Acute myocardial infarction – consequences of new treatment modalities and smoking status

Observations from two prospective cohort studies

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Contents

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Erlend Aune, May 2011

Abstract

This thesis is based upon a comparison of two cohorts of consecutive patients admitted with chest pain suspected to be acute coronary syndrome (ACS) in 2003 (n = 755) and 2006 (n = 934). In 2003 the predominant reperfusion strategy for patients with ST-segment elevation myocardial infarction (STEMI) was prehospital fibrinolysis. Patients with non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP) were managed with an ischemia-driven approach for invasive procedures.

In September 2005, following the introduction of new European guidelines on invasive treatment, an early invasive strategy was implemented. Patients with STEMI were transported 100 km to Rikshospitalet University Hospital in Oslo for primary percutaneous coronary intervention. Those with NSTEMI or UAP were routinely transported for invasive management within 48-72 hours in the absence of contraindicating factors. In 2003, 48% of patients qualified for a diagnosis of ACS as compared with 39% in 2006 ($p<0.001$). In both cohorts NSTEMI patients were older and had greater co-morbidity than patients with STEMI.

From 2003 to 2006 the incidence rate for STEMI decreased from 100 to 77 cases per 100,000 person-years, whereas for NSTEMI this decrease was 147 to 143 cases per 100,000 person-years. The one-year all-cause mortality for NSTEMI decreased from 32% in 2003 to 19% ($p = 0.002$) in 2006. The corresponding figures for STEMI were 20% and 11% ($p = 0.086$). After adjustment for age, sex, previous acute myocardial infarction (AMI), previous stroke, diabetes, smoking status, previous left ventricular dysfunction and serum creatinine on admission, patients with AMI in the 2006 cohort had a significantly lower risk for one-year mortality than those managed for AMI in 2003 (hazard ratio 0.54, 95% confidence interval 0.38-0.78, $p = 0.001$).

In a post-hoc analysis, smokers with NSTEMI seemed to be a subset of patients with a particular survival benefit of early invasive management, but smoking on admission was still an independent predictor of death. In a systematic literature search on studies addressing the occurrence of the "smoker's paradox" in ACS (i.e. that smokers have lower adjusted case fatality than non-smokers), we found that studies supporting the existence of the paradox were from the pre-thrombolytic and thrombolytic era. No studies of patients with contemporary management found support for the paradox. The "smoker's paradox" most probably represents a historical phenomenon without relevance for today's practice.

In conclusion, the implementation of routine early invasive management for unselected patients with AMI was followed by a 41% reduction in one-year total mortality. For NSTEMI this survival benefit

was especially pronounced for smokers, but smoking was still an independent predictor of one-year mortality.

List of papers

I. Aune E, Hjelmesæth J, Fox KAA, Endresen K, Otterstad JE. High mortality rates in conservatively managed patients with acute coronary syndrome. Scand Cardiovasc J 2006; 40: 137-44.

II. Aune E, Endresen K, Fox KAA, Steen-Hansen JE, Røislien J, Hjelmesæth J, Otterstad JE. Effect of implementing routine early invasive strategy on 1-year mortality in patients with an acute myocardial infarction. Am J Cardiol 2010; 105: 36-42.

III. Aune E, Endresen K, Røislien J, Hjelmesæth J, Otterstad JE. The effect of tobacco smoking and treatment strategy on the one-year mortality of patients with acute non-ST-segment elevation myocardial infarction. BMC Cardiovasc Disord 2010; 10: 59.

IV. Aune E, Røislien J, Mathisen M, Thelle DS, Otterstad JE. The "smoker's paradox" in patients with acute coronary syndrome: a systematic review. BMC Medicine. Resubmitted after minor revision.

Abbreviations and acronyms

ACC	American college of cardiology
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ACTION	Assessment of combination therapy in obstructed native coronary arteries
AMI	Acute myocardial infarction
CABG	Coronary artery bypass grafting
CCU	Coronary care unit
CHD	Coronary heart disease
CI	Confidence interval
CKMB	Creatine kinase-myocardial band
CURE	Clopidogrel in unstable angina to prevent recurrent events
DANAMI-2	Danish trial in acute coronary angioplasty in acute myocardial infarction 2
ECG	Electrocardiogram
ESC	European society of cardiology
GISSI	Gruppo italiano per lo studio Della streptochinasi nell'infarcto miocardico
GRACE	Global registry of acute coronary events
HR	Hazard ratio
ISIS	International study of infarct survival
IV	Intravenous
LBBB	Left bundle branch block
MI	Myocardial infarction
MONICA	Multinational monitoring of trends and determinants in cardiovascular disease
NSTE-ACS	Non-ST-segment elevation acute coronary syndrome
NSTEMI	Non-ST-segment elevation myocardial infarction
OASIS	Organization to assess strategies for ischemic syndrome
PCI	Percutaneous coronary intervention
PRAGUE	Primary angioplasty in patients transferred from general community hospitals to specialized PTCA units with or without emergency thrombolysis
PTCA	Percutaneous transluminal coronary angioplasty
STEMI	ST-segment elevation myocardial infarction
TIMACS	Timing of intervention in acute coronary syndromes
UAP	Unstable angina pectoris

WARIS	Warfarin aspirin reinfarction study
WHO	World Health Organisation

1. Introduction

1.1. Background and motivation

The causes of the decline in cardiovascular mortality in Europe [2,3], including Norway [4], are complex. Factors include lifestyle changes (e.g. less saturated fat, lower low-density lipoprotein cholesterol, less tobacco smoking) and the introduction of new treatment strategies in the last three decades [5,6]. The single most frequent cause of death in Norway is still acute myocardial infarction (AMI) [7]. In 2000 new criteria for the diagnosis of AMI were presented [8], with a focus on the rise of sensitive markers of cardiac injury following ischemic symptoms. According to changes in the electrocardiogram (ECG), patients with a significant rise in cardiac markers were subdivided into ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). Patients without such a rise were classified as unstable angina pectoris (UAP) provided they had transient ST-segment deviation and/or negative T waves in the ECG. These three groups accordingly represented the entity of acute coronary syndrome (ACS). A common cause of myocardial underperfusion in ACS is atherosclerotic plaque rupture or erosion with varying degrees of thrombosis and distal embolization [9,10].

Following the introduction of these criteria there was a huge move to characterise patients with STEMI or NSTEMI. Little was known about the incidence and prognosis of these subsets of patients. So far, a national registry of AMI has not been established in Norway. To obtain such knowledge about these patients, we initiated in 2003 a prospective cohort study of unselected patients hospitalised with suspected AMI. All patients were followed up for one year with total mortality as the only endpoint, and all revascularisation procedures and medical treatment were carefully registered. At that time the management of AMI comprised prehospital fibrinolysis of STEMI and a conservative, ischemia-driven approach for invasive management of NSTEMI. It transpired that one-year mortality was surprisingly high, and questions were raised as to whether the management applied could be improved. In 2005, the new guidelines on percutaneous coronary intervention (PCI) were in favour of primary PCI for STEMI and early invasive management for patients with NSTEMI and UAP [11]. Such a treatment policy was also highly recommended at a large European Society of Cardiology (ESC) meeting at the European Heart House the same year. In view of the high mortality of 2003's conservative approach, we initiated a second prospective cohort study including consecutive patients admitted in 2006. The purpose was to include similar patients to those included in 2003, with the only difference being the introduction of the early invasive management for all three subgroups of ACS.

The study of the first cohort was planned in 2002 and the second in 2005. The results were presented in 2006 and 2010, respectively. In this time period new diagnostic criteria for AMI and treatment algorithms were introduced. In addition, some interesting results emerged from analyses performed, especially regarding the influence of smoking status. Therefore, this thesis also includes a post-hoc analysis (Paper III) exploring the impact of smoking status on mortality. These findings motivated us to perform a systematic literature review (Paper IV) of a phenomenon termed the "smoker's paradox" (i.e. that smokers have better post-AMI survival than non-smokers when differences in baseline confounders are adjusted for). It should be emphasised that the production of this thesis has been a dynamic process, with the two last papers conceived of during the course of our other studies and not at the initiation of the thesis.

1.2. Historical perspectives

1.2.1. The criteria for AMI

Until 2000 the most commonly used criteria for MI were those published by the World Health Organisation (WHO) in 1979 [12]. AMI was defined by a combination of two out of three characteristics: typical symptoms, rise in enzymes and typical patterns in the ECG involving development of Q-waves. The advent of more sensitive and specific biomarkers of myocardial necrosis and a need for a more precise definition of AMI led to a consensus conference in July 1999. A joint ESC/American College of Cardiology (ACC) consensus document was published in 2000 [8]. AMI was defined as myocardial cell death due to prolonged ischemia, and the diagnosis was now based upon a rise in cardiac biomarkers (preferably troponin T or I) accompanied by electrocardiographic findings or clinical symptoms supporting myocardial ischemia. Advances in the diagnosis and management of AMI, in addition to a need for improved epidemiological data, led to further refinement of the criteria published in 2007 [13]. A clinical classification of five types of myocardial infarction was introduced. In addition to type 1 and 2, a type 3 was introduced in relation to sudden cardiac death, type 4 for PCI-associated AMI and type 5 for AMI following coronary artery bypass grafting (CABG).

1.2.2. Treatment of AMI

Prefibrinolytic era

A diagnosis of AMI was first verified by typical ECG changes in the 1930s. Bed rest for six weeks and symptomatic treatment was the only management provided. The development of external cardiac defibrillators to treat life-threatening arrhythmias throughout the 1950s [14] was one of the main reasons for introducing coronary care units (CCU). Such a unit was established at Vestfold Hospital

Trust in 1968. At that time the "warning arrhythmia" theory was predominant in the management of AMI, and intravenous (IV) lidocaine to prevent lethal arrhythmias was frequently used. It turned out, however, that although the incidence of ventricular fibrillation was reduced with lidocaine, the mortality was not [15]. In the 1970s i.v. nitroglycerine was very popular, but although a symptomatic effect on chest pain and heart failure was obtained, an effect on mortality was only documented in meta-analyses [16,17].

At that time a growing interest in the use of intravenous beta-blockade emerged, but the results of the first ever mega-trial in cardiology, ISIS-1, were quite disappointing for IV atenolol [18]. On the other hand, post AMI treatment with oral beta-blockers like timolol [19] and propranolol [20] was proven to increase long-term survival. In the 1980s oral treatment of heart failure and systolic dysfunction following AMI with angiotensin converting enzyme (ACE)-inhibitors was also associated with improved long-term survival [21,22]. These favourable results prompted a mega-trial on IV ACE-inhibition in the acute phase. As in the IV beta-blocker studies, the results were quite disappointing [23]. The beneficial effect of warfarin in survivors of AMI was documented in the two WARIS-studies published in 1990 and 2002 [24,25].

Fibrinolytic era

The large GISSI study was the first to demonstrate a favourable effect of IV fibrinolysis in AMI [26]. This finding was corroborated by the even larger ISIS-2 trial, where the combined use of IV streptokinase and oral aspirin reduced 5-weeks vascular mortality when compared with placebo infusion and tablets [27]. More efficient fibrinolytic therapies were developed and put into practice based on results from several large trials [28-32]. It had also become apparent that the preferred scenario for such treatment would be in the prehospital setting [33-35].

Invasive treatment

Andreas Grüntzig performed the first percutaneous transluminal coronary angioplasty (PTCA) in 1977 [36], and the first PTCA in Scandinavia was undertaken at Rikshospitalet University Hospital in Oslo by Karleif Vatne and Kjell Levorstad in 1981. Balloon angioplasty was initially compared with intracoronary thrombolytic therapy by O'Neill et al. in 1986 [37]. In the following years a number of trials compared primary PTCA with IV fibrinolysis for STEMI. These trials were summarised in a comprehensive, although debated meta-analysis by Keeley et al. in 2003 [38]. At that time, the term PTCA had been replaced by the term PCI with the introduction of additional stenting. The conclusion was that primary PCI is more efficient than fibrinolytic therapy. However, the problem of

transporting patients with STEMI from a hospital without PCI facilities to an invasive centre was not addressed in this meta-analysis.

At that time there was still some reluctance to transport patients with a diagnosis of STEMI to a remote invasive hospital. Both the DANAMI-2 [39] and PRAGUE-1 and -2 [40,41] studies were clearly in favour of transportation for primary PCI vs. fibrinolytic therapy in the local hospital.

During an international meeting at the European Heart House in June 2005 there was a large debate on fibrinolysis vs. primary PCI for STEMI and invasive vs. conservative strategy for NSTEMI [42]. Both at this meeting and in guidelines for PCI published the same year [11], the opinion of most experts was clearly in favour of primary PCI for STEMI and an early invasive strategy for patients with NSTEMI. Of special interest to us in Vestfold was the personal communication with Henning R. Andersen following the European meeting at the airport in Nice. He assured us that ambulance transportation for patients with STEMI to an invasive hospital was quite safe. In general, the company of a physician or specially trained nurse was not deemed to be necessary based upon his experiences from conducting the DANAMI-2 study. The population density in most areas of Denmark is quite similar to that in Vestfold, the geographically smallest county in Norway.

Non-ST-segment elevation ACS (NSTE-ACS), was, until the change of millennium, treated with medical stabilisation by the use of anti-ischemic and antithrombotic agents, including aspirin and heparin. Following the CURE study [43], clopidogrel for nine months was added. At that time, there was a considerable debate on the optimal invasive management of these patients, be it routine early invasive treatment or an ischemia-driven strategy. The results of the first trials were mixed, but after introduction of glycoprotein IIb/IIIa inhibitors and intracoronary stents a number of large trials published in the beginning of the new millennium showed a significant reduction of major cardiovascular events with the use of an early invasive vs. a conservative strategy [44-46]. These results were corroborated in two meta-analyses presented in 2005 [47] and 2008 [48].

In 2002, the principal management of STEMI in Norway was prehospital fibrinolysis, with an open mind kept for primary PCI for patients hospitalised in invasive centres. Patients with NSTEMI were managed with an ischemia-driven approach implying invasive management in case of recurrent ischemic episodes or a positive exercise test. As with STEMI, the presentation of new guidelines and the meeting at the European Heart House in Nice in 2005 prompted the implementation of an early invasive strategy of patients with NSTEMI. There is still a debate on how early such patients should undergo coronary angiography. So far, most centres in Norway aim to have an angiography performed within 48(-72) hours after admission to hospital in patients with moderate or high risk [49].

Introduction of early invasive treatment in Vestfold 2005

Based upon the combined information available at that time, in September of 2005 we changed our policy in order to transport all patients with STEMI to Rikshospitalet University Hospital in Oslo for primary PCI . The distance was 100 km and we decided that two certified paramedics were sufficient medical assistance. In addition, invasive management of patients with NSTEMI within 48-72 hours was introduced as a routine. This treatment policy was also a consequence of the disappointing mortality results observed in 2003's conservatively treated cohort of patients with AMI [50]. The change of treatment strategy allowed us to both perform a prospective study of all patients in 2006 with an ACS and to evaluate a possible mortality reduction in comparison with the cohort treated conservatively in 2003. The prospective nature of this new study gave us an opportunity to use identical inclusion criteria and cut-off level of troponin T as in the former cohort.

Present state of optimal AMI treatment

In the 2007 recommendation of the Norwegian Society of Cardiology [49] primary PCI is declared the preferred treatment for STEMI, provided a transportation time of <90 minutes is feasible. Due to obvious geographical reasons, fibrinolysis is still an option in rural areas with longer transportation time. Patients with NSTEMI and intermediate or high risk should be subjected to early invasive management (within 48-72 hours) unless they have co-morbidities contradicting such management. In the most recent ESC guidelines on myocardial revascularisation from 2010 [51], in cases with persistent ST-elevation after fibrinolysis then rapid transfer to an invasive centre for rescue-PCI should be considered. In case of successful fibrinolytic therapy, patients should be referred the next day for angiography. It is further stated that NSTEMI-ACS is the most frequent manifestation of ACS. They constitute a very heterogeneous group of patients with a highly variable prognosis.

The optimal timing of coronary angiography in NSTE-ACS patients is still under debate. In a recent meta-analysis on optimal timing for coronary angiography in NSTE-ACS patients, early catheterisation (median time ranged from 1.16 to 14 hours from admission) and potential intervention reduced the risk of recurrent ischemia and shortened hospital stay when compared with delayed catheterisation (median time ranged from 20.8 to 86 hours from admission) [52]. Early risk stratification is essential for medical as well as interventional strategies. In the TIMACS trial of 3031 NSTE-ACS patients a clinical benefit of early invasive management (<24 hours after randomisation), as opposed to delayed intervention (≥36 hours after randomisation), was observed in high risk patients only (GRACE risk score for in-hospital mortality >140) [53].

In the most recent guidelines on revascularisation [51], there is a class 1A recommendation for an early invasive strategy (<24 h) in NSTE-ACS patients with GRACE risk score >140 for in-hospital

mortality [54] or multiple other high-risk criteria. There is also a class 1A recommendation for an invasive strategy in patients with GRACE risk score >140 or at least one high-risk criterion, recurrent symptoms, or inducible ischemia at stress test.

2. Aims of the thesis

1. To obtain one-year mortality data from unselected, conservatively treated patients with the three categories of ACS, in addition to non-ACS patients with or without evidence of CHD admitted to a hospital without PCI-facilities in 2003.
2. To investigate whether the introduction of an early invasive strategy for unselected patients with AMI was associated with reduced one-year mortality compared to a previous conservative strategy.
3. Study the influence of smoking on the effect of early invasive strategy in a post-hoc analysis of patients with NSTEMI.
4. Perform a systematic literature search on the existence and characteristics of the "smoker's paradox" (i.e. that smokers have lower adjusted case fatality than non-smokers) in patients with ACS.

3. Materials and methods

3.1. Study population

This study recruited consecutive patients admitted to our hospital with suspected ACS. During two one-year periods all patients were prospectively registered. The conservative strategy cohort included patients admitted from 1st February 2003 through to 31st January 2004. The invasive strategy cohort included patients admitted from 15th February 2006 through to 14th February 2007. The catchment population totalled 126,000 in 2003, but was increased to 165,000 in September 2006 from an area of similar socioeconomic status. For estimation of incidence figures, and due to the increased catchment area, we have calculated and used an average catchment population of 139,500 for the 2006 cohort.

3.2. Diagnosis and classification of patients

Patients were categorised into five groups: 1) STEMI, 2) NSTEMI, 3) UAP, 4) coronary heart disease (CHD) without ACS and 5) non-coronary chest pain. The latter two groups did not qualify for ACS and were classified according to whether there was evidence of CHD or not, based upon documented

prior AMI, a positive stress test, angiographic findings or prior PCI/CABG. The diagnosis of AMI in both cohorts was made in accordance with the ESC/ACC criteria of 2000 [8]. Patients were diagnosed with AMI if they had typical symptoms and elevated cardiac markers (troponin T ≥0.1 μg/L or creatine kinase-myocardial band [CKMB] >10 μg/L). In the latter cohort only troponin T was used. The subtype of AMI was classified according to ECG findings. STEMI was considered present if persistent ST-segment elevation occurred in two adjacent leads (>0.1 mV in limb leads, >0.2 mV in V1-V3, and >0.1 mV in V4-V6). Patients qualifying for AMI but without persistent ST-segment elevation were classified as having NSTEMI. In the presence of left bundle branch block (LBBB), AMI patients were categorised as STEMI if LBBB was presumed to be of recent onset, otherwise as NSTEMI. The diagnosis of UAP was based upon the clinical syndrome and the occurrence of transient ST-segment deviation or T-wave inversion on the resting ECG but with cardiac markers below cut-off for AMI.

If ACS was excluded and CHD could not be entirely ruled out after observation, eligible patients routinely underwent an exercise ECG before discharge. In case of a positive stress test, patients were classified as CHD without ACS, irrespective of whether the angina was of recent onset or not. The attending physician referred such patients to elective angiography based on individual judgment. Since there were no guidelines for management of non-ACS patients hospitalised for chest pain, those with a negative or no stress test were left to further clinical management by their attending physician. In the literature this large group of patients has been termed “non-specific chest pain” regardless of whether they have pre-existing CHD or not [55-58], with a considerable percentage of them representing frequent readmissions to hospital; the so-called “frequent flyers” [59,60]. In the present thesis we aimed to characterise this large group of patients and to assess how their one-year mortality was associated with pre-existent CHD or not. The study was neither designed to explore non-coronary causes for chest pain, nor to characterise those who ended up as “frequent flyers”, since readmissions were not systematically recorded. Note that patients who were admitted with an identified non-coronary cause of chest pain (e.g. pneumonia, pulmonary embolism, esophagitis, myo-pericarditis and aortic dissection) were excluded by the two investigators (Erlend Aune and Jan Erik Otterstad) who made all the final diagnoses at the time of discharge for the index event in both cohorts. In case of an unclear diagnosis, a consensus was reached through discussion.

The AMI-criteria from 2000 required blood samples in order to discover a rise in serum troponin. Therefore, those patients with cardiac arrest on admission who were not successfully resuscitated were excluded even if the ECG was indicative of an AMI.

Patients who reported to have smoked within the last three months before admission were categorised as current smokers. Never-smokers and those who had stopped more than three months prior to hospitalisation were classified as non-smokers [61].

3.3. Prehospital STEMI triage in 2006 vs. 2003

A 12-lead ECG was recorded in all patients with a suspected AMI and sent by telemetry to our CCU for analysis by the physician on duty. Prehospital activation of reperfusion therapy (both fibrinolysis and the invasive centre in case of primary PCI) was done by this physician. In 2003, patients with ST-segment elevations or LBBB presumed to be of recent onset were hospitalised in our CCU for observation after fibrinolysis. STEMI patients in the 2006 cohort routinely bypassed our hospital en route to primary PCI. The average transportation time from Vestfold County to the invasive centre is approximately 60 minutes, whilst the door-to-balloon time is 20-25 minutes. However, these time intervals were not systematically recorded.

3.4. Treatment algorithm for STEMI

In both cohorts, patients treated with fibrinolysis who had <50% ST-segment recovery and/or recurrent symptoms after 60 minutes were transferred for rescue-PCI. Patients with a successful fibrinolysis in the 2003 cohort were subjected to ischemia-driven diagnostics and referred for coronary angiography in the presence of symptoms and/or objective evidence of ischemia. Patients in the 2006 cohort were routinely subjected to coronary angiography within 24-48 hours following fibrinolysis. Patients treated with primary PCI were returned to our department and observed for a few days. Most patients had an echocardiogram performed in order to evaluate left ventricular function and the possible initiation of an ACE-inhibitor. All surviving ACS patients in both cohorts were offered participation in our cardiac rehabilitation program [62] and given secondary medical prophylaxis according to the guidelines of the Norwegian Society of Cardiology [63]. Patients were only subjected to an exercise test in case of symptoms or residual coronary stenosis on the angiogram performed during primary PCI. A subsequent, elective PCI was performed after four to six weeks whenever found indicated.

3.5. Treatment algorithm for NSTE-ACS

In 2003, a “cool-down” policy was applied according to the then current guidelines [63-65]. Only those with ongoing ischemic symptoms accompanied by ST-segment depression and/or negative T-waves were transferred for invasive management within the first 48-72 hours after onset of symptoms. Otherwise they underwent a submaximal exercise ECG at discharge and a maximal test after six weeks. Patients were only referred for elective coronary angiography in case of a positive test and/or ischemic symptoms. In 2006, NSTE-ACS patients were referred for coronary angiography

within 48-72 hours regardless of symptoms or evidence of ongoing ischemia provided the absence of dementia or severe co-morbidities. Patients were returned to our department the following day and the majority underwent an echocardiogram before discharge. All NSTE-ACS patients in both cohorts were offered participation in the cardiac rehabilitation program.

3.6. Management at the invasive centre

The diagnostic and therapeutic procedures were performed with standard techniques, mainly through radial access. In STEMI patients, only the culprit lesion was treated (and stented if possible) in the acute setting, unless cardiogenic shock was present. Other lesions were treated after some weeks if clinically indicated. For patients with NSTEMI, all lesions were (in principle) treated with stenting whenever technically possible. In patients with advanced age or severe comorbidities complete revascularisation procedures were not always performed. Patients with extensive triple vessel disease including left main or proximal left anterior descending coronary artery stenosis were referred for surgery, which in general was performed within 1-7 days if not contraindicated. After completion of the study, all angiographic data from the 2006 cohort was carefully evaluated by EA. In case of questionable findings, a consensus was reached between Erlend Aune and Knut Endresen with respect to the results presented in Papers II and III.

3.7. Follow-up

In the 2003 cohort 147/366 patients, and in the 2006 cohort 154/363 patients, with ACS refused or were not considered capable of follow-up visits owing to dementia and/or severe co-morbidity. We confirmed vital status for all patients included (both ACS and non-ACS), regardless of their follow-up status. Because of regulatory restrictions, the causes of death were not available. Data was collected from the invasive centre for all patients, including patients bypassing our hospital en route to primary PCI.

3.8. Baseline Global Registry of Acute Coronary Events (GRACE) risk score

Data for the GRACE risk score for six-month mortality [54] was collected among patients with AMI to compare the baseline risk in the two cohorts in Paper II and III. Data was prospectively recorded for patients in the 2006 cohort, and retrospectively collected through examination of all patient records for the 2003 cohort. GRACE risk score was available for 281 of 311 AMI patients (90%) in the 2003 cohort and 299 of 307 (97%) in the 2006 cohort, i.e. 94% of all AMI patients.

3.9. Ethics

The 2003 cohort study was approved by the local ethics committee and the 2006 cohort study by the regional ethics committee for South-East Norway Health Authority and the Norwegian Social Sciences Service Data Services.

3.10. Statistics

The primary outcome was all-cause death after one year. Mann-Whitney U test or Kruskal-Wallis test were used for comparison of continuous data between different groups of patients. Proportions were analysed by χ^2 test or Fischer's exact test. Kaplan-Meier plots and Log rank tests were used for unadjusted comparison of survival between different subsets of patients. Cox proportional hazards regression models were used for additional survival analyses. The assumption of proportional hazards was explored with partial residual plots.

In paper I, such models were used to analyse the effects of STEMI, NSTEMI, UAP, CHD without ACS, and non-coronary chest pain (reference variable) on patient survival. Diagnostic categories were included as the first variable in the regression analysis; non-coronary chest pain = 0, CHD without ACS = 1, UAP = 2, STEMI = 3 and NSTEMI = 4, with non-coronary chest pain as the reference group. Variables associated with patient survival in the univariate analysis ($p<0.20$) were included in the multiple Cox regression analysis [66].

In paper II, the cohort was used as a surrogate variable for treatment strategy in the Cox proportional hazards regression analyses. Interaction terms between cohort/age, cohort/smoking and previous AMI/previous left ventricular systolic dysfunction were included and tested. An apriori power analysis was performed before the inclusion of patients in the second cohort. Given the same number of AMI patients in the second cohort, the study had a power >80% ($\alpha = 0.05$) to demonstrate a reduced mortality of at least 40% for NSTEMI and at least 35% for NSTEMI and STEMI combined.

In paper III, two Cox proportional hazards regression models were used. In model 1, explanatory variables with a p-value ≤0.05 from paper II were included in the multiple regression analysis (treatment strategy, age, s-creatinine and previous left ventricular systolic dysfunction). In addition, smoking status at admission, as well as aspirin and statin usage during hospitalisation were used to assess the hazard ratio (HR) for death after one year. Interaction terms between age/strategy and smoking/strategy were included and tested. In model 2, GRACE risk score [54] (including age, heart rate, systolic blood pressure, s-creatinine, Killip class, cardiac arrest at admission, ST-segment deviation and elevated cardiac markers) was used for the adjustment of differences in baseline risk,

with the analysis presented separately for smokers and non-smokers. As in paper II, cohort was used as a surrogate variable for the treatment strategy.
Two-tailed p-values below 0.05 were considered statistically significant. The analyses were implemented using SPSS® 12.0 (paper I) and 16.0 (paper II and III) (SPSS Inc, Chicago, IL).

4. Summary of results

4.1. Paper I

This paper presents one-year mortality data for 755 conservatively managed unselected chest pain patients with or without an ACS in 2003. A total of 366 patients had ACS, of whom 126 (34%) had STEMI, 185 (51%) had NSTEMI and 55 (15%) had UAP. Among the remaining 389 patients without ACS, 42% showed evidence of CHD and 58% did not. In patients with STEMI, 61% received immediate reperfusion therapy (ratio fibrinolysis: primary PCI = 18:1). The proportion of NSTEMI patients who had early PCI was 3% within 48 hours and 6% within 7 days. All-cause one-year mortality rates for STEMI, NSTEMI, UAP, CHD without ACS, and non-coronary chest pain were 20%, 32%, 7%, 10%, and 3%, respectively. Adjusted for age, sex, diabetes mellitus and prior AMI, the HR for one-year mortality (using non-coronary chest pain patients as reference) was similar in the two subgroups with AMI (5.7 [95% CI 2.4-13.8] for NSTEMI and 5.8 [95% CI 2.3-14.0] for STEMI).
In conclusion, this conservatively managed population of consecutive patients with ACS had one-year mortality rates that were significantly higher than seen in most registries and clinical trials.

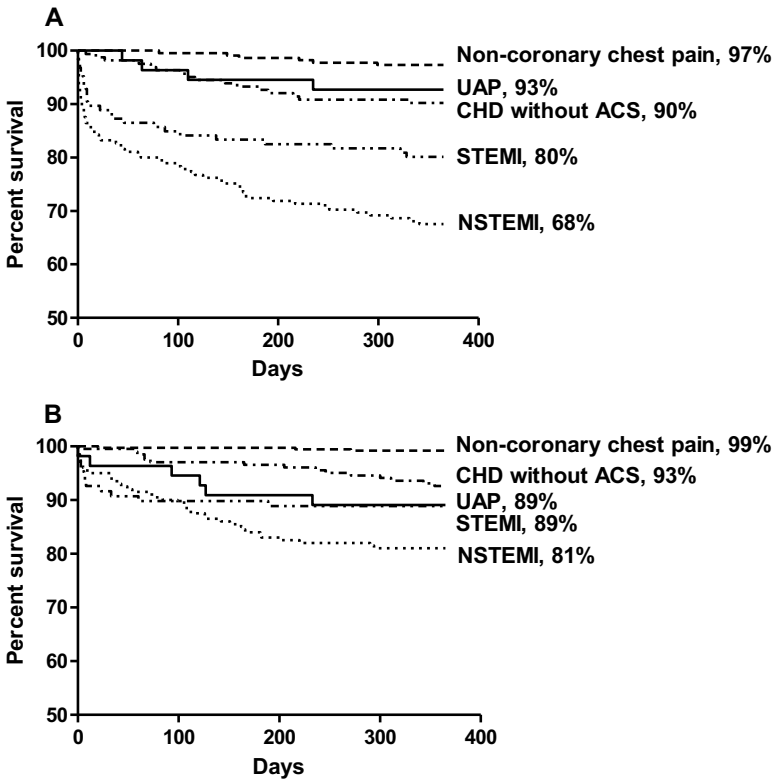
4.2. Paper II

This paper explores the effect of implementing a routine early invasive strategy in unselected patients with an AMI. We compared one-year all-cause mortality in consecutive AMI patients hospitalised in 2006 (n = 307) with the conservatively managed AMI cohort from 2003 (n = 311). The incidence of AMI was 247 cases per 100,000 person-years in 2003 and 220 cases per 100,000 person-years in 2006. There was a non-significant trend for younger STEMI patients in the 2006 cohort, with s-creatinine slightly higher in the 2003 cohort. Otherwise, baseline characteristics were similar in the two cohorts, including GRACE risk score. Primary PCI in STEMI was performed in 57% of patients in 2006 and 3% in 2003 ($p<0.001$). The corresponding numbers for fibrinolysis were 8% and 58% ($p<0.001$). Early PCI for NSTEMI (<72 hours) was performed in 25% of patients in 2006, in contrast to 4% in 2003 ($p<0.001$). The angiograms showed no statistically significant difference in the number of diseased epicardial vessels between the two cohorts, but 1-vessel disease was more prevalent in patients with STEMI compared with NSTEMI, who had more 3-vessel disease. More patients in the

invasive cohort were prescribed clopidogrel, aspirin, and statins during follow-up than in the conservative cohort, otherwise the secondary prevention measures were similar between the two cohorts. The one-year mortality rate for all AMI patients was 27% in the 2003 cohort and 16% in the 2006 cohort, an absolute reduction of 11% and a relative reduction of 41% (p=0.001). The relative mortality reduction among patients with NSTEMI and STEMI was 41% (p = 0.002) and 45% (p = 0.086), respectively. The mortality reduction of all AMI patients were consistent after adjustment for age, sex, prior AMI, prior stroke, diabetes mellitus, smoking status, prior left ventricular systolic dysfunction, serum creatinine (HR 0.54, 95% confidence interval [CI] 0.38-0.78) and GRACE risk score at admission (HR 0.67, 95% CI 0.46-0.97).

In conclusion, the introduction of a strategy for routine early transfer to a high-volume invasive centre was accompanied by a substantial reduction in one-year mortality among unselected patients with AMI.

Figure 1. One-year survival in 2003 (A) and 2006 (B) according to various categories of chest pain.



4.3. Paper III

In a post-hoc analysis we explored whether the survival benefit of early invasive management reported in paper II might differ when smoking status and age were taken into consideration. This analysis addresses only patients with NSTEMI, since it would be underpowered to explore the smaller subset of STEMI patients. We report on the 381 (out of 385) NSTEMI patients in both cohorts with information on smoking status at admission. Smokers were significantly younger than non-smokers in both cohorts (median age 60 vs. 81 years in 2006 and 66 vs. 79 years in 2003). Smokers in the 2006 cohort had a slightly lower serum creatinine and more prior PCI than smokers in the 2003 cohort. Otherwise, baseline risk factors were similar among smokers and non-smokers within both cohorts. One-year all-cause mortality for smokers was 37% in the 2003 cohort and 6% in the 2006 cohort ($p<0.001$). The respective numbers for non-smokers were 30% and 23% ($p = 0.18$). Revascularisation (PCI or CABG) within seven days increased from 9% in 2003 to 53% in 2006 for smokers ($p<0.001$). The corresponding numbers for non-smokers were 5% and 27% ($p<0.001$). A significant interaction was observed between strategy and smoking status ($p = 0.024$), implying a significantly different invasive strategy effect for smokers vs. non-smokers. No interaction was observed between strategy and age, supporting an age-independent effect of the invasive strategy. In spite of the apparently favourable effect of early invasive management, current smoking was still an independent predictor of fatal outcome (HR 2.61, 95% CI 1.43-4.79).

In conclusion, unselected smokers with NSTEMI represent a subset of patients whom receive particular clinical benefit from an early invasive strategy.

4.4. Paper IV

The findings in Paper III brought focus on previous reports of the so-called “smoker’s paradox”, reflecting a lower mortality post AMI among current smokers when compared with non-smokers. In order to obtain information on possible associations between such a “paradox” and treatment strategy we performed a systematic literature search. Relevant studies published by September 2010 were identified through literature searches using EMBASE, MEDLINE and the Cochrane Central Register of Controlled Trials. English-language original articles were included if they presented data on hospitalised patients with defined ACS, reported at least in-hospital mortality, had a clear definition of smoking status (including ex-smokers), presented crude and adjusted mortality data with effect estimates, and had a study sample of >100 smokers and >100 non-smokers. A total of 978 citations were identified, and 18 citations form 17 studies fulfilled our predefined criteria. Six studies (one observational, three registries and two randomised controlled trials on fibrinolytic therapy)

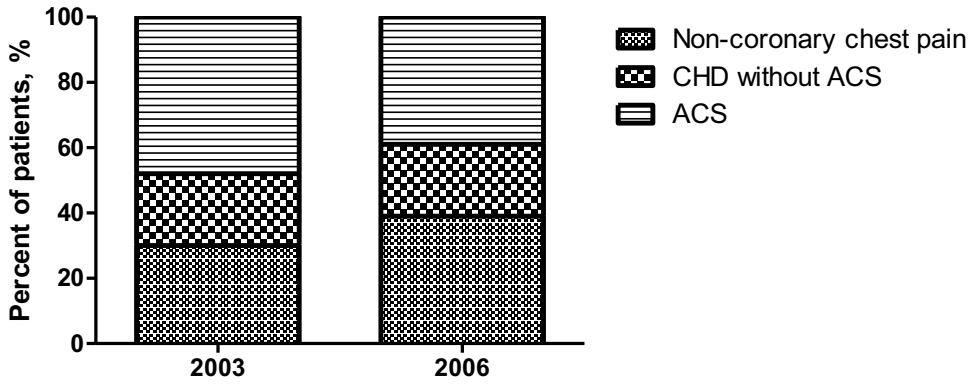
could verify a “smoker’s paradox”. These studies enrolled patients managed in the pre-fibrinolytic and fibrinolytic era. No studies of a contemporary population with acute coronary syndrome found evidence for such a paradox.

In conclusion, the “smoker’s paradox” has been observed in AMI populations from the 1980s and 1990s, but is no longer present among patients with diagnosed ACS managed according to contemporary recommendations.

4.5. Non-ACS patients

Data on the characteristics and mortality of non-ACS patients in the 2003 cohort is presented in paper I. The corresponding findings in the second cohort were not published, since the focus in paper II was the implementation of new treatment modalities in patients with AMI only. The percentage of patients admitted who did not qualify for ACS increased from 52% in 2003 to 61% in 2006 ($p<0.001$). This increase was driven by a higher proportion of the non-coronary chest pain group (39% in 2006 vs. 30% in 2003, $p<0.001$), whereas no change was observed for non-ACS patients with evidence of CHD (22% in both cohorts) (Figure 2). Non-ACS patients were treated according to the individual assessment of the attending physician, and this policy was identical for the two cohorts studied. For non-ACS without CHD, the one-year mortality was 3% in 2003 and 1% in 2006 (log rank $p = 0.074$). The corresponding figures for non-ACS with CHD were 10% and 7% (log rank $p = 0.40$). Accordingly, the profound mortality reduction among patients with AMI could not be demonstrated in the non-ACS group.

Figure 2. Proportion of patients with ACS vs. non-ACS in 2003 and 2006.



5. Discussion

5.1. Population

This thesis is based upon data obtained from a single county (Vestfold) in Norway, and the results may not be regarded as representative for other regions. Both incidence and case fatality of AMI have been shown to vary between geographical areas worldwide and in countries with large variations in population density [67-72]. In order to obtain a study population without selection bias we included all patients admitted for chest pain and a suspected ACS to our hospital.
Most information on treatment and prognosis of patients with ACS has been derived from randomised trials with various inclusion and selection criteria. The impression has therefore been that the incidences of subgroups among ACS patients and their long-term prognoses reported may have been hampered by selection bias. Because of the modest sample size in this study, no separate analyses have been performed for females and males.

5.2. Diagnostic criteria

5.2.1. AMI

The diagnostic criteria for AMI were identical for both cohorts and in accordance with the ESC/ACC consensus from 2000 [8]. Both Troponin T and CKMB were used as biomarkers of myocardial cell necrosis. In the 2003 cohort, one patient was classified as having NSTEMI because of elevated CKMB, but had troponin T just below cut-off. Otherwise, all AMI patients in both cohorts had Troponin T values above cut-off. In 2006, only Troponin T was used for detection of cardiac injury, regardless of CKMB level, concurrent with recommendations for a one-marker strategy [73]. Identical ECG assessment to differentiate between STEMI and NSTEMI was done prospectively by two of the investigators (Erlend Aune and Jan Erik Otterstad) for both cohorts.
During the time span of this study both the biomarker of choice and the cut-off for myocardial infarction varied between hospitals and countries. In 2005, a survey was conducted by Hjortshøj et al. to investigate the diagnostic approach to AMI in Nordic hospitals [74]. All users of Troponin T in Denmark and a large majority in Norway reported a cut-off value of 0.1 µg/L, whereas 67% of Troponin T users in Finland and 81% in Sweden reported a cut-off of 0.05 µg/L or less. In our study a cut-off for troponin T of ≥0.1 µg/L was applied for both cohorts. Later, and based on the new MI criteria published in 2007 [13], the cut-off value for troponin T was reduced to ≥0.04 µg/L. With the implementation of a high-sensitive assay in 2009, this cut-off was further lowered to ≥30 ng/L. The proportion of patients in both cohorts with UAP, CHD without ACS and non-coronary chest pain who had a maximal troponin T below cut-off for AMI but above 0.03 µg/L were 13% (n = 14), 4% (n = 15)

and 3% (n = 15%), respectively. Accordingly, 44 additional patients (11% increase from 385 cases in both cohorts) would have been classified to have NSTEMI if today's cut-off had been applied. However, a less sensitive assay with poorer precision at values <0.1 µg/l was used in the study. Such a reclassification must therefore be interpreted with caution.

5.2.2. UAP

This term has been used for angina pectoris of recent onset or deterioration of stable angina regardless of ECG changes or not. In this thesis we applied a stricter definition, requiring patients to have the clinical syndrome, transient ST-segment deviation or T-wave inversion in the resting ECG, and maximum troponin T below the cut-off value of AMI. Such a policy was in keeping with the criteria applied in the CURE study [43]. The investigators of that trial chose to introduce these more stringent criteria after having analysed the observed vs. expected event rate after 3000 patients had been included. We adopted these criteria since we felt it right to include patients who had at least one objective criterion for coronary ischemia.

5.2.3. Non-ACS patients

Patients who did not qualify for ACS were subdivided into whether or not there was evidence of CHD according to prespecified criteria. In keeping with our experience from the ACTION study [75], a prior diagnosis of angina pectoris based on symptoms alone was not accepted as sufficient evidence of CHD. With the stringent criteria for UAP applied, we cannot exclude the possibility that some of the patients in the non-ACS group may have had UAP. In order to cope with this problem, patients with suspected CHD were in general subjected to a maximal exercise test and categorised as having CHD in case of a positive test.

5.3. Follow-up

Follow-up for all patients was one year from index admission. A few patients who were initially enrolled as non-ACS were later on hospitalised with an ACS, and then reclassified to the ACS population and followed for one year. The percentage of patients with ACS who refused or were not considered capable of follow-up visits was 47% in 2003 and 50% in 2006. Data on medical secondary prophylaxis and rehospitalisation is therefore incomplete. The design of this study did not incorporate any follow-up requiring informed consent from the non-ACS population. However, it is important to emphasise that data on mortality and invasive procedures among patients with ACS are complete for both cohorts since the collection of these data was independent of follow-up visits. Finally, complete data on one-year mortality was available for both groups with and without ACS.

5.4. Endpoints

One-year all-cause mortality was the endpoint in this thesis. During the planning of this study, the inclusion of major adverse cardiovascular events was considered. Due to regulatory restrictions requiring informed consent from all patients, such an inclusion was rejected. Similar limitations also existed for the causes of death, and the study did therefore not allow for differentiation between cardiovascular and non-cardiovascular deaths.

5.5. Incidences of ACS

The incidence of STEMI in 2003 was reduced from 100 cases per 100,000 person-years to 77 cases per 100,000 person-years in 2006. The respective figures for NSTEMI were 147 and 143 cases per 100,000 person-years. There is no AMI registry in Norway, but according to estimates from PCI-registries the incidence of STEMI in 2007 was 83 cases per 100,000 person-years and 193 cases per 100,000 person-years for NSTEMI [76]. There is, however, some uncertainty surrounding these data, which in principal are based upon so-called “expert opinion”. Our data indicates that at least in Vestfold there has been a decline in incidences of STEMI between 2003 and 2006, but not in NSTEMI cases. Data was collected from the invasive centre for all patients, including patients bypassing our hospital en route for primary PCI. In addition, all STEMI patients undergoing primary PCI were routinely transferred back to our hospital before discharge. Accordingly, a less complete capture of STEMI cases in 2006 cannot explain this decline in incidence. Our findings are in accordance with the reduced CHD death rate in Norway of 21% in the period 2003 to 2006 [77].

In a large Californian population based study the incidence of STEMI was reduced from 133 cases per 100,000 person-years in 1999 to 50 cases per 100,000 person-years in 2008 [78]. The respective figures for NSTEMI were 154 and 158 cases per 100,000 person-years. The authors suggest that increasing measures to reduce risk factors at the individual and community levels have resulted in improved control over risk factors over time. In addition, the uses of certain cardioprotective medications have increased over time. These agents may have beneficial effects even in primary prophylaxis. The combined effects from lifestyle measures and medication might have been counteracted by the increasing prevalence of obesity and diabetes. The results from the large Californian population based study and our own study suggest that the net effect has been a lower incidence of STEMI, but not necessarily of NSTEMI.

The incidences of UAP in our study were only 44 and 40 cases per 100,000 person-years for the 2003 and 2006 cohorts. Our stringent inclusion criteria for this diagnosis may explain these rather low

figures. With that reservation in mind, there was no trend of a significant decrease in the incidence of UAP.

5.6. Incidences of non-ACS

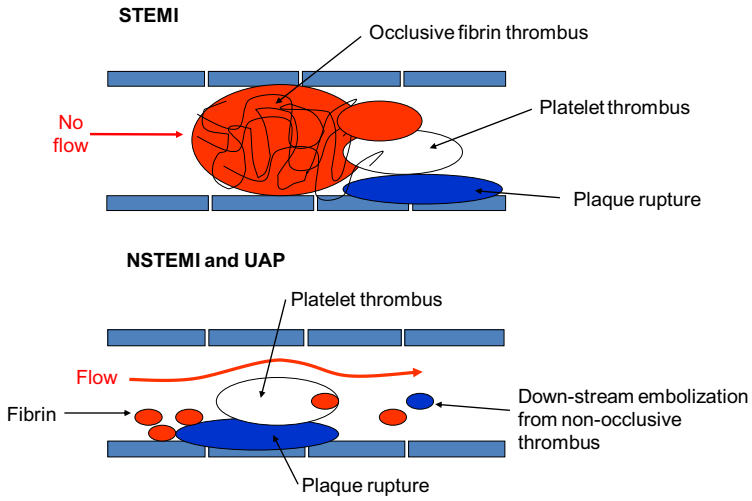
The incidence rate of non-ACS patients admitted for chest pain increased from 309 cases per 100,000 person-years in 2003 to 409 cases per 100,000 person-years in 2006. This 32% increase is difficult to explain and underlines the importance of proper handling for these patients. Not only do they impose a large burden on our health resources, but they are not offered any systematic management as is offered to the smaller group with ACS. Notably, the subset of non-ACS without evidence of CHD increased from 58% of all non-ACS patients in 2003 to 64% in 2006. In both cohorts this subset of patients represented the largest of the five subgroups with chest pain. Although their one-year mortality rate is low, they impose a challenging diagnostic task, and many may have reduced quality of life whilst a number of them may represent frequent readmissions, the so-called "frequent fliers". The increased number of non-ACS hospital admissions may reflect increased awareness of symptoms suggesting possible coronary ischemia. In the media people are reminded of the importance of taking chest pain symptoms seriously, and the importance of early treatment of ACS is stressed. Since this study primarily aimed at characterising patients with ACS, its prognosis and the influence of treatment, there was no systematic protocol for further characterisation of the large and increasing non-ACS group.

5.7. Baseline characteristics of ACS patients

The findings in paper I clearly outlined the differences between the younger STEMI vs. the much older NSTEMI patients. The latter group accordingly had more comorbidity and in general a far higher risk. Angiographic findings from the 2006 cohort revealed a significantly higher incidence of 3-vessel disease among patients with NSTEMI than those with STEMI, who had a higher incidence of 1-vessel disease. In an editorial following the study by Terkelsen et al. [79] which presented similar results to ours in paper I, Philip Urban summarises the difference as follows: "Younger patients with less prior cardiac and non-cardiac events in their medical history ("the rookie hearts") tend more frequently to present with transmural ischemia when they are admitted for their AMI. Older patients who more frequently have suffered prior damage to their left ventricle, and also have more non-cardiac comorbidity ("the veterans hearts") tend to have less acute myocardial damage and no ST-segment elevation" [80]. The difference in the composition of the thrombus in STEMI and NSTE-ACS is schematically presented in figure 3.

The smaller subset of patients with UAP had similar age to those with STEMI, whilst the percentage with previous AMI was even higher than among NSTEMI patients. They represented more females and previous revascularisations than the two other groups.

Figure 3. Schematic composition of thrombi in STEMI and NSTE-ACS (Courtesy of Prof. Frank Brosstad).



5.8. Baseline characteristics of non-ACS patients with or without CHD in paper I

Patients in the group with non-ACS and CHD were 10 years older and represented more males than the non-ACS group without CHD. One of the patients in the latter group had previously been treated with CABG and was erroneously included in that group. In retrospect, this patient had a pulmonary embolism and should not have been included in this study according to our protocol requirements.

5.9. Prognosis in ACS in 2003 vs. 2006

The mortality rates in the 2003 cohort were high when compared with data from randomised trials and registries which may have been hampered by selection bias [38,81-85]. Interestingly, the unadjusted one-year death rates were quite similar to those described from an unselected cohort of patients with AMI in Randers, Denmark from the time period 1999-2001 [79]. This hospital was located 35 km from the intervention centre. It is remarkable that the one-year mortality for patients with NSTEMI in that study was 30.5% in spite of the fact that 48% of those patients had coronary angiography during hospitalisation or where scheduled for such a procedure at discharge. In our

2003 cohort, only 8% of patients with NSTEMI had angiography within seven days, and the one-year mortality was 32%. In the 2006 cohort 25% of NSTEMI patients had early PCI and the one-year mortality dropped to 19%. It should be noted that the study by Terkelsen et al. was retrospective, and that the percentage reported was for invasive strategy rather than the number of PCIs performed.

In a recent study Reikvam et al. reported a substantial reduction in total mortality from AMI in Norway since the 1990s [4]. According to Statistics Norway and the Cause of Death Registry there was a decrease in deaths from AMI (ICD-10 I21-22) of 23% from 2003 to 2006 [7]. This reduced mortality probably reflects a combination of a reduction in both incidence [86] and case fatality of AMI. In data from the WHO MONICA survey published in 1999, coronary event-rates contributed to two third of the reduced mortality from AMI, whereas case fatality accounted for only one third [87].

5.10. Prognosis in non-ACS in 2003 and 2006

This study did not aim at exploring differences in mortality for non-ACS patients, nor was it an apriori power calculation for such an analysis. In both cohorts the one-year mortality of patients without CHD was quite low, with 2.7% in 2003 and 0.8% in 2006. Interestingly, the mortality rate of 9.8% among those with CHD in 2003 was quite similar to that among patients with UAP. In 2006 the mortality in the subset with non-ACS and CHD was with 7.4%, similar to that among patients with UAP and only slightly lower than 11.2% among patients with STEMI (predominantly reperfused with primary PCI). These figures underline the importance of proper management of non-ACS patients with CHD who are hospitalised for chest pain. Possibly, the introduction of more sensitive assays for cardiac markers will be of help in the risk stratification of such patients. All non-ACS patients were subjected to an exercise test whenever this was felt needed, and referred for coronary angiography in case of a positive test. This management did not change from 2003 to 2006, but we cannot exclude the possibility that a higher proportion of patients were subjected to elective invasive management in 2006.

5.11. Implementation of the early invasive strategy

The implementation of immediate transportation by ambulance with two certified paramedics for primary PCI, and the less time-dependent early invasive management of patients with NSTEMI, was feasible and safe. Only one patient (with STEMI) in the 2006 cohort died during transfer. The LIFEPAK® 12 Defibrillator/Monitor was used for telemetry of a 12-channel ECG and for monitoring during transportation. The paramedics administered morphine, aspirin, clopidogrel, nitroglycerine,

and (low-molecular weight) heparin. We did not use routine injection of beta-blockers. In a few cases, patients transferred from our hospital to the invasive centre were followed by an anaesthetist or a nurse anaesthetist.

5.12. Impact of tobacco smoking

Tobacco smoking is a well established risk factor for CHD and represents a potential confounding factor in this study. The prevalence of current smoking among STEMI patients was 47% in 2003 and 45% in 2006. In the older NSTEMI populations the respective figures were 30% and 25%. Our study did not include data on smoking cessation due to regulatory limitations requiring informed consent for the clinical follow-up. A possible explanation for the reduced mortality observed in the 2006 cohort could be differences in the rate of smoking cessation. Patients in both cohorts underwent the same rehabilitation program which included comprehensive information on the importance of smoking cessation. In older studies of smoking cessation after myocardial infarction [61] and in patients with stable CHD [88] the survival benefit appeared at a later stage than one year. In a recent report from the OASIS-5 study of NSTE-ACS patients, giving up smoking was associated with a lower rate of reinfarctions but had no effect on mortality after six months [89]. Based on these considerations it seems unlikely that differences in smoking cessation could explain the mortality reduction observed.

The effect of smoking and treatment strategy on mortality was explored exclusively in patients with NSTEMI, since this was the largest subgroup and with the highest number of events. The significant interaction between smoking and strategy, but not between age and strategy, implies that the effect of an invasive strategy was significantly different between smokers and non-smokers. In spite of this favourable effect, current smoking was an independent predictor of death (HR 2.61, 95% CI 1.43-4.49).

Another possible confounding factor that could partly explain our results is the introduction of a smoking ban in restaurants and public places in Norway in 2004. In a meta-analysis the introduction of such smoking bans was followed by a 17% decreased risk of AMI [90]. This beneficial effect was attributed to a reduction in second-hand smoke, since passive smoking is associated with a 25-30% increased risk of AMI [91-93]. The meta-analysis did not, however, address any survival benefit following the introduction of such bans.

5.13. Why include the review on “smoker’s paradox”?

In paper III we found that smokers with NSTEMI seem to be a subset of AMI patients with a particular survival benefit from an early invasive strategy, but smoking at admission was still an independent predictor of death in the multiple regression analysis.

Contrasting with our findings, we were aware of large studies, in which smokers suffering AMI had a better prognosis than non-smokers, even when analyses adjusting for baseline differences were included [94,95]. In Norway, Mølstad had described the existence of such a paradox in patients managed in the period 1982-1984 [96]. Nevertheless, in Braunwald’s recent text book on cardiovascular medicine [97], it is stated that the paradox is entirely explained by the fact that the younger smokers are more likely to undergo reperfusion strategies and have on average lower co-morbidity.

Since the studies supporting the paradox were, to our knowledge, large and well performed, we found it worthwhile to perform a systematic literature search in order to explore a possible common denominator in studies supporting the existence of the paradox vs. those that did not. In this systematic review, 18 citations out of 978 unique citations were selected on basis of predefined criteria. These studies included 442,200 patients and reflected both older and more recent definitions of AMI/ACS. We found that all six studies in favour of the paradox were pre 2000 and included patients with AMI based upon WHO criteria and were managed in the pre-thrombolytic and thrombolytic era. Thus, our results in paper III are quite in concordance with contemporary studies of patients with ACS.

5.14. Limitations

As in any observational study, potential residual confounding may have been present. Due to the prospective design of this study, information bias has probably not influenced our findings significantly. A potential difference in pre-hospital death rates between the two cohorts could constitute a selection bias, since only patients who were alive at admission were included.

In light of the relatively modest population size, potential differences between the groups might not be statistically significant because of type 2 errors. Data on medical treatment and lifestyle measures such as smoking cessation after discharge was incomplete or even absent. Adjustments for these confounders could therefore not be performed, casting doubt on the on the validity of the mortality reduction observed being exclusively related to the introduction of an early invasive strategy.

Comorbidity during the index hospitalisation (i.e. pneumonia, sepsis, respiratory failure or malignant disease) was not systematically recorded. It cannot be excluded that different rates of comorbidity in

the two cohorts may have influenced our results. On the other hand, all patients were carefully evaluated for serious non-coronary conditions causing their chest pain, and subsequently excluded from the study. These principles were identical for both cohorts.

For some reason it was not possible to obtain the time from onset of symptoms to reperfusion among patients with STEMI. Although the median time from telephone call to the emergency medical systems to arrival of an ambulance was nine minutes in both cohorts, possible differences in patient delay may have influenced outcome. Data on GRACE risk score was available for 90% of patients with AMI in 2003 and 97% of the 2006 cohort. These small differences may represent a confounding factor in the assessment of baseline risk, but are probably not of major importance. Due to the low number of patients with UAP and few number of events reported (four deaths in 2003 and six deaths in 2006) we did not incorporate any analysis of mortality in relation to the change of paradigm in that group.

6. Perspectives

Since this study was conceived in the end of 2002, there have been improvements and clarifications in the diagnosis and treatment of ACS. For STEMI patients focus has been on pre-hospital infarct triage and immediate reperfusion, with increasing use of primary PCI as the preferred modality rather than fibrinolysis. For NSTE-ACS patients there have been considerable improvements in antithrombotic treatment, with more potent thienopyridines [98,99] parallel to the introduction of early invasive management [44-46,53,100,101]. The introduction of drug-eluting stents reduced restenosis and associated clinical events [102-105]. Based upon the results from randomised trials this change of paradigm has resulted in better outcome. The present study has added knowledge to the effect of changed treatment algorithm in unselected AMI patients based upon a historical evaluation of implementing early invasive treatment strategies.

The diagnostic classification of AMI has changed since this study was conceived [13]. The introduction of five clinical subtypes of AMI will help to obtain better epidemiologic data, as well as clarifying different etiologic causes of myocardial necroses secondary to myocardial ischemia. The use of cardiac troponins with interpretation of elevated values has been challenging. There has been increased awareness of non-ischemic causes of troponin elevation [106,107], as well as of separating AMIs with a primary coronary event (type I) from those caused by a mismatch in oxygen supply/demand from other reasons (type II). Such information is important, since guidelines on antithrombotic and invasive management (in principle) only apply to type I AMI, and not to those with type II AMI or non-thrombotic troponin elevation.

In the future a multi-marker strategy for prognostication in chest pain patients will probably be applied. There is increasing evidence supporting the usage of natriuretic peptides in the risk stratification of ACS patients [108].

A large and growing group is those patients admitted with non-specific chest pain (both with and without CHD). Some of these patients become “frequent flyers” with repeated visits to the emergency room. No guidelines exist for the optimal management of these patients. The establishment of specialised chest pain clinics with the possibility of routine assessment including evaluation of gastrointestinal, musculoskeletal and psychiatric disorders could potentially improve quality of life for these patients and reduce their health utility resources. Patients with CHD admitted for chest pain, but without ACS, represent a large population with a long-term mortality within the range of patients with a diagnosis of UAP and those treated with primary PCI for STEMI. Possibly, new sensitive assays of cardiac troponins and newer biomarkers, such as copeptin, may be of help in risk stratification and management of these patients [109-112]. However, the use of such highly sensitive troponin assays comes with a cost of decreased specificity [113], and their clinical application needs to be established [114].

6.1. Randomised controlled trials (RCT) vs. observational studies

The role of observational studies in the evaluation of treatments is an important and continually debated topic [115]. Such analyses cannot control for the effects of all potential confounding variables. A wrong conclusion about causal inference can therefore be drawn [116]. Pocock and Elbourne have stated that all observational studies have one crucial deficiency: the design is not an experimental one [115]. Only randomised treatment assignment can provide a reliably unbiased estimate of treatment effects, but RCTs must generally be supplemented by evidence from effectiveness studies to inform best clinical practice [117]. Observational data can give additional information which can inform whether efficacy under RCTs on selected patient groups translates into effective treatment in routine practice. RCTs represent the “gold standard” study design to prove a treatment effect, but observational studies should be seen as complementary to these studies [118]. They are needed to evaluate the effectiveness of health care [119]. Our observational study indicates that the treatment effect of early invasive management of AMI is more profound in unselected patients than has been reported in RCTs on selected patients with a lower risk profile.

6.2. The role of a general county hospital in clinical research

The majority of clinical research in Norway is conducted at university hospitals. The main advantage of clinical research at general county hospitals is the possibility to include unselected patient groups and obtain results that may be more representative of routine clinical practice. The present thesis is based upon study populations that could not have been recruited at a tertiary referral hospital. On the other hand, it could not be completed without close co-operation with our referral hospital. Research at smaller institutions is dependent on establishing networks with other institutions or persons with complementary qualifications, e.g. biostatisticians, geneticists or senior scientists with more experience and competence. Participation in international multicentre studies as a principal investigator or as a member of the steering committees is of value in establishing contact with international expertise in clinical research. Such contact has been of great value both before and during the present study, and is highly recommended for similar hospitals to ours.
Another exciting prospect would be to combine clinical science at local hospitals with basic science at universities, with the establishment of networks that could lead to more translational research. Since all public Norwegian hospitals are now required by law to conduct research, the need for co-operation with university hospitals will most probably increase. This underlines the importance of institutional research strategies that should both encourage and facilitate close co-operation with universities and other external institutions.

7. Conclusions

1. A conservative treatment strategy of unselected patients with AMI was associated with higher one-year mortality than seen in most trials and registries. The highest mortality was observed in NSTEMI patients followed by STEMI patients. Non-ACS patients with established CHD who are hospitalised with chest pain had one-year mortality similar to patients with UAP.

2. The introduction of routine early invasive management in unselected AMI patients was followed by significantly reduced one-year mortality compared with a previous conservative strategy.

3. Unselected smokers with NSTEMI received a particular clinical benefit from an early invasive strategy when compared with non-smokers, but current smoking was still an independent predictor of one-year mortality.

4. The “smoker’s paradox” was observed in some studies of AMI patients during the 1980s and 1990s. During that time period fibrinolysis was the dominant reperfusion strategy. This “paradox” has not been reported in more recent studies using routine early invasive management.

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RESEARCH ARTICLE Open Access

The effect of tobacco smoking and treatment strategy on the one-year mortality of patients with acute non-ST-segment elevation myocardial infarction

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Abstract

Background: The aim of the present study was to investigate whether a previously shown survival benefit resulting from routine early invasive management of unselected patients with acute non-ST-segment elevation myocardial infarction (NSTEMI) may differ according to smoking status and age.

Methods: Post-hoc analysis of a prospective observational cohort study of consecutive patients admitted for NSTEMI in 2003 (conservative strategy cohort [CS]; n = 185) and 2006 (invasive strategy cohort [IS]; n = 200). A strategy for transfer to a high-volume invasive center and routine early invasive management was implemented in 2005. Patients were subdivided into current smokers and non-smokers (including ex-smokers) on admission.

Results: The one-year mortality rate of smokers was reduced from 37% in the CS to 6% in the IS ($p < 0.001$), and from 30% to 23% for non-smokers ($p = 0.18$). Non-smokers were considerably older than smokers (median age 80 vs. 63 years, $p < 0.001$). The percentage of smokers who underwent revascularization (angioplasty or coronary artery bypass grafting) within 7 days increased from 9% in the CS to 53% in the IS ($p < 0.001$). The corresponding numbers for non-smokers were 5% and 27% ($p < 0.001$). There was no interaction between strategy and age ($p = 0.25$), as opposed to a significant interaction between strategy and smoking status ($p = 0.024$). Current smoking was an independent predictor of one-year mortality (hazard ratio 2.61, 95% confidence interval 1.43-4.79, $p = 0.002$).

Conclusions: The treatment effect of an early invasive strategy in unselected patients with NSTEMI was more pronounced among smokers than non-smokers. The benefit for smokers was not entirely explained by differences in baseline confounders, such as their younger age.

Background

Early invasive management of non-ST-segment elevation myocardial infarction (NSTEMI) has been shown, when contrasted with a conservative treatment approach, to improve clinical outcome [1]. Whether such an effect differs between smokers and non-smokers is difficult to explore, since smokers with NSTEMI are substantially younger than non-smokers. To the best of our knowledge, such an exploration has only been attempted in a sub-analysis of the FRISC II study [2], where allocation to early invasive treatment for non-ST-segment elevation acute coronary syndrome (NSTE-ACS) was associated with a clinical benefit in non-smokers only [3]. The risk level was moderate, as reflected in a 6 months mortality rate of 2%. The favorable effect of early invasive management was exclusively driven by a reduction of recurrent MI and no information on age-differences was provided. In a study of unselected patients with acute myocardial infarction (AMI), we found that for NSTEMI the one-year mortality rates were 32% with conservative management and 21% with an early invasive approach [4]. The purpose of the present analysis was to investigate whether this survival benefit may differ according to smoking status and age.

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Methods

Details on the study design and methodology are published elsewhere [4]. In brief, all patients referred to our non-invasive hospital during two one-year periods with a suspected AMI were prospectively registered. The diagnosis of AMI was made in accordance with the European Society of Cardiology/American College of Cardiology criteria of 2000 [5]. The conservative strategy cohort (CS) included patients admitted from February 1, 2003 through to January 31, 2004. The invasive strategy cohort (IS) included patients admitted from February 15, 2006 through to February 14, 2007. Patients were transferred approximately 100 km (63 miles) to the closest high-volume invasive center (Rikshospitalet University Hospital, Oslo, Norway).

A diagnosis of AMI was, in the case of both cohorts, made in the presence of typical symptoms and elevated troponin T greater than a cutoff level of ≥ 0.1 μg/L. According to the electrocardiographic findings, AMI was sub-classified into ST-segment elevation myocardial infarction (STEMI) and NSTEMI. Current smokers included those who had smoked within the last three months. Non-smokers were defined as never-smokers and ex-smokers who had stopped more than three months prior to admission. Data on smoking cessation was not collected due to the fact that informed consent was required in order to undergo one-year follow-up on morbidity and medication. This, however, could only be obtained in 55% of the study group due to limitations such as patient refusal, old age, dementia and geographical factors. Baseline risk evaluation for both cohorts included the Global Registry of Acute Coronary Events (GRACE) risk score for 6-month mortality [6]. The primary outcome was all-cause death after one year.

Patients with NSTEMI have platelet-rich thrombi, as opposed to predominantly fibrin-rich thrombi in STEMI [7]. We therefore felt it appropriate to evaluate separately the impact of tobacco smoking for each type of AMI. The present report addresses NSTEMI patients only, since it would be underpowered to explore the impact of smoking status in the smaller subset of STEMI patients.

Both the regional ethics committee for South-East Norway Regional Health Authority and the Norwegian Social Science Data Services approved the study.

Statistical analysis

In the post-hoc analysis, Mann-Whitney U test was used for comparison of continuous data between different groups of patients. Proportions were analyzed by χ^2 test or Fisher's exact test. Kaplan-Meier plots and Log rank tests were used for unadjusted comparison of survival between different subsets of patients, i.e. smokers and cohort. Two multiple Cox proportional hazards regression models were used for additional survival analyses. In model 1, explanatory variables with a p-value ≤ 0.05 in the main study's multiple regression analysis [4] (treatment strategy, age, s-creatinine and previous left ventricular systolic dysfunction), in addition to smoking status at admission, as well as aspirin and statin usage during hospitalization, were used to assess the hazard ratio (HR) for death after one year. Interaction terms between age/strategy and smoking/strategy were included and tested. In model 2, GRACE risk score (including age, heart rate, systolic blood pressure, s-creatinine, Killip Class, cardiac arrest at admission, ST-segment deviation and elevated cardiac markers) was used for the adjustment of differences at baseline risk, with the analysis presented separately for smokers and non-smokers. In both models, the cohort was used as a surrogate variable for the treatment strategy. The assumption of proportional hazards was explored with partial residual plots. Two-tailed p-values below 0.05 were considered statistically significant. The analyses were implemented using SPSS® 16.0 (SPSS Inc, Chicago, IL).

Results

In 2003 (CS) 185 patients were admitted with NSTEMI. Data on smoking status was obtained in 181 cases (98%), of whom 54 (30%) were current smokers. In 2006 (IS) 200 patients were admitted with NSTEMI. Data on smoking status was complete, with 49 (25%) patients found to be current smokers (p = 0.29 versus CS). Baseline characteristics according to smoking status at admission and treatment cohort are presented in Table 1. Smokers were significantly younger than non-smokers both in the IS (median age 60 vs. 81 years, p < 0.001) and the CS (median age 66 vs. 79 years, p < 0.001). Smokers in the IS had a significantly lower s-creatinine (median [25^{th}-75^{th} percentile] 76 [69-96] vs. 95 [75-113] μmol/L, p = 0.014) compared with smokers in the CS. More smokers in the IS had prior PCI when compared to smokers in the CS. Otherwise, baseline risk factors, including GRACE risk score, were similar among smokers and non-smokers within both cohorts.

Total mortality

The Kaplan-Meier estimates of one-year survival according to smoking status and treatment strategy are shown in Figure 1. Smokers in the CS had a one-year mortality of 37% (20/54) as compared with 6% (3/49) in the IS (p < 0.001). The corresponding numbers for non-smokers were 30% (38/127) and 23% (35/151) (p = 0.18).

The results from the Cox proportional hazards regression analyses are presented in Table 2 (model 1) and Table 3 (model 2). In model 1, a statistically significant interaction was found between strategy and smoking (p = 0.024). Current smoking was an independent

Table 1 Baseline characteristics for NSTEMI patients.

	Non-smokers			Smokers*		
	CS (n = 127)	IS (n = 151)	p-value	CS (n = 54)	IS (n = 49)	p-value
Age (years)	79 (72-86)	81 (69-86)	0.61	66 (56-76)	60 (55-72)	0.17
Male	74 (58%)	87 (58%)	1.00	39 (72%)	34 (69%)	0.92
Medical history						
Diabetes	21 (17%)	29 (19%)	0.67	6 (11%)	6 (12%)	1.00
Previous AMI	42 (33%)	53 (35%)	0.82	14 (26%)	12 (25%)	1.00
Previous LVSD†	10 (8%)	19 (13%)	0.30	7 (13%)	3 (6%)	0.40
Hypertension	46 (36%)	45 (30%)	0.31	17 (32%)	13 (27%)	0.74
Stroke	6 (5%)	17 (11%)	0.080	6 (11%)	2 (4%)	0.34
CABG	11 (9%)	20 (13%)	0.31	5 (9%)	3 (6%)	0.82
PCI	6 (5%)	10 (7%)	0.68	3 (6%)	10 (20%)	0.049
Presenting characteristics						
S-Creatinine, μmol/L‡	95 (76-128)	90 (77-115)	0.30	95 (75-116)	76 (69-97)	0.014
GRACE risk score	140 (113-166)	139 (110-164)	0.53	112 (84-160)	108 (80-131)	0.28

Categorical data presented as n (%) and continuous data as median (25^{th} -75^{th} percentile). *Smoking within last three months. †Defined as prior left ventricular ejection fraction < 40%. ‡Conversion factor 0.0113 for mg/dL.

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CS, conservative strategy cohort; GRACE, global registry of acute coronary events; IS, invasive strategy cohort; LVSD, left ventricular systolic dysfunction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

predictor of mortality (HR 2.61, 95% confidence interval [CI] 1.43-4.79, p = 0.002). No interaction was observed between strategy and age (p = 0.25). When adjusted for GRACE risk score at admission (model 2) IS was associated with a statistically significant reduction of one-year mortality for smokers (HR 0.20, 95% CI 0.06-0.68, p = 0.010), but not for non-smokers (HR 0.79, 95% CI 0.49-1.28, p = 0.34).

Invasive procedures and mortality within 7 days

Among smokers, the proportion of patients who underwent coronary angiography within 7 days increased from 11% in the CS to 78% in the IS. This was accompanied by a 6-fold increase in percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) during the same time period (Figure 2a). The 7-days mortality rate reduced from 17% in the CS to 0% in the IS (Figure 2b).

The proportion of non-smokers who underwent coronary angiography within 7 days was 6% in the CS and 49% in the IS. The corresponding data for early revascularization and death are presented in Figure 3a and Figure 3b, indicating a less pronounced and non-significant decrease in mortality as compared with smokers.

Non-smokers in the IS who had revascularization within 7 days were significantly younger than those not undergoing this treatment (median [25^{th}-75^{th} percentile] age 71 [62-77] vs. 83 [74-88] years, p < 0.001). The corresponding figures for smokers were 58 (50-70) vs. 63 (59-78) years (p = 0.035). Similar age-differences were observed in the CS.

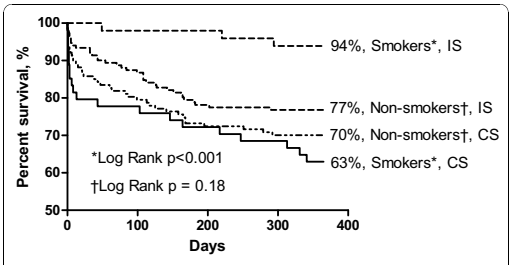

Figure 1 One-year survival in non-ST-segment elevation myocardial infarction (NSTEMI) patients with invasive strategy (IS) and conservative strategy (CS).

Table 2 Hazard ratios (HR) of death in patients with NSTEMI (n = 381) during one-year follow-up using multiple Cox proportional hazards regression (Model 1).

	HR	95% CI	p-value
Invasive strategy	0.80	0.50-1.27	0.34
Age per year	1.05	1.02-1.08	< 0.001
S-creatinine per unit (μmol/L)	1.005	1.003-1.007	< 0.001
Current smoking	2.61	1.43-4.79	0.002
Previous LVSD*	1.63	0.97-2.75	0.064
Statin during hospitalization	0.46	0.29-0.71	0.001
Aspirin during hospitalization	0.57	0.35-0.90	0.017
Interaction term (current smoker/strategy)	0.22	0.06-0.82	0.024

*Defined as previous left ventricular ejection fraction < 40%.

CI, confidence interval; LVSD, left ventricular systolic dysfunction; NSTEMI, non-ST-segment elevation myocardial infarction.

Table 3 Hazard ratios (HR) of death in patients with NSTEMI (n = 381) during one-year follow-up using multiple Cox proportional hazards regression according to smoking status (Model 2).

	Non-smokers (n = 278)			Smokers (n = 103)		
	HR	95% CI	p-value	HR	95% CI	p-value
Invasive strategy	0.79	0.49-1.28	0.34	0.20	0.06-0.68	0.010
GRACE risk score (per point)	1.03	1.02-1.04	<0.001	1.04	1.02-1.05	<0.001

CI, confidence interval; GRACE, global registry of acute coronary events; NSTEMI, non-ST-segment elevation myocardial infarction.

Among patients treated with PCI, 95% had stents. There was no difference in the usage of drug-eluting stents (DES) in the IS between smokers and non-smokers (24% vs. 21%, respectively, p = 1.00).

Medical treatment

Data on medical treatment during hospitalization are provided in Table 4. A non-significant tendency for more statin usage in the IS and for more aspirin usage among smokers than non-smokers was observed. Otherwise, the medication prescribed was similar within the two treatment cohorts, both for smokers and non-smokers.

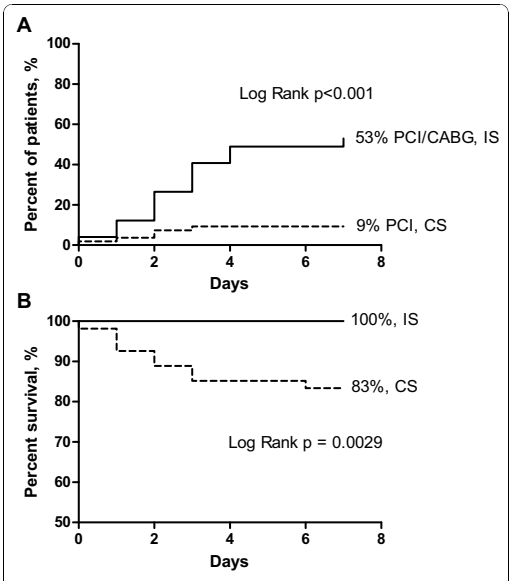

Figure 2 Revascularization (a) and survival (b) during first 7 days in smokers with non-ST-segment elevation myocardial infarction (NSTEMI).

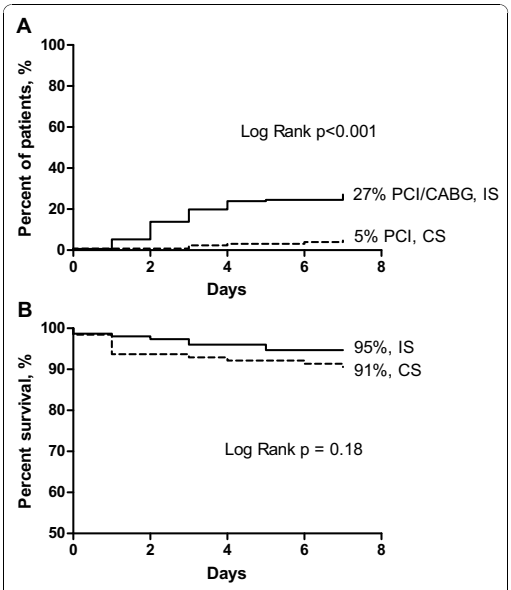

Figure 3 Revascularization (a) and survival (b) during first 7 days in non-smokers with non-ST-segment elevation myocardial infarction (NSTEMI).

Discussion

Principal findings

The main finding of this study is that smokers with NSTEMI benefit the most from an early invasive treatment strategy, and that the treatment effect seems independent of age. For all-cause mortality the interaction term between current smoker and strategy was

Table 4 Medical treatment during index hospitalization in NSTEMI patients.

	Non-smokers			Smokers		
	CS (n = 127)	IS (n = 151)	p-value	CS (n = 54)	IS (n = 49)	p-value
Aspirin	103 (81%)	124 (82%)	0.95	48 (90%)	45 (92%)	0.86
Clopidogrel	92 (72%)	118 (78%)	0.34	46 (85%)	46 (94%)	0.27
Beta-blocker	110 (87%)	123 (82%)	0.32	46 (85%)	42 (86%)	1.00
ACE-I/ARB	53 (42%)	77 (51%)	0.16	22 (41%)	19 (39%)	1.00
Statins	74 (58%)	106 (70%)	0.051	40 (74%)	44 (90%)	0.072

Categorical data presented as n (%).

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CS, conservative strategy cohort; IS, invasive strategy cohort; NSTEMI, non-ST-segment elevation myocardial infarction.

significant, implying that the effect of an invasive strategy was significantly different between smokers and non-smokers. In this unselected population one-year mortality for smokers decreased from 37% in the CS to 6% in the IS. Half of the fatal events among smokers in the CS occurred within 7 days. Such a profound reduction in early mortality could not be demonstrated among the non-smokers, where the increased use of early invasive management was less pronounced. In spite of the favorable findings among smokers undergoing early invasive treatment, current smoking was still an independent predictor of one-year mortality.

Comparisons with previous studies

Several studies and registries of patients with NSTE-ACS have compared the outcome of smokers vs. non-smokers in order to evaluate the possible existence of a "smoker's paradox" [1,8-10]. The consensus has been that the apparently favorable outcome among younger smokers is eliminated when adjustments for baseline risk factors are made in various multiple regression analyses. To the best of our knowledge, the only study that has compared the influence of early invasive vs. a conservative approach in smokers vs. non-smokers with NSTE-ACS is the FRISC II trial [2]. In contrast with our study, a clinical benefit resulting from early invasive treatment was observed for non-smokers but not for smokers. It must be emphasized that the study populations were different, with a much higher mortality rate in our observational study of unselected NSTEMI patients. In FRISC II only 68% of the patients had elevated troponin and age > 75 years was an exclusion criterion. In our study, 53% of the patients were > = 75 years old. Patients treated with PCI in FRISC II were unable to be treated with DES and only 61% had stents in the invasive group, whilst anti-platelet therapy comprised of ticlopidine treatment for only 3-4 weeks after the procedure. This is in contrast to our study, where the majority had stents, and all had clopidogrel prior to and 9 months after the procedure. In FRISC II, early invasive vs. conservative treatment had no influence on total mortality. As is reflected in the favorable influence on mortality in our study, it seems fair to assume that the introduction of early invasive management may have induced a reduction in both cardiac morbidity and total mortality.

Most studies on the prognostic impact of smoking in acute coronary syndromes have compared younger smokers with older non-smokers, and, in part, ex-smokers [8,9,11-13]. It may be speculated that smokers and non-smokers of similar age suffering from an AMI would differ in terms of other risk factors as well as the composition of the atherosclerotic lesion rendering them open to different treatment results.

Differences in baseline confounding factors

Smokers were considerably younger and more likely to undergo early revascularization than non-smokers. It could therefore be argued that the favorable effect of an invasive strategy in the younger subgroup of smokers can be explained solely by this difference in age and the lower proportion of early revascularization in non-smokers. However, we found no interaction between strategy and age, as opposed to a significant interaction between strategy and smoking status at admission. Accordingly, the survival benefit of an invasive strategy in our study seems independent of age. This is consistent with previous findings from randomized trials. In the RITA 3 trial [14] patients assigned an early intervention for NSTE-ACS had a more favorable outcome than those with a conservative strategy, with the results consistent across various subgroups, including age. In two other large randomized studies [2,15] exploring the effect of early invasive strategy versus a conservative approach in NSTE-ACS there were no differences in outcome among patients subdivided into age groups ≥ 65 years and < 65 years. Based upon these considerations, it seems unlikely that differences in age and the proportion of smokers and non-smokers treated with early invasive strategy can solely explain the favorable results obtained among smokers undergoing early invasive versus conservative management.

Another potential confounding factor is the different concomitant medical therapy given to each cohort. It should be emphasized that there were no changes in the recommendations for adjunctive medical treatment from the first to the second cohort. In spite of this, we observed a non-significant tendency for more statin usage among smokers in the IS than in the CS. Statin and aspirin use during hospitalization were associated with a lower hazard ratio for mortality (model 1), but when included in the adjusted analysis, such treatment had no influence on the interaction between smoking and treatment strategy.

Strengths and limitations of the study

The present study is a post-hoc analysis of a prospective observational cohort study including all patients with NSTEMI admitted to our hospital. This unselected study population is representative of Norwegian patients with NSTEMI in general, as opposed to patients included in randomized trials with various inclusion and exclusion criteria. On the other hand, due to the observational and nonrandomized design, our findings may have been influenced by unidentified confounders. In light of the relatively modest population size, potential differences between the groups might not be statistically significant because of type 2 errors. Due to the same reason it did not seem appropriate to stratify age

groups. Data on important confounding factors during follow-up, such as secondary medical prophylaxis and smoking cessation after discharge were not available. According to observations made in studies of smoking cessation in patients with coronary heart disease, an apparent affect on mortality is not seen until after 2-4 years [16-18]. In recently published data from the OASIS 5 study of NSTE-ACS patients, smoking cessation was associated with a lower rate of reinfarctions but had no effect on mortality after 6 months [19]. The early mortality reduction observed in our study can therefore not be explained by a higher percentage of quitters in the IS than in the CS. Although smokers in the IS were slightly younger, had significantly lower s-creatinine and more statin treatment during the index hospitalization, the favorable mortality results were still statistically significant after adjustment for these confounders. Due to regulatory limitations we were not able to study the influence on recurrent myocardial infarctions. Finally, non-smokers were due to higher age and more co-morbidity less likely to undergo invasive treatment. This could have influenced our results in some way not accounted for.

Conclusions

Unselected smokers with NSTEMI represent a subset of patients who receive particular clinical benefit from an early invasive strategy. This benefit seems to be independent of age.

Abbreviations

ACE-I: angiotensin converting enzyme inhibitor; AMI: acute myocardial infarction; ARB: angiotensin-II receptor blocker; CABG: coronary artery bypass grafting; CI: confidence interval; CS: conservative strategy cohort; DES: drug-eluting stent; GRACE: global registry of acute coronary events; HR: hazard ratio; IS: invasive strategy cohort; LVSD: left ventricular systolic dysfunction; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

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Authors' contributions

This study was conceived and designed by EA, KE, JJ and JEO. EA, KE and JEO acquired the data. EA, KE, JR, JJ and JEO analyzed and interpreted the data. EA and JR conducted the statistical analysis. EA, JJ and JEO drafted the original version of the manuscript. EA, KE, JR, JJ and JEO revised the manuscript critically for important intellectual content. All authors have read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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IV

The "smoker's paradox" in patients with acute coronary syndrome: a systematic review

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Abstract

Background:

Smokers have been shown to have lower mortality after acute coronary syndrome than non-smokers. This has been attributed to the younger age, lower co-morbidity, more aggressive treatment and lower risk profile of the smoker. Some studies, however, have used multivariate analyses to show a residual survival benefit for smokers; i.e. the "smoker's paradox". The aim of this study was therefore to perform a systematic review of the literature and evidence surrounding the existence of the "smoker's paradox".

Methods:

Relevant studies published by September 2010 were identified through literature searches using EMBASE (from 1980), MEDLINE (from 1963) and the Cochrane Central Register of Controlled Trials, with a combination of text words and subject headings used. English-language original articles were included if they presented data on hospitalised patients with defined acute coronary syndrome, reported at least in-hospital mortality, had a clear definition of smoking status (including ex-smokers), presented crude and adjusted mortality data with effect estimates, and had a study sample of >100 smokers and >100 non-smokers. Two investigators independently reviewed all titles and abstracts in order to identify potentially relevant articles, with any discrepancies resolved by repeated review and discussion.

Results:

A total of 978 citations were identified, with 18 citations from 17 studies included thereafter. Six studies (one observational study, three registries and two randomised controlled trials on thrombolytic treatment) observed a "smoker's paradox". Between the 1980s and 1990s these studies enrolled patients with acute myocardial infarction (AMI) according to criteria similar

to the World Health Organisation criteria from 1979. Among the remaining 11 studies not supporting the existence of the paradox, five studies represented patients undergoing contemporary management.

Conclusion:

The “smoker’s paradox” was observed in some studies of AMI patients in the pre-thrombolytic and thrombolytic era, whereas no studies of a contemporary population with acute coronary syndrome have found evidence for such a paradox.

Background

The term "smoker's paradox" was introduced into scientific discourse more than 25 years ago following observations that smokers (in comparison to non-smokers) experience decreased mortality following an acute myocardial infarction (AMI) [1-4]. Braunwald's recent textbook on heart disease argues that the observation that smoking predicts better outcome following various reperfusion strategies is not because of any benefit from smoking but simply because smokers are likely to undergo such procedures at a much younger age and hence have on average lower comorbidity [5].

In a recent study we observed a 41% reduction in one-year mortality in unselected AMI patients following the switch from a conservative approach in 2003 to the introduction of routine early invasive management in 2006 [6]. In a sub-analysis of patients with non-ST-segment elevation myocardial infarction (NSTEMI) this treatment effect was especially pronounced for smokers. In spite of this favourable effect, current smoking was still an independent predictor for one-year mortality [7]. These observations motivated us to perform a systematic review of the literature (observational studies and randomised trials) surrounding the "smoker's paradox" in order to explore possible differences between study populations with or without this phenomenon.

Methods

Literature search and study selection

We searched three electronic databases: EMBASE (from 1980 onward), MEDLINE (from 1963 onward) and the Cochrane Register of Controlled Trials. Our search strategy combined text words and subject headings identifying reports relating to acute coronary syndrome/AMI, smoking status and mortality. The search included literature published by 22nd September 2010. Due to the long time spans of the databases we decided to perform two slightly different

searches in MEDLINE and EMBASE, one from 1963/1980 to 1995, the other from 1996 to date of search. (See additional file 1 for the full search strategy.) The reference lists of identified studies were also scanned to identify any other relevant studies, with the search strategy expanding accordingly.

Two investigators (EA and JEO) independently reviewed all titles and abstracts to identify potentially relevant articles and resolved discrepancies by repeated review and discussion. If two or more studies presented the same data from a single patient population, we included these data only once in the review.

No review protocol was used, but we prospectively defined the following criteria for the inclusion of studies into our review:

- Studies of patients hospitalized for acute coronary syndrome (ACS), including the previous World Health Organization (WHO) criteria for AMI [8] and the more recent definition of ACS, including ST-segment elevation myocardial infarction (STEMI), NSTEMI and unstable angina pectoris (UAP) [9].
- The publication should provide a clear definition of smoking status into current, former and never-smokers, including baseline characteristics of each group with age as a minimum. In case former smokers were not defined separately, a minimum requisite was that they had to be defined and characterised either as smokers, non-smokers or per definition were excluded from the analysis.
- Both crude and adjusted total mortality rates should be presented. Effect estimates should be provided, and “age” was a minimum requirement as a covariate.
- The length of follow-up should be reported and include at least hospital mortality. Studies reporting only post-discharge mortality were excluded.
- Only English-language original articles were included.
- The study should include >100 smokers and >100 non-smokers.

Our own study exploring one-year mortality among smokers vs. non-smokers with NSTEMI was published after the literature search was finalised, but the results were known to us by September 2010, and the study has therefore been included in this review [7].

Results

The study selection process is presented in Figure 1. In total, 978 unique citations were identified. Based upon titles and abstracts, 903 citations could be excluded. Accordingly, 75 full-length original articles were considered in depth for inclusion, with 18 publications from 17 studies (7 randomized trials and 10 observational studies/registries) meeting all inclusion criteria [7,10-26]. The Superior Yield of the New strategy of Enoxaparin, Revascularization and GlYcoprotein IIb/IIIa inhibitors (SYNERGY) trial is presented by two publications, one demonstrating crude mortality rates [21] and another adjusted mortality rates [23]. The studies were published between 1991 and 2009 and enrolled patients from 1982 through till 2007. Five studies [7,13,15,18,21,23] were considered to represent a contemporary population of ACS and mainly included patients according to the diagnostic criteria from 2000 [9]. The other studies were based upon patients included according to the WHO criteria [8] in the 1980s and 1990s.

Study categories and adjusted mortality rates

Study characteristics, with crude and adjusted mortality rates expressed as odds ratios and hazard ratios and relative risks with 95% confidence intervals according to smoking status, are presented in Table 1. The studies have been sub-divided into six categories according to study design. The effect estimates for adjusted mortality rates are presented in Figure 2.

Randomised controlled trials (RCT) in patients treated with fibrinolysis for STEMI

Both the International Tissue Plasminogen Activator/Streptokinase Mortality Trial [11] and the Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial [12] demonstrated higher adjusted mortality rates among non-smokers, i.e. supporting a smoker's paradox. For the latter study, no such effect was observed in the angiographic substudy of 2437 patients. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Micardico (GISSI-2) trial [22] included patients with the same factorial study design as the international study [11], but did not demonstrate any reduced adjusted in-hospital mortality for smokers compared with never-smokers.

RCT in STEMI treated with percutaneous coronary intervention (PCI)

In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial 2082 patients with STEMI undergoing primary PCI were randomised to either angioplasty or stenting with or without abciximab [26]. Although current smokers had a lower crude mortality rate, the adjusted analysis did not find a lower mortality than that of non-smokers.

RCT of non-ST-segment elevation acute coronary syndrome (NSTE-ACS) subjected to invasive management

In the SYNERGY trial [27] patients with NSTE-ACS were randomised to enoxaparin or unfractionated heparin and then underwent coronary angiography and subsequent PCI or coronary artery bypass grafting (CABG). The crude mortality rate after one year was similar among smokers and non-smokers [23]. In the adjusted analysis there was a significant mortality excess among smokers vs. non-smokers, supporting the unfavourable effect of current smoking at baseline [21].

Multi-centre post-AMI studies from RCTs

The TRAndolapril Cardiac Evaluation (TRACE) study consisted of 2606 patients and aimed to determine whether patients with left ventricular dysfunction post AMI would benefit from long-term treatment with trandolapril vs. placebo [28]. In a study of 6676 consecutive AMI patients screened for participation in the TRACE study, the long-term mortality was far lower among smokers than either ex- or non-smokers. In spite of this, the adjusted analysis did not give any evidence to support the existence of a smoker's paradox in this population [20].
The Optimal Trial In Myocardial Infarction with the Angiotensin Antagonist Losartan (OPTIMAAL) study included selected patients with AMI and evidence of heart failure for randomized treatment with captopril vs. losartan [19]. The unadjusted mortality rate among current smokers was 17% lower than among non-smokers, but this decreased risk was eliminated after adjustment for age and other baseline differences.

Single centre observational studies of patients with AMI

Mølstad included 484 unselected AMI patients between 1982 and 1984 [24]. The 3-months mortality rate among current smokers was only 1/3 of that among ex- and never-smokers combined. In a "final" multivariate model, current smoking had a significant protective effect.
Bettencourt et al. [13] and Gaspar et al. [15] included consecutive patients with ACS and could not verify the existence of the smoker's paradox. In the latter study the adjusted analysis indicated a higher 6-months mortality rate among current and former vs. never-smokers (Figure 1).
In our own study of 381 unselected NSTEMI patients, smokers had significantly higher adjusted one-year mortality than non-smokers (including ex-smokers) [7], although, the treatment effect of an early invasive strategy was more pronounced among smokers than non-smokers.

Registries

A nationwide prospective survey comprised of patients admitted with AMI in all coronary care units (CCU) operating in Israel during a 2-month period [16]. Although the 6-months mortality rate among smokers was approximately 1/3 of that among ex- and never-smokers combined, the adjusted analysis could not verify the smoker's paradox.

Within the Hellenic registry of patients admitted to hospital with AMI [10] there was also no evidence of any adjusted in-hospital survival benefit among current vs. non-smokers.

The by far largest registry in this overview was the National Registry of Myocardial Infarction 2 (NRMI 2) [17], with data from 297 458 patients with confirmed AMI admitted to participating hospitals but without hospital transfer. Crude in-hospital mortality among smokers was 50% lower than among the on average 14 years older non-smokers. A highly significant OR for reduced mortality in the adjusted analysis supported the existence of a "smoker's paradox".

The Análisis del Retraso en el Infarcto Agudo de Miocardio (ARIAM) registry from Spain included patients with AMI and UAP admitted to a CCU/Intensive Care Unit (ICU) [25]. In patients with AMI, the CCU/ICU mortality was nearly 1/3 among smokers when compared with non-smokers. The adjusted OR for smokers was significantly in favour of the paradox.

The Investigación, Búsqueda Específica y Registro de Isquemia Cooronaria Aguda (IBERICA) registry included patients between 25 and 74 years of age admitted to hospital with AMI. Within this registry, smokers had a lower adjusted 28-days mortality rate than the non-smokers used as evidence in favour of the paradox.

The Global Registry of Acute Coronary Events (GRACE) included patients admitted to hospital with a diagnosis of ACS. In an analysis of 19 325 patients the in-hospital mortality rate among smokers was only half of that among never-smokers (3.3% vs. 6.9%). There was

no significant difference in adjusted OR for current smokers compared with never-smokers. These results were consistent in all three subgroups of the ACS population studied (STEMI, NSTEMI and unstable angina pectoris).

Confounding factors included in the adjusted analyses

The confounding variables used in the multivariate analyses (in addition to smoking status) are presented in Table 2. The studies include a wide range of covariates both for baseline risk factors and treatment provided. Four observational studies did not adjust for any treatment provided during hospitalisation [13,15,24,25]. Three registries [14,16,18], in addition to the CADILLAC trial [26], included invasive treatment in the multivariate analyses. The NRMI 2 registry adjusted for "any reperfusion therapy" without specifying the proportion of patients undergoing invasive procedures [17]. Only two studies included renal function in the multivariate analyses [23,24].

Comments

Main findings

The smoker's paradox was observed in six of the 17 studies included as the basis of this review. One of these studies was an observational single-centre study enrolling unselected AMI patients between 1982 and 1984 [24]. The five other studies dated from the late 1980s and early 1990s and included patients according to the former WHO classification and before the routine use of invasive revascularization [11,12,14,17,25].

Possible explanations of the smoker's paradox

The possible explanations for the reported paradoxical findings can be categorised as being either due to systematic errors, residual confounding or different pathogenesis: the latter

therefore representing a true effect of smoking. Systematic errors would include publication bias. The declining frequency of papers reporting the "smoker's paradox" during the last decade supports our argument that the paradox was the result of skewed reports during the 1980-90s. Another systematic error might be that smokers with an acute cardiac event could have a greater case fatality before admission to hospital than non-smokers [14,29,30]. Those admitted alive to the hospital would therefore already represent the survivors. This notion is supported by the fact that the smoker's paradox has only been demonstrated in hospitalised patients.

Adjustment for age and co-morbidity did reduce the magnitude of the smoking effect in many of the studies, but not all. Part of the remaining effect could be due to residual confounding, both because of measurement errors in the co-factors and lack of information about relevant risk factors. The six studies supporting a smoker's paradox have included STEMI patients, with fibrinolysis the dominant reperfusion strategy. This may indicate that there are slight differences in the pathogenesis of the acute coronary event in smokers as compared to non-smokers. It has previously been shown that smokers with STEMI have improved myocardial perfusion after fibrinolysis compared to non-smokers, despite adjustment for differences in age and co-morbidities [31,32]. Tobacco smoking is also associated with increased levels of circulating fibrinogen and tissue factor. This suggests a more fibrin-rich thrombus in smokers with STEMI which would leave them more amenable to fibrinolytic therapy [33] and thus an improved survival rate. All these explanations may operate in unison to contribute to the observation that smokers perform better than non-smoker after an AMI.

Studies favouring the paradox

Randomized trials

The International Tissue Plasminogen Activator/Streptokinase Mortality Trial [11] and GISSI-2 [22] had a similar design and enrolled STEMI patients within the same time period. A "smoker's paradox" was observed in the International study, whereas only a non-significant trend for better outcome for smokers was demonstrated in GISSI-2. These two studies bring forward the problem of the classification of former smokers. In the International study the OR for 6-month mortality was presented for never-smokers vs. current + former smokers, whilst the contrasting GISSI-2 only reported in-hospital mortality in current vs. never-smokers.
In the GUSTO-1 study 40 599 patients were included in an analysis of 30-days mortality in relation to smoking status. To the best of our knowledge it is in this study that concept of the smokers paradox is first coined. Although not stated expressively in the abstract of the original article, the results from the adjusted analysis were significantly in favour of the paradox in the overall population studied. The abstract refers to the adjusted OR among 2431 patients subjected to the angiographic substudy, among which the paradox was not apparent.

Registries

NRMI 2 reports on 297 458 patients (58%) without hospital transfer out of 510 044 included patients from 1994 to 1997 [17]. The findings are clearly in favour of the paradox. In this report 24% were current smokers compared with 27-28% in the overall NRMI 2 population [34]. This indicates that the smokers were more likely to be transferred to other hospitals and hence excluded from the analysis. The rather surprising "paradoxical" protective effects of a family history of CAD, hypercholesterolemia and various medical treatments observed in that model were not commented upon by the authors.
The authors of ARIAM point out that registries in general may have inherent defects due to the possibility of unidentified confounders not included in the analyses [25]. A selection bias may have been present since only patients admitted to the participating hospitals ICU/CCU

were included. The IBERICA registry is the only registry supporting the presence of the paradox that incorporated primary PCI in the multivariate regression model. In spite of that, only a minority of patients were subject to such treatment.

The treatment scenario in the late 1980s and early 1990s was quite different from today's practice. Although the preferred treatment for STEMI now is primary PCI, fibrinolysis remains an important alternative to mechanical revascularisation. In Europe, 5-85% of patients with STEMI undergo primary PCI [35]. Transfer delays may be unacceptably long before primary PCI is performed, especially for patients living in rural areas or reporting to non-PCI centres. As opposed to the thrombolytic era where the paradox was observed, patients who have had successful thrombolysis should be referred within 24 hours for angiography and revascularization as required [36]. In none of the studies and registries supporting the smoker's paradox was such a treatment strategy applied.

The single centre study

The strength of Mølstad's study is the inclusion of consecutive, unselected patients [24]. At that time no reperfusion modalities were available, and the results are purely of historic interest. This study demonstrates the problems related to multivariate analyses of a small patient population, with results being reliant upon the nature and number of the covariates put into the model. When usage of diuretics was added as a fifth covariate in the multivariate model, there was no longer a significant survival benefit for smokers.

Studies not supporting the paradox

Randomized trials

In TRACE some different confounders to those used in the thrombolytic studies were included, with the study recruiting screenees for a randomised trial [20]. The study population

that was screened for entry into TRACE is probably representative of unselected AMI patients admitted to hospital alive with an AMI. On the other hand, OPTIMAAL included highly selected patients with AMI and heart failure [19]. The percentage of patients given fibrinolysis was 54% in OPTIMAAL screenees and 39% in TRACE screenees, as opposed to 100% in the fibrinolytic trials. Such differences, along with selection criteria, may explain the different conclusions reached by these studies and the fibrinolytic studies.

In the more recent CADILLAC trial, in which patients were selected to undergo primary PCI for STEMI, the paradox could not be verified [26]. This suggests that the possible existence of a smoker's paradox does not extend into the invasive era.

In SYNERGY, the only randomised trial including NSTE-ACS with patients scheduled for invasive management, a significantly increased adjusted HR for one-year mortality in current vs. never-smokers was found [23].

Registries

Both the Israeli [16] and Hellenic [10] registries included hospitalised patients with AMI in the fibrinolytic era. Similar to NRMI 2 [17], IBERICA [14] and ARIAM [25], the mortality rate was compared among current vs. non-smokers, with the results contradictory. It is possible that the number of patients was too small to register the differences noted in the three larger registries.

The GRACE registry was the only study to include patients based upon the current definition of ACS and included in-hospital invasive procedures as a covariate [18]. Neither in the total population of nearly 20 000 patients, nor in the subgroups of patients with STEMI, NSTEMI or UAP, could the existence of the paradox be verified.

Single centre studies

In neither of the two single centre studies from Portugal [13,15] could the paradox be demonstrated, with one showing a non-significant increase in odds ratio for current vs. non-smokers for 6-months mortality [15] (in keeping with the findings from SYNERGY). The same trend was observed in our own study [7]. These three studies are relatively small, but they include a substantial number of patients undergoing invasive management and confirm the results from GRACE.

Limitations of the overview

In a systematic search there will always be a conflict between completeness and accuracy. We tried to perform as wide a search as possible and tested the initial search for possible omissions according to known important publications. Nevertheless, we cannot exclude the possibility of having omitted relevant important studies. In that context, two recent studies that did not meet our inclusion criteria are of interest. They address the important smoking interaction of clopidogrel. Desai et al. presented data from 3427 STEMI patients [37]. They found that the beneficial effect of clopidogrel was especially pronounced among those who smoked ≥10 cigarettes per day. The other study by Bliden et al. of 259 patients undergoing elective stenting shows that clopidogrel induced increased platelet inhibition and lower aggregation as compared with non-smokers [38]. The design of these studies, however, did not allow for the exploration of the existence of the "paradox".

Due to expected variations in the definition of non-fatal cardiovascular events, as well as the sub-classification of fatal events from 1963 onwards, this overview does not explore possible associations between smoking status and events other than total mortality. In addition, the overview does not include any mechanistic studies. Because of the heterogeneity of the data we did not find it meaningful to make a formal meta-analysis.

Conclusions

The "smoker's paradox" was predominantly observed in AMI patients selected according to the WHO criteria of the 1980s and 1990s. During that time period fibrinolysis was the dominant reperfusion strategy for such patients. The paradox, however, has not been demonstrated in more recent studies using routine early invasive management, although, in one recent study smokers with NSTEMI have been shown to benefit more from an early invasive strategy than non-smokers. It can therefore be argued that the "smoker's paradox" is a historical rather than contemporary phenomenon. As such, we would be wise to encourage smoking cessation rather than relying on the "positive effects" of the so-called paradox.

Abbreviations

ACE-I: angiotensin converting enzyme inhibitor; ACS: acute coronary syndrome; AMI: acute myocardial infarction; CABG: coronary artery bypass grafting; CAD; coronary artery disease; CCU: coronary care unit; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; ER: emergency room; GRACE: global registry of acute coronary events; HR: hazard ratio; ICU: intensive care unit; LAD: left anterior descending artery; LMWH: low molecular weight heparin; MI: myocardial infarction; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; NSTEMI: non-ST-segment elevation myocardial infarction; OR: odds ratio; PCI: percutaneous coronary intervention; PTCA: percutaneous transluminal coronary angioplasty; RCT: randomised controlled trial; RR: relative risk; STEMI: ST-segment elevation myocardial infarction; UAP: unstable angina pectoris; UFH: unfractionated heparin; WHO: world health organization.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

This study was conceived and designed by EA, MM and JEO. The literature search was performed by MM. EA and JEO independently reviewed all titles and abstracts to identify potentially relevant articles. EA, JR, DST and JEO analysed and interpreted the data. EA, DST and JEO drafted the original version of the manuscript. EA, JR, MM, DST and JEO revised the manuscript for critically important intellectual content. All authors have read and approved the final manuscript.

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Figure legends

Figure 1.

Selection of studies

Figure 2.

Odds ratios (OR)/Hazard ratios (HR) with 95% confidence intervals for death during follow-up for smokers compared with non-smokers in the studies included. Circles indicate data derived from randomised trials. Squares indicate data derived from observational studies or registries. Open symbols indicate contemporary studies enrolling patients mainly after 2000. Closed symbols indicate older studies enrolling patients in the pre-thrombolytic and thrombolytic era. Symbol size reflects the sample size of the studies and registries. *Inverted OR from original paper.

Table 1: Study characteristics and mortality rates according to smoking status at index event.

Study	Paradox?	Time symptoms to inclusion	Publ.	Enroll.	Index Event	n	Current (C) n (age)	Former (F) n (age)	Never (N) n (age)	Follow-up	Total mortality C	Total mortality F	Total mortality N	Adjusted mortality rates with 95% confidence interval
Randomised clinical trials in STEMI patients (thrombolytic treatment)														
GUSTO-1 [12]	Yes	3.2 ±1.65h	1995	90-93	STEMI	40599	17507 (55)	11117 (64)	11975 (66)	30d	4.0%	6.7%	10.3%	OR 1.25 (1.11-1.39) N vs. C
Barbash et al. [11]	Yes	3.0±1.6h	1993	88-89	STEMI	8259	3649 (58)	2244 (64)	2366 (67)	6m	7.7%	12.1%	17.6%	OR 1.35 (1.12-1.61) N vs. C+F
GISSI-2 [22]	No	<3 h in 70%	1998	88-89	STEMI	9694	5151 (57)	1932 (64)	2611 (68)	Inhosp.	4.7%	7.6%	13.8%	OR 0.80 (0.60-1.07) C vs. N OR 0.97 (0.70-1.35) F vs. N
Randomised clinical trials in STEMI patients (invasive treatment)														
CADILLAC [26]	No	<12h	2004	97-99	STEMI	2082	898 (53)	546 (64)	638 (65)	1y	2.9%	3.7%	6.6%	HR 0.96 (0.52-1.76) C vs. N
Randomised clinical trials in patients with NSTE-ACS (invasive treatment)														
SYNERGY [21,23]	No	<24h	2008	01-02	NSTE-ACS	9971	2404 (61)	3491 (69)	4076 (70)	1y	6.5%	9.1%	6.7%	HR 1.77 (1.42-2.21) C vs. N
Multi-centre post-AMI randomised trials														
TRACE [20]	No	2-6d	1999	90-92	AMI	6485	3341 (64)	1420 (71)	1724 (74)	3y	26-27%	38-39%	42-43%	HR 1.04 (0.93-1.15) C vs. N
OPTIMAAL [19]	No	<10d	2004	98-99	AMI	5475	1832 (62)	1867 (69)	1776 (71)	2.7y	16.3%	Incl. in C	19.3%	HR 1.08 (0.93-1.25) C+F vs. N
Single-centre observational studies of patients with AMI														
Mølstad [24]	Yes	NA	1991	82-84	AMI	484	184 (61)	Incl. in N	456 (70)	3m	11-13%	Incl. in N	32-34%	HR 0.62 (0.36-1.04) C vs. N+F HR 0.55 (0.33-0.93) C vs. N+F
Bettencourt et al. [13]	No	NA	2004	01-02	ACS	901	369 (58)	Incl. in C	532 (69)	Inhosp.	2.6%	Incl. in F	6.6%	OR 0.96 (0.38-2.41) C+F vs. N
Gaspar et al. [15]	No	NA	2009	04-07	ACS	1228	450 (58)	Incl. in C	778 (68)	6m	9.3%	Incl. in C	13.1%	OR 1.25 (0.61-2.54) C+F vs. N

Aune et al. [7]	No	NA	2010	03-07	NSTEMI	381	103 (63)	Incl. in N	278 (80)	12m	22%	Incl. in N	27%	HR 2.61 (1.43-4.79) C vs. N+F
Registries														
Gottlieb et al. [16]	No	NA	1996	94	AMI	999	367 (57)	Incl. in N	632 (67)	6m	7.9%	Incl. in N	21.5%	HR 0.84 (0.54-1.30) C vs. N+F
Andrikopoulos et al. [10]	No	<24h	2001	93-94	AMI	5507	3853 (59)	Excluded	1654 (70)	Inhosp.	7.4%	NA	14.5%	RR 1.12 (0.86-1.44) C vs. N
NRMI 2 [17]	Yes	NA	2002	94-97	AMI	297458	72585 (58)	Incl. in N	224871 (72)	Inhosp.	8.0%	Incl. in N	16.4%	OR 0.86 (0.83-0.90) C vs. N+F
ARIAM [25]	Yes	<24 h criterion	2004	95-01	AMI	17761	5796 (57)	3494 (67)	8471 (70)	ICU/CCU	5.0%	9.3%	13.3%	OR 0.77 (0.66-0.91) C vs. N
					UAP	7795	1721	1950	4124	ICU/CCU	0.7%	1.0%	1.5%	OR 0.81 (0.48-1.36) C vs. N
IBERICA [14]	Yes	<12h in 82%	2007	97-98	AMI	7796	3057 (56)	1730	2839 (65)	28d	8.9%	16.9%	20.1%	OR 0.57 (0.42-0.78) C vs. N
GRACE [18]	No	NA	2005	99-02	ACS	19325	5276 (57)	5691 (67)	8358 (71)	Inhosp.	3.3%	4.5%	6.9%	OR 1.01 (0.80-1.27) C vs. N

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CCU, coronary care unit; HR, hazard ratio; ICU, intensive care unit; OR, odds ratio; NA, not available; NST-ACS, non-ST-segment acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; RR, relative risk; STEMI, ST-segment elevation myocardial infarction; UAP, unstable angina pectoris

Table 2: Covariates in addition to smoking status used in the multivariate analyses.

Study	Baseline and clinical characteristics	Reperfusion and medication
Studies supporting the existence of a smoker's paradox		
Mølstad [24]	Age, atrial fibrillation, s-creatinine, s-potassium	None
Barbash et al. [11]	Age, sex, MI site, diabetes, previous MI, antecedent angina, hypertension, hypotension at entry, Killip class, body mass index, hypercholesterolemia, family history of CAD	Time to lysis
GUSTO-1 [12]	Age, sex, systolic blood pressure, Killip class, heart rate, MI site, previous MI, previous CABG, height, diabetes, hypertension, cerebrovascular disease	Time to lysis, type of thrombolytic treatment
NRMI 2 [17]	Age, sex, MI site, previous MI, previous CABG, weight, diabetes, hypertension, hypercholesterolemia, family history of CAD, black race, other race, previous heart failure, previous PTCA, previous stroke, Q vs. non-Q,	Any reperfusion therapy, aspirin first 24 hours, any heparin, intravenous nitroglycerine, beta-blocker, i.v. lidocaine, i.v. magnesium, ACE-inhibitor, calcium channel blocker, other anti-thrombin, other antiplatelet
ARIAM [25]	Age, Killip class, MI site, diabetes, Q-wave, non-Q-wave with ST elevation, non-Q-wave with ST decent	None
IBERICA [14]	Age, sex, MI site, previous MI, diabetes, hypertension, previous angina, spline function for symptoms monitoring, cardiogenic shock or acute pulmonary oedema, severe arrhythmias	Thrombolysis, primary angioplasty, aspirin, beta-blocker
Studies not supporting the existence of a smoker's paradox		
Gottlieb et al. [16]	Age, sex, systolic blood pressure <100 mmHg, heart rate >100/min, Killip class ≥2, anterior MI, diabetes, hypertension, previous MI, previous angina, Q-wave MI, family history of CAD, CHF during index hospitalization, atrial fibrillation during hospitalization	Thrombolytic therapy, invasive coronary procedures
GISSI-2 [22]	Age, sex, Killip class, MI site, hypertension, diabetes, previous angina, body mass index, number of leads with ST elevation	Time to lysis

TRACE [20]	Age, sex, body mass index, COPD, previous angina, previous MI, hypertension, family history of CAD, CHF, wall motion index, Q wave anterior MI	Thrombolytic treatment
Andrikopoulos et al. [10]	Age, sex, diabetes, hypertension, previous MI	Thrombolytic treatment
OPTIMAAL [19]	Age, sex, COPD, cerebrovascular accidents, diabetes, hypercholesterolemia, hypertension, previous MI, Killip Class, Q wave MI, MI site, peripheral vascular disease	Thrombolytic treatment, discharge medication
Bettencourt et al. [13]	Age, sex	None
GRACE [18]	Age, sex, geographical region, previous angina, previous MI, previous PCI/CABG, hypertension, diabetes, hyperlipidemia, chronic heart failure, Killip class, blood pressure, heart rate	Thrombolytic treatment, catheterization, PCI, CABG, aspirin, UFH, LMWH, Glycoprotein IIb/IIIa inhibitor, ACE-inhibitor, calcium channel blocker, beta-blocker, statin
CADILLAC [26]	Age, sex, Killip class ≥2, MI site, previous MI, previous CABG, diabetes, hypertension, hypercholesterolemia, LAD culprit vessel, triple vessel disease, baseline TIMI 0 or 3	Stent randomization, abciximab randomization, time from MI to ER, time from ER to first balloon
SYNERGY[23]	Age, gender, creatinine clearance, heart rate, history of CHF, diabetes, baseline rales, ST depression on baseline ECG, weight, peripheral vascular disease, Killip class 3 or 4, No positive biomarkers at randomization, T-wave inversion on baseline ECG	Enoxaparin vs. UFH
Gaspar et al. [15]	Age, left ventricular dysfunction, Killip class >1, ST-elevation ACS	None
Aune et al. [7]	Age, s-creatinine, previous left ventricular systolic dysfunction, interaction term (current smoking/strategy)	Invasive strategy, aspirin, statin

ACE-inhibitor, angiotensin converting enzyme inhibitor; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ER, emergency room; LAD, left anterior descending artery; LMWH, low molecular weight heparin; MI, myocardial infarction; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; UFH, unfractionated heparin.

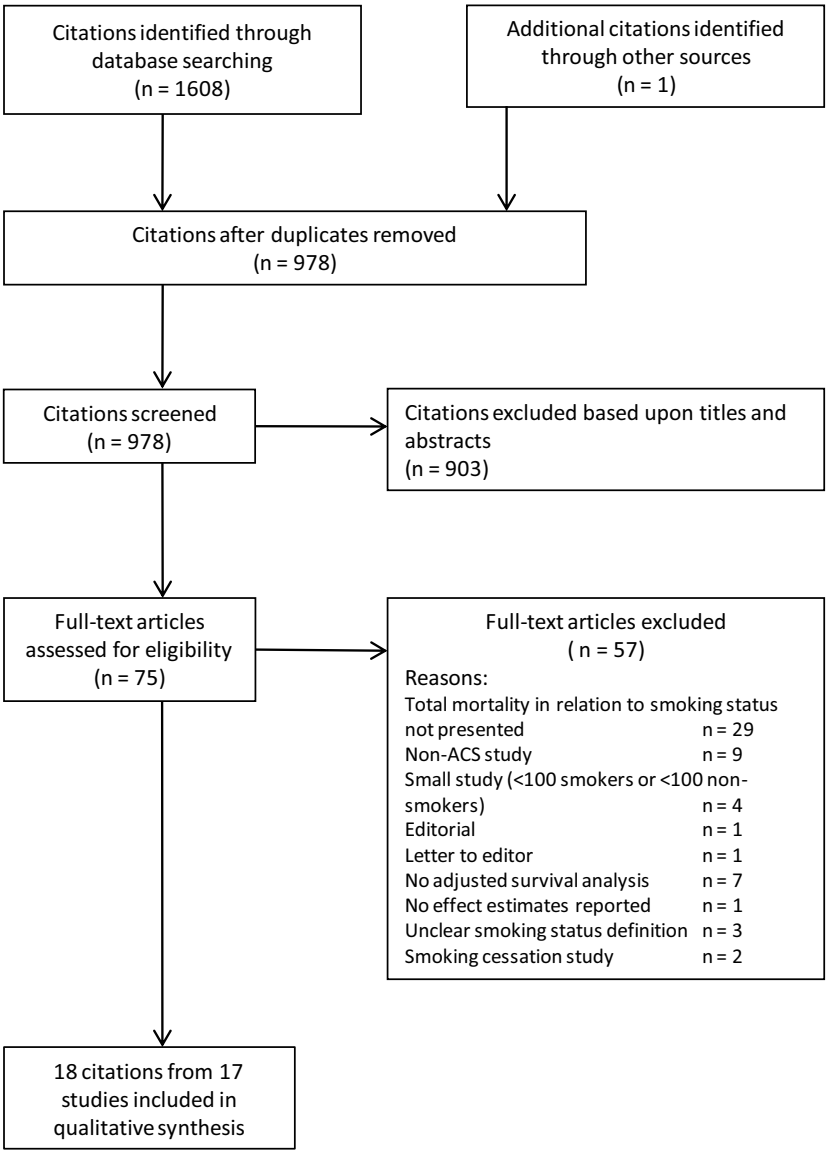
Description of additional data file

File name: Additional file 1

File format: PDF

Title of data: Full search strategy in EMBASE, MEDLINE and Cochrane Central Register of Controlled Trials

Figure 1.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Citations after duplicates removed (n = 978)
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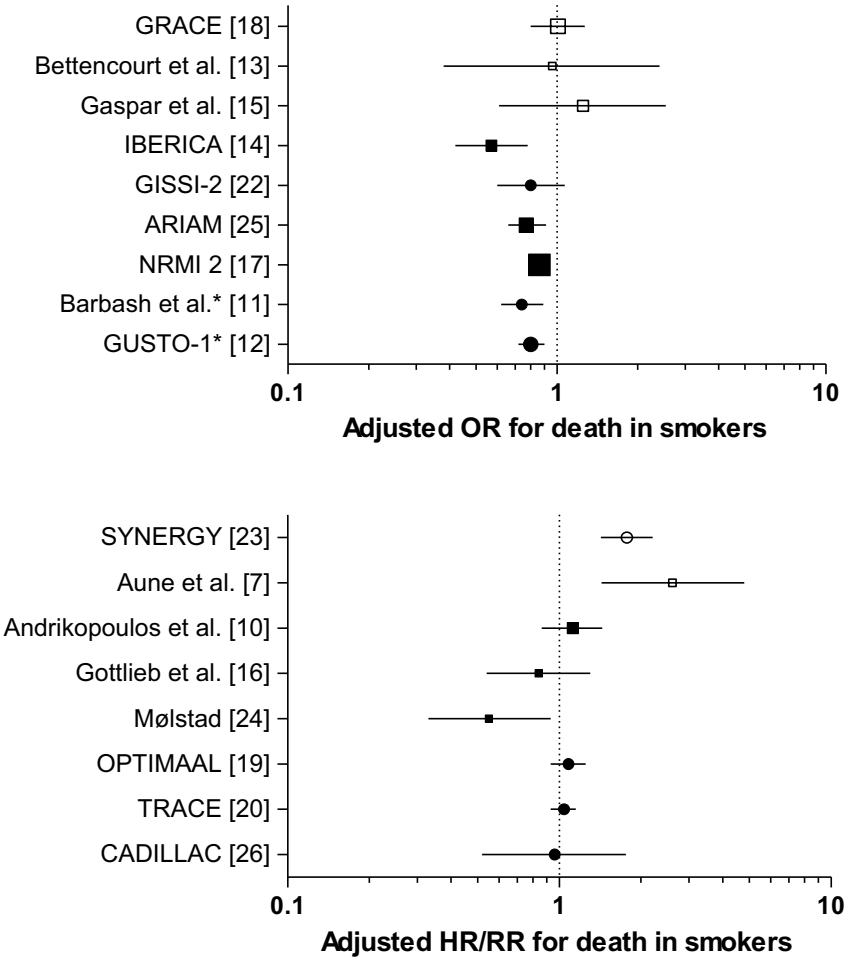
Full-text articles excluded (n = 57)
Reasons:
Total mortality in relation to smoking status not presented n = 29
Non-ACS study n = 9
Small study (<100 smokers or <100 non-smokers) n = 4
Editorial n = 1
Letter to editor n = 1
No adjusted survival analysis n = 7
No effect estimates reported n = 1
Unclear smoking status definition n = 3
Smoking cessation study n = 2
18 citations from 17 studies included in qualitative synthesis

Figure 2.


GRACE [18]
Bettencourt et al. [13]
Gaspar et al. [15]
IBERICA [14]
GISSI-2 [22]
ARIAM [25]
NRMI 2 [17]
Barbash et al.* [11]
GUSTO-1* [12]
0.1
1
10
Adjusted OR for death in smokers
SYNERGY [23]
Aune et al. [7]
Andrikopoulos et al. [10]
Gottlieb et al. [16]
Mølstad [24]
OPTIMAAL [19]
TRACE [20]
CADILLAC [26]
0.1
1
10
Adjusted HR/RR for death in smokers