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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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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 ustable 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), 121.4 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.

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 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 catherization 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.

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)

NSTEMI		Diagnosis at initial examination			Diagnosis registered after CAG					
		CAG within 60 days			PCI within 60 days (Grouped according to after CAG diagnosis)			CABG within 60 days from CAG		
		Treatment rate %	n	% in 3 days*	Treatment rate %	N	% in 3 days*	Treatment rate %	n	% in 7 days*
Overall	18.757	62.2	11,676	31.5	52.3	6,233	30.6	16.2	1,933	26.5
Year of diagnosis	2001	49.0	792	18.2	48.6	269	27.2	22.8	126	28.4
	2002	54.0	1,112	19.0	49.3	489	25.1	23.1	229	24.8
	2003	57.2	1,292	25.4	51.2	643	22.4	19.0	239	38.9
	2004	60.2	1,356	22.2	53.8	708	23.5	17.5	230	35.4
	2005	66.6	1,437	25.8	55.9	804	23.4	16.2	233	26.2
	2006	67.0	1,373	28.5	54.3	814	24.2	13.4	201	22.8
	2007	65.6	1,420	30.9	49.2	750	26.9	16.7	254	15.5
	2008	69.1	1,545	46.5	50.1	847	38.9	13.4	226	25.0
	2009	68.7	1,349	55.2	55.2	909	52.1	11.8	195	23.0
Gender	Men	69.8	7,850	32.0	55.9	4,423	30.5	18.6	1,497	25.9
	Women	51.0	3,697	29.3	46.6	1,681	27.0	11.2	410	27.9
Age	30 or younger	64.9	24	36.4	13.6	3	66.7	-	-	-
	30-39	83.8	223	45.7	51.8	113	42.5	2.2	5	60.0
	40-49	89.0	1,073	41.4	58.5	627	41.6	7.2	78	35.2
	50-59	88.3	2,439	33.2	60.9	1,525	30.0	12.4	315	28.6
	60-69	82.9	3,459	29.3	52.2	1,762	27.8	20.6	702	25.0
	70-79	65.2	3,253	27.2	47.4	1,530	26.0	21.6	706	24.5
	80 or older	21.3	1,076	30.5	49.2	544	27.4	9.0	101	32.6
LMCA** involvement	Yes				20.3	46	27.9	64.3	146	50.0
	No				54.3	5,228	31.4	14.4	1,384	24.5
Number of occluded vessels	0				4.5	60	23.2	0.5	6	33.3
	1 vessel				78.0	2,743	35.4	1.6	56	32.1
	2 vessels				71.4	1,492	31.0	12.7	266	24.2
	3 vessels				29.8	676	29.7	49.7	1,126	29.2

* 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

Unstable angina		Diagnosis at initial examination			Diagnosis registered after CAG					
		CAG within 60 days			PCI within 60 days (Grouped according to after CAG diagnosis)			CABG within 60 days from CAG		
		Treatment rate %	n	% in 3 days*	Treatment rate %	n	% in 3 days*	Treatment rate %	n	% in 7 days*
Overall	15,469	52.5	8,114	44.8	48.4	2,134	38.4	18.0	795	42.6
Year of diagnosis	2001	43.1	778	29.4	51.4	238	25.1	25.9	120	46.8
	2002	43.4	900	33.5	46.3	211	30.5	28.1	128	42.7
	2003	45.0	897	40.0	47.7	213	32.8	22.8	102	54.3
	2004	49.3	915	35.6	41.4	178	22.3	20.2	87	52.5
	2005	51.4	951	45.2	50.7	243	38.4	14.8	71	36.4
	2006	57.1	946	46.7	50.5	245	40.2	15.3	74	38.2
	2007	61.0	895	51.0	47.5	222	42.0	16.1	75	30.8
	2008	67.9	942	56.0	48.8	329	52.1	12.2	82	41.0
	2009	64.7	890	61.8	50.1	255	50.0	11.0	56	28.0
Gender	Men	57.0	4,894	44.8	50.5	1,394	38.7	21.3	598	42.7
	Women	46.2	2,921	40.0	46.6	684	33.6	11.9	177	41.6
Age	30 or younger	23.3	27	61.5	-	-	-	-	-	-
	30-39	35.1	226	47.7	36.4	36	51.4	14.3	1	25.0
	40-49	47.2	922	45.2	48.1	219	44.8	3.9	4	51.7
	50-59	59.4	1,999	40.6	52.2	560	39.2	6.9	32	35.2
	60-69	64.0	2,373	43.7	49.7	648	35.3	14.1	153	45.2
	70-79	56.5	1,730	41.7	45.5	443	32.4	21.6	287	41.5
	80 or older	26.0	538	46.2	53.6	172	35.8	26.2	258	52.6
LMCA* involvement	yes				16.0	24	45.8	12.3	40	58.6
	No				51.2	1,810	38.9	74.0	111	39.1
Number of occluded vessels	0				3.6	24	39.1	15.6	551	33.3
	1 vessel				78.2	1,068	42.6	0.6	4	37.9
	2 vessels				66.4	487	36.5	2.5	34	42.0
	3 vessels				26.2	205	32.5	19.1	140	43.1

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

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Figure 1: Flowchart patient population
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Patients with 1st time ACS from 2001 to 2009
n= 99,473

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Prior heart disease
n= 19,440

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

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 %)

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No CAG within 60 days,
n= 26,326

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Dead within 60 days,
n= 7,544

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CAG within 60 days,
n = 46,163

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

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 %)

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Patients med ACS
n= 36,083

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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

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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

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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.
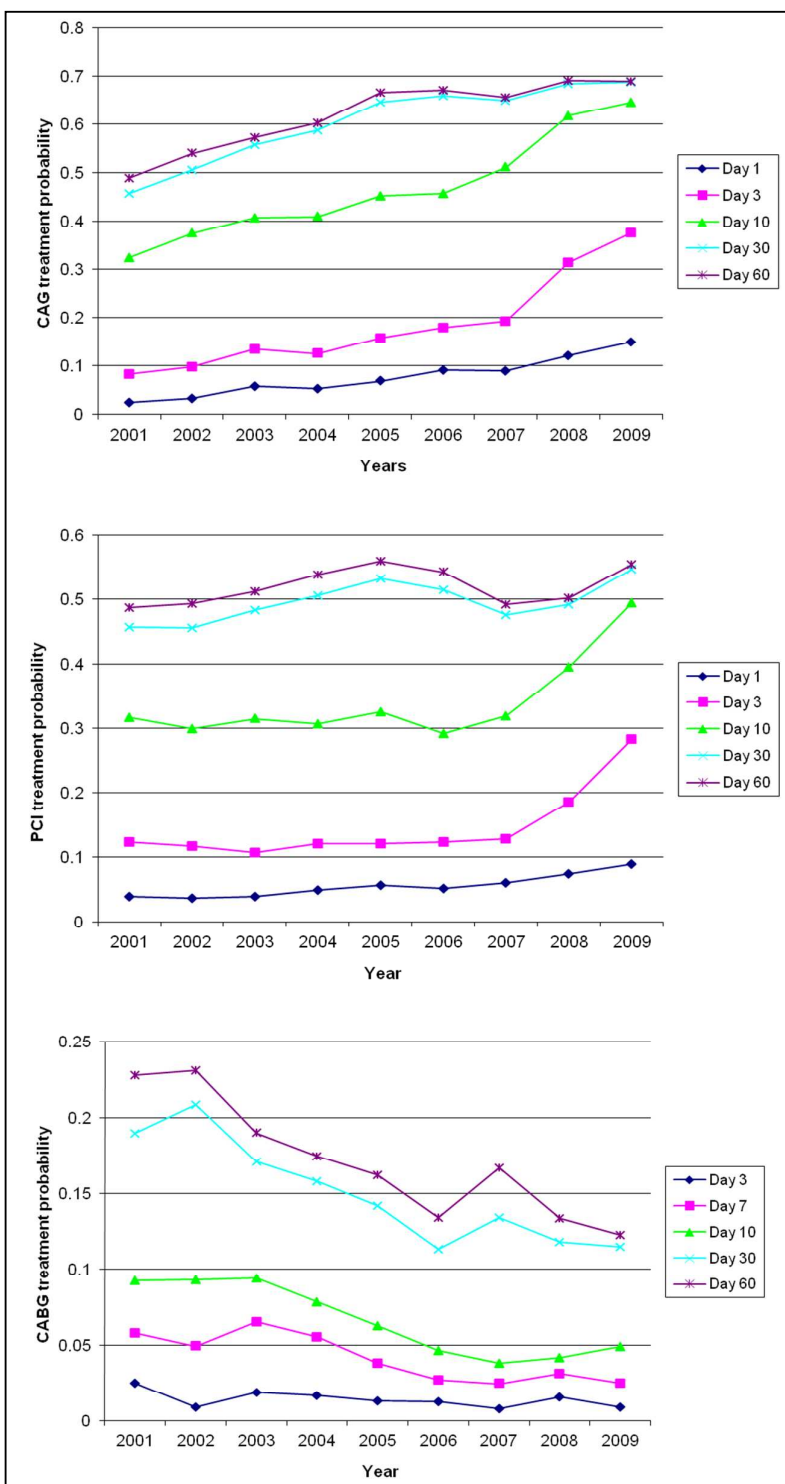
§ For PCI and CABG only among those who receive CAG
# For CABG time is measured from time of CAG

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
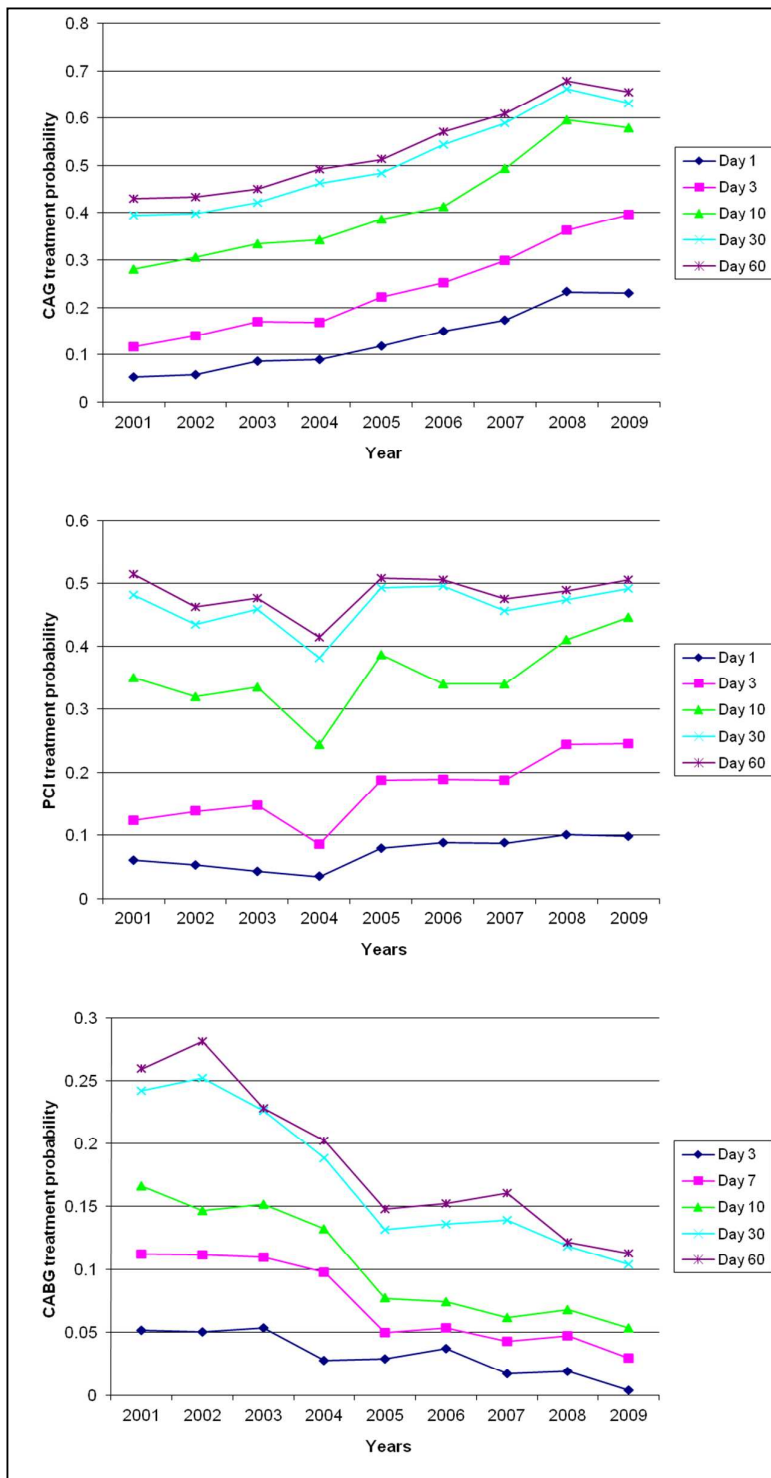
§ For PCI and CABG only among those who receive CAG
# For CABG time is measured from time of CAG

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 stilled 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

Specification	SKS-code	Number	%
Hypertension arterialis essentialis	DI109	161	1.6
Other form of angina pectoris	DI100	100	1.0
Angina pectoris no specification	DI209	3,721	36.9
Angina pectoris (stable)	DI251	1,610	16.0
Former myokardial infarction	DI252	620	6.2
Chronic ischemic heart disease without specification	DI259	320	3.2
Aorta valve stenose, non reumatoid	DI350	184	1.8
Heart failure no specification	DI509	159	1.6
Chest pain no specification	DR079	152	1.5
Cardiogenic shock	DR570	109	1.1
Observation myocardial infarction	DZ034	296	2.9
Observation heart disease	DZ035	764	7.6
Sub total		**8,196**	**81.3**
Other	Other	1,884	18.7
Total		**10,080**	**100**

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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

NSTEMI	Year categorical n =18,757		Year continuous n =18,757		+ fixed treatment protocols n =18,757		+ age n=18,482		+ sex n=18,482	
Year	β	CI 95	β	CI 95	β	CI 95	β	CI 95	β	CI 95
2001	0		0.21	0.20-0.23	0.19	0.18-0.21	0.19	0.18-0.21	0.19	0.18-0.21
2002	0.18	-0.04-0.40								
2003	0.53	0.33-0.66								
2004	0.45	0.25-0.66								
2005	0.70	0.50-0.90								
2006	0.86	0.66-1.06								
2007	0.93	0.73-1.13								
2008	1.48	1.30-1.67								
2009	1.70	1.50-1.88								
Fixed treatment protocols					0.18	0.08-0.28	0.22	0.11-0.32	0.22	0.12-0.32
Age										
Ref: < 50							0		0	
50-59							-0.21	-0.32-(-0.10)	-0.22	-0.33-(-0.11)
60-79							-0.62	-0.72-(-0.53)	-0.61	-0.70-(-0.51)
>80							-1.90	-2.04-(-1.76)	-1.84	-1.99-(-1.70)
Sex										
Men									0	
Women									-0.20	-0.28-(-0.13)

4.1.b PCI

NSTEMI	Year categorical n=11,915		Year continuous n=11,915		+ fixed treatment protocols n=11,915		+ age n=11,680		+ sex n=11,680		+ Number of occluded vessels and main trunk disease n=7,592	
Year	β	CI 95	β	CI 95	β	CI 95	β	CI 95	β	CI 95	β	CI 95
2001	0		0.14	0.11-0.16	0.07	0.04-0.10	0.07	0.04-0.09	0.07	0.04-0.10	0.03	-0.003-0.06
2002	-0.05	-0.35-0.24										
2003	-0.15	-0.44-0.14										
2004	-0.01	-0.30-0.27										
2005	-0.01	-0.29-0.27										
2006	0.01	-0.27-0.29										
2007	0.05	-0.22-0.33										
2008	0.45	0.19-0.71										
2009	0.91	0.66-1.17										
Fixed treatment protocols					0.57	0.43-0.71	0.62	0.47-0.76	0.61	0.47-0.76	0.55	0.40-0.71
Age (ref = < 50)							0		0		0	
50-59							-0.20	-0.34-(-0.05)	-0.20	-0.35-0.06	-0.29	-0.45-(-0.14)
60-79							-0.59	-0.72-(-0.45)	-0.57	-0.70-(-0.44)	-0.54	-0.68-(0.40)
>80							-0.67	-0.88-(-0.47)	-0.62	-0.83-(-0.42)	-0.54	-0.76-(-0.33)
Sex (ref=men)									0		0	
Women									-0.27	-0.38-(-0.16)	-0.10	-0.21-0.02
LMCA involvement (ref=no)											0	
Yes											0.68	0.07-1.29
Number of occluded vessels (ref=1)											0	
2											-0.13	-0.24-(-0.01)
3											-1.03	-1.20-(-0.87)

4.1.c. CABG

NSTEMI	Year categorical n=11,915		Year continuous n=11,915		+ fixed treatment protocols n=11,915		+ age n=11,680		+ sex n=11,680		+ Number of occluded vessels and main trunk disease n=7,592	
Year	β	CI 95	β	CI 95	β	CI 95	B	CI 95	β	CI 95	β	CI 95
2001	0		-0.13	-0.17-(-0.09)	-0.14	-0.18-(-0.09)	-0.13	-0.17-(-0.09)	-0.13	-0.17-(-0.09)	-0.18	-0.23-(-0.12)
2002	-0.17	-0.62-0.28										
2003	0.12	-0.29-0.53										
2004	-0.05	-0.47-0.37										
2005	-0.43	-0.87-0.01										
2006	-0.77	-1.23-(-0.30)										
2007	-0.86	-1.34-(-0.39)										
2008	-0.63	-1.07-(-0.19)										
2009	-0.86	-1.33-(-0.40)										
Fixed treatment protocols					0.06	-0.31-0.44	0.02	-0.36-0.41	-0.01	-0.37-0.39	0.09	-0.42-0.61
Age (ref = < 50)							0		0		0	
50-59							0.46	0.03-0.90	0.45	-0.01-0.88	-0.07	-0.57-0.42
60-79							0.86	0.47-1.25	0.89	0.50-1.29	-0.16	-0.61-0.29
>80							0.38	-0.14-0.90	0.48	-0.05-1.00	-0.96	-1.61-(-0.32)
Sex (ref=men)									0		0	
Women									-0.48	-0.71-(-0.26)	-0.23	-0.52-0.04
LMCA involvement (ref=no)											0	
Yes											-1.22	-1.53-(-0.92)
Number of occluded vessels (ref=1)											0	
2											1.67	1.07-2.27
3											3.26	2.71-3.82

4.2. Results from the Fine Grey model for NSTEMI at 60 days

4.2.a CAG

NSTEMI	Year categorical n =18,757		Year continuous n n =18,757		+ age n=18,482		+ sex n= 18,482	
Year	β	CI 95	β	CI 95	β	CI 95	β	CI 95
2001	0		0.09	0.09-0.10	0		0	
2002	0.15	0.06-0.23			0.18	0.10-0.27	0.18	0.09-0.27
2003	0.25	0.16-0.33			0.30	0.21-0.38	0.30	0.22-0.38
2004	0.31	0.22-0.39			0.40	0.32-0.48	0.40	0.32-0.48
2005	0.47	0.38-0.55			0.52	0.44-0.60	0.52	0.44-0.60
2006	0.49	0.41-0.58			0.54	0.46-0.62	0.54	0.46-0.62
2007	0.52	0.43-0.60			0.62	0.54-0.71	0.62	0.54-0.71
2008	0.73	0.64-0.82			0.89	0.80-0.98	0.89	0.80-0.98
2009	0.81	0.72-0.90			1.01	0.91-1.10	1.01	0.91-1.10
Age								
Ref: < 50					0		0	
50-59					-0.06	-0.13-0.01	-0.06	-0.13-0.01
60-79					-0.49	-0.55-(-0.42)	-0.47	-0.53-(-0.40)
>80					-2.22	-2.31-(-2.13)	-2.16	-2.25-(-2.07)
Sex								
Men							0	
Women							-0.22	-0.26-(-0.18)

4.2.b PCI

NSTEMI	Year categorical n=11,915		Year continuous n=11,915		+ age n=11,680		+ sex n=11,680		+ Number of occluded vessels and main trunk disease n=7,592	
Year	β	CI 95	β	CI 95	B	CI 95	β	CI 95	B	CI 95
2001	0		0.03	0.02-0.04	0		0		0	
2002	0.004	-0.14-0.15			0.01	-0.13-0.16	0.01	-0.14-0.16	-0.12	-0.32-0.08
2003	0.06	-0.08-0.20			0.05	-0.09-0.19	0.05	-0.06-0.22	0.01	-0.20-0.17
2004	0.11	-0.02-0.25			0.12	-0.02-0.25	0.12	-0.02-0.25	-0.02	-0.21-0.17
2005	0.17	0.04-0.31			0.17	0.04-0.31	0.17	0.04-0.32	0.005	-0.18-0.17
2006	0.12	-0.02-0.25			0.14	0.002-0.27	0.14	0.01-0.28	-0.07	-0.25-0.11
2007	0.03	-0.11-0.17			0.03	-0.11-0.17	0.04	-0.10-0.17	-0.12	-0.30-0.06
2008	0.12	-0.01-0.26			0.14	0.001-0.28	0.14	0.01-0.29	0.06	-0.12-0.24
2009	0.35	0.21-0.49			0.39	0.25-0.53	0.39	0.25-0.53	0.22	0.04-0.41
Age (ref = < 50)					0		0		0	
50-59					0.07	-0.02-0.17	0.07	-0.04-0.14	-0.04	-0.14-0.07
60-79					-0.24	-0.33-(-0.16)	-0.23	-0.33-(-0.17)	-0.22	-0.31-(-0.12)
>80					-0.28	-0.39-(-0.16)	-0.24	-0.37-(0.14)	-0.20	-0.33-(-0.06)
Sex (ref=men)							0		0	
Women							-0.24	-0.29-(-0.18)	-0.06	-0.13-0.003
LMCA involvement (ref=no)									0	
Yes									0.81	0.51-1.11
Number of occluded vessels (ref=1)									0	
2									-0.13	-0.19-(-0.06)
3									-1.33	-1.42-(-1.24)

4.2.c CABG

NSTEMI	Year categorical n=11,915		Year continuous n=11,915		+ age n=11,680		+ sex n=11,680		+ Number of occluded vessels and main trunk disease n=7,592	
Year	β	CI 95	β	CI 95	B	CI 95	β	CI 95	β	CI 95
2001	0		-0.09	-0.11-(-0.07)	0		0		0	
2002	0.04	-0.20-0.24			-0.02	-0.23-0.20	-0.03	-0.24-0.19	0.21	-0.09-0.51
2003	-0.19	-0.40-0.03			-0.19	-0.40-0.03	-0.19	-0.41-0.03	0.13	-0.17-0.42
2004	-0.29	-0.50-(-0.07)			-0.29	-0.51-(-0.07)	-0.30	-0.52-(-0.08)	-0.01	-0.31-0.29
2005	-0.38	-0.59-(-0.16)			-0.36	-0.57-(-0.14)	-0.37	-0.58-(-0.15)	-0.06	-0.35-0.22
2006	-0.59	-0.81-(-0.36)			-0.57	-0.79-(-0.35)	-0.58	-0.80-(-0.35)	-0.46	-0.77-(-0.16)
2007	-0.37	-0.58-(-0.15)			-0.36	-0.57-(-0.15)	-0.35	-0.56-(-0.13)	0.05	-0.34-0.23
2008	-0.59	-0.80-(-0.37)			-0.58	-0.79-(-0.36)	-0.57	-0.80-(-0.37)	-0.31	-0.61-(-0.02)
2009	-0.69	-0.91-(-0.47)			-0.69	-0.91-(-0.46)	-0.70	-0.93-(-0.48)	-0.25	-0.55-0.05
Age (ref = < 50)					0		0		0	
50-59					0.70	0.46-0.95	0.69	0.45-0.93	0.25	-0.03-0.54
60-79					1.30	1.07-1.52	1.34	1.12-1.56	0.31	-0.05-0.58
>80					0.45	0.16-0.74	0.57	0.27-0.86	-1.07	-1.44-(-0.69)
Sex (ref=men)							0		0	
Women							-0.59	-0.70-(-0.48)	-0.26	-0.40-(-0.12)
LMCA involvement (ref=no)									0	
Yes									-0.74	-0.97-(-0.52)
Number of occluded vessels (ref=1)									0	
2									2.04	1.73-2.34
3									3.76	3.47-4.04

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

Unstable angina	Year categorical n =15,469		Year continuous n =15,469		+ fixed treatment protocols n =15,469		+ age n=14,913		+ sex n= 14,913	
Year	β	CI 95	β	CI 95	β	CI 95	β	CI 95	β	CI 95
2001	0		0.18	0.17-0.19	0.18	0.17-0.20	0.18	0.16-0.19	0.18	0.16-0.20
2002	0.20	0.03-0.38								
2003	0.42	0.25-0.59								
2004	0.41	0.23-0.58								
2005	0.72	0.56-0.89								
2006	0.87	0.71-1.04								
2007	1.07	0.91-1.23								
2008	1.31	1.16-1.48								
2009	1.41	1.25-1.56								
Fixed treatment protocols					-0.04	-0.16-0.07	-0.04	-0.16-0.08	-0.04	-0.16-0.08
Age										
Ref: < 50							0		0	
50-59							0.21	0.10-0.32	0.21	0.10-0.32
60-79							0.30	0.20-0.40	0.32	0.23-0.42
>80							-0.51	-0.66-(-0.35)	-0.43	-0.58-(-0.27)
Sex										
Men									0	
Women									-0.34	-0.42-(-0.27)

5.1.b PCI

Unstable angina	Year categorical n=4,410		Year continuous n=4,410		+ fixed treatment protocols n=4,410		+ age n=4,299		+ sex n=4,299		+ Number of occluded vessels and main trunk disease n=2,776	
Year	β	CI 95	β	CI 95	β	CI 95	β	CI 95	β	CI 95	β	CI 95
2001	0		0.11	0.08-0.14	0.11	0.08-0.15	0.12	0.08-0.15	0.12	0.08-0.15	0.12	0.08-0.16
2002	0.12	-0.24-0.47										
2003	0.19	-0.17-0.54										
2004	-0.38	-0.79-0.04										
2005	0.45	0.12-0.79										
2006	0.46	0.13-0.79										
2007	0.46	0.13-0.80										
2008	0.76	0.46-1.06										
2009	0.76	0.45-1.07										
Fixed treatment protocols					-0.03	-0.26-0.20	-0.02	-0.25-0.22	-0.01	-0.24-0.23	0,003	-0.25-0.24
Age (ref = < 50)							0		0		0	
50-59							0.01	-0.22-0.24	-0.01	-0.22-0.24	-0.17	-0.42-0.07
60-79							-0.25	-0.46-(-0.03)	-0.24	-0.45-(-0.02)	-0.35	-0.59-(-0.12)
>80							-0.17	-0.50-0.15	-0.13	-0.44-(-0.20)	-0.22	-0.57-0.12
Sex (ref=men)												
Women									0		0	
									-0.28	-0.43-(-0.12)	-0.09	-0.26-0.08
LMCA involvement (ref=no)												
Yes											0	
											0.59	-0.08-1.27
Number of occluded vessels (ref=1)												
2											0	
											-0.31	-0.49-(-0.13)
3											-1.30	-1.57-(-1.03)

5.1.c CABG

Unstable angina	Year categorical n=4,410		Year continuous n=4,410		+ fixed treatment protocols n=4,458		+ age n=4,299		+ sex n=4,299		+ Number of occluded vessels and main trunk disease n=2,776	
Year	β	CI 95	β	CI 95	β	CI 95	B	CI 95	β	CI 95	β	CI 95
2001	0		-0.17	-0.21-(-0.13)	-0.16	-0.21-(-0.11)	-0.17	-0.22-(-0.12)	-0.16	-0.21-(-0.11)	-0.12	-0.18-(-0.06)
2002	-0.004	-0.39-0.38										
2003	-0.02	-0.41-0.37										
2004	-0.15	-0.56-0.25										
2005	-0.83	-1.32-(-0.35)										
2006	-0,76	-1.24-(-0.29)										
2007	-1,00	-1.51-(-0.48)										
2008	-0.89	-1.33-(-0.45)										
2009	-1.40	-1.95-(-0.81)										
Fixed treatment protocols					-0.21	-0.79-0.36	-0.22	-0.79-0.36	-0.21	-0.78-0.37	-0.56	-1.42-0.30
Age (ref = < 50)							0		0		0	
50-59							0.50	-0.07-1.06	0.48	-0.08-1.04	-0.11	0.74-0.52
60-79							1.26	0.76-1.77	1.29	0.79-1.80	0.20	-0.37-0.77
>80							0.92	0.26-1.58	1.02	0.37-1.69	-0.69	-1.55-0.16
Sex (ref=men)									0		0	
Women									-0.63	-0.90-(-0.36)	-0.32	-0.65-0.02
LMCA involvement (ref=no)												
Yes											0 -1.12	-1.48-(-0.76)
Number of occluded vessels (ref=1)												
2											0 2.31	1.57-3.06
3											3.40	2.68-4.11

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

5.2.a CAG

Unstable angina	Year categorical n =15,469		Year continuous n =15,469		+ age n=14,913		+ sex n= 14,913	
Year	β	CI 95	β	CI 95	β	CI 95	β	CI 95
2001	0		0.11	0.10-0.12	0		0	
2002	0.03	-0.06-0.12			0.08	-0.01-0.18	0.09	-0.004-0.18
2003	0.09	0.01-0.20			0.11	0.02-0.21	0.11	0.02-0.21
2004	0.20	0.10-0.28			0.23	0.14-0.32	0.24	0.15-0.33
2005	0.29	0.16-0.35			0.33	0.23-0.42	0.33	0.24-0.42
2006	0.44	0.29-0.48			0.44	0.35-0.54	0.45	0.35-0.54
2007	0.58	0.45-0.64			0.56	0.46-0.65	0.57	0.47-0.67
2008	0.82	0.66-0.86			0.81	0.71-0.90	0.81	0.72-0.91
2009	0.78	0.63-0.83			0.77	0.67-0.87	0.78	0.68-0.88
Age Ref: < 50					0		0	
50-59					0.43	0.36-0.50	0.44	0.36-0.51
60-79					0.48	0.41-0.54	0.50	0.43-0.57
>80					-0.61	-0.72-(-0.51)	-0.55	-0.65-(-0.44)
Sex Men							0	
Women							-0.27	-0.32-(-0.23)

5.2.b PCI

Unstable angina	Year categorical n=4,410		Year continuous n=4,410		+ age n=4,299		+ sex n=4,299		+ Number of occluded vessels and main trunk disease n=2,776	
Year	β	CI 95	β	CI 95	β	CI 95	β	CI 95	B	CI 95
2001	0		0.02	0.00-0.04	0		0		0	
2002	-0.12	-0.29-0.06			-0.13	-0.31-0.05	-0.13	-0.31-0.05	-0.07	-0.26-0.12
2003	-0.08	-0.26-0.09			-0.10	-0.28-0.08	-0.10	-0.28-0.08	-0.04	-0.23-0.16
2004	-0.30	-0.49-(-0.12)			-0.30	-0.48-(-0.11)	-0.29	-0.48-(-0.10)	-0.15	-0.35-0.05
2005	0.04	-0.14-0.21			0.04	-0.13-0.22	0.04	-0.13-0.22	0.06	-0.13-0.25
2006	0.01	-0.16-0.18			-0.02	-0.19-0.16	-0.02	-0.20-0.15	0.03	-0.15-0.21
2007	-0.06	-0.24-0.12			-0.10	-0.28-0.09	-0.09	-0.27-0.09	0.004	-0.19-0.20
2008	0.04	-0.13-0.21			0.05	-0.12-0.22	0.05	-0.11-0.22	0.19	0.003-0.37
2009	0.10	-0.08-0.28			0.08	-0.10-0.26	0.09	-0.09-0.27	0.30	0.11-0.50
Age (ref = < 50)					0		0		0	
50-59					0.19	0.04-0.34	0.19	0.03-0.34	-0.01	-0.19-0.16
60-79					0.04	-0.10-0.18	0.05	-0.09-0.18	-0.12	-0.31-0.02
>80					0.17	0.02-0.37	0.19	0.002-0.39	-0.01	-0.26-0.20
Sex (ref=men)							0		0	
Women							-0.13	-0.22-(-0.04)	0.05	-0.05-0.16
LMCA involvement (ref=no)										
Yes									0 / 1.25	0.85-1.78
Number of occluded vessels (ref=1)										
2									0 / -0.22	-0.33-(-0.11)
3									-1.45	-1.62-(-1.31)

5.2.b CABG

Unstable angina	Year categorical n=4,410		Year continuous n=4,410		+ age n=4,299		+ sex n=4,299		+ Number of occluded vessels and main trunk disease n=2,776	
Year	β	CI 95	β	CI 95	B	CI 95	β	CI 95	β	CI 95
2001	0		-0.13	-0.16-(-0.10)	0		0		0	
2002	0.08	-0.17-0.32			-0.06	-0.20-0.31	0.06	-0.20-0.31	0.01	-0.30-0.31
2003	-0.13	-0.40-0.13			-0.16	-0.43-0.11	-0.14	-0.42-0.13	0.34	0.02-0.66
2004	-0.28	-0.56-0.002			-0.29	-0.57-(-0.003)	-0.24	-0.52-0.05	-0.19	-0.55-(-0.16)
2005	-0.64	-0.93-(-0.34)			-0.69	-0.98-(-0.39)	-0.68	-0.98-(-0.39)	-0.55	-0.90-(-0.20)
2006	-0.61	-0.90-(-0.32)			-0.60	-0.90-(-0.31)	-0.61	-0.90-(-0.32)	-0.42	-0.77-(-0.06)
2007	-0.56	-0.85-(-0.27)			-0.56	-0.85-(-0.26)	-0.53	-0.82-(-0.24)	-0.42	-0.78-(-0.05)
2008	-0.84	-1.13-(-0.56)			-0.87	-1.16-(-0.59)	-0.86	-1.15-(-0.58)	-0.41	-0.77-(-0.05)
2009	-0.95	-1.26-(-0.63)			-0.98	-1.30-(-0.66)	-0.96	-1.27-(-0.64)	-0.43	-0.80-(-0.05)
Age (ref = < 50)					0		0		0	
50-59					0.80	0.44-1.16	0.79	0.43-1.15	0.26	-0.18-0.70
60-79					1.41	1.07-1.74	1.45	1.11-1.78	0.43	0.01-0.84
>80					0.75	0.30-1.20	0.87	0.41-1.32	-0.97	-1.59-(-0.36)
Sex (ref=men)							0		0	
Women							-0.66	-0.83-(-0.49)	-0.22	-0.42-(-0.02)
LMCA involvement (ref=no)										
Yes									0 / -1.03	-1.31-(-0.76)
Number of occluded vessels (ref=1)										
2									0 / 2.11	1.71-2.52
3									3.51	3.12-3.89

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

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

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.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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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.

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Number of words in main text: 3,873

Abstract

Objective:

To investigate trends in time to invasive examination and 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 (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

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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), 121.4 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

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). 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)

NSTEMI		Diagnosis at initial examination			Diagnosis registered after CAG					
		CAG within 60 days			PCI within 60 days (Grouped according to after CAG diagnosis)			CABG within 60 days from CAG		
		Examination rate %	n	% in 3 days*	Treatment rate %	N	% in 3 days*	Treatment rate %	n	% in 7 days*
Overall	18.947	63.3	11,997	31.8	52.7	5984	30.7	16.2	1836	26.3
Year of diagnosis	2001	49.8	823	18.2	48.4	255	27.5	23.0	121	29.5
	2002	54.9	1,177	19.9	49.6	465	24.8	22.8	214	23.7
	2003	58.7	1,355	26.2	51.4	597	21.2	19.5	226	38.5
	2004	61.3	1,422	23.2	54.3	673	24.2	17.8	221	35.5
	2005	67.7	1,480	26.6	56.7	771	23.7	16.2	220	25.7
	2006	68.0	1,401	28.9	55.1	792	24.6	13.1	188	23.3
	2007	66.9	1,438	30.7	49.5	728	27.4	16.5	243	15.3
	2008	70.5	1,533	46.2	50.3	817	38.9	13.2	214	24.7
	2009	70.0	1,368	55.7	55.3	886	52.0	11.8	189	23.0
Gender	Men	70.8	8,072	32.3	56.3	4247	30.8	18.8	1424	25.7
	Women	52.1	3,791	29.4	47.0	1615	26.9	11.2	386	28.0
Age	30 or younger	86.7	26	37.5	15.0	3	66.7	-	-	-
	30-39	91.5	225	44.3	53.1	111	42.9	2.3	5	60.0
	40-49	91.4	1,093	40.6	59.2	599	42.2	7.0	72	33.8
	50-59	89.4	2,521	33.2	61.0	1459	29.8	12.5	302	28.3
	60-69	84.0	3,543	29.8	52.5	1703	28.3	20.8	675	25.6
	70-79	66.1	3,337	27.6	47.9	1472	25.9	21.7	665	23.7
	80 or older	21.8	1,118	31.2	49.7	515	27.5	8.7	91	33.3
LMCA** involvement	Yes				18.7	39	33.3	65.6	137	50.4
	No				54.6	4885	32.1	14.3	1276	24.9
Number of occluded vessels	0				1.9	22	31.8	0.3	4	50.0
	1 vessel				78.5	2592	36.2	1.5	49	36.7
	2 vessels				71.7	1393	32.0	12.7	246	23.4
	3 vessels				30.0	630	30.1	49.3	1034	29.6

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

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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

Unstable angina		Diagnosis at initial examination			Diagnosis registered after CAG					
		CAG within 60 days			PCI within 60 days (Grouped according to after CAG diagnosis)			CABG within 60 days from CAG		
		Examination rate %	n	% in 3 days*	Treatment rate %	n	% in 3 days*	Treatment rate %	n	% in 7 days*
Overall	8,820	71.4	6,300	44.2	49.7	2031	38.9	18.0	735	43.7
Year of diagnosis	2001	59.9	631	30.2	51.3	224	24.9	26.8	117	47.2
	2002	61.0	649	32.0	47.6	200	31.2	28.8	121	44.5
	2003	64.5	633	37.1	49.5	206	33.5	22.8	95	55.3
	2004	72.3	663	33.1	43.4	170	23.3	20.4	80	53.4
	2005	74.1	705	43.1	51.2	229	38.1	14.5	65	36.7
	2006	74.3	753	44.6	52.3	228	39.9	14.0	61	42.1
	2007	78.3	720	51.9	49.2	214	43.0	15.9	69	30.0
	2008	82.1	823	55.5	50.4	317	52.6	11.6	73	42.0
	2009	79.0	723	62.0	50.9	243	51.1	11.3	54	29.2
Gender	Men	74.9	3,719	44.6	51.6	1318	39.5	21.4	549	44.1
	Women	66.7	2,305	37.7	48.2	658	33.4	12.0	166	41.7
Age	30 or younger	64.3	18	61.1	-	-	-	14.3	1	0
	30-39	71.4	177	43.0	39.1	34	52.9	4.5	4	25.0
	40-49	75.6	684	43.7	49.5	207	45.8	7.3	31	50.0
	50-59	80.4	1,562	40.0	54.0	534	39.9	13.8	137	37.0
	60-69	78.3	1,841	42.7	50.3	609	36.1	21.8	265	46.7
	70-79	70.7	1,350	40.8	46.9	429	32.3	26.7	244	42.7
	80 or older	37.8	392	45.8	55.3	163	34.7	11.0	33	50.0
LMCA* involvement	yes				14.8	21	47.6	75.4	107	60.0
	No				52.6	1684	39.7	15.5	496	39.8
Number of occluded vessels	0				1.9	11	50.0	0.5	3	0
	1 vessel				79.1	1010	44.1	2.3	30	40.0
	2 vessels				67.1	451	36.7	19.6	132	42.3
	3 vessels				26.5	186	31.8	58.3	409	43.8

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

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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 <u>invasive examination and</u> 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 (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 <u>invasive examination</u>

<u>and</u> 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

Gr<u>a</u>~~e~~y 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 <u>invasive examination and</u> treatment

probability at 3 days for CAG and PCI was seen especially from 2007 through to 2009. For

NSTEMI the CAG ~~treatment~~ <u>examination</u> probability at 3 days leaped from 2<u>0</u> ~~1~~% in 2007 to 3<u>2</u>~~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~~ investigate a potential ~~explanation~~causes of the significant improvement in prognosis by ~~investigating~~ describing ~~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.

5

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), 121.4 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. DDiagnosis 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 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 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)(12). 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)(12). 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

COMPRISK to draw Aalen-Johansen plot provided open access by the MAYO Institute.

Results:

Of the 65,909~~80,033~~ patients ~~who were registered with first time ACS and no prior heart disease~~identified 28.7~~3.4~~ % were admitted with NSTEMI, 13,4~~9.3~~ % with unstable angina, 25.5~~3.3~~ % with STEMI and 32.4~~4.0~~ % with non-specified MI. A total of 8,412~~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 35~~3~~.0 % of patients were admitted with NSTEMI, 12.6~~2~~ % with unstable angina, 33.2~~5.7~~ with STEMI and 19.2~~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 55.7~~2~~ %. For PCI a similar development was seen with 52.0~~1~~ % treated within 3 days in 2009 compared to 27.5~~2~~ % 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 ~~investigation~~ 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~~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 19.5~~3~~ % in 2007 to 31.5~~9~~ % in 2008 and a

further increase to 38.7~~7.5~~ % 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~~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=7.44~~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

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=0.50~~32~~ p=0.62~~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 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 CAG~~cag~~ (*z*=-0.50~~76~~

p=0.62~~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*=-0.32~~23~~ p=0.75~~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. 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)(1, 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)(18).

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 thean early strategy (22). This

reflects shows the importance of early invasive treatment however theise 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~~721~~ patients with a~~A~~ngina 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 <u>invasive examination and </u>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~~ <u>examination </u>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 8<u>4.7</u>~~5.6~~ % and 82.1~~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 <u>-</u>Gr<u>a</u>~~e~~y 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~~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.

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.

Funding

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.

18

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)

NSTEMI		Diagnosis at initial examination			Diagnosis registered after CAG					
		CAG within 60 days			PCI within 60 days (Grouped according to after CAG diagnosis)			CABG within 60 days from CAG		
		Treatment Examination rate %	n	% in 3 days*	Treatment rate %	N	% in 3 days*	Treatment rate %	n	% in 7 days*
Overall		18.947757 63.362.2	11,997 1,676	31.831.5	52.752.3	59846,233	30.730.6	16.216.2	18361,933	26.326.5
Year of diagnosis	2001	49.849.0	823792	18.218.2	48.448.6	25526	27.527.2	23.022.8	121126	29.528.4
	2002	54.954.0	1,1771,112	19.919.0	49.649.3	46548 9	24.825.1	22.823.1	214229	23.724.8
	2003	58.757.2	1,3551,292	26.225.4	51.451.2	59764 3	21.222.4	19.519.0	226239	38.538.9
	2004	61.360.2	1,4221,356	23.222.2	54.353.8	67370 8	24.223.5	17.817.5	221230	35.535.4
	2005	67.766.6	1,4801,437	26.625.8	56.755.9	77180 4	23.723.4	16.216.2	220233	25.726.2
	2006	68.067.0	1,4011,373	28.928.5	55.154.3	79281 4	24.624.2	13.113.4	188201	23.322.8
	2007	66.965.6	1,4381,420	30.730.9	49.549.2	72875 0	27.426.9	16.516.7	243254	15.315.5
	2008	70.569.1	1,5331,545	46.246.5	50.350.1	81784 7	38.938.9	13.213.4	214226	24.725.0
	2009	70.068.7	1,3681,349	55.755.2	55.355.2	88690 9	52.052.1	11.811.8	189195	23.023.0
Gender	Men	70.869.8	8,0727,850	32.332.0	56.355.9	42474,423	30.830.5	18.818.6	14241,497	25.725.9
	Women	52.151.0	3,7913,697	29.429.3	47.046.6	16151,681	26.927.0	11.211.2	386410	28.027.9
Age	30 or younger	86.764.9	2624	37.536.4	15.013.6	33	66.766.7	--	--	--
	30-39	91.583.8	225223	44.345.7	53.151.8	11111 3	42.942.5	2.32.2	55	60.060.0
	40-49	91.489.0	1,0931,073	40.641.4	59.258.5	59962 7	42.241.6	7.07.2	7278	33.835.2
	50-59	89.488.3	2,5212,439	33.233.2	61.060.9	14591,525	29.830.0	12.512.4	302315	28.328.6
	60-69	84.082.9	3,5433,459	29.829.3	52.552.2	17031,762	28.327.8	20.820.6	675702	25.625.0
	70-79	66.165.2	3,3373,253	27.627.2	47.947.4	14721,530	25.926.0	21.721.6	665706	23.724.5
	80 or older	21.821.3	1,1181,076	31.230.5	49.749.2	51555 4	27.527.4	8.79.0	91101	33.332.6
LMCA** involvement	Yes				18.720.3	3946	33.327.9	65.664.3	137146	50.450.0
	No				54.654.3	48855,228	32.131.4	14.314.4	12761,384	24.924.5
Number of occluded vessels	0				1.94.5	2260	31.823.2	0.30.5	46	50.033.3
	1 vessel				78.578.0	25922,743	36.235.4	1.51.6	4956	36.732.1
	2 vessels				71.771.4	13931,492	32.031.0	12.712.7	246266	23.424.2
	3 vessels				30.029.8	63067 6	30.129.7	49.349.7	10341,126	29.629.2

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

19

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

Unstable angina		Diagnosis at initial examination			Diagnosis registered after CAG					
		CAG within 60 days			PCI within 60 days (Grouped according to after CAG diagnosis)			CABG within 60 days from CAG		
		Treatment Examination rate %	n	% in 3 days*	Treatment rate %	n	% in 3 days*	Treatment rate %	n	% in 7 days*
Overall	8,82015,469	71.452.5	6,3008,114	44.244.8	49.748.4	20312,134	38.938.4	18.018.0	735795	43.742.6
Year of diagnosis	2001	59.943.1	631778	30.229.4	51.351.4	224238	24.925.1	26.825.9	117120	47.246.8
	2002	61.043.4	649900	32.033.5	47.646.3	200211	31.230.5	28.828.1	121128	44.542.7
	2003	64.545.0	633897	37.140.0	49.547.7	206213	33.532.8	22.822.8	95102	55.354.3
	2004	72.349.3	663915	33.135.6	43.441.4	170178	23.322.3	20.420.2	8087	53.452.5
	2005	74.151.4	705951	43.145.2	51.250.7	229243	38.138.4	14.514.8	6571	36.736.4
	2006	74.357.1	753946	44.646.7	52.350.5	228245	39.940.2	14.015.3	6174	42.138.2
	2007	78.361.0	720895	51.951.0	49.247.5	214222	43.042.0	15.916.1	6975	30.030.8
	2008	82.167.9	823942	55.556.0	50.448.8	317329	52.652.1	11.612.2	7382	42.041.0
	2009	79.064.7	723890	62.061.8	50.950.1	243255	51.150.0	11.311.0	5456	29.228.0
Gender	Men	74.957.0	3,7194,894	44.644.8	51.650.5	13181,394	39.538.7	21.421.3	549598	44.142.7
	Women	66.746.2	2,3052,921	37.740.0	48.246.6	658684	33.433.6	12.011.9	166177	41.741.6
Age	30 or younger	64.323.3	1827	61.161.5	-	--	--	14.3-	1-	-0
	30-39	71.435.1	177226	43.047.7	39.136.4	3436	52.951.4	4.514.3	41	25.025.0
	40-49	75.647.2	684922	43.745.2	49.548.1	207219	45.844.8	7.33.9	314	50.051.7
	50-59	80.459.4	1,5621,999	40.040.6	54.052.2	534560	39.939.2	13.86.9	13732	37.035.2
	60-69	78.364.0	1,8412,373	42.743.7	50.349.7	609648	36.135.3	21.814.1	265153	46.745.2
	70-79	70.756.5	1,3501,730	40.841.7	46.945.5	429443	32.332.4	26.721.6	244287	42.741.5
	80 or older	37.826.0	392538	45.846.2	55.353.6	163172	34.735.8	11.026.2	33258	50.052.6
LMCA* involvement	yes				14.816.0	2124	47.645.8	75.412.3	10740	60.058.6
	No				52.651.2	16841,810	39.738.9	15.574.0	496111	39.839.1
Number of occluded vessels	0				1.93.6	1124	50.039.1	0.515.6	3551	033.3
	1 vessel				79.178.2	10101,068	44.142.6	2.30.6	304	40.037.9
	2 vessels				67.166.4	451487	36.736.5	19.62.5	13234	42.342.0
	3 vessels				26.526.2	186205	31.832.5	58.319.1	409140	43.843.1

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

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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

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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 stilled 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.

2

Appendix 3: Distribution of diagnosis for patients with a non acute coronary heart syndrome diagnosis at coronary angiography

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

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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

NSTEMI	Year categorical n =18,947		Year continuous n =18,947		+ fixed treatment protocols n =18,947		+ age n=18,676		+ sex n=18,676	
Year	β	CI 95	β	CI 95	β	CI 95	β	CI 95	β	CI 95
2001	0		0.21	0.19-0.22	0.19	0.17-0.20	0.19	0.17-0.20	0.19	0.17-0.20
2002	0.22	0.01-0.43								
2003	0.57	0.37-0.77								
2004	0.49	0.29-0.69								
2005	0.74	0.54-0.93								
2006	0.86	0.67-1.06								
2007	0.92	0.73-1.11								
2008	1.48	1.29-1.66								
2009	1.71	1.53-1.89								
Fixed treatment protocols					0.22	0.11-0.32	0.25	0.15-0.35	0.25	0.15-0.35
Age										
Ref: < 50							0		0	
50-59							-0.23	-0.34-(-0.12)	-0.23	-0.34-(-0.12)
60-79							-0.63	-0.72-(-0.53)	-0.61	-0.71-(-0.51)
>80							-1.89	-2.03-(-1.75)	-1.83	-1.97-(-1.69)
Sex										
Men									0	
Women									-0.19	-0.26-(-0.12)

4.1.b PCI

NSTEMI	Year categorical n=11,357		Year continuous n=11,357		+ fixed treatment protocols n=11,357		+ age n=11,131		+ sex n=11,131		+ Number of occluded vessels and LMCA involvement, n=7,076	
Year	β	CI 95	β	CI 95	β	CI 95	β	CI 95	β	CI 95	β	CI 95
2001	0		0.14	0.11-0.16	0.07	0.05-0.10	0.07	0.04-0.10	0.07	0.04-0.10	0.01	-0.02-0.05
2002	-0.07	-0.38-0.23										
2003	-0.20	-0.51-0.10										
2004	0.02	-0.27-0.31										
2005	0.02	-0.27-0.31										
2006	0.03	-0.25-0.32										
2007	0.07	-0.21-0.35										
2008	0.45	0.18-0.71										
2009	0.91	0.65-1.17										
Fixed treatment protocols					0.55	0.40-0.69	0.59	0.45-0.74	0.59	0.44-0.74	0.57	0.41-0.73
Age (ref = < 50)							0		0		0	
50-59							-0.24	-0.38-(-0.09)	-0.24	-0.39-(-0.09)	-0.31	-0.47-(-0.15)
60-79							-0.60	-0.74-(-0.47)	-0.59	-0.72-(-0.45)	-0.55	-0.70-(0.41)
>80							-0.70	-0.90-(-0.49)	-0.64	-0.85-(-0.43)	-0.57	-0.79-(-0.35)
Sex (ref=men)									0		0	
Women									-0.28	-0.40-(-0.17)	-0.13	-0.24-(-0.01)
LMCA involvement (ref=no)											0	
Yes											0.65	0.05-1.26
Number of occluded vessels (ref=1)											0	
2											-0.13	-0.24-(-0.01)
3											-1.06	-1.22-(-0.89)

4.1.c. CABG

NSTEMI	Year categorical n=11,357		Year continuous n=11,357		+ fixed treatment protocols n=11,357		+ age n=11,131		+ sex n=11,131		+ Number of occluded vessels and LMCA involvement, n=7,076	
Year	β	CI 95	β	CI 95	β	CI 95	B	CI 95	β	CI 95	β	CI 95
2001	0		-0.13	-0.17-(-0.10)	-0.14	-0.19-(-0.10)	-0.13	-0.18-(-0.09)	-0.13	-0.18-(-0.09)	-0.20	-0.25-(-0.14)
2002	-0.25	-0.70-0.20										
2003	0.08	-0.33-0.50										
2004	-0.08	-0.50-0.34										
2005	-0.50	-0.94-(-0.05)										
2006	-0.83	-1.30-(-0.36)										
2007	-0.93	-1.41-(-0.45)										
2008	-0.70	-1.14-(-0.25)										
2009	-0.91	-1.37-(-0.44)										
Fixed treatment protocols					0.09	-0.29-0.48	0.05	-0.34-0.44	0.04	-0.35-0.43	0.19	-0.34-0.71
Age (ref = < 50)							0		0		0	
50-59							0.47	0.02-0.92	0.45	-0.00-0.90	0.01	-0.53-0.51
60-79							0.88	0.47-1.29	0.91	0.49-1.32	-0.12	-0.59-0.35
>80							0.40	-0.14-0.94	0.50	-0.05-1.04	-1.00	-1.69-(-0.32)
Sex (ref=men)									0		0	
Women									-0.48	-0.71-(-0.25)	-0.28	-0.57-0.01
LMCA involve-ment (ref=no)												
Yes											0	
											-1.27	-1.58-(-0.95)
Number of occluded vessels (ref=1)												
2											0	
											1.61	1.00-2.22
3											3.20	2.65-3.76

4.2. Results from the Fine Grey model for NSTEMI at 60 days

4.2.a CAG

NSTEMI	Year categorical n =18,947		Year continuous n n =18,947		+ age n=18,676		+ sex n= 18,676	
Year	β	CI 95	β	CI 95	β	CI 95	β	CI 95
2001	0		0.10	0.09-0.10	0		0	
2002	0.16	0.07-0.24			0.21	0.12-0.29	0.21	0.12-0.29
2003	0.27	0.19-0.36			0.35	0.26-0.43	0.35	0.27-0.43
2004	0.32	0.24-0.40			0.44	0.36-0.52	0.43	0.36-0.51
2005	0.48	0.40-0.56			0.52	0.48-0.64	0.57	0.49-0.64
2006	0.50	0.42-0.58			0.54	0.48-0.65	0.57	0.48-0.65
2007	0.53	0.44-0.61			0.62	0.58-0.74	0.66	0.57-0.74
2008	0.75	0.67-0.84			0.89	0.87-1.04	0.96	0.87-1.04
2009	0.84	0.75-0.93			1.01	0.98-1.17	1.08	0.98-1.17
Age								
Ref: < 50					0		0	
50-59					-0.06	-0.22-0.08	-0.15	-0.22-0.08
60-79					-0.49	-0.65-(-0.53)	-0.56	-0.63-(-0.50)
>80					-2.22	-2.41-(-2.25)	-2.27	-2.36-(-2.19)
Sex								
Men							0	
Women							-0.20	-0.24-(-0.16)

4.2.b PCI

NSTEMI	Year categorical n=11,357		Year continuous n=11,357		+ age n=11,131		+ sex n=11,131		+ Number of occluded vessels and LMCA involvement, n=7,076	
Year	β	CI 95	β	CI 95	B	CI 95	β	CI 95	B	CI 95
2001	0		0.03	0.02-0.04	0		0		0	
2002	0.004	-0.14-0.15			0.02	-0.13-0.17	0.02	-0.13-0.17	-0.12	-0.34-0.11
2003	0.06	-0.08-0.20			0.06	-0.09-0.20	0.06	-0.09-0.20	-0.08	-0.29-0.13
2004	0.11	-0.02-0.25			0.14	-0.00-0.28	0.13	-0.01-0.28	-0.05	-0.26-0.16
2005	0.17	0.04-0.31			0.20	0.06-0.34	0.20	0.06-0.34	0.03	-0.23-0.17
2006	0.12	-0.02-0.25			0.16	0.03-0.30	0.17	0.03-0.31	-0.13	-0.33-0.07
2007	0.03	-0.11-0.17			0.04	-0.10-0.18	0.05	-0.09-0.19	-0.18	-0.38-0.02
2008	0.12	-0.01-0.26			0.15	0.01-0.29	0.15	0.01-0.29	-0.00	-0.20-0.20
2009	0.35	0.21-0.49			0.40	0.25-0.54	0.40	0.26-0.54	0.17	0.04-0.37
Age (ref = < 50)					0		0		0	
50-59					0.05	-0.04-0.15	0.05	-0.05-0.14	-0.05	-0.16-0.06
60-79					-0.25	-0.34-(-0.16)	-0.24	-0.32-(-0.15)	-0.22	-0.32-(-0.12)
>80					-0.29	-0.41-(-0.17)	-0.25	-0.36-(0.13)	-0.20	-0.34-(-0.06)
Sex (ref=men)							0		0	
Women							-0.24	-0.30-(-0.18)	-0.07	-0.14-0.01
LMCA involvement (ref=no)									0	
Yes									0.95	0.62-1.28
Number of occluded vessels (ref=1)									0	
2									-0.14	-0.20-(-0.07)
3									-1.35	-1.44-(-1.25)

4.2.c CABG

NSTEMI	Year categorical n=11,357		Year continuous n=11,357		+ age n=11,131		+ sex n=11,131		+ Number of occluded vessels and LMCA involvement,n=7,076	
Year	**β**	**CI 95**	**β**	**CI 95**	**B**	**CI 95**	**β**	**CI 95**	**β**	**CI 95**
2001	0		-0.09	-0.11-(-0.07)	0		0		0	
2002	-0.00	-0.23-0.22			-0.04	-0.27-0.18	-0.05	-0.28-0.17	0.11	-0.21-0.43
2003	-0.17	-0.39-0.05			-0.17	-0.39-0.05	-0.18	-0.40-0.05	0.09	-0.23-0.40
2004	-0.28	-0.50-(-0.05)			-0.28	-0.50-(-0.05)	-0.29	-0.51-(-0.07)	-0.02	-0.33-0.29
2005	-0.39	-0.61-(-0.17)			-0.36	-0.59-(-0.14)	-0.37	-0.60-(-0.15)	-0.14	-0.35-0.22
2006	-0.62	-0.85-(-0.39)			-0.60	-0.83-(-0.37)	-0.61	-0.83-(-0.38)	-0.53	-0.85-(-0.22)
2007	-0.39	-0.60-(-0.17)			-0.37	-0.59-(-0.16)	-0.36	-0.58-(-0.15)	-0.10	-0.40-0.19
2008	-0.61	-0.84-(-0.39)			-0.60	-0.82-(-0.37)	-0.61	-0.83-(-0.39)	-0.41	-0.71-(-0.10)
2009	-0.70	-0.93-(-0.47)			-0.69	-0.92-(-0.46)	-0.71	-0.94-(-0.48)	-0.30	-0.62-0.01
Age (ref = < 50)					0		0		0	
50-59					0.73	0.48-0.98	0.71	0.46-0.97	0.28	-0.01-0.58
60-79					1.31	1.08-1.54	1.35	1.12-1.59	0.33	-0.06-0.61
>80					0.43	0.13-0.74	0.55	0.24-0.86	-1.16	-1.58-(-0.77)
Sex (ref=men)							0		0	
Women							-0.59	-0.71-(-0.48)	-0.31	-0.46-(-0.16)
LMCA involve-ment (ref=no)									0	
Yes									-0.85	-1.08-(-0.61)
Number of occluded vessels (ref=1)									0	
2									2.11	1.79-2.44
3									3.84	3.53-4.14

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

Unstable angina	Year categorical n =8,820		Year continuous n =8,820		+ fixed treatment protocols n =8,820		+ age n=8,419		+ sex n= 8,419	
Year	β	CI 95	β	CI 95	β	CI 95	β	CI 95	β	CI 95
2001	0		0.17	0.15-0.18	0.17	0.15-0.19	0.17	0.15-0.19	0.17	0.15-0.19
2002	0.15	-0.05-0.36								
2003	0.36	0.16-0.56								
2004	0.38	0.18-0.58								
2005	0.72	0.53-0.90								
2006	0.75	0.57-0.94								
2007	1.02	0.84-1.20								
2008	1.18	1.01-1.36								
2009	1.31	1.13-1.48								
Fixed treatment protocols					-0.03	-0.15-0.09	-0.02	-0.15-0.11	-0.03	-0.15-0.11
Age Ref: < 50							0		0	
50-59							0.00	-0.13-0.10	0.00	-0.13-0.13
60-79							0.02	0.13-0.10	0.00	-0.12-0.12
>80							-0.68	-0.86-(-0.49)	-0.61	-0.80-(-0.43)
Sex Men									0	
Women									-0.29	-0.37-(-0.21)

5.1.b PCI

Unstable angina	Year categorical n=4,089		Year continuous n=4,089		+ fixed treatment protocols n=4,089		+ age n=3,981		+ sex n=3,981		+ Number of occluded vessels and LMCA involvement, n=2,556	
Year	β	CI 95	β	CI 95	β	CI 95	β	CI 95	β	CI 95	B	CI 95
2001	0		0.11	0.08-0.14	0.11	0.08-0.15	0.12	0.08-0.16	0.12	0.08-0.16	0.11	0.07-0.15
2002	0.20	-0.16-0.57										
2003	0.26	-0.10-0.62										
2004	-0.27	-0.69-0.15										
2005	0.47	0.12-0.81										
2006	0.51	0.16-0.85										
2007	0.55	0.20-0.89										
2008	0.82	0.51-1.14										
2009	0.82	0.50-1.15										
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)							0		0		0	
50-59							0.01	-0.24-0.23	-0.01	-0.24-0.22	-0.18	-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							-0.25	-0.59-0.08	-0.20	-0.54-0.14	-0.28	-0.64-0.09
Sex (ref=men) Women									0		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											-1.34	-1.62-(-1.05)

5.1.c CABG

Unstable angina	Year categorical n=4,089		Year continuous n=4,089		+ fixed treatment protocols n=4,089		+ age n=3,981		+ sex n=3,981		+ Number of occluded vessels and LMCA involvement, n=2,556	
Year	β	CI 95	β	CI 95	β	CI 95	B	CI 95	β	CI 95	β	CI 95
2001	0		-0.18	-0.22-(-0.13)	-0.17	-0.22-(-0.12)	-0.18	-0.22-(-0.12)	-0.17	-0.23-(-0.12)	-0.13	-0.20-(-0.06)
2002	0.02	-0.37-0.41										
2003	-0.05	-0.45-0.34										
2004	-0.17	-0.59-0.24										
2005	-0.89	-1.39-(-0.39)										
2006	-0,78	-1.26-(-0.29)										
2007	-1,07	-1.61-(-0.54)										
2008	-0.96	-1.42-(-0.50)										
2009	-1.36	-1.93-(-0.78)										
Fixed treatment protocols					-0.11	-0.69-0.47	-0.11	-0.69-0.48	-0.10	-0.68-0.48	-0.41	-1.28-0.45
Age (ref = < 50)							0		0		0	
50-59							0.49	-0.09-1.07	0.48	-0.10-1.05	-0.15	-0.80-0.49
60-79							1.26	0.74-1.79	1.30	0.77-1.82	0.14	-0.45-0.73
>80							0.76	0.05-1.46	0.87	0.16-1.58	-1.12	-2.12-(-0.11)
Sex (ref=men)									0		0	
Women									-0.64	-0.92-(-0.36)	-0.33	-0.69-0.02
LMCA involve-ment (ref=no)											0	
Yes											-1.14	-1.50-(-0.77)
Number of occluded vessels (ref=1)											0	
2											2.28	1.53-3.02
3											3.33	2.61-4.05

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

5.2.a CAG

Unstable angina	Year categorical n =8,820		Year continuous n =8,820		+ age n=8,419		+ sex n= 8,419	
Year	β	CI 95	β	CI 95	β	CI 95	β	CI 95
2001	0		0.11	0.10-0.12	0		0	
2002	0.05	-0.05-0.15			0.13	-0.03-0.24	0.13	-0.03-0.24
2003	0.16	0.05-0.27			0.16	0.05-0.27	0.15	0.05-0.26
2004	0.31	0.21-0.41			0.32	0.22-0.42	0.32	0.22-0.43
2005	0.42	0.32-0.52			0.45	0.35-0.55	0.45	0.34-0.55
2006	0.41	0.31-0.52			0.42	0.32-0.52	0.42	0.32-0.52
2007	0.61	0.50-0.72			0.57	0.46-0.68	0.57	0.46-0.68
2008	0.79	0.69-0.90			0.79	0.68-0.90	0.79	0.68-0.90
2009	0.78	0.67-0.89			0.77	0.66-0.89	0.77	0.66-0.89
Age								
Ref: < 50					0		0	
50-59					0.14	0.05-0.22	0.14	0.05-0.22
60-79					0.03	-0.05-0.11	0.04	-0.04-0.12
>80					-1.01	-1.14-(-0.89)	-0.97	-1.10-(-0.85)
Sex								
Men							0	
Women							-0.17	-0.23-(-0.12)

5.2.b PCI

Unstable angina	Year categorical n=4,089		Year continuous n=4,089		+ age n=3,981		+ sex n=3,981		+ Number of occluded vessels and LMCA involve-ment, n=2,556	
Year	β	CI 95	β	CI 95	β	CI 95	β	CI 95	B	CI 95
2001	0		0.02	0.01-0.04	0		0		0	
2002	-0.07	-0.26-0.11			-0.08	-0.27-0.10	-0.08	-0.27-0.10	-0.03	-0.23-0.17
2003	-0.02	-0.21-0.16			-0.04	-0.23-0.14	-0.04	-0.22-0.14	0.01	-0.19-0.21
2004	-0.23	-0.42-(-0.05)			-0.23	-0.42-(-0.04)	-0.22	-0.41-(-0.03)	-0.12	-0.34-0.09
2005	0.06	-0.12-0.24			0.07	-0.11-0.25	0.07	-0.11-0.25	0.07	-0.12-0.27
2006	0.06	-0.12-0.24			0.04	-0.14-0.22	0.03	-0.15-0.21	0.06	-0.13-0.24
2007	0.00	-0.18-0.18			0.04	-0.22-0.15	-0.03	-0.22-0.15	0.02	-0.18-0.22
2008	0.10	-0.07-0.27			0.11	-0.07-0.28	0.11	-0.06-0.28	0.22	0.03-0.41
2009	0.14	-0.04-0.32			0.12	-0.06-0.31	0.13	-0.06-0.32	0.33	0.12-0.53
Age (ref = < 50)					0		0		0	
50-59					0.19	0.03-0.34	0.18	0.03-0.34	-0.02	-0.21-0.16
60-79					0.02	-0.12-0.16	0.02	-0.12-0.17	-0.17	-0.34-0.00
>80					0.16	0.04-0.36	0.18	-0.02-0.38	-0.04	-0.27-0.20
Sex (ref=men)							0		0	
Women							-0.12	-0.21-(-0.02)	0.08	-0.03-0.18
LMCA involvement (ref=no)										
Yes									1.43	0.92-1.94
Number of occluded vessels (ref=1)									0	
2									-0.22	-0.33-(-0.11)
3									-1.45	-1.62-(-1.29)

5.2.b CABG

Unstable angina	Year categorical n=4,089		Year continuous n=4,089		+ age n=3,981		+ sex n=3,981		+ Number of occluded vessels and LMCA involve-ment, n=2,556	
Year	β	CI 95	β	CI 95	B	CI 95	β	CI 95	β	CI 95
2001	0		-0.14	-0.17-(-0.11)	0		0		0	
2002	0.07	-0.18-0.33			-0.05	-0.21-0.31	0.05	-0.21-0.31	0.10	-0.21-0.42
2003	-0.17	-0.44-0.11			-0.19	-0.47-0.08	-0.18	-0.46-0.10	0.34	0.02-0.67
2004	-0.30	-0.59-(-0.02)			-0.32	-0.62-(-0.03)	-0.28	-0.57-0.02	-0.19	-0.56-(-0.19)
2005	-0.69	-1.00-(-0.39)			-0.75	-1.06-(-0.45)	-0.75	-1.06-(-0.45)	-0.56	-0.93-(-0.20)
2006	-0.73	-1.04-(-0.42)			-0.73	-1.05-(-0.42)	-0.74	-1.05-(-0.42)	-0.54	-0.93-(-0.15)
2007	-0.61	-0.91-(-0.32)			-0.60	-0.90-(-0.30)	-0.59	-0.89-(-0.29)	-0.41	-0.79-(-0.04)
2008	-0.93	-1.22-(-0.63)			-0.96	-1.26-(-0.66)	-0.95	-1.25-(-0.65)	-0.45	-0.83-(-0.07)
2009	-0.95	-1.27-(-0.63)			-0.99	-1.31-(-0.66)	-0.97	-1.29-(-0.64)	-0.42	-0.81-(-0.03)
Age (ref = < 50)					0		0		0	
50-59					0.71	0.34-1.07	0.70	0.33-1.06	0.07	-0.38-0.52
60-79					1.35	1.01-1.69	1.39	1.04-1.73	0.30	0.12-0.73
>80					0.57	0.01-1.05	0.69	0.21-1.17	-1.30	-1.97-(-0.62)
Sex (ref=men)							0		0	
Women							-0.65	-0.82-(-0.47)	-0.25	-0.47-(-0.04)
LMCA involve-ment (ref=no)									0	
Yes									-1.04	-1.32-(-0.76)
Number of occluded vessels (ref=1)									0	
2									2.14	1.73-2.56
3									3.49	3.09-3.90

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

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

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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
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.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.