related death

The risk of adverse events and events with special focus will be examined as total number and by Kaplan Meier risk estimators at the end of follow-up

Statistical plan for long term outcome analyses

The long term analysis will be performed when the last patients has been followed for at least 4 years or when at least 300 patients have died, whichever comes first.

Analyses will be performed as described for the primary and secondary analyses.