Trends in invasive examination, treatment rate and time to treatment from 2001 to 2009 in patients admitted first time with non ST-elevation Myocardial Infarction or unstable angina in Denmark.

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</table>
Title

Trends in invasive examination, treatment rate and time to treatment from 2001 to 2009 in patients admitted first time with non ST-elevation Myocardial Infarction or unstable angina in Denmark.

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Abstract

Objective:

To investigate time trends in invasive examination and time to treatment for patient with first time diagnosis of non-ST-elevation Myocardial infarction (NSTEMI) and unstable angina in the period from 2001 to 2009 in Denmark

Design: From 1 January 2001 to 31 December 2009 all first time hospitalisations with NSTEMI and unstable angina were identified in the National Patient Registry. Time from admission to initiation of coronary angiography (CAG), percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) was calculated. We described the development in treatment probability (CAG, PCI and CABG at 3, 7, 10, 30 and 60 days) for the years 2001 to 2009, taking the competing risk of death into account using Aalen-Johansen estimators and a Fine Grey model.

Setting: Nationwide Danish cohort

Results: The proportion of patients with receiving a CAG and PCI increased substantially over time while the proportion receiving a CABG decreased for both NSTEMI and unstable angina. For both NSTEMI and unstable angina a significant increase in treatment probability at 3 days for CAG and PCI was seen especially from 2007 through to 2009. For example for NSTEMI the CAG treatment probability at 3 days leaped from 21% in 2007 to 34 % in 2008 and 39 % in 2009. For PCI the same was true with a leap in treatment probability from 19 % to 28 % from 2008 to 2009.
Conclusions: In Denmark the use of CAG and PCI in treatment of NSTEMI and unstable angina has increased from 2001 to 2009 while the use of CABG has decreased. During the same period there was a marked increase in treatment probability at 3 days i.e. more patients were treated faster which is in line with the political aim of reducing time to treatment.

Main strengths:
- Large unselected patient population n=80,033
- Detailed register based data
- Use of statistical methods that account for competing risks
- Information on extension and severity of the disease

Main limitations:
- No information on biomarkers to validate register based data
- No information on why patients died before treatment

Keywords: acute coronary heart syndrome, NSTEMI, Unstable angina, time to treatment, time trends, cohort design
Introduction

Treatment of acute coronary heart disease has advanced substantially during the latest decades, and improved clinical outcome has been seen (1). A recent register based Danish cohort study by Schmidt et al. found that short term mortality after first time hospitalisation with AMI was nearly halved from 1984 to 2008 (2). It has been suggested that part of this decline can be attributed to improved treatment including introduction of thrombolysis, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) and improved medical prevention after diagnosis (3). Coronary angiography (CAG) is recommended as part of the diagnostic process for all patients with acute myocardial infarction with PCI as the primary intervention (4). Since the mid nineties there has been a strong political focus on time to treatment in order to reduce case fatality (5). For coronary heart disease this focus in Denmark has among other initiatives led to the development of fixed treatment protocols for patients with non ST elevation myocardial infarction (NSTEMI) and unstable angina. These protocols were implemented during 2009. The protocol stipulates that the maximum time from admission with NSTEMI to invasive examination (CAG) should be less than 3 calendar days (72 hours) and time to appropriate invasive treatment less than 3 calendar days for PCI, and 7 calendar days for coronary artery bypass graft surgery (CABG) (6). These protocols are based on the shared European guidelines (4, 7).

The purpose of this study is to explore the potential causes of the significant improvement in prognosis by investigating time trends in invasive examination, treatment and time to treatment for patients with first time diagnosis of NSTEMI or unstable angina in the period from 2001 to 2009 in Denmark using a nationwide cohort design and taking into account vessel disease severity as well as using appropriate methods of analysis that account for the competing risk of death. This study is the first nationwide cohort study to describe time waited for CAG, PCI and CABG over a decade.
where large changes in treatment of NSTEMI and unstable angina were introduced including the introduction of fixed treatment protocols.
Method

The Danish health care system provides universal coverage for all citizens. Since 1995, all contacts with the health care system including emergency, ambulatory and inpatient have been registered in the National Patient Registry (NPR) with information about time and date of admission and discharge along with information about diagnosis as well as type and date of potential invasive treatment or examination (8). Furthermore there are several registers and clinical quality databases with patient specific information (9) that can be linked with the data from the NPR through the use of the unique ten-digit person identifier. The registers used for this study are the NPR (8), the National Prescription Registry, which collects information on redeemed prescriptions (10), the Danish Heart Registry, which registers information regarding patients undergoing invasive cardiac procedure (11) and the Medical Cause of Death Registry, which contains information on time and cause of death (12).

Study population:

From January 1 2001 to December 31 2009 all first time hospitalisations of acute coronary heart syndrome (ACS) were identified in the National Patient Registry (n= 99,473) by the following ICD10 codes (I20.0 Unstable angina pectoris, I21.0-I21.3 ST-elevation myocardial infarction (STEMI), I21.4 non ST-elevation myocardial infarction (NSTEMI) and I21.9 AMI – Unspecified) using discharge diagnoses (see figure 1). Patients with prior heart disease (ICD10: I20-I25) were excluded using information from the NPR going back to 1995 (n= 19,440) leaving 80,033 cases for analysis. Diagnosis can change after the result of CAG therefore we used the diagnosis registered after the CAG in the analysis of time to PCI and CABG. For this reason the number of patients in the different sub-diagnosis groups vary between analyses of CAG, PCI and CABG (see figure 1 for distribution of patients with acute coronary heart syndrome within sub diagnosis group at initial
examination and after coronary angiography). Patients with STEMI and unspecified MI are only included in the initial descriptive analysis of the patient population.

Variables

**Time to treatment (from admission to CAG, PCI and CABG)**

Time (measured in hours) from admission to a hospital to initiation of coronary angiography (CAG), percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) was calculated using information from the NPR (the specific SKS codes can be seen in appendix 1). Only treatment and examination within the first 60 days after initial symptom presentation was included. Further information regarding this variable can be found in appendix 2.

**Severity and extent of disease**

Severity and the extent of disease will influence the perceived urgency of treatment. Information on number of occluded vessels and LMCA involvement was available from the Danish Heart Register in 82.2% and 85.6% of the cases that received a CAG, respectively.

**Statistical methods**

In the descriptive analysis the number of patients receiving CAG, PCI or CABG was reported along with the number of patients receiving the respective treatment within 3 days for CAG and PCI and 7 days from CAG for CABG for each diagnosis and for each of the covariates: age, sex, number of occluded vessels and LMCA involvement. When investigating time to treatment for a specific disease, it is important to account for the competing risk of death in order to account for the time waited by patients who die before they are treated (13). Reporting a median time to treatment is not
relevant as it will only describe the time waited by patients who manage to be treated. Furthermore, if we wish to model cumulated probability of treatment (not intensities) and applied standard methods (e.g. Cox regression method or Kaplan Meier plots), then we would regard death without treatment as independent censoring and would only be able to make inference for a hypothetical population where patients do not die without being treated (13). This would not represent a true picture of reality. The problem of competing risk is especially important for a potentially fatal disease like ACS where some sub diagnosis have a relative high mortality rate (14, 15).

Furthermore, as first line treatments are mutually exclusive (patients receive either PCI or CABG) we need to account for the competing risk of receiving the other treatment, respectively. To account for this competing risk problem we used Aalen-Johansen plots where we described the development in treatment probability (CAG, PCI and CABG) for the years 2001 to 2009. These plots account for the competing risk of death and treatment (PCI or CABG, respectively) by showing the estimated percentage of the original population, which at a given time has received the treatment (CAG, PCI or CABG). The plot has no distributional assumptions (13). From these plots we derived treatment probability at 1, 3, 7 (only for CABG), 10, 30 and 60 days after diagnosis. These probabilities are presented in graphs in order to show the development from 2001 to 2009.

To test whether the effects seen in the plots were statistically significant, we used the Fine Gray model, a regression model that accounts for competing risk and adjusts for covariates (13). In this model we find the effect of the calendar years when controlling for covariates (age, sex, LMCA involvement and number of occluded vessels).

When analysing the impact of the fixed treatment protocols implemented during 2009, a proper evaluation with a control group was not feasible due to lack of an appropriate comparison group.
Consequently we applied a second-best solution where we looked at whether the change in times to
treatment in the year 2009 differed from the time trend observed in the time period from 2001 to
2008 extrapolated to 2009. The use of this method was inspired by the methods used by Lee et al
when evaluating the effects of Pay for Performance in the UK (16). We tested this in the Fine Gray
model and report the test statistics as z. Year 2001 is the reference when year is included
categorically. In all analyses a 5% significance level was used. Data were analysed with SAS
version 9.3, STATA version 12.1 and by using the macro COMRISK to draw Aalen-Johansen plot
provided open access by the MAYO Institute.

Results:

Of the 80,033 patients who were registered with first time ACS and no prior heart disease 23.4 %
were admitted with NSTEMI, 19.3 % with unstable angina, 23.3 % with STEMI and 34.0 % with
non-specified MI. A total of 10,080 patients were after the CAG registered with a non ACS
diagnosis and subsequently excluded from the further analysis of PCI and CABG (see appendix 3
where the diagnoses that account for 80% of these patients are listed). After CAG the distribution of
diagnosis were as follows 33.0 % of patients were admitted with NSTEMI, 12.2 % with unstable
angina, 35.7 with STEMI and 19.0 with non-specific MI.

Table 1 show that from 2001 to 2009 the proportion of patients with NSTEMI receiving a CAG and
PCI increased substantially, while the proportion receiving a CABG decreased. During the same
period the fraction of patients examined with a CAG who received this within 3 days increased
from 18.2 % to 55.2 %. For PCI a similar development was seen with 52.1 % treated within 3 days
in 2009 compared to 27.2 % in 2001. For CABG within 7 days the percentage slightly declined over
the time period with some fluctuations.
For unstable angina the activity rate increased for CAG, but not for PCI in the period from 2001 to 2009 (table 3) however for both CAG and PCI the rates of patient who received these procedures within 3 days doubled in this time period. For CABG the treatment rate was more than halved.

Insert table 2

Figure 2a shows the development in the probability of invasive investigation using CAG from 2001 to 2009 for NSTEMI accounting for the competing risk of death. The figure shows a statistically significant increase in the use of CAG in the period from 2001 to 2005 with an increase in probability from 49 % for CAG at 60 days in 2001 to 66.6 % in 2005 (tested using the Fine Gray model see results in appendix 4). From 2005 and onwards only a slight increase in probability of CAG at 60 days was seem. The figure also shows a steady increase in the probability of CAG within 3 days from 2001 to 2007 followed by a leap from 19.3 % in 2007 to 31.5 % in 2008 and a further increase to 37.5 % in 2009. The fixed treatment protocol seemed to have a significant effect on the probability of receiving a CAG within 3 days (z=3.45 p=0.001). For PCI (figure 2b) there was only a slight increase in the probability of treatment with PCI at 60 days from 2001 to 2009. Further the probability of PCI treatment within 3 days increased markedly from 2007 to 2008 and again from 2008 to 2009. The effect of the implementation of the fixed treatment protocols also revealed a significant effect for PCI (z=7.82 p<0.001). For CABG the development in treatment probability was somewhat different with a significant drop in probability of receiving this type of treatment over the period 2001 to 2006 with subsequent stagnation (figure 1c). The probability of
treatment within 7 days of CAG decreased significantly over the period and there seemed to be no effect of the fixed treatment protocols ($z=0.32$, $p=0.75$).

*Insert figure 2*

Figure 3 shows the similar graphs for patient with unstable angina. In general the development was very similar to that of patients with NSTEMI, but with the increase in the invasive examination/treatment rate later in the observation period (from 2004 to 2008). The probability of receiving CAG within 3 days increased four-fold from 2001 to 2009 with an almost constant increase (figure 2a). We saw no effect of the fixed treatment protocols on timing of cag ($z=-0.76$, $p=0.44$). The PCI treatment rate at 60 days was somewhat stable in the time period with a small drop in 2004, while the probability of treatment within 3 days increased almost constantly from 2001 to 2009. There was no effect of the fixed treatment protocols ($z=-0.23$, $p=0.82$) (figure 2b). For CABG the treatment probability at 60 days decreased in the time period as well as the treatment probability at 7 days (figure 2c). There was no significant effect of the fixed treatment protocols. For both NSTEMI and unstable angina there was no significant development in death before treatment over time i.e. the competing risk (analysis not shown).

*Insert figure 3*

When including age, sex, number of occluded vessels and LMCA involvement (last two only for PCI and CABG) we found that for NSTEMI the development in CAG treatment probability at 3 days and 60 days was the same as seen in the unadjusted analyses, and the effect of the fixed treatment protocols remained significant. For PCI the same pattern was observed, however when
adjusting for number of occluded vessels, the linear effect of year became insignificant, but the
effect of the fixed treatment protocols remained. For CABG the picture did not change after the
adjustment except that the decrease in treatment probability seen at 60 days was not as noticeable as
in the unadjusted analysis. Performing the same adjustments did not change the conclusions for
unstable angina either (See all results from the Fine Gray model in appendix 5).
Discussion

In this nationwide cohort study, we found a significant increase in the proportions of patients with NSTEMI and unstable angina receiving a CAG and PCI in Denmark between 2001 and 2009, while the proportion receiving CABG decreased. In the analysis accounting for competing risks there was an increase in the probability of treatment within 3 days for CAG and PCI after 2001 and there seemed to be a significant effect of the introduction of a fixed treatment protocol with recommended maximum time from diagnosis to invasive examination and treatment for NSTEMI, but not for unstable angina.

Our results are in agreement with studies from the US, which showed an increase in the use of CAG and PCI over the last two decades, and a decrease in CABG (1, 17, 18). The study also contributes to the interpretation of the findings from a recent Danish study (2), which showed a significant reduction in 30-day and 1-year mortality risk after first time hospitalisation for MI between 1999-2003 and 2004-2008. Part of this reduction could be due to a decrease in time to treatment. When comparing with this study one should keep in mind that we did not include patients with STEMI who are included in Schmidt et al.'s study and that these have a succinct treatment path with the need for more urgent treatment. There seems to be no other nationwide studies on trends in time from diagnosis to invasive treatment; however in 2009 Bradley et al reported a decrease in door to balloon time for patients with STEMI after enrolment in a national quality campaign with the aim to reduce the door to balloon time to less than 90 minutes for this group (19).

We did find a significant decline in time for CAG and PCI corresponding to implementation of the fixed treatment protocol for NSTEMI. However, for both NSTEMI and unstable angina, we found a steady increase in treatment rate from 2001 and onwards and for NSTEMI a steep increase in
probability already in 2008. This indicates that focus on improvement on time to treatment is not new. Furthermore the treatment protocols were first implemented during 2009, but they were already discussed in 2008 and this could have led to early implementation and hence an increase in speed of treatment before the actual implementation. In this time period there seemed to be a general agreement on the benefits of an invasive strategy vs. medical management for patients with NSTEMI (20, 21). However the optimal timing of invasive interventions was not clearly agreed upon. Mehta et al published in 2009 their results from the large TIMACS trial which included 3031 patients with unstable angina or NSTEMI. They found a significantly lower risk of death, myocardial infarction or stroke at 6 months for high risk patients when comparing an early (less than 24 h) with a delayed strategy (more than 36 h). Furthermore they found no safety issues related to an early strategy (22). This reflects the importance of early treatment however this result reflects the difference between very early and early invasive intervention which is a slightly other discussion than ours. In 2010 a meta analysis was published combining four trials which concluded that early angiography and if relevant treatment for patients with NSTEMI reduces the risk of recurrent ischemia and shortens hospital stay (23). These results were however not reflected in the European Society of Cardiology guidelines until 2011 (4). However the previous guideline from 2007 (p. 27) also stated: "...Accordingly, currently available evidence does not mandate a systematic approach of immediate angiography in NSTE-ACS patients stabilized with a contemporary pharmacological approach. Likewise, routine practice of immediate transfer of stabilized patients admitted in hospitals without onsite catheterization facilities is not mandatory, but should be organized within 72 h" (7). It should also be noticed that our study is an observational trend study and we cannot exclude that other organizational or treatment factors than the introduction of the fixed treatment protocol has contributed to the observed reduction in time to
treatment. This study only evaluates the immediate effects of the fixed treatment protocols; however a longer follow up would also be of interest.

Strengths and weaknesses

The primary strength of this study is the large unselected patient population, as it covers all patients admitted with first time ACS in the period from 2001 to 2009 in Denmark. The patients were identified in the NPR and data from this register are considered to have a high quality for patients with a coronary heart disease diagnosis. Thus, a previous study found a positive predictive value for myocardial infarction in the NPR of 98% (24). However this means that we do not have information on biomarkers but solely rely on the correctness on what is registered in the NPR. The data in the NPR allowed us to follow patients through the course of diagnosis and treatment path, and we utilised this to change patients’ diagnoses after the CAG in case another diagnosis was registered at this point in time. This was done in order to imitate the clinical situation. At CAG 10,080 patients had a diagnosis other than ACS. The largest group was 3,721 patients with Angina no specification. This group of patients could potentially be patients with unstable angina however including this group did not change the conclusions (analysis not shown). We had information on the specific hour of admission and used this information to calculate time to treatment. Although the validity of this information can be questioned, we used it in order to calculate the time as precisely as possible. We only included treatment and examination within 60 days as ACS is an acute disease for which treatment if relevant should be initiated as soon as possible. We analysed our data by use of statistical methods that accounted for the competing risk of death, which is very important when we estimate trends in time to treatment in a population with a high risk of death. However we do not know whether patients who died were not treated because the risk of treatment was deemed too high, or because the treatment was not considered relevant. Our analysis showed that the group of
patients not receiving CAG was reduced in the period from 2001 to 2009, which was primarily due
to an increase in treatment of elderly patients (analysis not shown). We also included information
on the number of occluded vessels and LMCA involvement as a measure of the extension and
severity of the disease in the analysis. This information was only available for 85.6 % and 82.2 % of
the patients and especially patients from 2001 and 2002 had missing information on this variable.
However, we have no reason to believe that this missing data should be non-random and related to
time to treatment. Further we did not use age standardised data in the trend analyses because the
fixed treatments protocols include all patient groups. However, we tested whether there was an
effect of the treatment protocols in the Fine-Grey model which adjusted for age, gender, LMCA
involvement and number of occluded vessels. The analyses showed that these variables did not
change the effect of the treatment protocols. It should also be noticed that we did not include
patients who died before admission to hospital as these patients are not included in the NPR.

In conclusion, this study contributes to the interpretation of the recent decline in mortality after
hospitalisation for MI by showing a contemporary increase in the proportion of patients receiving a
CAG and PCI. The study also suggest that the introduction of fixed treatment protocols with a
recommended maximum time from diagnosis to invasive examination and treatment may have
impacted on time to treatment as more patients receive a CAG and PCI within the time limit of 3
days around the time of the introduction of the protocols.

Contributors: SM, DGH, EP, ADOZ, MO contributed to the design of the study. SM carried
out statistical analysis with guidance from PKA and MO. SM wrote initial draft and all
authors critically revised the manuscript.
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Competing interest: None

Ethics

This register based study was approved the Danish Data Protection Agency (Approval number 2010-41-5263). Register based studies does not need approval by a medical ethics committee in Denmark.
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<th>CAG within 60 days</th>
<th>PCI within 60 days (Grouped according to after CAG diagnosis)</th>
<th>CABG within 60 days from CAG</th>
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<td>Treatment rate %</td>
<td>n</td>
<td>% in 3 days*</td>
<td>Treatment rate %</td>
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<td>3</td>
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<td>29.7</td>
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* National guidelines recommend CAG and PCI within 3 days of diagnosis and CABG within 7 days of CAG.
** Left Main Coronary Artery
Table 2: Coronary angiography (CAG), Percutaneous coronary intervention (PCI) and Coronary artery bypass grafting (CABG) treatment rates and number treated within 3/7 days distributed according to covariates for patients with first time Unstable Angina

<table>
<thead>
<tr>
<th>Unstable angina</th>
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<th>Diagnosis registered after CAG</th>
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<td>CAG within 60 days</td>
<td>PCI within 60 days (Grouped according to after CAG diagnosis)</td>
<td>Treatment rate %</td>
</tr>
<tr>
<td></td>
<td>Treatment rate %</td>
<td>n</td>
<td>% in 3 days*</td>
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<tr>
<td>Overall 15,469</td>
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<td>8,114</td>
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<td></td>
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<tr>
<td>30 or younger</td>
<td>23.3</td>
<td>27</td>
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<td>LMCA* involvement</td>
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<td>0</td>
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<tr>
<td>3 vessels</td>
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<td>205</td>
<td>32.5</td>
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</table>

* National guidelines recommend CAG and PCI within 3 days of diagnosis and CABG within 7 days of CAG.

** Left Main Coronary Artery
Reference List


Figure 1: Flowchart patient population

Patients with 1st time ACS from 2001 to 2009
n= 99,473

Prior heart disease
n= 19,440

Patients with 1st time ACS from 2001 to 2009
No prior heart disease
n= 80,033

No CAG within 60 days,
n= 26,326

No treatment within 60 days
from diagnosis
n= 15,992

Dead within 60 days,
n= 7,544

CAG within 60 days,
n= 46,163

After CAG, a non ACS diagnosis registered
n=10,080

Patients med ACS
n= 36,083

Distribution of ACS diagnoses before CAG:

Unstable angina n= 15,469 (19.3 %)
STEMI n= 18,631 (23.3 %)
NSTEMI n= 18,757 (23.4 %)
AMI non specific n= 27,176 (34.0 %)

Distribution of ACS diagnoses after CAG:

Unstable angina n= 4,410 (12.2 %)
STEMI n= 12,890 (35.7 %)
NSTEMI n= 11,915 (33.0 %)
AMI non specific n=6,868 (19.0 %)

PCI within 60 days from
diagnosis
n=15,173

CABG within 60 days from
diagnosis
n=3,914

Death within 60 days from
diagnosis
n= 1,004

No treatment within 60 days from diagnosis
n= 15,992

PCI within 60 days from CAG
n=15,229

CABG within 60 days from CAG
n=3,996

Death within 60 days from CAG
n=1,016

No treatment within 60 days from CAG
n= 15,842

ACS: Acute coronary heart syndrome
STEMI: ST elevation myocardial infarction
NSTEMI: Non ST elevation myocardial infarction
AMI: Acute myocardial infarction
CAG: Coronary angiography
CABG: Coronary artery bypass grafting
PCI: Percutaneous coronary intervention
Figure 2a, b and c: Development in Coronary angiography (CAG), Percutaneous coronary intervention (PCI) and Coronary artery bypass grafting (CABG) treatment probability from year 2001 to 2009 for patients with Non ST elevation myocardial infarction at day 1, 3, 7 (CABG only), 10, 30 and 60.

§ For PCI and CABG only among those who receive CAG
# For CABG time is measured from time of CAG
Figure 3 a, b, c: Development in Coronary angiography (CAG), Percutaneous coronary intervention (PCI) and Coronary artery bypass grafting (CABG) treatment probability from year 2001 to 2009 for patients with unstable angina at day 1, 3, 7 (CABG only), 10, 30 and 60

§ For PCI and CABG only among those who receive CAG
# For CABG time is measured from time of CAG
Appendix 1: Treatment codes (SKS codes)

CAG: UXAC85, UXAC85A, UXAC85B, UXAC85C or UXAC85D;

PCI: KFNG, KFNG00, KFNG02, KFNG05, KFNG10, KFNG12, KFNG20, KFNG22, KFNG30, KFNG40, KFNG96;

CABG: KFNA, KFNA00, KFNA10, KFNA20, KFNC, KFNC10, KFNC20, KFNC30, KFNC40, KFNC50, KFNC60, KFNC96, KFND, KFND10, KFND20, KFND96, KFNE, KFNE00, KFND10, KFNE20, KFND96.

ACS: Acute coronary heart syndrome
STEMI: ST elevation myocardial infarction
NSTEMI: Non ST elevation myocardial infarction
AMI: Acute myocardial infarction
CAG: Coronary angiography
CABG: Coronary artery bypass grafting
PCI: Percutaneous coronary intervention
Appendix 2: Definition of time to treatment

Both date and clock-time is important in relation to the definition of time to treatment. Date is available for all patients for both admission and procedure while clock-time was missing in some cases. For patients for whom information on clock time of admission was missing, time of admission was defined as one hour before the time registration for the CAG (n=498). For example, if a patient was admitted on the 10th of June with missing time information and had a CAG on June 11th at 10 AM then the waiting time would be set at 25 hours. Conversely, if time information on CAG (n=109), PCI (n=195) or CABG (n=335) was missing, then the hour of CAG, PCI and CABG was defined as one hour after the time registered at the initial admission. This ensured that the dates of admission were still used, but that the waiting time could not end up being negative. Patients without information on both the time of initial presentation and time of CAG (n=2), PCI (n=1) and CABG (n=5) respectively were excluded from the analysis. If a patient received both PCI and CABG, then only the first treatment received was included in the analysis.
Appendix 3: Distribution of diagnosis for patients with a non acute coronary heart syndrome diagnosis at coronary angiography

<table>
<thead>
<tr>
<th>Specification</th>
<th>SKS-code</th>
<th>Number</th>
<th>%</th>
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<td>Hypertension arterialis essentias</td>
<td>DI109</td>
<td>161</td>
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<tr>
<td>Other form of angina pectoris</td>
<td>DI100</td>
<td>100</td>
<td>1.0</td>
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<tr>
<td>Angina pectoris no specification</td>
<td>DI209</td>
<td>3,721</td>
<td>36.9</td>
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<tr>
<td>Angina pectoris (stable)</td>
<td>DI251</td>
<td>1,610</td>
<td>16.0</td>
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<tr>
<td>Former myokardial infarction</td>
<td>DI252</td>
<td>620</td>
<td>6.2</td>
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<tr>
<td>Chronic ischemic heart disease without specification</td>
<td>DI259</td>
<td>320</td>
<td>3.2</td>
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<tr>
<td>Aorta valve stenose, non reumatoid</td>
<td>DI350</td>
<td>184</td>
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<tr>
<td>Heart failure no specification</td>
<td>DI509</td>
<td>159</td>
<td>1.6</td>
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<tr>
<td>Chest pain no specification</td>
<td>DR079</td>
<td>152</td>
<td>1.5</td>
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<tr>
<td>Cardiogenic shock</td>
<td>DR570</td>
<td>109</td>
<td>1.1</td>
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<tr>
<td>Observation myocardial infarction</td>
<td>DZ034</td>
<td>296</td>
<td>2.9</td>
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<td>Observation heart disease</td>
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<td>764</td>
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<tr>
<td><strong>Sub total</strong></td>
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<td><strong>Other</strong></td>
<td>Other</td>
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<td><strong>Total</strong></td>
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<td><strong>10,080</strong></td>
<td><strong>100</strong></td>
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Appendix 4: Additional results for NSTEMI

4.1. Results from the Fine Grey model for NSTEMI at 3 days (CAG/PCI) and 7 days (CABG)

### 4.1.a CAG

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<th>Year</th>
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<th>CI 95</th>
<th>Year</th>
<th>β</th>
<th>CI 95</th>
<th>+ fixed treatment protocols</th>
<th>+ age n=18,482</th>
<th>+ sex n=18,482</th>
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<tbody>
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<td>2001</td>
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<td>0.19</td>
<td>0.18-0.21</td>
<td>0.19-0.21</td>
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<td>-0.02</td>
<td>-0.33-(-0.11)</td>
<td>-0.02-(-0.11)</td>
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<td>-1.84</td>
<td>-1.99-(-1.70)</td>
<td>-1.99-(-1.70)</td>
</tr>
<tr>
<td>2005</td>
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<td>2005</td>
<td>-1.90</td>
<td>-2.04-(-1.76)</td>
<td>-1.84</td>
<td>-1.99-(-1.70)</td>
<td>-1.99-(-1.70)</td>
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<td>2006</td>
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<td>0.66-1.06</td>
<td>2006</td>
<td>-1.90</td>
<td>-2.04-(-1.76)</td>
<td>-1.84</td>
<td>-1.99-(-1.70)</td>
<td>-1.99-(-1.70)</td>
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<td>2007</td>
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<tr>
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<td>1.00-1.96</td>
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<td>-1.99-(-1.70)</td>
<td>-1.99-(-1.70)</td>
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<tr>
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**Fixed treatment protocols**

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<th>CI 95</th>
<th>Age</th>
<th>β</th>
<th>CI 95</th>
<th>Age</th>
<th>β</th>
<th>CI 95</th>
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</thead>
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<td>Ref: &lt; 50</td>
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<td>0.18-0.28</td>
<td>50-59</td>
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<td>-0.34-(-0.05)</td>
<td>60-79</td>
<td>-0.20</td>
<td>-0.34-(-0.05)</td>
</tr>
<tr>
<td>50-59</td>
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<td>-0.34-(-0.05)</td>
<td>60-79</td>
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<td>&gt;80</td>
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<td>-0.34-(-0.05)</td>
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<table>
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<th>β</th>
<th>CI 95</th>
<th>Sex</th>
<th>β</th>
<th>CI 95</th>
<th>Sex</th>
<th>β</th>
<th>CI 95</th>
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<tbody>
<tr>
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<td>Women</td>
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### 4.1.b PCI

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<th>Year</th>
<th>β</th>
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<th>+ sex n=11,680</th>
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<td>0.04-0.10</td>
<td>0.03-0.06</td>
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<td>0.04-0.10</td>
<td>0.03-0.06</td>
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<td>0.04-0.10</td>
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<td>0.04-0.10</td>
<td>0.03-0.06</td>
</tr>
<tr>
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<td>0.04-0.10</td>
<td>0.03-0.06</td>
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<tr>
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<td>2006</td>
<td>-0.07</td>
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**Fixed treatment protocols**

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<th>Age (ref = &lt; 50)</th>
<th>β</th>
<th>CI 95</th>
<th>Age (ref = &lt; 50)</th>
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<td>60-79</td>
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<td>-0.34-(-0.05)</td>
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<td>-0.34-(-0.05)</td>
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</table>

<table>
<thead>
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<th>Sex (ref=men)</th>
<th>β</th>
<th>CI 95</th>
<th>Sex (ref=men)</th>
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<td>0.70-1.29</td>
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<td>0.70-1.29</td>
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<table>
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<th>LMCA involvement</th>
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<table>
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<th>Number of occluded vessels</th>
<th>β</th>
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### 4.1.c. CABG

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<th>+ sex n=11,680</th>
<th>+ Number of occluded vessels and main trunk disease n=7,592</th>
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<td><strong>β</strong></td>
<td><strong>CI 95</strong></td>
<td><strong>β</strong></td>
</tr>
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<td><strong>CI 95</strong></td>
<td><strong>β</strong></td>
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<td><strong>β</strong></td>
<td><strong>CI 95</strong></td>
<td><strong>β</strong></td>
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<td><strong>β</strong></td>
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### 4.2. Results from the Fine Grey model for NSTEMI at 60 days

#### 4.2.a CAG

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#### Age

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#### 4.2.b PCI

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<th>+ sex n=11,680</th>
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#### Age

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#### LMCA involvement

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#### Number of occluded vessels

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### 4.2.c CABG

#### NSTE MI

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#### Age

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#### Sex

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<th>+ sex n=11,680</th>
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#### LMCA involvement

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<th>+ sex n=11,680</th>
<th>+ Number of occluded vessels and main trunk disease n=7,592</th>
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<td>0</td>
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#### Number of occluded vessels

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<th>+ sex n=11,680</th>
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### Appendix 5: Additional result for unstable angina

#### 5.1. Results from the Fine Grey model for unstable angina at 3 days (CAG/PCI) and 7 days (CABG)

#### 5.1.a CAG

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#### 5.1.b PCI

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<th>+ sex n=4,299</th>
<th>+ Number of occluded vessels and main trunk disease n=2,776</th>
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<td>β</td>
<td>CI 95</td>
<td>β</td>
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#### Data for PCI includes:
- Fixed treatment protocols
- Age (Ref: < 50, 50-59, 60-79, >80)
- Sex (Men, Women)
- LMCA involvement (Ref=no, Yes)
- Number of occluded vessels (Ref=1, 2, 3)
### 5.1.c CABG

Unstable angina

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### 5.2. Results from the Fine Grey model for unstable angina at 60 days

#### 5.2.a CAG

Unstable angina

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### 5.2.b PCI

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## 5.2.b CABG

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STROBE Statement—checklist of items that should be included in reports of observational studies

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<td>(b) Provide in the abstract an informative and balanced summary of what was done and what was found</td>
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<td>Explain the scientific background and rationale for the investigation being reported</td>
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<td>State specific objectives, including any prespecified hypotheses</td>
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<td>Present key elements of study design early in the paper</td>
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<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</td>
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<td>(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</td>
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<td>Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants</td>
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<td>Case-control study—For matched studies, give matching criteria and the number of controls per case</td>
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<td>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</td>
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<td>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group</td>
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<td>Describe any efforts to address potential sources of bias</td>
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<td>(a) Describe all statistical methods, including those used to control for confounding</td>
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<td>(b) Describe any methods used to examine subgroups and interactions</td>
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<td>(e) Describe any sensitivity analyses</td>
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Results

Participants 13*
(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
(b) Give reasons for non-participation at each stage
(c) Consider use of a flow diagram

Descriptive data 14*
(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
(b) Indicate number of participants with missing data for each variable of interest
(c) Cohort study—Summarise follow-up time (eg, average and total amount)

Outcome data 15*
Cohort study—Report numbers of outcome events or summary measures over time
Case-control study—Report numbers in each exposure category, or summary measures of exposure
Cross-sectional study—Report numbers of outcome events or summary measures

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(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
(b) Report category boundaries when continuous variables were categorized
(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

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Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

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Key results 18
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Discuss both direction and magnitude of any potential bias

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Other information

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Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Trends in time to invasive examination and treatment from 2001 to 2009 in patients admitted first time with non ST-elevation Myocardial Infarction or unstable angina in Denmark.

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Title

Trends in time to invasive examination and treatment from 2001 to 2009 in patients admitted first time with non ST-elevation Myocardial Infarction or unstable angina in Denmark.

Solvej Mårtensson MSc Public Health 1*, prof. Dorte Gyrd-Hansen 2, prof. Eva Prescott MD, DMSc 3, prof. Per Kragh Andersen 4, Ann-Dorthe Olsen Zwisler MD PhD 5, prof. Merete Osler MD, DMSc 1,6

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Number of words in main text: 3,873

Keywords: acute coronary heart syndrome, NSTEMI, Unstable angina, time to treatment, time trends, cohort design
Abstract

Objective:
To investigate trends in time to invasive examination and treatment for patients with first time
diagnosis of non-ST-elevation Myocardial infarction (NSTEMI) and unstable angina in the period
from 2001 to 2009 in Denmark

Design: From 1 January 2001 to 31 December 2009 all first time hospitalisations with NSTEMI and
unstable angina were identified in the National Patient Registry (n=65,909). Time from admission
to initiation of coronary angiography (CAG), percutaneous coronary intervention (PCI) or coronary
artery bypass graft (CABG) was calculated. We described the development in invasive examination
and treatment probability (CAG, PCI and CABG at 3, 7, 10, 30 and 60 days) for the years 2001 to
2009, taking the competing risk of death into account using Aalen-Johansen estimators and a Fine
Gray model.

Setting: Nationwide Danish cohort

Results: The proportion of patients receiving a CAG and PCI increased substantially over time
while the proportion receiving a CABG decreased for both NSTEMI and unstable angina. For both
NSTEMI and unstable angina a significant increase in invasive examination and treatment
probability at 3 days for CAG and PCI was seen especially from 2007 through to 2009. For
NSTEMI the CAG examination probability at 3 days leaped from 20 % in 2007 to 32 % in 2008
and 39 % in 2009 and PCI the same was true with a leap in treatment probability from 19 % to 28 %
from 2008 to 2009.
Conclusions: In Denmark the use of CAG and PCI in treatment of NSTEMI and unstable angina has increased from 2001 to 2009 while the use of CABG has decreased. During the same period there was a marked increase in invasive examination and treatment probability at 3 days i.e. more patients were treated faster which is in line with the political aim of reducing time to treatment.

Main strengths:
- Large unselected patient population n=65,909
- Detailed register based data
- Use of statistical methods that account for competing risks
- Information on extension and severity of the disease

Main limitations:
- No information on biomarkers to validate register based data
- No information on why patients died before treatment
Introduction

Treatment of acute coronary heart disease has advanced substantially during the latest decades, and improved clinical outcome has been seen (1). A recent register based Danish cohort study by Schmidt et al. found that short term mortality after first time hospitalisation with AMI was nearly halved from 1984 to 2008 (2). It has been suggested that part of this decline can be attributed to improved treatment including introduction of thrombolysis, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) and improved medical prevention after diagnosis (3). Coronary angiography (CAG) is recommended as part of the diagnostic process for all patients with acute myocardial infarction with PCI as the primary intervention (4). Since the mid nineties there has been a strong political focus on time to treatment in order to reduce case fatality (5). For coronary heart disease this focus in Denmark has among other initiatives led to the development of fixed treatment protocols for patients with non ST elevation myocardial infarction (NSTEMI) and unstable angina. These protocols were implemented during 2009. The protocol stipulates that the maximum time from admission with NSTEMI to invasive examination (CAG) should be less than 3 calendar days (72 hours) and time to appropriate invasive treatment less than 3 calendar days for PCI, and 7 calendar days for CABG (6). These protocols are based on the shared European guidelines (4, 7).

The purpose of this study is to investigate a potential explanation of the significant improvement in prognosis by describing time to invasive examination and treatment for patients with first time diagnosis of NSTEMI or unstable angina in the period from 2001 to 2009 in Denmark using a nationwide cohort design and taking into account vessel disease severity as well as using appropriate methods of analysis that account for the competing risk of death. This study is the first nationwide cohort study to describe time waited for CAG, PCI and CABG over a decade where
large changes in treatment of NSTEMI and unstable angina were introduced including the introduction of fixed treatment protocols.
Method

The Danish health care system provides universal coverage for all citizens. Since 1995, all contacts with the health care system including emergency, ambulatory and inpatient have been registered in the National Patient Registry (NPR) with information about time and date of admission and discharge along with information about diagnosis as well as type and date of potential invasive treatment or examination (8). Furthermore there are several registers and clinical quality databases with patient specific information (9) that can be linked with the data from the NPR through the use of the unique ten-digit person identifier. The registers used for this study are the NPR, the Danish Heart Registry, which registers information regarding patients undergoing invasive cardiac procedure (10) and the Medical Cause of Death Registry, which contains information on time and cause of death (11).

Study population:

From January 1 2001 to December 31 2009 all first time hospitalisations of acute coronary heart syndrome (ACS) were identified in the National Patient Registry (n= 99,473) by the following ICD10 codes (I20.0 Unstable angina pectoris, I21.0-I21.3 ST-elevation myocardial infarction (STEMI), I21.4 non ST-elevation myocardial infarction (NSTEMI) and I21.9 AMI – Unspecified) using discharge diagnoses (see figure 1). Patients with prior heart disease (ICD10: I20-I25) were excluded using information from the NPR going back to 1995 (n= 19,440) leaving 80,033 patients. A previous study by Joensen et al. found that the ACS diagnosis registered in the NPR should be used with caution especially the unstable angina diagnosis (12). Joensen et al. recommend restricting the analysis to patients discharged from wards when other validation is not possible. We therefor excluded outpatients (n=2,564) and patients with a NSTEMI or unstable angina diagnosis from an emergency room that was not verified in the subsequent admission (n=11,560) still
allowing for a shift from NSTEMI to unstable angina or vice versa. Consequently, the final population consisted of 65,909 patients. Diagnosis can change after the result of CAG therefore we used the diagnosis registered after the CAG in the analysis of time to PCI and CABG. For this reason the number of patients in the different sub-diagnosis groups vary between analyses of CAG, PCI and CABG (see figure 1 for distribution of patients with acute coronary heart syndrome in sub diagnosis groups at initial examination and after coronary angiography). Patients with STEMI and unspecified MI are only included in the initial descriptive analysis of the patient population.

Variables

**Time to examination or treatment (from admission to CAG, PCI and CABG)**

Time (measured in hours) from admission to initiation of coronary angiography (CAG), percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) was calculated using information from the NPR (the specific SKS codes can be seen in appendix 1) Only treatment and examination within the first 60 days after initial symptom presentation was included. Further information regarding this variable can be found in appendix 2.

**Severity and extent of disease**

Severity and the extent of disease will influence the perceived urgency of treatment. Information on number of occluded vessels and Left Main Coronary Artery (LMCA) involvement was available from the Danish Heart Register (DHR) in 82.1% and 84.7% of the cases that received a CAG, respectively. We allowed for a slip of ±2 days between NPR CAG date and DHR CAG date when identifying CAG information.
Other covariates include sex, age and year of diagnosis.

**Statistical methods**

In the descriptive analysis the number of patients receiving CAG, PCI or CABG was reported along with the number of patients receiving the respective examination or treatment within 3 days for CAG and PCI and 7 days from CAG for CABG for each diagnosis and for each of the covariates: age, sex, number of occluded vessels and LMCA involvement. When investigating time to treatment for a specific disease, it is important to account for the competing risk of death in order to account for the time waited by patients who die before they are treated (13). Reporting a median time to treatment is not relevant as it will only describe the time waited by patients who manage to be treated. Furthermore, if we wish to model cumulated probability of treatment (not intensities) and applied standard methods (e.g. Cox regression method or Kaplan Meier plots), then we would regard death without treatment as independent censoring and would only be able to make inference for a hypothetical population where patients do not die without being treated (13). The problem of competing risks is especially important for a potentially fatal disease like ACS where some sub diagnosis have a relative high mortality rate (14, 15). Furthermore, as first line invasive treatments are mutually exclusive (patients receive either PCI or CABG) we need to account for the competing risk of receiving the other treatment, respectively. To account for this competing risks problem we used Aalen-Johansen plots where we described the development in invasive examination (CAG) and treatment probability (PCI and CABG) for the years 2001 to 2009. These plots account for the competing risks of death and treatment (PCI or CABG, respectively) by showing the estimated percentage of the original population, which at a given time has received the examination (CAG) and treatment (PCI or CABG). The plot has no distributional assumptions (13). From these plots we
derived probability at 1, 3, 7 (only for CABG), 10, 30 and 60 days after diagnosis. These probabilities are presented in graphs in order to show the development from 2001 to 2009.

To test whether the effects seen in the plots were statistically significant, we used the Fine Gray model, a regression model that accounts for competing risks and adjusts for covariates (13). In this model we find the effect of the calendar years when controlling for covariates (age, sex, LMCA involvement and number of occluded vessels).

When analysing the impact of the fixed treatment protocols implemented during 2009, a proper evaluation with a control group was not feasible due to lack of an appropriate comparison group. Consequently we applied a second-best solution where we looked at whether the change in times to examination or treatment in the year 2009 differed from the time trend observed in the time period from 2001 to 2008 extrapolated to 2009. The use of this method was inspired by the methods used by Lee et al when evaluating the effects of Pay for Performance in the UK (16). We tested this in the Fine Gray model and report the test statistics as z. Year 2001 is the reference when year is included categorically. In all analyses a 5 % significance level was used.

Data were analysed with SAS version 9.3, STATA version 12.1 and by using the macro COMPRISK to draw Aalen-Johansen plot provided open access by the MAYO Institute.

Results:

Of the 65,909 patients identified 28.7 % were admitted with NSTEMI, 13.4 % with unstable angina, 25.5 % with STEMI and 32.4 % with non-specified MI. A total of 8,412 patients were after the CAG registered with a non ACS diagnosis and subsequently excluded from the further analysis.
of PCI and CABG (see appendix 3 where the diagnoses that account for 80% of these patients are listed). After CAG the distribution of diagnosis were as follows 35.0 % of patients were admitted with NSTEMI, 12.6 % with unstable angina, 33.2 with STEMI and 19.2 with non-specific MI.

Table 1 show that from 2001 to 2009 the proportion of patients with NSTEMI receiving a CAG and PCI increased substantially, while the proportion receiving a CABG decreased. During the same period the fraction of patients examined with a CAG who received this within 3 days increased from 18.2 % to 55.7 %. For PCI a similar development was seen with 52.0 % treated within 3 days in 2009 compared to 27.5 % in 2001. For CABG within 7 days the percentage slightly declined over the time period with some fluctuations.

Insert table 1

For unstable angina the activity rate increased for CAG, but not for PCI in the period from 2001 to 2009 (table 2) however for both CAG and PCI the rates of patient who received these procedures within 3 days doubled in this time period. For CABG the treatment rate was more than halved.

Insert table 2

Figure 2a shows the development in the probability of invasive examination using CAG from 2001 to 2009 for NSTEMI accounting for the competing risk of death. The figure shows a significant increase in the use of CAG in the period from 2001 to 2005 with an increase in probability from 49.8 % for CAG at 60 days in 2001 to 70.4 % in 2005 (tested using the Fine Gray model see results in appendix 4). From 2005 and onwards only a slight increase in probability of CAG at 60 days was seem. The figure also shows a steady increase in the probability of CAG within 3 days from 2001 to
2007 followed by a leap from 19.5% in 2007 to 31.9% in 2008 and a further increase to 38.7% in 2009. The fixed treatment protocol seemed to have a significant effect on the probability of receiving a CAG within 3 days (z=4.16 p<0.001). For PCI (figure 2b) there was only a slight increase in the probability of treatment with PCI at 60 days from 2001 to 2009. Further the probability of PCI treatment within 3 days increased markedly from 2007 to 2008 and again from 2008 to 2009. The effect of the implementation of the fixed treatment protocols also revealed a significant effect for PCI (z=7.44 p<0.001). For CABG the development in treatment probability was somewhat different with a significant drop in probability of receiving this type of invasive treatment over the period 2001 to 2006 with subsequent stagnation (figure 1c). The probability of CABG within 7 days of CAG decreased significantly over the period and there seemed to be no effect of the fixed treatment protocols (z=0.50 p=0.62).

Insert figure 2

Figure 3 shows the similar graphs for patient with unstable angina. In general the development was very similar to that of patients with NSTEMI, but with the increase in the invasive examination and treatment rate later in the observation period (from 2004 to 2008). The probability of receiving CAG within 3 days increased three-fold from 2001 to 2009 with an almost constant increase (figure 2a). We saw no effect of the fixed treatment protocols on timing of CAG (z=0.50 p=0.62). The PCI treatment rate at 60 days was somewhat stable in the time period with a small drop in 2004, while the probability of treatment within 3 days increased almost constantly from 2001 to 2009. There was no effect of the fixed treatment protocols (z=-0.32 p=0.75) (figure 2b). For CABG the treatment probability at 60 days decreased in the time period as well as the treatment probability at 7 days (figure 2c). There was no significant effect of the fixed treatment protocols. For both
NSTEMI and unstable angina there was no significant development in death before treatment over time i.e. a competing risk (analysis not shown).

*Insert figure 3*

When including age, sex, number of occluded vessels and LMCA involvement (last two only for PCI and CABG) we found that for NSTEMI the development in CAG examination probability at 3 days and 60 days was the same as seen in the unadjusted analyses, and the effect of the fixed treatment protocols remained significant. For PCI the same pattern was observed, however when adjusting for number of occluded vessels, the linear effect of year became insignificant, but the effect of the fixed treatment protocols remained. For CABG the picture did not change after the adjustment except that the decrease in treatment probability seen at 60 days was not as noticeable as in the unadjusted analysis. Performing the same adjustments did not change the conclusions for unstable angina either (See all results from the Fine Gray model in appendix 5).
Discussion

In this nationwide cohort study, we found a significant increase in the proportions of patients with NSTEMI and unstable angina receiving a CAG and PCI in Denmark between 2001 and 2009, while the proportion receiving CABG decreased. In the analysis accounting for competing risks there was an increase in the probability of examination and treatment within 3 days for CAG and PCI after 2001 and there seemed to be a significant effect of the introduction of a fixed treatment protocol with recommended maximum time from diagnosis to invasive examination and treatment for NSTEMI, but not for unstable angina.

Our results are in agreement with studies from the US, which showed an increase in the use of CAG and PCI over the last two decades, and a decrease in CABG (1, 17, 18). The study also contributes to the interpretation of the findings from a recent Danish study (2), which showed a significant reduction in 30-day and 1-year mortality risk after first time hospitalisation for MI between 1999-2003 and 2004-2008. Part of this reduction could be due to a decrease in time to treatment. When comparing with this study one should keep in mind that we did not include patients with STEMI who are included in Schmidt et al.‘s study and that these patients have a succinct treatment path with the need for more urgent treatment. There seems to be no other nationwide studies on trends in time from diagnosis to invasive treatment; however in 2009 Bradley et al reported a decrease in door to balloon time for patients with STEMI after enrolment in a national quality campaign with the aim to reduce the door to balloon time to less than 90 minutes for this group (19).

We did find a significant decline in time for CAG and PCI corresponding to implementation of the fixed treatment protocol for NSTEMI. However, for both NSTEMI and unstable angina, we found a steady increase in treatment rate from 2001 and onwards and for NSTEMI a steep increase in
probability already in 2008. This indicates that focus on improvement on time to invasive
eexamination and treatment is not new. Furthermore the treatment protocols were first implemented
during 2009, but they were already discussed in 2008 and this could have led to early
implementation and hence an increase in speed of invasive examination and treatment before the
actual implementation. In this time period there seemed to be a general agreement on the benefits of
an invasive strategy vs. medical management for patients with NSTEMI (20, 21). However the
optimal timing of invasive interventions was not clearly agreed upon. Mehta et al published in 2009
their results from the large TIMACS trial which included 3031 patients with unstable angina or
NSTEMI. They found a significantly lower risk of death, myocardial infarction or stroke at 6
months for high risk patients when comparing an early (less than 24 h) with a delayed strategy
(more than 36 h). Furthermore they found no safety issues related to the early strategy (22). This
shows the importance of early invasive treatment however these results only reflect the difference
between very early and early invasive intervention which is a slightly other discussion than ours. In
2010 a metaanalysis was published combining four trials which concluded that early angiography
and if relevant treatment for patients with NSTEMI reduces the risk of recurrent ischemia and
shortens hospital stay (23). These results were however not reflected in the European Society of
Cardiology guidelines until 2011 (4). However the previous guideline from 2007 (p. 27) also
stated: "...Accordingly, currently available evidence does not mandate a systematic approach of
immediate angiography in NSTE-ACS patients stabilized with a contemporary pharmacological
approach. Likewise, routine practice of immediate transfer of stabilized patients admitted in
hospitals without onsite catherization facilities is not mandatory, but should be organized within 72
h” (7). We found that the number of patients receiving the recommended invasive examination and
treatment within the recommend time frame increased from 2001 to 2009, however a large group of
patient still received no invasive investigation or were treated later than the guideline recommends
in 2009. This patient group consists of three possible groups: patients that don’t have the disease in question due to lack of validity of data (see later discussion of strengths and weaknesses), patients who are too ill to be treated and patients who receive a less than optimal treatment. The basic idea behind the fixed treatment protocol i.e. same treatment for patients presenting with the same clinical symptoms irrespective of when or where patients come in contact with the health care system should ensure that the latter group is proportionally smaller in 2009 than in 2001. However, there could still be patients who don’t receive optimal treatment and unexplained variation between hospitals. Therefor monitoring by health authorities is of great importance.

**Strengths and weaknesses**

The primary strength of this study is the large unselected patient population, as it covers all patients admitted with first time ACS in the period from 2001 to 2009 in Denmark. The patients were identified in the NPR, however this means that we do not have information on biomarkers but solely rely on the correctness on what is registered in the NPR. We excluded outpatients and patients with a diagnosis from an emergency room which was not verified in a ward subsequently, however especially the unstable angina diagnosis is still problematic. Thus, it has been found that the positive predictive value of unstable angina for patients discharged from a ward only seems to around 40 % (12). Therefor one reason for the lack of effect of the fixed treatment protocols for this group of patients could be that a substantial part of this group does not have unstable angina. The data in the NPR allowed us to follow patients through the course of diagnosis and treatment path, and we utilised this to change patients’ diagnoses after the CAG in case another diagnosis was registered at this point in time. This was done in order to imitate the clinical situation. At CAG 8,412 patients had a diagnosis other than ACS. The largest group was 3,230 patients with angina no specification. This group of patients could potentially be patients with unstable angina however
including this group did not change the conclusions (analysis not shown). We had information on
the specific hour of admission and used this information to calculate time to treatment. Although the
validity of this information can be questioned, we used it in order to calculate the time as precisely
as possible. We only included treatment and examination within 60 days as ACS is an acute disease
for which treatment if relevant should be initiated as soon as possible. We analysed our data by use
of statistical methods that accounted for the competing risk of death, which is very important when
we estimate trends in time to treatment in a population with a high risk of death. However we do not
know whether patients who died were not treated because the risk of invasive examination and
treatment was deemed too high, or because the treatment was not considered relevant. Our analysis
showed that the group of patients not receiving CAG was reduced in the period from 2001 to 2009,
which was primarily due to an increase in examination of elderly patients (analysis not shown). We
also included information on the number of occluded vessels and LMCA involvement as a measure
of the extension and severity of the disease in the analysis. This information was only available for
84.7% and 82.1 % of the patients and especially patients from 2001 and 2002 had missing
information on this variable. However, we have no reason to believe that this missing data should
be non-random and related to time to treatment. Further we did not use age standardised data in the
trend analyses because the fixed treatments protocols include all patient groups. However, we tested
whether there was an effect of the treatment protocols in the Fine Gray model which adjusted for
age, gender, LMCA involvement and number of occluded vessels. The analyses showed that these
variables did not change the effect of the treatment protocols. It should also be noticed that we did
not include patients who died before arrival to a hospital as these patients are not included in the
NPR. It should also be noticed that our study is an observational trend study and we cannot exclude
that other organizational or treatment factors than the introduction of the fixed treatment protocol
has contributed to the observed reduction in time to examination and treatment. This study only
evaluates the immediate effects of the fixed treatment protocols; however a longer follow up would also be of interest.

In conclusion, this study contributes to the interpretation of the recent decline in mortality after hospitalisation for MI by showing a contemporary increase in the proportion of patients receiving a CAG and PCI as well as an increase in the probability of patients receiving CAG and PCI within the recommended time. The study also suggest that the introduction of fixed treatment protocols with a recommended maximum time from diagnosis to invasive examination and treatment may have impacted on time to treatment as more patients receive a CAG and PCI within the time limit of 3 days around the time of the introduction of the protocols.
Table 1: Coronary angiography (CAG), Percutaneous coronary intervention (PCI) and Coronary artery bypass grafting (CABG) treatment rates and number treated within 3/7 days distributed according to covariates for patients with first time Non ST elevation myocardial infarction (NSTEMI)

<table>
<thead>
<tr>
<th>NSTEMI</th>
<th>Diagnosis at initial examination</th>
<th>Diagnosis registered after CAG</th>
<th>CABG within 60 days from CAG</th>
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<td>CAG within 60 days</td>
<td>Examinati n rate % n % in 3 days</td>
<td>PCI within 60 days (Grouped according to after CAG diagnosis)</td>
<td>Treatment rate % n % in 7 days</td>
</tr>
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<td>Overall</td>
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<td>2001</td>
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<td>54.9 1,177 19.9 49.6 465 24.8 22.8</td>
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<td>61.3 1,422 23.2 54.3 673 24.2 17.8</td>
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<tr>
<td>2005</td>
<td>67.7 1,480 26.6 56.7 771 23.7 16.2</td>
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<td>91.4 1,093 40.6 59.2 599 42.2 7.0</td>
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<td>21.8 1,118 31.2 49.7 515 27.0 8.7</td>
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<td>3 vessels</td>
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<td>4</td>
<td>30.0 630 30.1 49.3 1034 29.6</td>
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</table>

* National guidelines recommend CAG and PCI within 3 days of diagnosis and CABG within 7 days of CAG.

** Left Main Coronary Artery
Table 2: Coronary angiography (CAG), Percutaneous coronary intervention (PCI) and Coronary artery bypass grafting (CABG) treatment rates and number treated within 3/7 days distributed according to covariates for patients with first time Unstable Angina

<table>
<thead>
<tr>
<th>Unstable angina</th>
<th>Diagnosis at initial examination</th>
<th>Diagnosis registered after CAG</th>
<th>CABG within 60 days from CAG</th>
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<tbody>
<tr>
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<td>CAG within 60 days</td>
<td>PCI within 60 days (Grouped according to after CAG diagnosis)</td>
<td>CABG within 60 days from CAG</td>
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<tr>
<td></td>
<td>Examination rate %</td>
<td>n % in 3 days*</td>
<td>Treatment rate %</td>
</tr>
<tr>
<td>Overall</td>
<td>8,820</td>
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<tr>
<td>Year of diagnosis</td>
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<td>59.9</td>
<td>631</td>
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<td>32.0</td>
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<tr>
<td>2 vessels</td>
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<tr>
<td>3 vessels</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

* National guidelines recommend CAG and PCI within 3 days of diagnosis and CABG within 7 days of CAG.
** Left Main Coronary Artery
Contributors: SM, DGH, EP, ADOZ, MO contributed to the design of the study. SM carried out statistical analysis with guidance from PKA and MO. SM wrote initial draft and all authors critically revised the manuscript.

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Competing interest: None

Ethics
This register based study was approved the Danish Data Protection Agency (Approval number 2010-41-5263). Register based studies does not need approval by a medical ethics committee in Denmark.

Data sharing: There are no available data
Reference List


Title

Trends in invasive examination, treatment rate and time to invasive examination and treatment from 2001 to 2009 in patients admitted first time with non ST-elevation Myocardial Infarction or unstable angina in Denmark.

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Number of words in main text: 3,873
Abstract

Objective:
To investigate time trends in invasive examination and time to invasive examination and treatment for patients with first time diagnosis of non-ST-elevation Myocardial infarction (NSTEMI) and unstable angina in the period from 2001 to 2009 in Denmark.

Design: From 1 January 2001 to 31 December 2009 all first time hospitalisations with NSTEMI and unstable angina were identified in the National Patient Registry (n=65,909). Time from admission to initiation of coronary angiography (CAG), percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) was calculated. We described the development in invasive examination and treatment probability (CAG, PCI and CABG at 3, 7, 10, 30 and 60 days) for the years 2001 to 2009, taking the competing risk of death into account using Aalen-Johansen estimators and a Fine-Gray model.

Setting: Nationwide Danish cohort

Results: The proportion of patients with receiving a CAG and PCI increased substantially over time while the proportion receiving a CABG decreased for both NSTEMI and unstable angina. For both NSTEMI and unstable angina a significant increase in invasive examination and treatment probability at 3 days for CAG and PCI was seen especially from 2007 through to 2009. For NSTEMI the CAG treatment-examination probability at 3 days leaped from 20.4% in 2007 to 32.4% in 2008 and 39% in 2009 and PCI the same was true with a leap in treatment probability from 19% to 28% from 2008 to 2009.
Conclusions: In Denmark the use of CAG and PCI in treatment of NSTEMI and unstable angina has increased from 2001 to 2009 while the use of CABG has decreased. During the same period there was a marked increase in invasive examination and treatment probability at 3 days i.e. more patients were treated faster which is in line with the political aim of reducing time to treatment.

Main strengths:
- Large unselected patient population n=65,909
- Detailed register based data
- Use of statistical methods that account for competing risks
- Information on extension and severity of the disease

Main limitations:
- No information on biomarkers to validate register based data
- No information on why patients died before treatment

Keywords: acute coronary heart syndrome, NSTEMI, Unstable angina, time to treatment, time trends, cohort design
Introduction

Treatment of acute coronary heart disease has advanced substantially during the latest decades, and improved clinical outcome has been seen (1). A recent register based Danish cohort study by Schmidt et al. found that short term mortality after first time hospitalisation with AMI was nearly halved from 1984 to 2008 (2). It has been suggested that part of this decline can be attributed to improved treatment including introduction of thrombolysis, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) and improved medical prevention after diagnosis (3). Coronary angiography (CAG) is recommended as part of the diagnostic process for all patients with acute myocardial infarction with PCI as the primary intervention (4). Since the mid nineties there has been a strong political focus on time to treatment in order to reduce case fatality (5). For coronary heart disease this focus in Denmark has among other initiatives led to the development of fixed treatment protocols for patients with non ST elevation myocardial infarction (NSTEMI) and unstable angina. These protocols were implemented during 2009. The protocol stipulates that the maximum time from admission with NSTEMI to invasive examination (CAG) should be less than 3 calendar days (72 hours) and time to appropriate invasive treatment less than 3 calendar days for PCI, and 7 calendar days for CABG (6). These protocols are based on the shared European guidelines (4, 7).

The purpose of this study is to explore the potential explanation of the significant improvement in prognosis by investigating time trends in invasive examination, treatment and time to invasive examination and treatment for patients with first time diagnosis of NSTEMI or unstable angina in the period from 2001 to 2009 in Denmark using a nationwide cohort design and taking into account vessel disease severity as well as using appropriate methods of analysis that account for the competing risk of death. This study is the first
nationwide cohort study to describe time waited for CAG, PCI and CABG over a decade where large changes in treatment of NSTEMI and unstable angina were introduced including the introduction of fixed treatment protocols.
Method
The Danish health care system provides universal coverage for all citizens. Since 1995, all contacts with the health care system including emergency, ambulatory and inpatient have been registered in the National Patient Registry (NPR) with information about time and date of admission and discharge along with information about diagnosis as well as type and date of potential invasive treatment or examination (8). Furthermore there are several registers and clinical quality databases with patient specific information (9) that can be linked with the data from the NPR through the use of the unique ten-digit person identifier. The registers used for this study are the NPR, the National Prescription Registry, which collects information on redeemed prescriptions (10), the Danish Heart Registry, which registers information regarding patients undergoing invasive cardiac procedure (10) and the Medical Cause of Death Registry, which contains information on time and cause of death (11).

Study population:
From January 1 2001 to December 31 2009 all first time hospitalisations of acute coronary heart syndrome (ACS) were identified in the National Patient Registry (n= 99,473) by the following ICD10 codes (I20.0 Unstable angina pectoris, I21.0-I21.3 ST-elevation myocardial infarction (STEMI), I21.4 non ST-elevation myocardial infarction (NSTEMI) and I21.9 AMI – Unspecified) using discharge diagnoses (see figure 1). Patients with prior heart disease (ICD10: I20-I25) were excluded using information from the NPR going back to 1995 (n= 19,440) leaving 80,033 patients. A previous study by Joensen et al. found that the ACS diagnosis registered in the NPR should be used with caution especially the unstable angina diagnosis (12). Joensen et al. recommend restricting the analysis to patients discharged from wards when other validation is not possible. We therefor excluded outpatients (n=2,564) and patients with a NSTEMI or unstable angina diagnosis.
from an emergency room that was not verified in the subsequent admission (n=11,560) still allowing for a shift from NSTEMI to unstable angina or vice versa. Consequently, the final population consisted of 65,909 patients for analysis. Diagnosis can change after the result of CAG therefore we used the diagnosis registered after the CAG in the analysis of time to PCI and CABG. For this reason the number of patients in the different sub-diagnosis groups vary between analyses of CAG, PCI and CABG (see figure 1 for distribution of patients with acute coronary heart syndrome within sub diagnosis groups at initial examination and after coronary angiography).

Patients with STEMI and unspecified MI are only included in the initial descriptive analysis of the patient population.

Variables

Time to examination or treatment (from admission to CAG, PCI and CABG)

Time (measured in hours) from admission to hospital to initiation of coronary angiography (CAG), percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) was calculated using information from the NPR (the specific SKS codes can be seen in appendix 1) Only treatment and examination within the first 60 days after initial symptom presentation was included. Further information regarding this variable can be found in appendix 2.

Severity and extent of disease

Severity and the extent of disease will influence the perceived urgency of treatment. Information on number of occluded vessels and Left Main Coronary Artery (LMCA) involvement was available from the Danish Heart Register (DHR) in 82.12\% and 845.76 \% of the cases that received a CAG,
respectively. We allowed for a slip of ±2 days between NPR CAG date and DHR CAG date when identifying CAG information.

Other covariates include sex, age and year of diagnosis.

Statistical methods

In the descriptive analysis the number of patients receiving CAG, PCI or CABG was reported along with the number of patients receiving the respective examination or treatment within 3 days for CAG and PCI and 7 days from CAG for CABG for each diagnosis and for each of the covariates: age, sex, number of occluded vessels and LMCA involvement. When investigating time to treatment for a specific disease, it is important to account for the competing risk of death in order to account for the time waited by patients who die before they are treated (13)(42). Reporting a median time to treatment is not relevant as it will only describe the -time waited by patients who manage to be treated. Furthermore, if we wish to model cumulated probability of treatment (not intensities) and applied standard methods (e.g. Cox regression method or Kaplan Meier plots), then we would regard death without treatment as independent censoring and would only be able to make inference for a hypothetical population where patients do not die without being treated (13)(42). This would not represent a true picture of reality. The problem of competing risks is especially important for a potentially fatal disease like ACS where some sub diagnosis have a relative high mortality rate (14, 15)(13, 14). Furthermore, as first line invasive treatments are mutually exclusive (patients receive either PCI or CABG) we need to account for the competing risk of receiving the other treatment, respectively. To account for this competing risks problem we used Aalen-Johansen plots where we described the development in invasive examination (CAG) and treatment probability (CAG, PCI and CABG) for the years 2001 to 2009. These plots account for the
competing risks of death and treatment (PCI or CABG, respectively) by showing the estimated percentage of the original population, which at a given time has received the examination (CAG) and treatment (CAG, PCI or CABG). The plot has no distributional assumptions \(^{(13)(12)}\). From these plots we derived treatment probability at 1, 3, 7 (only for CABG), 10, 30 and 60 days after diagnosis. These probabilities are presented in graphs in order to show the development from 2001 to 2009.

To test whether the effects seen in the plots were statistically significant, we used the Fine Gray model, a regression model that accounts for competing risks and adjusts for covariates \(^{(13)(12)}\). In this model we find the effect of the calendar years when controlling for covariates (age, sex, LMCA involvement and number of occluded vessels).

When analysing the impact of the fixed treatment protocols implemented during 2009, a proper evaluation with a control group was not feasible due to lack of an appropriate comparison group. Consequently we applied a second-best solution where we looked at whether the change in times to examination or treatment in the year 2009 differed from the time trend observed in the time period from 2001 to 2008 extrapolated to 2009. The use of this method was inspired by the methods used by Lee et al when evaluating the effects of Pay for Performance in the UK \(^{(16)(15)}\). We tested this in the Fine Gray model and report the test statistics as \(z\). Year 2001 is the reference when year is included categorically. In all analyses a 5 % significance level was used.

Data were analysed with SAS version 9.3, STATA version 12.1 and by using the macro COMPRI SK to draw Aalen-Johansen plot provided open access by the MAYO Institute.
Results:  
Of the 65,909,033 patients who were registered with first time ACS and no prior heart disease identified 28.73.4 % were admitted with NSTEMI, 13.49.3 % with unstable angina, 25.53.3 % with STEMI and 32.44.0 % with non-specified MI. A total of 8,412,080 patients were after the CAG registered with a non ACS diagnosis and subsequently excluded from the further analysis of PCI and CABG (see appendix 3 where the diagnoses that account for 80% of these patients are listed). After CAG the distribution of diagnosis were as follows 353.0 % of patients were admitted with NSTEMI, 12.62 % with unstable angina, 33.25.7 with STEMI and 19.20 with non-specific MI.

Table 1 show that from 2001 to 2009 the proportion of patients with NSTEMI receiving a CAG and PCI increased substantially, while the proportion receiving a CABG decreased. During the same period the fraction of patients examined with a CAG who received this within 3 days increased from 18.2 % to 55.72 %. For PCI a similar development was seen with 52.04 % treated within 3 days in 2009 compared to 27.52 % in 2001. For CABG within 7 days the percentage slightly declined over the time period with some fluctuations.

Insert table 1

For unstable angina the activity rate increased for CAG, but not for PCI in the period from 2001 to 2009 (table 3) however for both CAG and PCI the rates of patient who received these procedures within 3 days doubled in this time period. For CABG the treatment rate was more than halved.

Insert table 2
Figure 2a shows the development in the probability of invasive examination using CAG from 2001 to 2009 for NSTEMI accounting for the competing risk of death. The figure shows a significant increase in the use of CAG in the period from 2001 to 2005 with an increase in probability from 49.8% for CAG at 60 days in 2001 to 70.46% in 2005 (tested using the Fine Gray model see results in appendix 4). From 2005 and onwards only a slight increase in probability of CAG at 60 days was seen. The figure also shows a steady increase in the probability of CAG within 3 days from 2001 to 2007 followed by a leap from 19.53% in 2007 to 31.59% in 2008 and a further increase to 38.77% in 2009. The fixed treatment protocol seemed to have a significant effect on the probability of receiving a CAG within 3 days ($z=4.163.45, p<0.001$). For PCI (figure 2b) there was only a slight increase in the probability of treatment with PCI at 60 days from 2001 to 2009. Further the probability of PCI treatment within 3 days increased markedly from 2007 to 2008 and again from 2008 to 2009. The effect of the implementation of the fixed treatment protocols also revealed a significant effect for PCI ($z=7.4482, p<0.001$). For CABG the development in treatment probability was somewhat different with a significant drop in probability of receiving this type of invasive treatment over the period 2001 to 2006 with subsequent stagnation (figure 1c). The probability of treatment CABG within 7 days of CAG decreased significantly over the period and there seemed to be no effect of the fixed treatment protocols ($z=0.5032, p=0.6275$).

*Insert figure 2*

Figure 3 shows the similar graphs for patient with unstable angina. In general the development was very similar to that of patients with NSTEMI, but with the increase in the invasive examination and treatment rate later in the observation period (from 2004 to 2008). The probability of receiving CAG within 3 days increased four-three-fold from 2001 to 2009 with an almost constant increase
(figure 2a). We saw no effect of the fixed treatment protocols on timing of CAGcg (z=-0.5076 p=0.6244). The PCI treatment rate at 60 days was somewhat stable in the time period with a small drop in 2004, while the probability of treatment within 3 days increased almost constantly from 2001 to 2009. There was no effect of the fixed treatment protocols (z=-0.3223 p=0.7582) (figure 2b). For CABG the treatment probability at 60 days decreased in the time period as well as the treatment probability at 7 days (figure 2c). There was no significant effect of the fixed treatment protocols. For both NSTEMI and unstable angina there was no significant development in death before treatment over time i.e. a competing risk (analysis not shown).

Insert figure 3

When including age, sex, number of occluded vessels and LMCA involvement (last two only for PCI and CABG) we found that for NSTEMI the development in CAG treatment-examination probability at 3 days and 60 days was the same as seen in the unadjusted analyses, and the effect of the fixed treatment protocols remained significant. For PCI the same pattern was observed, however when adjusting for number of occluded vessels, the linear effect of year became insignificant, but the effect of the fixed treatment protocols remained. For CABG the picture did not change after the adjustment except that the decrease in treatment probability seen at 60 days was not as noticeable as in the unadjusted analysis. Performing the same adjustments did not change the conclusions for unstable angina either (See all results from the Fine Gray model in appendix 5).
Discussion

In this nationwide cohort study, we found a significant increase in the proportions of patients with NSTEMI and unstable angina receiving a CAG and PCI in Denmark between 2001 and 2009, while the proportion receiving CABG decreased. In the analysis accounting for competing risks there was an increase in the probability of examination and treatment within 3 days for CAG and PCI after 2001 and there seemed to be a significant effect of the introduction of a fixed treatment protocol with recommended maximum time from diagnosis to invasive examination and treatment for NSTEMI, but not for unstable angina.

Our results are in agreement with studies from the US, which showed an increase in the use of CAG and PCI over the last two decades, and a decrease in CABG \((1, 17, 18)\)(4, 16, 17). The study also contributes to the interpretation of the findings from a recent Danish study (2), which showed a significant reduction in 30-day and 1-year mortality risk after first time hospitalisation for MI between 1999-2003 and 2004-2008. Part of this reduction could be due to a decrease in time to treatment. When comparing with this study one should keep in mind that we did not include patients with STEMI who are included in Schmidt et al.s study and that these patients have a succinct treatment path with the need for more urgent treatment. There seems to be no other nationwide studies on trends in time from diagnosis to invasive treatment; however in 2009 Bradley et al reported a decrease in door to balloon time for patients with STEMI after enrolment in a national quality campaign with the aim to reduce the door to balloon time to less than 90 minutes for this group \((19)(48)\).

We did find a significant decline in time for CAG and PCI corresponding to implementation of the fixed treatment protocol for NSTEMI. However, for both NSTEMI and unstable angina, we found a
steady increase in treatment rate from 2001 and onwards and for NSTEMI a steep increase in probability already in 2008. This indicates that focus on improvement on time to invasive examination and treatment is not new. Furthermore the treatment protocols were first implemented during 2009, but they were already discussed in 2008 and this could have led to early implementation and hence an increase in speed of invasive examination and treatment before the actual implementation. In this time period there seemed to be a general agreement on the benefits of an invasive strategy vs. medical management for patients with NSTEMI (20, 21)(19, 20). However the optimal timing of invasive interventions was not clearly agreed upon. Mehta et al published in 2009 their results from the large TIMACS trial which included 3031 patients with unstable angina or NSTEMI. They found a significantly lower risk of death, myocardial infarction or stroke at 6 months for high risk patients when comparing an early (less than 24 h) with a delayed strategy (more than 36 h). Furthermore they found no safety issues related to the early strategy (22). This reflects shows the importance of early invasive treatment however these results only reflect the difference between very early and early invasive intervention which is a slightly other discussion than ours. In 2010 a meta-analysis was published combining four trials which concluded that early angiography and if relevant treatment for patients with NSTEMI reduces the risk of recurrent ischemia and shortens hospital stay (23). These results were however not reflected in the European Society of Cardiology guidelines until 2011 (4). However the previous guideline from 2007 (p. 27) also stated: ”...Accordingly, currently available evidence does not mandate a systematic approach of immediate angiography in NSTE-ACS patients stabilized with a contemporary pharmacological approach. Likewise, routine practice of immediate transfer of stabilized patients admitted in hospitals without onsite catherization facilities is not mandatory, but should be organized within 72 h” (7). We found that the number of patients receiving the recommended invasive examination and treatment within the recommend time frame increased from 2001 to 2009, however a large group of
patient still received no invasive investigation or were treated later than the guideline recommends in 2009. This patient group consists of three possible groups: patients that don’t have the disease in question due to lack of validity of data (see later discussion of strengths and weaknesses), patients who are too ill to be treated and patients who receive a less than optimal treatment. The basic idea behind the fixed treatment protocol i.e. same treatment for patients presenting with the same clinical symptoms irrespective of when or where patients come in contact with the health care system should ensure that the latter group is proportionally smaller in 2009 than in 2001. However, there could still be patients who don’t receive optimal treatment and unexplained variation between hospitals. Therefor monitoring by health authorities is of great importance.

Strengths and weaknesses

The primary strength of this study is the large unselected patient population, as it covers all patients admitted with first time ACS in the period from 2001 to 2009 in Denmark. The patients were identified in the NPR, however this means that we do not have information on biomarkers but solely rely on the correctness on what is registered in the NPR. We excluded outpatients and patients with a diagnosis from an emergency room which was not verified in a ward subsequently, however especially the unstable angina diagnosis is still problematic. Thus, it has been found that the positive predictive value of unstable angina for patients discharged from a ward only seems to around 40% (12). Therefor one reason for the lack of effect of the fixed treatment protocols for this group of patients could be that a substantial part of this group does not have unstable angina and data from this register are considered to have a high quality for patients with a coronary heart disease diagnosis. Thus, a previous study found a positive predictive value for myocardial infarction in the NPR of 98% (23). However this means that we do not have information on biomarkers but solely rely on the correctness on what is registered in the NPR. The data in the NPR allowed us to
follow patients through the course of diagnosis and treatment path, and we utilised this to change patients’ diagnoses after the CAG in case another diagnosis was registered at this point in time. This was done in order to imitate the clinical situation. At CAG 8,412 10,080 patients had a diagnosis other than ACS. The largest group was 3,230 724 patients with aAngina no specification. This group of patients could potentially be patients with unstable angina however including this group did not change the conclusions (analysis not shown). We had information on the specific hour of admission and used this information to calculate time to treatment. Although the validity of this information can be questioned, we used it in order to calculate the time as precisely as possible. We only included treatment and examination within 60 days as ACS is an acute disease for which treatment if relevant should be initiated as soon as possible. We analysed our data by use of statistical methods that accounted for the competing risk of death, which is very important when we estimate trends in time to treatment in a population with a high risk of death. However we do not know whether patients who died were not treated because the risk of invasive examination and treatment was deemed too high, or because the treatment was not considered relevant. Our analysis showed that the group of patients not receiving CAG was reduced in the period from 2001 to 2009, which was primarily due to an increase in treatment examination of elderly patients (analysis not shown). We also included information on the number of occluded vessels and LMCA involvement as a measure of the extension and severity of the disease in the analysis. This information was only available for 84.75 6% and 82.12 12% of the patients and especially patients from 2001 and 2002 had missing information on this variable. However, we have no reason to believe that this missing data should be non-random and related to time to treatment. Further we did not use age standardised data in the trend analyses because the fixed treatments protocols include all patient groups. However, we tested whether there was an effect of the treatment protocols in the Fine-Grar ey model which adjusted for age, gender, LMCA involvement and number of occluded vessels. The analyses
showed that these variables did not change the effect of the treatment protocols. It should also be noticed that we did not include patients who died before admission to a hospital as these patients are not included in the NPR. It should also be noticed that our study is an observational trend study and we cannot exclude that other organizational or treatment factors than the introduction of the fixed treatment protocol has contributed to the observed reduction in time to examination and treatment. This study only evaluates the immediate effects of the fixed treatment protocols; however a longer follow up would also be of interest.

In conclusion, this study contributes to the interpretation of the recent decline in mortality after hospitalisation for MI by showing a contemporary increase in the proportion of patients receiving a CAG and PCI as well as an increase in the probability of patients receiving CAG and PCI within the recommended time. The study also suggest that the introduction of fixed treatment protocols with a recommended maximum time from diagnosis to invasive examination and treatment may have impacted on time to treatment- as more patients receive a CAG and PCI within the time limit of 3 days around the time of the introduction of the protocols.

Contributors: SM, DGH, EP, ADOZ, MO contributed to the design of the study. SM carried out statistical analysis with guidance from PKA and MO. SM wrote initial draft and all authors critically revised the manuscript.

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**Competing interest:** None

**Ethics**

This register based study was approved the Danish Data Protection Agency (Approval number 2010-41-5263). Register based studies does not need approval by a medical ethics committee in Denmark.
Table 1: Coronary angiography (CAG), Percutaneous coronary intervention (PCI) and Coronary artery bypass grafting (CABG) treatment rates and number treated within 3/7 days distributed according to covariates for patients with first time Non ST elevation myocardial infarction (NSTEMI)

<table>
<thead>
<tr>
<th>NSTEMI</th>
<th>Diagnosis at initial examination</th>
<th>Diagnosis registered after CAG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAG within 60 days</td>
<td>PCI within 60 days (Grouped according to after CAG diagnosis)</td>
</tr>
<tr>
<td></td>
<td>Treatment Examining n rate %</td>
<td>Treatment rate %</td>
</tr>
<tr>
<td>Overall</td>
<td>18,457,221</td>
<td></td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>58,767,252</td>
<td>1,365,252</td>
</tr>
<tr>
<td>2004</td>
<td>61,360,262</td>
<td>1,422,262</td>
</tr>
<tr>
<td>2006</td>
<td>68,063,282</td>
<td>1,401,282</td>
</tr>
<tr>
<td>2008</td>
<td>70,604,302</td>
<td>1,533,302</td>
</tr>
<tr>
<td>2009</td>
<td>70,063,312</td>
<td>1,368,312</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>70,869,322</td>
<td>8,072,322</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 or younger</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>86,764,342</td>
<td>262,342</td>
</tr>
<tr>
<td>40-49</td>
<td>91,533,352</td>
<td>225,352</td>
</tr>
<tr>
<td>50-59</td>
<td>91,450,362</td>
<td>1,093,362</td>
</tr>
<tr>
<td>60-69</td>
<td>80,468,372</td>
<td>2,521,372</td>
</tr>
<tr>
<td>70-79</td>
<td>84,042,382</td>
<td>3,543,382</td>
</tr>
<tr>
<td>80 or older</td>
<td>66,016,392</td>
<td>3,374,392</td>
</tr>
<tr>
<td>LMCA** involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of occluded vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>187,203,402</td>
<td>354,402</td>
</tr>
<tr>
<td>1 vessel</td>
<td>54,644,412</td>
<td>1,114,412</td>
</tr>
<tr>
<td>2 vessels</td>
<td>80,203,422</td>
<td>2,262,422</td>
</tr>
<tr>
<td>3 vessels</td>
<td>19,422,432</td>
<td>1,141,432</td>
</tr>
</tbody>
</table>

* National guidelines recommend CAG and PCI within 3 days of diagnosis and CABG within 7 days of CAG.
** Left Main Coronary Artery
Table 2: Coronary angiography (CAG), Percutaneous coronary intervention (PCI) and Coronary artery bypass grafting (CABG) treatment rates and number treated within 3/7 days distributed according to covariates for patients with first time Unstable Angina

<table>
<thead>
<tr>
<th>Unstable angina</th>
<th>Diagnosis at initial examination</th>
<th>Diagnosis registered after CAG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAG within 60 days</td>
<td>PCI within 60 days (Grouped according to after CAG diagnosis)</td>
</tr>
<tr>
<td></td>
<td>Treatment rate %</td>
<td>n % in 3 days*</td>
</tr>
<tr>
<td>Overall</td>
<td>59.9%</td>
<td>3,279,675</td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td>2001</td>
<td>59.9%</td>
</tr>
<tr>
<td></td>
<td>2002</td>
<td>61.0%</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>64.5%</td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>72.3%</td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>74.1%</td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>74.3%</td>
</tr>
<tr>
<td></td>
<td>2007</td>
<td>78.3%</td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>82.1%</td>
</tr>
<tr>
<td></td>
<td>2009</td>
<td>79.0%</td>
</tr>
<tr>
<td>Gender</td>
<td>74.9%</td>
<td>3,199,347</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>51.6%</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>66.7%</td>
</tr>
<tr>
<td>Age</td>
<td>64.3%</td>
<td>188,277</td>
</tr>
<tr>
<td></td>
<td>younger</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>30-39</td>
<td>71.4%</td>
</tr>
<tr>
<td></td>
<td>40-49</td>
<td>75.6%</td>
</tr>
<tr>
<td></td>
<td>50-59</td>
<td>80.4%</td>
</tr>
<tr>
<td></td>
<td>60-69</td>
<td>78.3%</td>
</tr>
<tr>
<td></td>
<td>70-79</td>
<td>70.7%</td>
</tr>
<tr>
<td></td>
<td>80 or older</td>
<td>37.8%</td>
</tr>
<tr>
<td>LMCA* involvement</td>
<td>yes</td>
<td>18.4%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>62.6%</td>
</tr>
<tr>
<td>Number of occluded vessels</td>
<td>0</td>
<td>1.9%</td>
</tr>
<tr>
<td></td>
<td>1 vessel</td>
<td>79.7%</td>
</tr>
<tr>
<td></td>
<td>2 vessels</td>
<td>67.1%</td>
</tr>
<tr>
<td></td>
<td>3 vessels</td>
<td>26.5%</td>
</tr>
</tbody>
</table>

* National guidelines recommend CAG and PCI within 3 days of diagnosis and CABG within 7 days of CAG.
** Left Main Coronary Artery
Reference List


6. Danish National Board of Health. Treatment protocols for unstable angina and acute myocardial infarction without ST-segment elevation


Appendix 1: Treatment codes (SKS codes)

CAG: UXAC85, UXAC85A, UXAC85B, UXAC85C or UXAC85D;

PCI: KFNG, KFNG00, KFNG02, KFNG05, KFNG10, KFNG12, KFNG20, KFNG22, KFNG30, KFNG40, KFNG96;

CABG: KFNA, KFNA00, KFNA10, KFNA20, KFNC, KFNC10, KFNC20, KFNC30, KFNC40, KFNC50, KFNC60, KFNC96, KFND, KFND10, KFND20, KFND96, KFNE, KFNE00, KFND10, KFNE20, KFND96.

ACS: Acute coronary heart syndrome
STEMI: ST elevation myocardial infarction
NSTEMI: Non ST elevation myocardial infarction
AMI: Acute myocardial infarction
CAG: Coronary angiography
CABG: Coronary artery bypass grafting
PCI: Percutaneous coronary intervention
Appendix 2: Definition of time to treatment

Both date and clock-time is important in relation to the definition of time to treatment. Date is available for all patients for both admission and procedure while clock-time was missing in some cases. For patients for whom information on clock time of admission was missing, time of admission was defined as one hour before the time registration for the CAG (n=498). For example, if a patient was admitted on the 10\textsuperscript{th} of June with missing time information and had a CAG on June 11\textsuperscript{th} at 10 AM then the waiting time would be set at 25 hours. Conversely, if time information on CAG (n=109), PCI (n=195) or CABG (n=335) was missing, then the hour of CAG, PCI and CABG was defined as one hour after the time registered at the initial admission. This ensured that the dates of admission were still used, but that the waiting time could not end up being negative. Patients without information on both the time of initial presentation and time of CAG (n=2), PCI (n=1) and CABG (n=5) respectively were excluded from the analysis. If a patient received both PCI and CABG, then only the first treatment received was included in the analysis.
Appendix 3: Distribution of diagnosis for patients with a non acute coronary heart syndrome diagnosis at coronary angiography

<table>
<thead>
<tr>
<th>Specification</th>
<th>SKS-code</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension arterialis essentialis</td>
<td>DI109</td>
<td>124</td>
<td>1.5</td>
</tr>
<tr>
<td>Angina pectoris no specification</td>
<td>DI209</td>
<td>3,231</td>
<td>38.4</td>
</tr>
<tr>
<td>Angina pectoris (stable)</td>
<td>DI251</td>
<td>1,414</td>
<td>16.8</td>
</tr>
<tr>
<td>Former myokardial infarction</td>
<td>DI252</td>
<td>572</td>
<td>6.8</td>
</tr>
<tr>
<td>Chronic ischemic heart disease without specification</td>
<td>DI259</td>
<td>297</td>
<td>3.5</td>
</tr>
<tr>
<td>Aorta valve stenose, non reumatoid</td>
<td>DI350</td>
<td>145</td>
<td>1.7</td>
</tr>
<tr>
<td>Heart failure no specification</td>
<td>DI509</td>
<td>122</td>
<td>1.5</td>
</tr>
<tr>
<td>Chest pain no specification</td>
<td>DR079</td>
<td>114</td>
<td>1.4</td>
</tr>
<tr>
<td>Observation myocardial infarction</td>
<td>DZ034</td>
<td>203</td>
<td>2.4</td>
</tr>
<tr>
<td>Observation heart disease</td>
<td>DZ035</td>
<td>574</td>
<td>6.8</td>
</tr>
<tr>
<td><strong>Sub total</strong></td>
<td></td>
<td>6,795</td>
<td>81.3</td>
</tr>
<tr>
<td>Other</td>
<td>Other</td>
<td>1,617</td>
<td>19.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>8,413</td>
<td>100</td>
</tr>
</tbody>
</table>
Appendix 4: Additional results for NSTEMI

4.1. Results from the Fine Grey model for NSTEMI at 3 days (CAG/PCI) and 7 days (CABG)

### 4.1.a CAG

<table>
<thead>
<tr>
<th>NSTEMI</th>
<th>Year categorical n=18,947</th>
<th>Year continuous n=18,947</th>
<th>+ fixed treatment protocols n=18,947</th>
<th>+ age n=18,676</th>
<th>+ sex n=18,676</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year β CI 95</td>
<td>β CI 95</td>
<td>β CI 95</td>
<td>β CI 95</td>
<td>β CI 95</td>
</tr>
<tr>
<td>2001</td>
<td>0</td>
<td>0.21 [0.19-0.22]</td>
<td>0.19 [0.17-0.20]</td>
<td>0.17 [0.17-0.20]</td>
<td>0.17 [0.17-0.20]</td>
</tr>
<tr>
<td>2002</td>
<td>0.22 [0.01-0.43]</td>
<td>0.57 [0.37-0.77]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>0.57 [0.37-0.77]</td>
<td>0.49 [0.29-0.69]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>0.74 [0.54-0.93]</td>
<td>0.86 [0.67-1.06]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>0.92 [0.73-1.11]</td>
<td>1.48 [1.29-1.66]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>1.71 [1.53-1.89]</td>
<td>0.22 [0.11-0.32]</td>
<td>0.25 [0.15-0.35]</td>
<td>0.25 [0.15-0.35]</td>
<td></td>
</tr>
<tr>
<td>Fixed treatment protocols</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Ref: &lt; 50</td>
<td>0.21 [0.19-0.22]</td>
<td>0.19 [0.17-0.20]</td>
<td>0.17 [0.17-0.20]</td>
<td>0.17 [0.17-0.20]</td>
<td>0.17 [0.17-0.20]</td>
</tr>
<tr>
<td>50-59</td>
<td>-0.23 [-0.34-(-0.12)]</td>
<td>-0.63 [-0.72-(-0.53)]</td>
<td>-0.34 [-0.4-(-0.22)]</td>
<td>-0.34 [-0.4-(-0.22)]</td>
<td>-0.34 [-0.4-(-0.22)]</td>
</tr>
<tr>
<td>60-79</td>
<td>-1.89 [-2.03-(-1.75)]</td>
<td>-1.83 [-1.97-(-1.69)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>-0.23 [-0.34-(-0.12)]</td>
<td>-0.63 [-0.72-(-0.53)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Men</td>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>-0.19 [-0.26-(-0.12)]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 4.1.b PCI

<table>
<thead>
<tr>
<th>NSTEMI</th>
<th>Year categorical n=11,357</th>
<th>Year continuous n=11,357</th>
<th>+ fixed treatment protocols n=11,357</th>
<th>+ age n=11,131</th>
<th>+ sex n=11,131</th>
<th>+ Number of occluded vessels and LMCA involvement, n=7,076</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year β CI 95</td>
<td>β CI 95</td>
<td>β CI 95</td>
<td>β CI 95</td>
<td>β CI 95</td>
<td>β CI 95</td>
</tr>
<tr>
<td>2001</td>
<td>0.14 [0.11-0.16]</td>
<td>0.07 [0.05-0.10]</td>
<td>0.07 [0.04-0.10]</td>
<td>0.07 [0.04-0.10]</td>
<td>0.01 [-0.02-0.05]</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>-0.07 [-0.38-0.23]</td>
<td>0.02 [-0.51-0.10]</td>
<td>0.02 [-0.27-0.31]</td>
<td>0.02 [-0.27-0.31]</td>
<td>0.02 [-0.27-0.31]</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>-0.20 [-0.51-0.10]</td>
<td>0.02 [-0.27-0.31]</td>
<td>0.02 [-0.27-0.31]</td>
<td>0.02 [-0.27-0.31]</td>
<td>0.02 [-0.27-0.31]</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>0.02 [-0.27-0.31]</td>
<td>0.03 [-0.25-0.32]</td>
<td>0.03 [-0.25-0.32]</td>
<td>0.03 [-0.25-0.32]</td>
<td>0.03 [-0.25-0.32]</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>0.07 [-0.21-0.35]</td>
<td>0.45 [0.18-0.71]</td>
<td>0.91 [0.65-1.17]</td>
<td>0.55 [0.40-0.69]</td>
<td>0.59 [0.45-0.74]</td>
<td></td>
</tr>
<tr>
<td>Fixed treatment protocols</td>
<td>0.59 [0.44-0.74]</td>
<td>0.57 [0.41-0.73]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (ref = &lt; 50</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>-0.24 [-0.38-(-0.09)]</td>
<td>-0.34 [-0.4-(-0.22)]</td>
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### 4.1.c. CABG

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<th>+ Number of occluded vessels and LMCA involvement, n=7,076</th>
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**Fixed treatment protocols**

<table>
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<th>β (CI 95)</th>
<th>LMCA involvement (ref=no)</th>
<th>β (CI 95)</th>
<th>Number of occluded vessels (ref=1)</th>
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<td>0.91 (0.49-1.32)</td>
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<td>0.91 (0.49-1.32)</td>
<td>0.91 (0.49-1.32)</td>
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</table>

|                  |           |                |           |                |           | 2                                 | 3         |
|                  |           |                |           |                |           | 0.45 (0.00-0.90) | 0.45 (0.00-0.90) | 0.45 (0.00-0.90) | 0.45 (0.00-0.90) |

CI 95: Confidence Interval 95%
### 4.2. Results from the Fine Grey model for NSTEMI at 60 days

#### 4.2.a CAG

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#### 4.2.b PCI

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<tr>
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### 4.2.c CABG

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#### Age (ref = < 50)

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#### Number of occluded vessels (ref=1)

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### Appendix 5: Additional result for unstable angina

#### 5.1. Results from the Fine Grey model for unstable angina at 3 days (CAG/PCI) and 7 days (CABG)

##### 5.1.a CAG

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<td>β CI 95</td>
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<td>1.13-1.48</td>
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</table>

**Fixed treatment protocols**

- CAG: -0.03, -0.15-0.09, -0.02, -0.15-0.11, -0.03, -0.15-0.11

**Age**

- Ref: < 50: 0, 0.00, 0.00, 0.00, -0.13-0.13
- 50-59: 0.02, 0.13-0.10, 0.00, 0.12-0.12
- 60-79: -0.68, -0.86-(-0.49), -0.61, -0.80-(-0.43)
- > 80: 0, -0.29, -0.37-(-0.21)

**Sex**

- Men: 0
- Women: -0.29, -0.37-(-0.21)

##### 5.1.b PCI

<table>
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<td>-0.69-0.15</td>
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<td></td>
<td></td>
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<tr>
<td>2005</td>
<td>0.47</td>
<td>0.12-0.81</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>2006</td>
<td>0.51</td>
<td>0.16-0.88</td>
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<td>2007</td>
<td>0.55</td>
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<tr>
<td>2008</td>
<td>0.82</td>
<td>0.51-1.14</td>
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<td></td>
</tr>
<tr>
<td>2009</td>
<td>0.82</td>
<td>0.50-1.15</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Fixed treatment protocols**

- 0.04, -0.27-0.19, -0.02, -0.26-0.22, -0.01, -0.25-0.23, 0.03, -0.22-0.27

**Age (ref = < 50)**

- 50-59: 0.01, -0.24-1.23, 0.01, -0.24-0.22, 0.01, -0.43-0.07
- 60-79: -0.28, -0.50+(-0.06), -0.27, -0.48+(-0.05), -0.37, -0.61+(-0.13)
- > 80: 0, -0.25, -0.59-0.08, 0.20, -0.54-0.14, 0.28, -0.64-0.09

**Sex (ref=men)***

- Women: 0, -0.29, -0.45+(-0.12), -0.10, -0.28-0.07

**LMCA involvement (ref=no)***

- Yes: 0, 0.66, -0.06-1.37

**Number of occluded vessels (ref=1)**

- 2: 0, 0.35, -0.54+(-0.16)
- 3: 0, -1.34, -1.62+(-1.05)
### 5.1.c CABG

<table>
<thead>
<tr>
<th>Year</th>
<th>β</th>
<th>CI 95</th>
<th>+ fixed treatment protocols</th>
<th>+ age n=3,981</th>
<th>+ sex n=3,981</th>
<th>+ Number of occluded vessels and LMCA involvement, n=2,556</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>-0.18</td>
<td>-0.22(-0.13)</td>
<td>-0.17</td>
<td>-0.22(-0.12)</td>
<td>-0.17</td>
<td>-0.23(-0.12)</td>
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<td>2002</td>
<td>0.02</td>
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<td>0.05</td>
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<td>-0.17</td>
<td>-0.59(-0.24)</td>
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<tr>
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<td>-0.45(-0.34)</td>
<td>-0.17</td>
<td>-0.59(-0.24)</td>
<td>-0.89</td>
<td>-1.39(-0.39)</td>
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<tr>
<td>2004</td>
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<td>2005</td>
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<td>-0.69(0.47)</td>
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### 5.2. Results from the Fine Grey model for unstable angina at 60 days

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<td>0.05-0.27</td>
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<tr>
<td>2004</td>
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<td>0.35-0.55</td>
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<td>2006</td>
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<td>0.32-0.52</td>
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<tr>
<td>2007</td>
<td>0.61</td>
<td>0.50-0.72</td>
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<td>0.46-0.68</td>
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<td>2008</td>
<td>0.79</td>
<td>0.69-0.90</td>
<td>0.79</td>
<td>0.68-0.90</td>
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<td>2009</td>
<td>0.78</td>
<td>0.67-0.89</td>
<td>0.77</td>
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### 5.2.a CAG

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
### 5.2.b PCI

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<tr>
<th>Year</th>
<th>Year categorical n=4,089</th>
<th>+ age n=3,981</th>
<th>+ sex n=3,981</th>
<th>+ Number of occluded vessels and LMCA involve-ment, n=2,556</th>
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<tbody>
<tr>
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<td>-0.27-0.10</td>
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<tr>
<td>2003</td>
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<td>-0.23-0.14</td>
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<td>-0.42-(-0.05)</td>
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<tr>
<td>2007</td>
<td>0.00</td>
<td>-0.18-0.18</td>
<td>0.04</td>
<td>-0.22-0.15</td>
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<tr>
<td>2008</td>
<td>0.10</td>
<td>-0.07-0.27</td>
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<td>-0.06-0.28</td>
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<tr>
<td>2009</td>
<td>0.14</td>
<td>-0.04-0.32</td>
<td>0.12</td>
<td>-0.06-0.32</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (ref = &lt; 50)</th>
<th>50-59</th>
<th>60-79</th>
<th>&gt;80</th>
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</thead>
<tbody>
<tr>
<td>Sex (ref=men)</td>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMCA involvement (ref=no)</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of occluded vessels (ref=1)</td>
<td>2</td>
<td>3</td>
<td></td>
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</tbody>
</table>

### 5.2.b CABG

<table>
<thead>
<tr>
<th>Year</th>
<th>Year categorical n=4,089</th>
<th>+ age n=3,981</th>
<th>+ sex n=3,981</th>
<th>+ Number of occluded vessels and LMCA involve-ment, n=2,556</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>0</td>
<td>-0.02</td>
<td>0.01-0.04</td>
<td>0</td>
</tr>
<tr>
<td>2002</td>
<td>0.07</td>
<td>-0.18-0.33</td>
<td>-0.05</td>
<td>-0.21-0.31</td>
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<tr>
<td>2003</td>
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<td>-0.44-0.11</td>
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<td>-0.47-0.08</td>
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<tr>
<td>2004</td>
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<td>-0.59-(-0.02)</td>
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<td>-0.62-(-0.03)</td>
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<td>-1.26-(-0.66)</td>
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<td>2009</td>
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<td>-1.27-(-0.63)</td>
<td>-0.99</td>
<td>-1.31-(-0.66)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (ref = &lt; 50)</th>
<th>50-59</th>
<th>60-79</th>
<th>&gt;80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (ref=men)</td>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMCA involvement (ref=no)</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of occluded vessels (ref=1)</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
STROBE Statement—checklist of items that should be included in reports of observational studies

<table>
<thead>
<tr>
<th>Item No</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(a) Indicate the study's design with a commonly used term in the title or the abstract.</td>
</tr>
<tr>
<td></td>
<td>(b) Provide in the abstract an informative and balanced summary of what was done and what was found.</td>
</tr>
<tr>
<td>2</td>
<td>Explain the scientific background and rationale for the investigation being reported.</td>
</tr>
<tr>
<td>3</td>
<td>State specific objectives, including any prespecified hypotheses.</td>
</tr>
<tr>
<td>4</td>
<td>Present key elements of study design early in the paper.</td>
</tr>
<tr>
<td>5</td>
<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.</td>
</tr>
<tr>
<td>6</td>
<td>(a) <strong>Cohort study</strong>—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.</td>
</tr>
<tr>
<td></td>
<td><strong>Case-control study</strong>—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls.</td>
</tr>
<tr>
<td></td>
<td><strong>Cross-sectional study</strong>—Give the eligibility criteria, and the sources and methods of selection of participants.</td>
</tr>
<tr>
<td></td>
<td>(b) <strong>Cohort study</strong>—For matched studies, give matching criteria and number of exposed and unexposed.</td>
</tr>
<tr>
<td></td>
<td><strong>Case-control study</strong>—For matched studies, give matching criteria and the number of controls per case.</td>
</tr>
<tr>
<td>7</td>
<td>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.</td>
</tr>
<tr>
<td>8</td>
<td>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.</td>
</tr>
<tr>
<td>9</td>
<td>Describe any efforts to address potential sources of bias.</td>
</tr>
<tr>
<td>10</td>
<td>Explain how the study size was arrived at.</td>
</tr>
<tr>
<td>11</td>
<td>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.</td>
</tr>
<tr>
<td>12</td>
<td>(a) Describe all statistical methods, including those used to control for confounding.</td>
</tr>
<tr>
<td></td>
<td>(b) Describe any methods used to examine subgroups and interactions.</td>
</tr>
<tr>
<td></td>
<td>(c) Explain how missing data were addressed.</td>
</tr>
<tr>
<td></td>
<td>(d) <strong>Cohort study</strong>—If applicable, explain how loss to follow-up was addressed.</td>
</tr>
<tr>
<td></td>
<td><strong>Case-control study</strong>—If applicable, explain how matching of cases and controls was addressed.</td>
</tr>
<tr>
<td></td>
<td><strong>Cross-sectional study</strong>—If applicable, describe analytical methods taking account of sampling strategy.</td>
</tr>
<tr>
<td></td>
<td>(a) Describe any sensitivity analyses.</td>
</tr>
</tbody>
</table>

Continued on next page
Results

Participants 13* (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ✓

(b) Give reasons for non-participation at each stage ✓

(c) Consider use of a flow diagram ✓

Descriptive data 14* (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ✓

(b) Indicate number of participants with missing data for each variable of interest ✓

(c) Cohort study—Summarise follow-up time (eg, average and total amount) ✓

Outcome data 15* Cohort study—Report numbers of outcome events or summary measures over time ✓

Case-control study—Report numbers in each exposure category, or summary measures of exposure ✓

Cross-sectional study—Report numbers of outcome events or summary measures

Main results 16 (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ✓

(b) Report category boundaries when continuous variables were categorized ✓

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period ✓

Other analyses 17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ✓

Discussion

Key results 18 Summarise key results with reference to study objectives ✓

Limitations 19 Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ✓

Interpretation 20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ✓

Generalisability 21 Discuss the generalisability (external validity) of the study results ✓

Other information

Funding 22 Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Correction


In this paper, the variables ‘left main coronary artery involvement (LMCA)’ and ‘number of occluded vessels’ were not coded properly, so for patients where it was registered that they had LMCA involvement did not automatically have the maximum of three occluded vessels registered. When correcting this the number of cases included in the final ‘Fine Gray’ analysis, where these variables were used, increased from 7.076 to 7.106 for NSTEMI (Appendix 4, tables 4.1.b PCI, 4.1.c CABG, 4.2.b PCI, 4.2.c CABG) and from 2.556 to 2.572 for unstable angina (Appendix 5, tables 5.1.b PCI, 5.1.c CABG, 5.2.b PCI, 5.2.c CABG). After this correction the effect of LMCA involvement on likelihood of PCI and CABG within 3/7 days and within 60 days for both NSTEMI and unstable angina cases became smaller. The other estimates remained almost the same and this correction did not change the conclusions made in the article. The results can be seen in the corrected versions of appendix 4 and 5 available online.

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