Smoking and impaired glucose homeostasis predisposes to a more severe outcome in patients presenting with acute coronary syndrome: A cross-sectional study.

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Smoking and impaired glucose homeostasis predisposes to a more severe outcome in patients presenting with acute coronary syndrome: A cross-sectional study.

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Abstract

Objectives Smoking, diabetes, male sex, hypercholesterolemia and hypertension are well-established risk factors for the development of coronary artery disease (CAD). However, less is known about their role in influencing the outcome in the event of acute coronary syndrome (ACS). The aim of this study was to determine if these risk factors are associated specifically with acute myocardial infarction (MI) or unstable angina (UA) in patients with suspected ACS.

Design Cross sectional study

Setting Patients admitted to the coronary care unit, via the emergency room, at a central county hospital over a four-year period (1992-96).

Participants From 5292 patients admitted to the coronary care unit, 908 patients aged 30-74 years were selected, who at discharge had received the diagnosis of either MI (527) or UA (381). A control group consisted of 948 patients aged 30-74 years, where a diagnosis of ACS was excluded.

Main outcome measures MI or UA

Results Current smoking (OR 2.42 (1.61-3.62)), an impaired glucose homeostasis (OR 1.78 (1.19-2.67)) and male sex (OR 1.71 (1.21-2.40)) were significant factors predisposing to MI over UA, in an event of an ACS. Compared to the non-ACS group, impaired glucose homeostasis, male sex, cholesterol level and age were significantly associated with development of an ACS (both MI and UA). Interestingly, smoking was significantly associated with MI (OR 2.00 (1.32-3.02)), but not UA.

Conclusions Smoking, or impaired glucose homeostasis, are acquired risk factors for a severe ACS outcome in CAD patients. Importantly, smoking was not associated with UA, suggesting that it is not a risk factor for all clinical manifestations of CAD, but its influence is important mainly in the acute stages of ACS. Thus, on a diagnosis of CAD the cessation of smoking and management of glucose homeostasis are of upmost importance to avoid severe subsequent ACS consequences.

What is already known on this subject:

- Smoking, diabetes mellitus, hypertension, dyslipidemia and male sex are risk factors for the development of atherosclerotic coronary artery disease (CAD)
- The risk factors for the progression of CAD to a more severe acute coronary syndrome (ACS) outcome (myocardial infarction) are less understood.

What this study adds:

- Smoking and an impaired glucose homeostasis are risk factors for a more severe ACS outcome.
- The influence of smoking is important mainly in the acute stages of ACS, rather than all clinical manifestations of CAD *per se*.
- On a diagnosis of CAD the cessation of smoking and management of glucose homeostasis are of upmost importance to avoid severe subsequent ACS consequences.

Strengths and limitations of this study

Strengths:

- The patients were recruited before the introduction of PCI, CABG and modern antithrombotic drugs in the standard management of ACS. Thus, it was possible to identify progression to UA or MI as distinct outcome groups within the cohort, in the absence of interventions that would otherwise influence the thrombotic processes involved in ACS.
- The control group of non-ACS patients had a similar initial management routine following ER presentation i.e. transfer to a coronary care unit for observation until an ACS diagnosis was excluded, and upon discharge diagnosed as not even suffering from stable CAD.
- The study was based in a single centre with the same two cardiologists evaluating and categorising all 5292 patients, using consistent criteria.

Limitations:

- Some of the UA cases would likely have been diagnosed as NSTEMI using the most recent criteria of MI.
- Treatments and risk factor profiles have partly evolved since the study was performed.

Introduction

Smoking, diabetes mellitus, hypertension and dyslipidemia have, together with age and sex, been established as risk factors for the development of atherosclerotic coronary artery disease (CAD). Thus, these are targets for treatment to slow the progression of disease and to reduce the risk of acute coronary syndrome (ACS) consequences, such as myocardial infarction (MI) or unstable angina (UA)[1]. However, the influence of these risk factors on the nature of any CAD-associated ACS is less well understood.

The initiating event of ACS is thought to involve the exposure of a prothrombotic surface, either through atherosclerotic plaque rupture or disruption of the overlying endothelial surface. Resulting thrombosis formation can permanently occlude the lumen of a coronary artery, cause myocardial cell death and the induction of MI. However, in other cases it can be transient, or only partial occlude the vessel, inducing only UA[1]. It is not known why some CAD patients are predisposed to the former, rather than the latter outcome. The thrombogenicity of blood at the time of the acute event is likely to play a role, consistent with the clinical observation that rapid initiation of antithrombotic treatment (e.g. ASA, clopidogrel, fondaparinux) in ACS significantly improved the outcome[2]. However, the role of the established risk factors for the underlying CAD in the ACS outcome has not been well studied. The rationale of the current study was to further clarify this in the Carlscrona Heart Attack Prognosis Study (CHAPS).

CHAPS constitutes a patient cohort recruited before the introduction of percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery and modern antithrombotic drugs. Thus, to our knowledge, this study is unique in that UA and MI could be identified as distinct groups within an ACS population, and their respective risk factors (diabetes, hyperlipidemia, hypertension, smoking, age and sex) analysed separately.

Materials and methods:

Patient recruitment

The Carlscrona Heart Attack Prognosis Study (CHAPS) recruited 5292 consecutive patients admitted to the coronary intensive care unit with acute chest pain (indicative of a possible ACS) at Blekinge Hospital, Karlskrona, between January 26, 1992 and January 25, 1996. All included patients gave written informed consent. Of the total of 5292 admissions, 2967 were between 30-74 years of age at admittance. In patients with multiple admittances, only the first classifying admittance was included as case in the study.

Acute coronary syndrome patients

A diagnosis of ACS was ascertained in 908 of the eligible patients aged 30-74 years of age (644 men and 264 women). Two groups were identified: (i) patients experiencing at least one acute MI during the study (527) or (ii) patients experiencing no acute MI, but having at least one episode of UA during the study (381). Data on environmental and lifestyle factors, and blood samples, were collected on first admittance under the classifying diagnosis. The classifying diagnosis was set at discharge by one of two experienced cardiologists.

A diagnosis of acute MI was made when patients fulfilled at least two of the following criteria: (i) A history of chest pain of at least 15 min duration, (ii) an increase in activity of cardiac biomarkers (cardiac enzymes) to at least twice the upper limit of normality, or (iii) characteristic ECG changes for MI (typical sequence change of ST segment and/or of T-waves and/or appearance of new Q-waves). These criteria included both patients with ST-elevation MI (STEMI) and non-ST elevation MI (NSTEMI).

A diagnosis of UA was made when patients fulfilled all of the following criteria: (i) no evidence of MI, (ii) acute chest pain of increased/modified character to any previously experienced, during the preceding 48 h and (iii) angina pectoris diagnosed and medically treated before admission, or alternatively, angina pectoris ascertained by clinical evaluation, including a bicycle exercise test prior to discharge from the hospital. Post-infarction angina and patients with

secondary angina were not included.

Non-acute coronary syndrome patients

The study population also contained 948 patients aged 30-74 (569 men and 379 women) who were admitted with suspected ACS, but were subsequently diagnosed as non-ACS and, furthermore, were not diagnosed with stable coronary artery disease (CAD).

Ethical approval

Carlscrona Heart Attack Prognosis Study (CHAPS) was approved by the Regional Ethical Review Board, Lund, Sweden (EPN 2009/762 and LU 298-91).

Risk factors

The presence of CAD risk factors were identified based on laboratory analyses, patient history and/or medical records. Samples for laboratory analysis were collected at hospital admission and were analysed by the in-house routine diagnostic laboratory. Smoking status was defined as current- or non-smoker. Information on medical history of hypertension and diabetes were recorded at admission and extracted from earlier medical files, and the diagnosis and information were also verified at discharge from the hospital. Hypertension was defined as a physician's diagnosis prior to hospital admittance. In general, these patients were treated with blood pressure lowering medications. Patients with a previous diagnosis of diabetes were grouped for analysis as follows: (i) diet treated only, (ii) oral medication only, or (iii) insulin treated. In parallel, to identify patients with an impaired glucose homeostasis who had evidence of both acute and long-term insufficient glucose control, a laboratory-defined classification based on glucose ≥7.5 mM together with HbA1c ≥5.5 was used.

Statistical methods

STATA and IBM SPSS Statistics were used for data analyses. Standard methods were used for descriptive statistics. Associations between categorical variables were examined using binary logistic regression and expressed as odds ratios (OR) with 95% confidence intervals (CI). Principal analyses were made with men

and women combined in one group, but were repeated where men and women were analysed separately. Age was entered into the regressions in 10-year age groups. Confounding was considered by stratification and by multivariate regression models forcing age group, sex, impaired glucose homeostasis, serum cholesterol, hypertension and current smoking into the same model. Individuals with a missing variable were excluded in the respective analysis. Two-way interaction terms were used to explore the association of sex and the major risk factors with ACS outcome.

Results

Patient characteristics

The CHAPS study recruited 5292 patients of which 2992 were aged 30-74 years of age. Table I shows patient characteristics of the 908 eligible patients with ACS and the 948 eligible patients without ACS, or any current or previous medical history of CAD (non-ACS patients). Among patients with ACS we identified 46 patients (5%) with no previous diagnosis of diabetes as having impaired glucose homeostasis.

Risk factors predisposing to myocardial infarction in acute coronary syndrome

We tested the hypothesis that UA and MI are two separate outcomes in ACS, differently influenced by established risk factors for the underlying CAD. The results are shown in Table II. Current smoking (OR 2.42 (1.61-3.62)), an impaired glucose homeostasis defined as glucose ≥7.5 mM and HbA1c ≥5.5% (OR 1.78 (1.19-2.67)) and male sex (OR 1.71 (1.21-2.40)) were found to be more strongly associated with MI, compared to UA. The same was true with age, although this was a weaker association (OR 1.02 (1.00-1.04)). Neither cholesterol (total cholesterol level), nor a previous diagnosis of hypertension, was more strongly associated with MI than UA. These data indicate that different CAD risk factors are associated with different ACS outcomes.

Risk factors predisposing to myocardial infarction or unstable angina

Next, we compared the individual subgroups of MI patients or UA patients with non-ACS patients (Table III), to establish the association between the risk factors and the specific ACS outcome. Impaired glucose homeostasis, male sex, cholesterol level and age group were significantly associated with both MI and UA, when compared to patients with non-ACS. Interestingly, smoking was significantly associated only with MI (OR 2.00 (1.32-3.02)), but not with UA (OR 0.84 (0.53-1.33)).

We found no statistically significant interactions between sex and any of the major risk factors for CAD in the association with the outcome of ACS. In sex-

specific sub-analyses there was no significant difference between the results for men and women.

Discussion

In the current study we show that an impaired glucose homeostasis, smoking or male sex, in addition to being known major risk factors for CAD, are associated with a more severe outcome in the case of ACS (i.e. they predispose towards MI, rather than UA). Interestingly, when compared to the non-ACS group, smoking was significantly associated with MI, but not UA, suggesting its effects are mainly important in the determination of the ACS outcome, rather than the development of all clinical manifestations of CAD *per se*.

The major strength, and novelty, of this study is due to the unique nature of the Carlscrona Heart Attack Prognosis Study (CHAPS) patient cohort. The patients were recruited before the introduction of PCI, CABG and modern antithrombotic drugs in the standard management of ACS. The absence of these interventions, that would otherwise influence the thrombotic processes involved in ACS, made it possible to identify progression to UA or MI as distinct outcome groups within the cohort. Furthermore, we were also able to gather information on non-ACS patients who were admitted into the same hospital setting, during the same period. These patients were initially admitted with a suspected ACS diagnosis, but were discharged from the heart intensive unit assessed as not having experienced an ACS, or even suffering from stable CAD. Thus, the non-ACS patients provided an excellent control group, as they had a similar initial management routine following ER presentation i.e. transfer to a coronary care unit for observation until an ACS diagnosis was confirmed or excluded. A major strength of our study is that it was based in a single centre with the same two cardiologists evaluating and categorising all patients, using consistent criteria. This ensured a level of consistency that is not possible when using data from health care registries studies, which rely solely on diagnosis codes based on each treating physicians judgment, and are composed of data from multiple hospitals and collected for other purposes than research [3 4]

A number of limitations of the study should be acknowledged. Biochemical analyses were performed over a period of four years, although the hospital routine diagnostic laboratory used accredited standardised methods, providing consistency over time. The definition of MI continues to evolve as refined criteria and more sensitive and specific biomarkers are implemented. Some of the UA cases in our study would likely have now been diagnosed as NSTEMI, using recent criteria required for MI diagnosis [5] . Treatments and risk factor profiles have also partly developed since the study was performed. However, smoking remains a major health issue and type 2 diabetes is increasing in the western society, therefore, the results are still highly relevant for the care of patients with CAD today.

The determining role of thrombotic factors in the outcome of an ACS is underscored by the success of more aggressive antithrombotic treatment in recent years [2]. Previously, we have shown, using the CHAPS material, that genetic variations of thrombotic factors are associated with ACS outcome [6]. We show here that impaired glucose homeostasis confers an increased risk towards MI, rather than UA, in an ACS. Diabetes has been associated with both early and late mortality after presentation with ACS [7] and furthermore non-fasting elevated blood glucose has been associated with an increased risk of ischemic heart disease and MI [8]. A reason for a more adverse outcome in a patient with diabetes and/or impaired glucose homeostasis could be due to a prothrombotic effect, as also indicated by the more salutary effects of antithrombotic treatment in patients with diabetes [9]. In the present study we used the laboratory-based combination of an increased blood level of both glucose and Hb1Ac, to ascertain an acute, as well as a more longstanding, deregulated glucose homeostasis. Our finding that 46 of the patients with ACS, but no previously known diabetes, fulfilled these laboratory-based criteria is in line with previous reports of unknown diabetes in a significant proportion of patients with acute MI [10].
Our finding that current smoking is more common in patients with MI than with UA is supported by data from a recent registry-based longitudinal cohort study of patients with ACS in the national Swedish quality-of-care register (Riks-HIA) [4] and in the prospective population based CAREMA cohort study [11]. Interestingly,

our finding that smoking was associated with MI, but not UA, when compared to the non-ACS patients, shows that smoking has a significant effect mainly in the acute event, possibly through modulation of thrombogenicity at the site of a ruptured plaque [12]. Previous reports show that the increased risk for MI associated with smoking decreases rapidly after cessation [12-14], supporting the idea that smoking is a critical risk factor in the acute stages of ACS, rather than in all clinical manifestations of CAD.

In conclusion, our study shows that the presence of known major risk factors for CAD, such as an impaired glucose homeostasis, smoking and male sex are also significantly associated with a more severe outcome in the case of an ACS. Our finding that current smoking is strongly associated with MI, but not UA, emphasises the importance of the clinical practice of encouraging current smokers with a diagnosis of CAD to quit their smoking habits.

The observed differences in ACS outcome associated with smoking or dysregulated glucose metabolism highlight several hypotheses that warrant further investigation. Establishing the influence of these risk factors at the cellular level, e.g. on platelet function, coagulation and/or fibrinolysis, inflammation and other factors influencing the vessel micro-milieu, could lead to optimisation of pharmacological treatment for CAD and ACS.

Footnotes:

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Contributors:

LR, HO, and MF designed and initiated the original Carlscrona Heart Attack Prognosis Study on which the current study is based.

MF conducted the patient inclusion, reviewed all cases, collected patient information and compiled the data files.

JO, HF, IV, HO, AH, LR, UL conceived and designed the current study.

IV and MP collected and compiled the laboratory data.

HF and UL performed the statistical analyses and compiled the results.

JO, MF, HF, IV, HO, AH, LR, UL interpreted the results.

JO, HO, UL drafted the paper.

MF, HF, IV, LR contributed to critical revision for important intellectual content.

All authors approved the final manuscript.

JO is the guarantor.

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All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous

three years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing: No additional data available

The lead author, Jacob Odeberg, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table I. Patient characteristics

	Non-ACS		MI		UA	
	Men	Women	Men	Women	Men	Women
Patients	569	379	394	133	250	131
Age	57.4 (11.2)	60.1 (11.2)	63.3 (8.6)	65.8 (8.0)	62.5 (8.7)	65.1 (8.1)
Smoking	119 (24.4)	48 (14.2)	100 (27.0)	29 (23.2)	48 (19.8)	14 (11.1)
Hypertension	84 (17.0)	77 (22.7)	101 (26.8)	32 (25.2)	68 (27.9)	39 (31.0)
Cholesterol*	5.8 (1.4)	6.1 (1.4)	6.1 (1.3)	6.6 (1.5)	6.0 (1.1)	6.6 (1.3)
Diabetes all	29 (5.9)	30 (8.8)	65 (17.2)	28 (21.9)	27 (11.1)	22 (17.5)
DM (diet)	24 (4.9)	24 (7.0)	48 (12.7)	18 (14.1)	22 (9.0)	13 (10.3)
DM (p.o)	2 (0.4)	2 (0.6)	11 (2.9)	7 (5.5)	3 (1.2)	3 (2.4)
DM (insulin)	3 (0.6)	4 (1.2)	6 (1.6)	3 (2.3)	2 (0.8)	6 (4.8)
Glucos*	5.7 (2.6)	6.7 (4.6)	7.3 (3.8)	8.1 (4.1)	5.9 (2.3)	6.4 (3.3)
HbA1c *	4.6 (0.8)	5.0 (1.5)	5.3 (1.4)	5.5 (1.7)	5.1 (1.1)	5.3 (1.6)
Glucose control**	6 (4.3)	9 (11.4)	65 (18.6)	33 (30.6)	29 (13.3)	18 (16.4)

Non-acute coronary syndrome (Non-ACS), Myocardial Infarction (MI) and Unstable Angina (UA)
Data are means (SD), or numbers (%). DM (diet) no pharmacological treatment for diabetes, DM (p.o.) oral medication for diabetes, DM (insulin) treatment included insulin
* Routine laboratory analysis of admission samples.
** Glucose control defined as an impaired glucose homeostasis by HbA1c ≥5.5 % + Glucose ≥7.5 mM
Missing data Non-ACS (n): age (0), smoking (123), hypertension (114), cholesterol (720), diabetes (115), plasma glucose (715), HbA1c (725), glucose control (731). MI (n): age (0), smoking (31), hypertension (23), cholesterol (57), diabetes (115), plasma glucose (40), HbA1c (62), glucose control (98). UA (n): age (0), smoking (12), hypertension (11), cholesterol (45), diabetes (115), plasma glucose (42), HbA1c (46), glucose control (53).

Table II: The odds of myocardial infarction (MI) versus unstable angina (UA) in patients with acute coronary syndromes

	MI versus UA	
	OR	CI (95%)
Glucose control*	1.78	1.19-2.67
Age_group**	1.02	1.00-1.04
Sex (male)	1.71	1.21-2.40
Cholesterol	1.06	0.94-1.19
Smoking	2.42	1.61-3.62
Hypertension	0.84	0.60-1.18

* Impaired glucose homeostasis (HbA1c≥5.5% + blood glucose ≥7.5 mM)

**Age groups: 30-39, 40-49, 50-59, 60-69, 70-74 years

Associations were estimated by binary logistic regression and expressed as odds ratios (OR) with 95% confidence intervals (CI (95%)). MI versus UA was the dependent variable and age, sex, serum cholesterol, smoking, hypertension or glucose control were entered as covariates.

Table III: The odds of myocardial infarction (MI), or unstable angina (UA), versus patients without acute coronary syndrome (non-ACS)

	MI versus non-ACS		UA versus non-ACS	
	OR	CI (95%)	OR	CI (95%)
Glucose control*	4.22	2.35-7.56	2.14	1.15-3.95
Age group**	1.06	1.04-1.08	1.04	1.03-1.06
Sex (male)	2.44	1.68-3.55	1.48	1.02-2.15
Cholesterol	1.17	1.03-1.32	1.15	1.00-1.32
Smoking	2.00	1.32-3.02	0.84	0.53-1.33
Hypertension	1.06	0.71-1.58	1.29	0.87-1.92

* Impaired glucose homeostasis (HbA1c≥5.5% + blood glucose ≥7.5 mM)

** Age groups: 30-39, 40-49, 50-59, 60-69, 70-74 years

Associations were estimated by binary logistic regression and expressed as odds ratios (OR) with 95% confidence intervals (CI (95%)). MI and UA were the dependent variables and age, sex, serum cholesterol, smoking, hypertension or glucose control were entered as covariates.

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

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

Results		
( )Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ***Page 9***
		(b) Give reasons for non-participation at each stage ***Page 9***
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ***Page 9 and Table 1***
		(b) Indicate number of participants with missing data for each variable of interest ***Table 1 footnotes***
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures ***Table 1***
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ***Page 9, page 10 and Table 2, Table 3 footnotes***
		(*b*) Report category boundaries when continuous variables were categorized ***Table 2 and Table 3 footnote***
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period ***N.A***
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ***Page 9, page 10***
Discussion		
Key results	18	Summarise key results with reference to study objectives ***Page 11***
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ***Page 12***
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ***Page 11, page 12, page 13***
Generalisability	21	Discuss the generalisability (external validity) of the study results ***Page 13***
Other information		
( ) Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ***Page 14***

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

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

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The influence of smoking and impaired glucose homeostasis on the outcome in patients presenting with acute coronary syndrome: a cross sectional study

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The influence of smoking and impaired glucose homeostasis on the outcome in patients presenting with acute coronary syndrome: a cross sectional study

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Abstract

Objectives
Smoking, diabetes, male sex, hypercholesterolemia and hypertension are well-established risk factors for the development of coronary artery disease (CAD). However, less is known about their role in influencing the outcome in the event of acute coronary syndrome (ACS). The aim of this study was to determine if these risk factors are associated specifically with acute myocardial infarction (MI) or unstable angina (UA) in patients with suspected ACS

Design
Cross sectional study

Setting
Patients admitted to the coronary care unit, via the emergency room, at a central county hospital over a four-year period (1992-96)

Participants
From 5292 patients admitted to the coronary care unit, 908 patients aged 30-74 years were selected, who at discharge had received the diagnosis of either MI (527) or UA (381). A control group consisted of 948 patients aged 30-74 years, where a diagnosis of ACS was excluded

Main outcome measures
MI or UA

Results
Current smoking (OR 2.42 (1.61-3.62)), impaired glucose homeostasis defined as HbA1c≥5.5% + blood glucose ≥7.5mM (OR 1.78(1.19-2.67)) and male sex (OR 1.71 (1.21-2.40)) were significant factors predisposing to MI over UA, in an event of an ACS. Compared to the non-ACS group, impaired glucose homeostasis, male sex, cholesterol level and age were significantly associated with development of an ACS (both MI and UA). Interestingly, smoking was significantly associated with MI (OR 2.00(1.32-3.02)), but not UA

Conclusions
Smoking, or impaired glucose homeostasis, are acquired risk factors for a severe ACS outcome in CAD patients. Importantly, smoking was not associated with UA, suggesting that it is not a risk factor for all clinical manifestations of CAD, but its influence is important mainly in the acute stages of ACS. Thus, on a diagnosis of CAD the cessation of smoking and management of glucose homeostasis are of upmost importance to avoid severe subsequent ACS consequences.

What is already known on this subject:

- Smoking, diabetes mellitus, hypertension, dyslipidemia and male sex are risk factors for the development of atherosclerotic coronary artery disease (CAD)
- The risk factors for the progression of CAD to a more severe acute coronary syndrome (ACS) outcome (myocardial infarction) are less understood.

What this study adds:

- Smoking and an impaired glucose homeostasis are risk factors for a more severe ACS outcome.
- The influence of smoking is important mainly in the acute stages of ACS, rather than all clinical manifestations of CAD *per se*.
- On a diagnosis of CAD the cessation of smoking and management of glucose homeostasis are of upmost importance to avoid severe subsequent ACS consequences.

Strengths and limitations of this study

Strengths:

- The patients were recruited before the introduction of PCI, CABG and modern antithrombotic drugs in the standard management of ACS. Thus, it was possible to identify progression to UA or MI as distinct outcome groups within the cohort, in the absence of interventions that would otherwise influence the thrombotic processes involved in ACS.
- The control group of non-ACS patients had a similar initial management routine following presentation to the Emergency Room i.e. transfer to a coronary care unit for observation until an ACS diagnosis was excluded, and upon discharge diagnosed as not even suffering from stable CAD.
- The study was based in a single centre with the same two cardiologists evaluating and categorising all 5292 patients, using consistent criteria.

Limitations:

- Some of the UA cases would likely have been diagnosed as NSTEMI using the most recent criteria of MI.
- The control group is not representative of the general population
- Treatments and risk factor profiles have partly evolved since the study was performed.

Introduction

Smoking, diabetes mellitus, hypertension and dyslipidemia have, together with age and sex, been established as risk factors for the development of atherosclerotic coronary artery disease (CAD). Thus, these are targets for treatment to slow the progression of disease and to reduce the risk of acute coronary syndrome (ACS) consequences, such as myocardial infarction (MI) or unstable angina (UA)[1]. However, the influence of these risk factors on the nature of any CAD-associated ACS is less well understood.

The initiating event of ACS is thought to involve the exposure of a prothrombotic surface, either through atherosclerotic plaque rupture or disruption of the overlying endothelial surface. Resulting thrombosis formation can permanently occlude the lumen of a coronary artery, cause myocardial cell death and the induction of MI. However, in other cases it can be transient, or only partial occlude the vessel, inducing only UA[1]. It is not known why some CAD patients are predisposed to the former, rather than the latter outcome. The thrombogenicity of blood at the time of the acute event is likely to play a role, consistent with the clinical observation that rapid initiation of antithrombotic treatment (e.g. ASA, clopidogrel, fondaparinux) in ACS significantly improved the outcome[2]. However, the role of the established risk factors for the underlying CAD in the ACS outcome has not been well studied. The rationale of the current study was to further clarify this in the Carlscrona Heart Attack Prognosis Study (CHAPS).

CHAPS constitutes a patient cohort recruited before the introduction of percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery and modern antithrombotic drugs. Thus, to our knowledge, this study is unique in that UA and MI could be identified as distinct groups within an ACS population, and their respective risk factors (diabetes, hyperlipidemia, hypertension, smoking, age and sex) analysed separately.

Materials and methods:

Patient recruitment

The Carlscrona Heart Attack Prognosis Study (CHAPS) recruited 5292 consecutive patients admitted to the coronary intensive care unit with acute chest pain (indicative of a possible ACS) at Blekinge Hospital, Karlskrona, between January 26, 1992 and January 25, 1996. Patients that presented to the Emergency Room (ER) with recent or ongoing chest pain were at this time by routine directly transferred to the coronary intensive care unit. Patients were included after written informed consent. Patients unable to give informed consent because of their medical condition were excluded. Of the total of 5292 patient admissions included, 2992 were between 30-74 years of age at admittance. In patients with multiple admittances, only the first classifying admittance was included as case in the study. The selection of patients for the current study is outlined in figure 1.

Acute coronary syndrome patients

A diagnosis of ACS was ascertained in 908 of the eligible patients aged 30-74 years of age (644 men and 264 women). Two groups were identified: (i) patients experiencing at least one acute MI during the study (527) or (ii) patients experiencing no acute MI, but having at least one episode of UA during the study (381). Data on environmental and lifestyle factors, and blood samples, were collected on first admittance under the classifying diagnosis. The classifying diagnosis was set at discharge by one of two experienced cardiologists.

A diagnosis of acute MI was made when patients fulfilled at least two of the following criteria: (i) A history of chest pain of at least 15 min duration, (ii) an increase in activity of cardiac biomarkers (aspartate amino transferase and/or creatinine kinase) to at least twice the upper limit of normality, or (iii) characteristic ECG changes for MI (typical sequence change of ST segment

and/or of T-waves and/or appearance of new Q-waves). These criteria included both patients with ST-elevation MI (STEMI) and non-ST elevation MI (NSTEMI) corresponding to ICD 9 code 410

A diagnosis of UA was made when patients fulfilled all of the following criteria: (i) no evidence of MI, (ii) acute chest pain of increased/modified character to any previously experienced, during the preceding 48 h and (iii) angina pectoris diagnosed and medically treated before admission, or alternatively, angina pectoris ascertained by clinical evaluation, including a bicycle exercise test prior to discharge from the hospital. These patients correspond to ICD 9 code 411. Post-infarction angina and patients with secondary angina were not included.

Patients admitted to the coronary intensive care unit were initially treated with aspirin, and in case of on-going chest pain, also nitrates and morphine. In cases of clear diagnosis of ST elevation MI, thrombolysis with streptokinase was given (194 of 527 patients with MI). Patients with MI diagnosed by cardiac markers only were not given thrombolysis. At the time of the study, acute coronary artery intervention was not available at this hospital.

Non-acute coronary syndrome patients

The study population also contained 948 patients aged 30-74 (569 men and 379 women) who were admitted with suspected ACS, but were subsequently diagnosed as non-ACS and, furthermore, were not diagnosed with stable coronary artery disease (CAD). This group constitute patients with chest discomfort or chest pain without remaining suspicion of cardiac ischemic origin, thus excluding ICD 9 codes 410-414. Patients with dyspepsia, lower airway infection or musculoskeletal origin of chest pain are found in this group, however in many cases no specific medical condition had been established upon discharge from the coronary intensive care unit.

Ethical approval

Carlscrona Heart Attack Prognosis Study (CHAPS) was approved by the Regional Ethical Review Board, Lund, Sweden (EPN 2009/762 and LU 298-91).

Risk factors

The presence of CAD risk factors were identified based on laboratory analyses, patient history and/or medical records. Samples for laboratory analysis were collected at hospital admission and were analysed by the in-house routine diagnostic laboratory. Smoking status was defined as current- or non-smoker. Non-smoker included patients who quit smoking >1 month before admission. Information on medical history of hypertension and diabetes were recorded at admission and extracted from earlier medical files, and the diagnosis and information were also verified at discharge from the hospital. Hypertension was defined as a physician's diagnosis prior to hospital admittance. In general, these patients were treated with blood pressure lowering medications. Patients with a previous diagnosis of diabetes were grouped for analysis as follows: (i) diet treated only, (ii) oral medication only, or (iii) insulin treated. In parallel, to identify patients with an impaired glucose homeostasis who had evidence of both acute and long-term insufficient glucose control, a laboratory-defined classification based on glucose ≥7.5 mM together with HbA1c ≥5.5 was used. We had previously evaluated this classification by comparing to prior diagnosis of DM, and found that 89% of those treated by diet only, 95% of those treated by oral medication only, and 100% of those treated with insulin were identified as having impaired glucose homeostasis using this classification (unpublished).

Statistical methods

STATA and IBM SPSS Statistics were used for data analyses. Standard methods were used for descriptive statistics. Associations between categorical variables were examined using binary logistic regression and expressed as odds ratios (OR) with 95% confidence intervals (CI). Principal analyses were made with men and women combined in one group, but were repeated where men and women were analysed separately. Age was entered into the regressions in 10-year age groups. Confounding was considered by stratification for final diagnosis (as MI, ACS or not) and by multivariate regression models forcing age group, sex, impaired glucose homeostasis, serum cholesterol, hypertension and current smoking into the same model. Individuals with a missing variable were excluded

in the respective analysis. Two-way interaction terms were used to explore the association of sex and the major risk factors with ACS outcome.

Results

Patient characteristics

The CHAPS study recruited 5292 patients of which 2992 were aged 30-74 years of age. Table I shows patient characteristics of the 908 eligible patients with ACS and the 948 eligible patients without ACS, or any current or previous medical history of CAD (non-ACS patients). Among patients with ACS we identified 46 patients (5%) with no previous diagnosis of diabetes as having impaired glucose homeostasis.

Risk factors predisposing to myocardial infarction in acute coronary syndrome

We tested the hypothesis that UA and MI are two separate outcomes in ACS, differently influenced by established risk factors for the underlying CAD. The results are shown in Table II. Current smoking (OR 2.42 (1.61-3.62)), an impaired glucose homeostasis defined as glucose ≥7.5 mM and HbA1c ≥5.5% (OR 1.78 (1.19-2.67)) and male sex (OR 1.71 (1.21-2.40)) were found to be more strongly associated with MI, compared to UA. The same was true with age, although this was a weaker association (OR 1.02 (1.00-1.04)). Neither cholesterol (total cholesterol level), nor a previous diagnosis of hypertension, was more strongly associated with MI than UA. These data indicate that different CAD risk factors are associated with different ACS outcomes.

Risk factors predisposing to myocardial infarction or unstable angina

Next, we compared the individual subgroups of MI patients or UA patients with non-ACS patients (Table III), to establish the association between the risk factors and the specific ACS outcome. Impaired glucose homeostasis, male sex, cholesterol level and age group were significantly associated with both MI and UA, when compared to patients with non-ACS. Interestingly, smoking was significantly associated only with MI (OR 2.00 (1.32-3.02)), but not with UA (OR 0.84 (0.53-1.33)).

We found no statistically significant interactions between sex and any of the major risk factors for CAD in the association with the outcome of ACS. In sex-

specific sub-analyses there was no significant difference between the results for men and women.

Discussion

In the current study we show that an impaired glucose homeostasis, smoking or male sex, in addition to being known major risk factors for CAD, are associated with a more severe outcome in the case of ACS (i.e. they predispose towards MI, rather than UA). Interestingly, when compared to the non-ACS group, smoking was significantly associated with MI, but not UA, suggesting its effects are mainly important in the determination of the ACS outcome, rather than the development of all clinical manifestations of CAD *per se*.

The major strength, and novelty, of this study is due to the unique nature of the Carlscrona Heart Attack Prognosis Study (CHAPS) patient cohort. The patients were recruited before the introduction of PCI, CABG and modern antithrombotic drugs in the standard management of ACS. The absence of these interventions, that would otherwise influence the thrombotic processes involved in ACS, made it possible to identify progression to UA or MI as distinct outcome groups within the cohort.

Furthermore, we were also able to gather information on non-ACS patients who were admitted into the same hospital setting, during the same period. These patients were initially admitted with a suspected ACS diagnosis, but were discharged from the heart intensive unit assessed as not having experienced an ACS, or even suffering from stable CAD. Thus, the non-ACS patients provided an excellent control group, as they had a similar initial management routine following Emergency Room (ER) presentation i.e. transfer to a coronary care unit for observation until an ACS diagnosis was confirmed or excluded. A major strength of our study results from it being based in a single centre with the same two cardiologists evaluating and categorising all patients, using consistent criteria, and furthermore consistent management routines. This ensured a level of consistency that is not possible when using data from health care registries studies, which rely solely on diagnosis codes based on each treating physicians

judgment, and are composed of data from multiple hospitals and collected for other purposes than research [3] [4]

A number of limitations of the study should be acknowledged. Biochemical analyses were performed over a period of four years, although the hospital routine diagnostic laboratory used accredited standardised methods, providing consistency over time. Data for laboratory analyses were not complete for all patients. The definition of MI continues to evolve as refined criteria and more sensitive and specific biomarkers are implemented. Some of the UA cases in our study would likely have now been diagnosed as NSTEMI, using recent criteria required for MI diagnosis [5] . The control group is not representative of the general population as it is enriched for individuals seeking medical attention for non-coronary conditions presenting with chest pain or discomfort, of which some may also be associated with smoking (i.e. dyspepsia, bronchitis). Furthermore, CHAPS is a single centre study, and treatments and risk factor profiles have also partly developed since the study was performed. The results would therefore not necessarily be generalised to a broader modern population although our results are supported by more recent studies as discussed below [4 6]. However, smoking remains a major health issue and type 2 diabetes is increasing in the western society, therefore, the results are still highly relevant for the care of patients with CAD today.

The determining role of thrombotic factors in the outcome of an ACS is underscored by the success of more aggressive antithrombotic treatment in recent years [2]. Previously, we have shown, using the CHAPS material, that genetic variations of thrombotic factors are associated with ACS outcome [7]. We show here that impaired glucose homeostasis confers an increased risk towards MI, rather than UA, in an ACS. Diabetes has been associated with both early and late mortality after presentation with ACS [8] and furthermore non-fasting elevated blood glucose has been associated with an increased risk of ischemic heart disease and MI [9]. A reason for a more adverse outcome in a patient with diabetes and/or impaired glucose homeostasis could be due to a prothrombotic effect, as also indicated by the more salutary effects of antithrombotic treatment

in patients with diabetes [10]. In the present study we used the laboratory-based combination of an increased blood level of both glucose and Hb1Ac, to ascertain an acute, as well as a more longstanding, deregulated glucose homeostasis. Our finding that 46 of the patients with ACS, but no previously known diabetes, fulfilled these laboratory-based criteria is in line with previous reports of unknown diabetes in a significant proportion of patients with acute MI [11]. Our finding that current smoking is more common in patients with MI than with UA is supported by data from a recent registry-based longitudinal cohort study of patients with ACS in the national Swedish quality-of-care register (Riks-HIA) [4] and in the prospective population based CAREMA cohort study [6]. Interestingly, our finding that smoking was associated with MI, but not UA, when compared to the non-ACS patients, shows that smoking has a significant effect mainly in the acute event, possibly through modulation of thrombogenicity at the site of a ruptured plaque [12]. This is supported by the finding of Dudas et al that smoking was associated with MI but not with extensive CAD in need of a coronary bypass grafting [13]. Furthermore, Björck et al. found smoking to be an independent determinant for presenting with STEMI compared with non-STEMI in 93 416 consecutive patients aged 25 to 84 years and admitted to hospital between 1996 and 2004 with a first AMI. ([14]. Previous reports show that the increased risk for MI associated with smoking decreases rapidly after cessation [12 15 16], supporting the idea that smoking is a critical risk factor in the acute stages of ACS, rather than in all clinical manifestations of CAD.

In conclusion, our study shows that the presence of known major risk factors for CAD, such as an impaired glucose homeostasis, smoking and male sex are also significantly associated with a more severe outcome in the case of an ACS. Our finding that current smoking is strongly associated with MI, but not UA, emphasises the importance of the clinical practice of encouraging current smokers with a diagnosis of CAD to quit their smoking habits.

The observed differences in ACS outcome associated with smoking or dysregulated glucose metabolism highlight several hypotheses that warrant further investigation. Establishing the influence of these risk factors at the

cellular level, e.g. on platelet function, coagulation and/or fibrinolysis, inflammation and other factors influencing the vessel micro-milieu, could lead to optimisation of pharmacological treatment for CAD and ACS.

Footnotes:

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Contributors statement

LR, HO, and MF designed and initiated the original Carlscrona Heart Attack Prognosis Study on which the current study is based.

MF conducted the patient inclusion, reviewed all cases, collected patient information and compiled the data files.

JO, HF, IV, HO, AH, LR, UL conceived and designed the current study.

IV and MP collected and compiled the laboratory data.

HF and UL performed the statistical analyses and compiled the results.

JO, MF, HF, IV, HO, AH, LR, UL interpreted the results.

JO, HO, UL drafted the paper.

MF, HF, IV, LR contributed to critical revision for important intellectual content.

All authors approved the final manuscript.

JO is the guarantor.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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The funding agencies had no role in the design of the study; in the analysis and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.

Data sharing: No additional data available

The lead author, Jacob Odeberg, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table I. Patient characteristics

	Non-ACS		MI		UA		Number of patients with data
	Men	Women	Men	Women	Men	Women	
Patients	569	379	394	133	250	131	1856
Age	57.4 (11.2)	60.1 (11.2)	63.3 (8.6)	65.8 (8.0)	62.5 (8.7)	65.1 (8.1)	1856
Smoking	119 (24.4)	48 (14.2)	100 (27.0)	29 (23.2)	48 (19.8)	14 (11.1)	166
Hypertension	84 (17.0)	77 (22.7)	101 (26.8)	32 (25.2)	68 (27.9)	39 (31.0)	148
Cholesterol*	5.8 (1.4)	6.1 (1.4)	6.1 (1.3)	6.6 (1.5)	6.0 (1.1)	6.6 (1.3)	822
Diabetes all	29 (5.9)	30 (8.8)	65 (17.2)	28 (21.9)	27 (11.1)	22 (17.5)	201
DM (diet)	24 (4.9)	24 (7.0)	48 (12.7)	18 (14.1)	22 (9.0)	13 (10.3)	149
DM (p.o)	2 (0.4)	2 (0.6)	11 (2.9)	7 (5.5)	3 (1.2)	3 (2.4)	28
DM (insulin)	3 (0.6)	4 (1.2)	6 (1.6)	3 (2.3)	2 (0.8)	6 (4.8)	24
Glucose*	5.7 (2.6)	6.7 (4.6)	7.3 (3.8)	8.1 (4.1)	5.9 (2.3)	6.4 (3.3)	797
HbA1c *	4.6 (0.8)	5.0 (1.5)	5.3 (1.4)	5.5 (1.7)	5.1 (1.1)	5.3 (1.6)	833
Glucose control**	6 (4.3)	9 (11.4)	65 (18.6)	33 (30.6)	29 (13.3)	18 (16.4)	882

Non-acute coronary syndrome (Non-ACS), Myocardial Infarction (MI) and Unstable Angina (UA)
Data are means (SD), or numbers (%). DM (diet) no pharmacological treatment for diabetes, DM (p.o.) oral medication for diabetes, DM (insulin) treatment included insulin
* Routine laboratory analysis of admission samples.
** Glucose control defined as an impaired glucose homeostasis by HbA1c ≥5.5 % + Glucose ≥7.5 mM

Table II: The odds of myocardial infarction (MI) versus unstable angina (UA) in patients with acute coronary syndromes

	MI versus UA	
	OR	CI (95%)
Glucose control*	1.78	1.19-2.67
Age_group**	1.02	1.00-1.04
Sex (male)	1.71	1.21-2.40
Cholesterol	1.06	0.94-1.19
Smoking	2.42	1.61-3.62
Hypertension	0.84	0.60-1.18

* Impaired glucose homeostasis (HbA1c≥5.5% + blood glucose ≥7.5 mM)

**Age groups: 30-39, 40-49, 50-59, 60-69, 70-74 years

Associations were estimated by binary logistic multivariate regression and expressed as odds ratios (OR) with 95% confidence intervals (CI (95%)). MI versus UA was the dependent variable and age by 10 years age groups, sex, serum cholesterol, smoking, hypertension and glucose control were entered as covariates into the same model that included 742 subjects.

Table III: The odds of myocardial infarction (MI), or unstable angina (UA), versus patients without acute coronary syndrome (non-ACS)

	MI versus non-ACS		UA versus non-ACS	
	OR	CI (95%)	OR	CI (95%)
Glucose control*	4.22	2.35-7.56	2.14	1.15-3.95
Age group**	1.06	1.04-1.08	1.04	1.03-1.06
Sex (male)	2.44	1.68-3.55	1.48	1.02-2.15
Cholesterol	1.17	1.03-1.32	1.15	1.00-1.32
Smoking	2.00	1.32-3.02	0.84	0.53-1.33
Hypertension	1.06	0.71-1.58	1.29	0.87-1.92

* Impaired glucose homeostasis (HbA1c≥5.5% + blood glucose ≥7.5 mM)

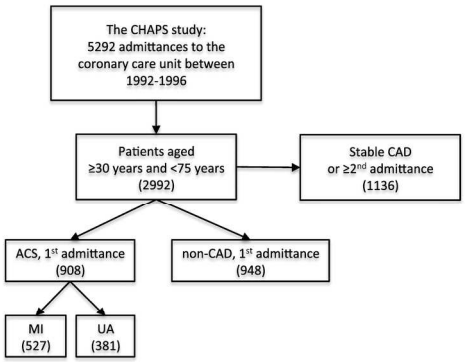
** Age groups: 30-39, 40-49, 50-59, 60-69, 70-74 years

Associations were estimated by multivariate binary logistic regression and expressed as odds ratios (OR) with 95% confidence intervals (CI (95%)). MI and UA were the dependent variables and age by 10 year age groups, sex, serum cholesterol, smoking, hypertension and glucose control were entered as covariates into the same model. Number of patients included in final models was 680 (MI versus non-ACS), and 564 (UA versus non-ACS), respectively.

Figure legend:

Figure 1

Flow chart outlining selection of patients for current study. For patients with more than one hospital admittance during the study, only the first admittance under classifying diagnosis was included in the current study. 1136 of patients ≥30 and < 75 years were excluded. These represent either patients with known CAD (stable angina, previous MI, prior diagnosis of ischemic heart failure, stroke) or patients included with a previous admission in either the ACS or non-ACS group.



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The influence of smoking~~Smoking~~ and impaired glucose homeostasis on the~~predisposes to a more severe~~ outcome in patients presenting with acute coronary syndrome: a~~A~~ cross -sectional study.

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Abstract

Objectives Smoking, diabetes, male sex, hypercholesterolemia and hypertension are well-established risk factors for the development of coronary artery disease (CAD). However, less is known about their role in influencing the outcome in the event of acute coronary syndrome (ACS). The aim of this study was to determine if these risk factors are associated specifically with acute myocardial infarction (MI) or unstable angina (UA) in patients with suspected ACS.

Design Cross sectional study

Setting Patients admitted to the coronary care unit, via the emergency room, at a central county hospital over a four-year period (1992-96).

Participants From 5292 patients admitted to the coronary care unit, 908 patients aged 30-74 years were selected, who at discharge had received the diagnosis of either MI (527) or UA (381). A control group consisted of 948 patients aged 30-74 years, where a diagnosis of ACS was excluded.

Main outcome measures MI or UA

Results Current smoking (OR 2.42 (1.61-3.62)), an impaired glucose homeostasis defined as HbA1c≥5.5% + blood glucose ≥7.5 mM (OR 1.78 (1.19-2.67)) and male sex (OR 1.71 (1.21-2.40)) were significant factors predisposing to MI over UA, in an event of an ACS. Compared to the non-ACS group, impaired glucose homeostasis, male sex, cholesterol level and age were significantly associated with development of an ACS (both MI and UA). Interestingly, smoking was significantly associated with MI (OR 2.00 (1.32-3.02)), but not UA.

Conclusions Smoking, or impaired glucose homeostasis, are acquired risk factors for a severe ACS outcome in CAD patients. Importantly, smoking was not associated with UA, suggesting that it is not a risk factor for all clinical manifestations of CAD, but its influence is important mainly in the acute stages of ACS. Thus, on a diagnosis of CAD the cessation of smoking and management of glucose homeostasis are of upmost importance to avoid severe subsequent ACS consequences.

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What is already known on this subject:

- Smoking, diabetes mellitus, hypertension, dyslipidemia and male sex are risk factors for the development of atherosclerotic coronary artery disease (CAD)
- The risk factors for the progression of CAD to a more severe acute coronary syndrome (ACS) outcome (myocardial infarction) are less understood.

What this study adds:

- Smoking and an impaired glucose homeostasis are risk factors for a more severe ACS outcome.
- The influence of smoking is important mainly in the acute stages of ACS, rather than all clinical manifestations of CAD *per se*.
- On a diagnosis of CAD the cessation of smoking and management of glucose homeostasis are of upmost importance to avoid severe subsequent ACS consequences.

Strengths and limitations of this study

Strengths:

- The patients were recruited before the introduction of PCI, CABG and modern antithrombotic drugs in the standard management of ACS. Thus, it was possible to identify progression to UA or MI as distinct outcome groups within the cohort, in the absence of interventions that would otherwise influence the thrombotic processes involved in ACS.
- The control group of non-ACS patients had a similar initial management routine following ~~ER~~ presentation to the Emergency Room i.e. transfer to a coronary care unit for observation until an ACS diagnosis was excluded, and upon discharge diagnosed as not even suffering from stable CAD.
- The study was based in a single centre with the same two cardiologists evaluating and categorising all 5292 patients, using consistent criteria.

Limitations:

- Some of the UA cases would likely have been diagnosed as NSTEMI using the most recent criteria of MI.
- The control group is not representative of the general population
- Treatments and risk factor profiles have partly evolved since the study was performed.

Introduction

Smoking, diabetes mellitus, hypertension and dyslipidemia have, together with age and sex, been established as risk factors for the development of atherosclerotic coronary artery disease (CAD). Thus, these are targets for treatment to slow the progression of disease and to reduce the risk of acute coronary syndrome (ACS) consequences, such as myocardial infarction (MI) or unstable angina (UA)[1].[1] However, the influence of these risk factors on the nature of any CAD-associated ACS is less well understood.

The initiating event of ACS is thought to involve the exposure of a prothrombotic surface, either through atherosclerotic plaque rupture or disruption of the overlying endothelial surface. Resulting thrombosis formation can permanently occlude the lumen of a coronary artery, cause myocardial cell death and the induction of MI. However, in other cases it can be transient, or only partial occlude the vessel, inducing only UA[1].[1] It is not known why some CAD patients are predisposed to the former, rather than the latter outcome. The thrombogenicity of blood at the time of the acute event is likely to play a role, consistent with the clinical observation that rapid initiation of antithrombotic treatment (e.g. ASA, clopidogrel, fondaparinux) in ACS significantly improved the outcome[2].[2] However, the role of the established risk factors for the underlying CAD in the ACS outcome has not been well studied. The rationale of the current study was to further clarify this in the Carlscrona Heart Attack Prognosis Study (CHAPS).

CHAPS constitutes a patient cohort recruited before the introduction of percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery and modern antithrombotic drugs. Thus, to our knowledge, this study is unique in that UA and MI could be identified as distinct groups within an ACS population, and their respective risk factors (diabetes, hyperlipidemia, hypertension, smoking, age and sex) analysed separately.

Materials and methods:

Patient recruitment

The Carlscrona Heart Attack Prognosis Study (CHAPS) recruited 5292 consecutive patients admitted to the coronary intensive care unit with acute chest pain (indicative of a possible ACS) at Blekinge Hospital, Karlskrona, between January 26, 1992 and January 25, 1996. Patients that presented to the Emergency Room (ER) with recent or ongoing chest pain were at this time by routine directly transferred to the coronary intensive care unit. Patients were~~All~~ included after~~patients gave~~ written informed consent. Patients unable to give informed consent because of their medical condition were excluded. Of the total of 5292 patient admissions included, 2992~~, 2967~~ were between 30-74 years of age at admittance. In patients with multiple admittances, only the first classifying admittance was included as case in the study. The selection of patients for the current study is outlined in figure 1.

Acute coronary syndrome patients

A diagnosis of ACS was ascertained in 908 of the eligible patients aged 30-74 years of age (644 men and 264 women). Two groups were identified: (i) patients experiencing at least one acute MI during the study (527) or (ii) patients experiencing no acute MI, but having at least one episode of UA during the study (381). Data on environmental and lifestyle factors, and blood samples, were collected on first admittance under the classifying diagnosis. The classifying diagnosis was set at discharge by one of two experienced cardiologists.

A diagnosis of acute MI was made when patients fulfilled at least two of the following criteria: (i) A history of chest pain of at least 15 min duration, (ii) an increase in activity of cardiac biomarkers (aspartate amino transferase and/or creatinine kinase~~cardiac enzymes~~) to at least twice the upper limit of normality, or (iii) characteristic ECG changes for MI (typical sequence change of ST segment

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and/or of T-waves and/or appearance of new Q-waves). These criteria included both patients with ST-elevation MI (STEMI) and non-ST elevation MI (NSTEMI) corresponding to ICD 9 code 410).

A diagnosis of UA was made when patients fulfilled all of the following criteria: (i) no evidence of MI, (ii) acute chest pain of increased/modified character to any previously experienced, during the preceding 48 h and (iii) angina pectoris diagnosed and medically treated before admission, or alternatively, angina pectoris ascertained by clinical evaluation, including a bicycle exercise test prior to discharge from the hospital. These patients correspond to ICD 9 code 411. Post-infarction angina and patients with secondary angina were not included.

Patients admitted to the coronary intensive care unit were initially treated with aspirin, and in case of on-going chest pain, also nitrates and morphine. In cases of clear diagnosis of ST elevation MI, thrombolysis with streptokinase was given (194 of 527 patients with MI). Patients with MI diagnosed by cardiac markers only were not given thrombolysis. At the time of the study, acute coronary artery intervention was not available at this hospital.

Non-acute coronary syndrome patients

The study population also contained 948 patients aged 30-74 (569 men and 379 women) who were admitted with suspected ACS, but were subsequently diagnosed as non-ACS and, furthermore, were not diagnosed with stable coronary artery disease (CAD). This group constitute patients with chest discomfort or chest pain without remaining suspicion of cardiac ischemic origin, thus excluding ICD 9 codes 410-414. Patients with dyspepsia, lower airway infection or musculoskeletal origin of chest pain are found in this group, however in many cases no specific medical condition had been established upon discharge from the coronary intensive care unit.

Ethical approval

Carlscrona Heart Attack Prognosis Study (CHAPS) was approved by the Regional Ethical Review Board, Lund, Sweden (EPN 2009/762 and LU 298-91).

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Risk factors

The presence of CAD risk factors were identified based on laboratory analyses, patient history and/or medical records. Samples for laboratory analysis were collected at hospital admission and were analysed by the in-house routine diagnostic laboratory. Smoking status was defined as current- or non-smoker. Non-smoker included patients who quit smoking >1 month before admission. Information on medical history of hypertension and diabetes were recorded at admission and extracted from earlier medical files, and the diagnosis and information were also verified at discharge from the hospital. Hypertension was defined as a physician's diagnosis prior to hospital admittance. In general, these patients were treated with blood pressure lowering medications. Patients with a previous diagnosis of diabetes were grouped for analysis as follows: (i) diet treated only, (ii) oral medication only, or (iii) insulin treated. In parallel, to identify patients with an impaired glucose homeostasis who had evidence of both acute and long-term insufficient glucose control, a laboratory-defined classification based on glucose ≥7.5 mM together with HbA1c ≥5.5 was used. We had previously evaluated this classification by comparing to prior diagnosis of DM, and found that 89% of those treated by diet only, 95% of those treated by oral medication only, and 100% of those treated with insulin were identified as having impaired glucose homeostasis using this classification (unpublished).

Statistical methods

STATA and IBM SPSS Statistics were used for data analyses. Standard methods were used for descriptive statistics. Associations between categorical variables were examined using binary logistic regression and expressed as odds ratios (OR) with 95% confidence intervals (CI). Principal analyses were made with men and women combined in one group, but were repeated where men and women were analysed separately. Age was entered into the regressions in 10-year age groups. Confounding was considered by stratification for final diagnosis (as MI, ACS or not)), and by multivariate regression models forcing age group, sex, impaired glucose homeostasis, serum cholesterol, hypertension and current smoking into the same model. Individuals with a missing variable were excluded

in the respective analysis. Two-way interaction terms were used to explore the association of sex and the major risk factors with ACS outcome.

Results

Patient characteristics

The CHAPS study recruited 5292 patients of which 2992 were aged 30-74 years of age. Table I shows patient characteristics of the 908 eligible patients with ACS and the 948 eligible patients without ACS, or any current or previous medical history of CAD (non-ACS patients). Among patients with ACS we identified 46 patients (5%) with no previous diagnosis of diabetes as having impaired glucose homeostasis.

Risk factors predisposing to myocardial infarction in acute coronary syndrome

We tested the hypothesis that UA and MI are two separate outcomes in ACS, differently influenced by established risk factors for the underlying CAD. The results are shown in Table II. Current smoking (OR 2.42 (1.61-3.62)), an impaired glucose homeostasis defined as glucose ≥7.5 mM and HbA1c ≥5.5% (OR 1.78 (1.19-2.67)) and male sex (OR 1.71 (1.21-2.40)) were found to be more strongly associated with MI, compared to UA. The same was true with age, although this was a weaker association (OR 1.02 (1.00-1.04)). Neither cholesterol (total cholesterol level), nor a previous diagnosis of hypertension, was more strongly associated with MI than UA. These data indicate that different CAD risk factors are associated with different ACS outcomes.

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Risk factors predisposing to myocardial infarction or unstable angina

Next, we compared the individual subgroups of MI patients or UA patients with non-ACS patients (Table III), to establish the association between the risk factors and the specific ACS outcome. Impaired glucose homeostasis, male sex, cholesterol level and age group were significantly associated with both MI and UA, when compared to patients with non-ACS. Interestingly, smoking was significantly associated only with MI (OR 2.00 (1.32-3.02)), but not with UA (OR 0.84 (0.53-1.33)).

We found no statistically significant interactions between sex and any of the major risk factors for CAD in the association with the outcome of ACS. In sex-

specific sub-analyses there was no significant difference between the results for men and women.

Discussion

In the current study we show that an impaired glucose homeostasis, smoking or male sex, in addition to being known major risk factors for CAD, are associated with a more severe outcome in the case of ACS (i.e. they predispose towards MI, rather than UA). Interestingly, when compared to the non-ACS group, smoking was significantly associated with MI, but not UA, suggesting its effects are mainly important in the determination of the ACS outcome, rather than the development of all clinical manifestations of CAD *per se*.

The major strength, and novelty, of this study is due to the unique nature of the Carlscrona Heart Attack Prognosis Study (CHAPS) patient cohort. The patients were recruited before the introduction of PCI, CABG and modern antithrombotic drugs in the standard management of ACS. The absence of these interventions, that would otherwise influence the thrombotic processes involved in ACS, made it possible to identify progression to UA or MI as distinct outcome groups within the cohort.

Furthermore, we were also able to gather information on non-ACS patients who were admitted into the same hospital setting, during the same period. These patients were initially admitted with a suspected ACS diagnosis, but were discharged from the heart intensive unit assessed as not having experienced an ACS, or even suffering from stable CAD. Thus, the non-ACS patients provided an excellent control group, as they had a similar initial management routine following Emergency Room (ER) presentation i.e. transfer to a coronary care unit for observation until an ACS diagnosis was confirmed or excluded. A major strength of our study results from~~is that~~ it being~~was~~ based in a single centre with the same two cardiologists evaluating and categorising all patients, using consistent criteria, and furthermore consistent management routines.~~.~~ This ensured a level of consistency that is not possible when using data from health care registries studies, which rely solely on diagnosis codes based on each

treating physicians judgment, and are composed of data from multiple hospitals and collected for other purposes than research [3] [4]~~3,4~~

A number of limitations of the study should be acknowledged. Biochemical analyses were performed over a period of four years, although the hospital routine diagnostic laboratory used accredited standardised methods, providing consistency over time. Data for laboratory analyses were not complete for all patients. The definition of MI continues to evolve as refined criteria and more sensitive and specific biomarkers are implemented. Some of the UA cases in our study would likely have now been diagnosed as NSTEMI, using recent criteria required for MI diagnosis [5] . The control group is not representative of the general population as it is enriched for individuals seeking medical attention for non-coronary conditions presenting with chest pain or discomfort, of which some may also be associated with smoking (i.e. dyspepsia, bronchitis). Furthermore, CHAPS is a single centre study, and treatments[5] ~~. Treatments~~ and risk factor profiles have also partly developed since the study was performed. The results would therefore not necessarily be generalised to a broader modern population although our results are supported by more recent studies as discussed below [4 6]. However, smoking remains a major health issue and type 2 diabetes is increasing in the western society, therefore, the results are still highly relevant for the care of patients with CAD today.

The determining role of thrombotic factors in the outcome of an ACS is underscored by the success of more aggressive antithrombotic treatment in recent years [2].~~2.~~ Previously, we have shown, using the CHAPS material, that genetic variations of thrombotic factors are associated with ACS outcome [7].~~6.~~ We show here that impaired glucose homeostasis confers an increased risk towards MI, rather than UA, in an ACS. Diabetes has been associated with both early and late mortality after presentation with ACS [8][7] and furthermore non-fasting elevated blood glucose has been associated with an increased risk of ischemic heart disease and MI [9].~~8.~~ A reason for a more adverse outcome in a patient with diabetes and/or impaired glucose homeostasis could be due to a prothrombotic effect, as also indicated by the more salutary effects of

antithrombotic treatment in patients with diabetes [10].[9] In the present study we used the laboratory-based combination of an increased blood level of both glucose and Hb1Ac, to ascertain an acute, as well as a more longstanding, deregulated glucose homeostasis. Our finding that 46 of the patients with ACS, but no previously known diabetes, fulfilled these laboratory-based criteria is in line with previous reports of unknown diabetes in a significant proportion of patients with acute MI [11].[10]

Our finding that current smoking is more common in patients with MI than with UA is supported by data from a recent registry-based longitudinal cohort study of patients with ACS in the national Swedish quality-of-care register (Riks-HIA) [4][4] and in the prospective population based CAREMA cohort study [6].[11]

Interestingly, our finding that smoking was associated with MI, but not UA, when compared to the non-ACS patients, shows that smoking has a significant effect mainly in the acute event, possibly through modulation of thrombogenicity at the site of a ruptured plaque [12]. This is supported by the finding of Dudas et al that smoking was associated with MI but not with extensive CAD in need of a coronary bypass grafting [13]. Furthermore, Björck et al. found smoking to be an independent determinant for presenting with STEMI compared with non-STEMI in 93 416 consecutive patients aged 25 to 84 years and admitted to hospital between 1996 and 2004 with a first AMI. ([14].[12]; Previous reports show that the increased risk for MI associated with smoking decreases rapidly after cessation [12 15 16],[12-14]; supporting the idea that smoking is a critical risk factor in the acute stages of ACS, rather than in all clinical manifestations of CAD.

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In conclusion, our study shows that the presence of known major risk factors for CAD, such as an impaired glucose homeostasis, smoking and male sex are also significantly associated with a more severe outcome in the case of an ACS. Our finding that current smoking is strongly associated with MI, but not UA, emphasises the importance of the clinical practice of encouraging current smokers with a diagnosis of CAD to quit their smoking habits.

The observed differences in ACS outcome associated with smoking or dysregulated glucose metabolism highlight several hypotheses that warrant

further investigation. Establishing the influence of these risk factors at the cellular level, e.g. on platelet function, coagulation and/or fibrinolysis, inflammation and other factors influencing the vessel micro-milieu, could lead to optimisation of pharmacological treatment for CAD and ACS.

Footnotes:

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Contributor statements~~:~~

LR, HO, and MF designed and initiated the original Carlscrona Heart Attack Prognosis Study on which the current study is based.

MF conducted the patient inclusion, reviewed all cases, collected patient information and compiled the data files.

JO, HF, IV, HO, AH, LR, UL conceived and designed the current study.

IV and MP collected and compiled the laboratory data.

HF and UL performed the statistical analyses and compiled the results.

JO, MF, HF, IV, HO, AH, LR, UL interpreted the results.

JO, HO, UL drafted the paper.

MF, HF, IV, LR contributed to critical revision for important intellectual content.

All authors approved the final manuscript.

JO is the guarantor.

Competing interests~~Funding:~~

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~~The funding agencies had no role in the design of the study; in the analysis and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.~~

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous

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three years; no other relationships or activities that could appear to have influenced the submitted work.

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The funding agencies had no role in the design of the study; in the analysis and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.

Data sharing: No additional data available

The lead author, Jacob Odeberg, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table I. Patient characteristics

	Non-ACS		MI		UA		Number of patients with data
	Men	Women	Men	Women	Men	Women	
Patients	569	379	394	133	250	131	1856
Age	57.4 (11.2)	60.1 (11.2)	63.3 (8.6)	65.8 (8.0)	62.5 (8.7)	65.1 (8.1)	1856
Smoking	119 (24.4)	48 (14.2)	100 (27.0)	29 (23.2)	48 (19.8)	14 (11.1)	166
Hypertension	84 (17.0)	77 (22.7)	101 (26.8)	32 (25.2)	68 (27.9)	39 (31.0)	148
Cholesterol*	5.8 (1.4)	6.1 (1.4)	6.1 (1.3)	6.6 (1.5)	6.0 (1.1)	6.6 (1.3)	822
Diabetes all	29 (5.9)	30 (8.8)	65 (17.2)	28 (21.9)	27 (11.1)	22 (17.5)	201
DM (diet)	24 (4.9)	24 (7.0)	48 (12.7)	18 (14.1)	22 (9.0)	13 (10.3)	149
DM (p.o)	2 (0.4)	2 (0.6)	11 (2.9)	7 (5.5)	3 (1.2)	3 (2.4)	28
DM (insulin)	3 (0.6)	4 (1.2)	6 (1.6)	3 (2.3)	2 (0.8)	6 (4.8)	24
Glucose~~Glucos~~*	5.7 (2.6)	6.7 (4.6)	7.3 (3.8)	8.1 (4.1)	5.9 (2.3)	6.4 (3.3)	797
HbA1c *	4.6 (0.8)	5.0 (1.5)	5.3 (1.4)	5.5 (1.7)	5.1 (1.1)	5.3 (1.6)	833
Glucose control**	6 (4.3)	9 (11.4)	65 (18.6)	33 (30.6)	29 (13.3)	18 (16.4)	882

Non-acute coronary syndrome (Non-ACS), Myocardial Infarction (MI) and Unstable Angina (UA)
Data are means (SD), or numbers (%). DM (diet) no pharmacological treatment for diabetes, DM (p.o.) oral medication for diabetes, DM (insulin) treatment included insulin
* Routine laboratory analysis of admission samples.
** Glucose control defined as an impaired glucose homeostasis by HbA1c ≥5.5 % + Glucose ≥7.5 mM
~~Missing data Non-ACS (n): age (0), smoking (123), hypertension (114), cholesterol (720), diabetes (115), plasma glucose (715), HbA1c (725), glucose control (731). MI (n): age (0), smoking (31), hypertension (23), cholesterol (57), diabetes (115), plasma glucose (40), HbA1c (62), glucose control (98). UA (n): age (0), smoking (12), hypertension (11), cholesterol (45), diabetes (115), plasma glucose (42), HbA1c (46), glucose control (53).~~

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Table II: The odds of myocardial infarction (MI) versus unstable angina (UA) in patients with acute coronary syndromes

	MI versus UA	
	OR	CI (95%)
Glucose control*	1.78	1.19-2.67
Age_group**	1.02	1.00-1.04
Sex (male)	1.71	1.21-2.40
Cholesterol	1.06	0.94-1.19
Smoking	2.42	1.61-3.62
Hypertension	0.84	0.60-1.18

* Impaired glucose homeostasis (HbA1c≥5.5% + blood glucose ≥7.5 mM)

**Age groups: 30-39, 40-49, 50-59, 60-69, 70-74 years

Associations were estimated by binary logistic multivariate regression and expressed as odds ratios (OR) with 95% confidence intervals (CI (95%)). MI versus UA was the dependent variable and age by 10 years age groups, sex, serum cholesterol, smoking, hypertension and~~or~~ glucose control were entered as covariates into the same model that included 742 subjects.

Table III: The odds of myocardial infarction (MI), or unstable angina (UA), versus patients without acute coronary syndrome (non-ACS)

	MI versus non-ACS		UA versus non-ACS	
	OR	CI (95%)	OR	CI (95%)
Glucose control*	4.22	2.35-7.56	2.14	1.15-3.95
Age group**	1.06	1.04-1.08	1.04	1.03-1.06
Sex (male)	2.44	1.68-3.55	1.48	1.02-2.15
Cholesterol	1.17	1.03-1.32	1.15	1.00-1.32
Smoking	2.00	1.32-3.02	0.84	0.53-1.33
Hypertension	1.06	0.71-1.58	1.29	0.87-1.92

* Impaired glucose homeostasis (HbA1c≥5.5% + blood glucose ≥7.5 mM)

** Age groups: 30-39, 40-49, 50-59, 60-69, 70-74 years

Associations were estimated by multivariate binary logistic regression and expressed as odds ratios (OR) with 95% confidence intervals (CI (95%)). MI and UA were the dependent variables and age by 10 year age groups, sex, serum cholesterol, smoking, hypertension and~~or~~ glucose control were entered as covariates into the same model. Number of patients included in final models was 680 (MI versus non-ACS), and 564 (UA versus non-ACS), respectively.

Figure legend:

Figure 1

Flow chart outlining selection of patients for current study. For patients with more than one hospital admittance during the study, only the first admittance under classifying diagnosis was included in the current study. 1136 of patients ≥30 and < 75 years were excluded. These represent either patients with known CAD (stable angina, previous MI, prior diagnosis of ischemic heart failure, stroke) or patients included with a previous admission in either the ACS or non-ACS group.

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

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

Results		
( )Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ***Page 9***
		(b) Give reasons for non-participation at each stage ***Page 9***
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ***Page 9 and Table 1***
		(b) Indicate number of participants with missing data for each variable of interest ***Table 1 footnotes***
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures ***Table 1***
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ***Page 9, page 10 and Table 2, Table 3 footnotes***
		(*b*) Report category boundaries when continuous variables were categorized ***Table 2 and Table 3 footnote***
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period ***N.A***
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ***Page 9, page 10***
Discussion		
Key results	18	Summarise key results with reference to study objectives ***Page 11***
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ***Page 12***
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ***Page 11, page 12, page 13***
Generalisability	21	Discuss the generalisability (external validity) of the study results ***Page 13***
Other information		
( ) Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ***Page 14***

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

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