Glucose Regulation in Acute Coronary Syndromes

Implications for outcome and outcome prediction

Maarten de Mulder

Stellingen bij het proefschrift

Glucose Regulation in Acute Coronary Syndromes

Implications for outcome and outcome prediction

1. Bij patiënten met een hartinfarct vraagt een goed risicomodel voor het voorspellen van uitkomsten om een beter risicomodel. (dit proefschrift)

2. Glucose is een onafhankelijke voorspeller van sterfte bij patiënten met een hartinfarct, ook in het huidige tijdperk van snelle reperfusie middels een percutane coronaire interventie. Derhalve kan zoet toch zuur zijn. (dit proefschrift)

3. Gezien het frequente vóórkomen, mag het belang van het tijdig opsporen van onontdekte diabetes bij patiënten met een hartinfarct niet worden vergeten. De praktijk is echter weerbarstig. (dit proefschrift)

4. Strikte glucose regulatie kan worden verkregen met weinig hypoglycemiëen, een dergelijk protocol is echter wel arbeidsintensief. (dit proefschrift)

5. Strikte glucose regulatie bij hyperglycemische hartinfarct patiënten die behandeld worden met een percutane coronair interventie leidt niet tot kleinere hartinfarcten. (dit proefschrift)

6. The good physician treats the disease; the great physician treats the patient who has the disease. (William Osler)

7. He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all. (William Osler)

8. Don't dream your life, live your dream. (Mark Twain)

9. Logic will take you from A to B, imagination will take you everywhere. (Albert Einstein)

10. Promoveren is een ander woord voor "stug volhouden" en "teamsport".

11. Je hoeft niet ziek te zijn om beter te worden.

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ERASMUS UNIVERSITEIT ROTTERDAM

Glucose Regulation in Acute Coronary Syndromes

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Glucose regulatie bij het acuut coronair syndroom

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Het verschijnen van dit proefschrift werd mede mogelijk gemaakt door de steun van de Nederlandse Hartstichting.

Inhoudsopgave

Chapter 1

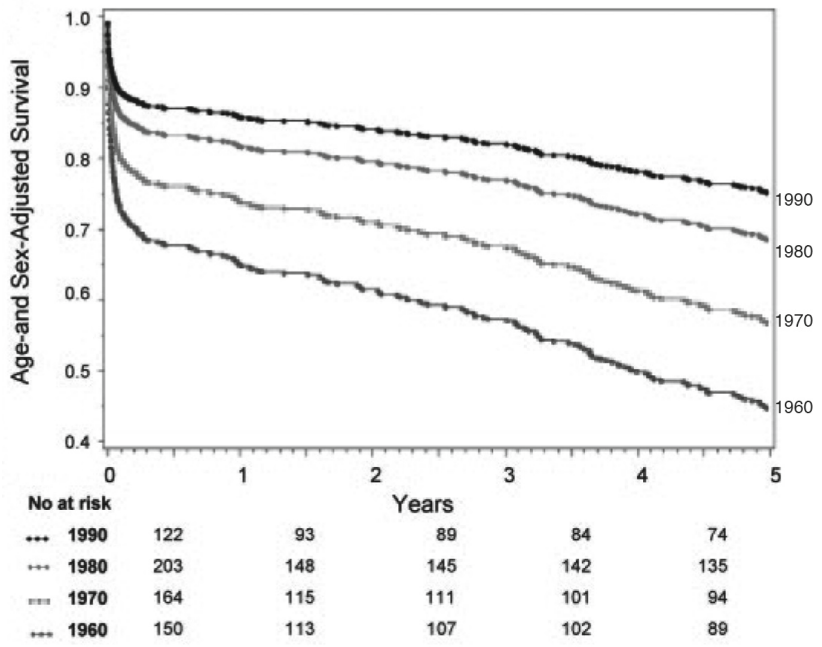
Introduction & Thesis Outline

INTRODUCTION

Cardiovascular disease: trends and current status

In the past decades the management of acute coronary syndromes (ACS), including myocardial infarction (MI) and unstable angina, has evolved from a strategy of watchful waiting to a highly technical intervention with anti-blood clotting drugs and percutaneous coronary intervention (PCI) with stent placement. As a result, the prognosis of patients has improved radically. In the 1960s in-hospital mortality in MI patients was as high as 30%. After the widespread introduction of coronary care units (CCU) in the 1970s this figure was reduced to approximately 15%, figure 1. Further improvements were made with the introduction of fibrinolytic drugs (1980s) and PCIs (1990s). Currently, 30 day mortality after MI admission has been reduced to 4 - 6 %. [1]

Figure 1 Survival after myocardial infarction; 1960's – 1990's



Up to 5-year case fatality after overall AMI by decade
From: Parikh et al 2009 [25]

Despite these developments, cardiovascular disease (CVD) still is a major cause of the loss of healthy life years in developed countries. For example, in The Netherlands, ± 90,000 patients are admitted each year for an ACS whereas the annual number of fatal ischemic coronary events is as high as ±10,600. [2] In fact, for three main reasons, the burden of CVD is expected to increase in the decades ahead. First, improved survival results in an increasing prevalence of patients with chronic disease, who continue to be at risk of recurrent events. Second, this process is amplified by the aging of the general population.[3] Third, a growing group of asymptomatic individuals are at risk of developing CVD due to mediating conditions such as tobacco consumption, abdominal obesity, dyslipidemia, insulin resistance and elevated blood pressure. Particularly the 'pandemic' of diabetes mellitus (DM) is worrisome in this respect.

Burden of diabetes mellitus

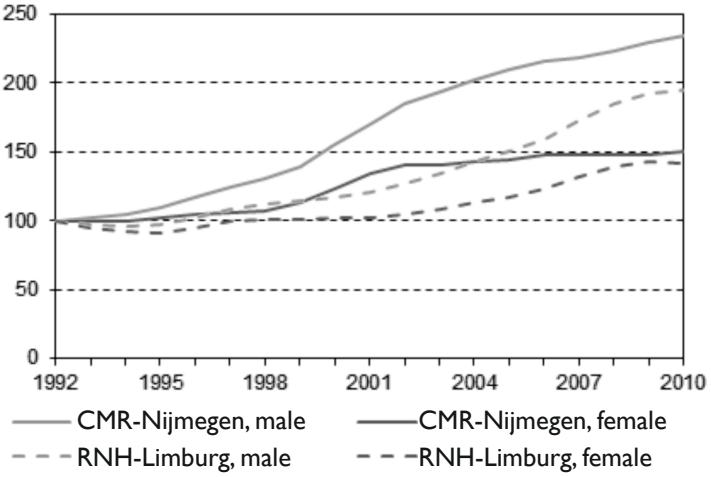
In the past decades the burden of DM has increased. According to the Dutch National Public Health Compass the prevalence of DM doubled in men between 1991 and 2011 and increased by 50% in women, figure 2. [4] It is estimated that the number of patients with known diabetes in The Netherlands will keep growing: from 800,000 (~5%) in 2011 to 1,3 million (~8%) inhabitants in 2025. [5] These increasing numbers are associated with increased obesity, decreased physical activity, and aging of the population. The (trends in the) prevalence of DM in The Netherlands are representative of prevalence figures in the Western World and around the globe. It is estimated that in 2012 approximately 371 million people were living with diabetes worldwide, figure 3, and this number is expected to rise to 552 million in 2030. [6]

Diabetes and hyperglycemia in acute coronary syndromes

Through several pathophysiological mechanisms, including chronic hyperglycemia and chronic vascular inflammation, patients with diabetes have accelerated atherosclerosis. [7] Indeed, DM is one of the main risk factors for CVD and ACS.[8] Furthermore, once CVD has been diagnosed, patients with DM have a 2 – 4 fold higher mortality as compared to their non-DM counterparts.[9]

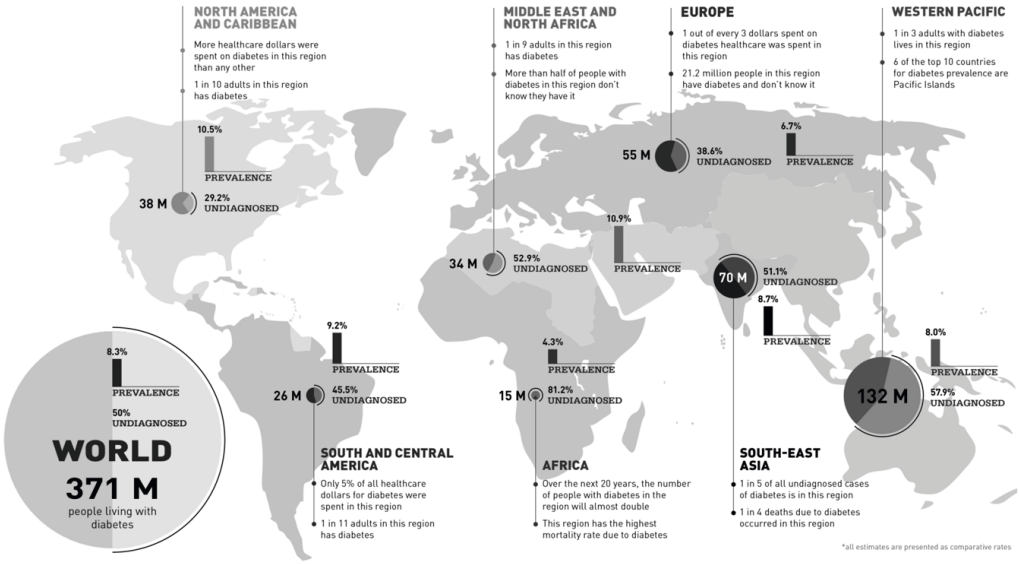
Glucose metabolism is a continuum that varies gradually from normal glucose metabolism to impaired glucose tolerance to clinically manifest diabetes. The first changes in glucose concentrations can be detected as much as 3–6 years before the diagnosis of DM is established.[10] Fortunately, timely lifestyle and pharmacological interventions can prevent or delay this process.[11 12] Obviously, this requires that disturbed glucose metabolism is timely recognized and that patients are motivated to actually change their lifestyle. Scoring models can aid to recognize those at high risk for DM.[13]

Figure 2 Prevalence of diabetes in The Netherlands; 1991 – 2011



Point prevalence of diabetes mellitus from 1991 – 2011 (3 year average), standardized and indexed to Dutch population in 2010 (1992 is 100)
CMR = Continuous Morbidity Registration;
RNH = RegistratieNet Huisartsenpraktijken (General Practitioners' Registry)
From: www.nationaalkompas.nl

Figure 3 Global burden of diabetes mellitus in 2012

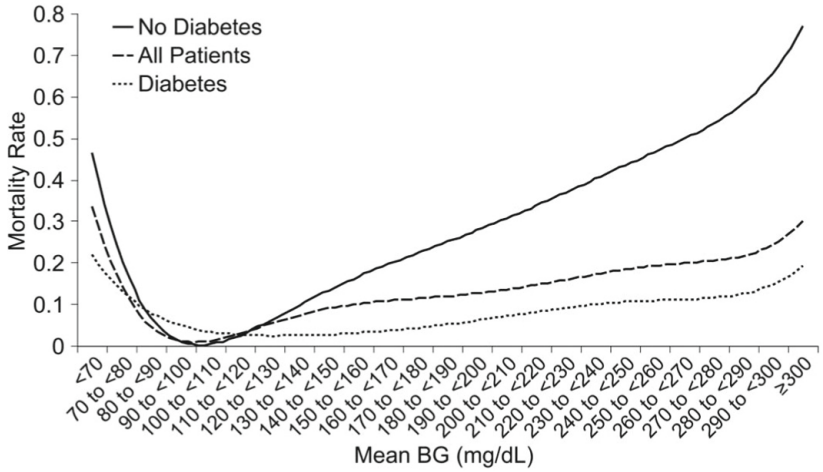


From: www.idf.org

Approximately 50% of ACS patients have an abnormal glucose metabolism, and their admission plasma glucose (APG) is elevated. Several observational studies in ACS patients have demonstrated that elevated APG levels are associated with adverse clinical outcomes, even if APG remains below 11 mmol/l, the diagnostic threshold for DM.[14-17] In fact, the prognosis of ACS patients with elevated APG might be even worse than patients with established diabetes, figure 4.

It is still unclear, however, if elevated APG should be considered a marker of disease severity (and thus can be considered as a more or less innocent bystander), or as a factor that by itself causes extended myocardial injury. One of the aims of this thesis is to find answers to this question.

Figure 4 Admission glucose and mortality



Nature of the relationship between mean hospitalization glucose and in-hospital mortality after acute myocardial infarction (unadjusted analysis). BG = blood glucose.
From: Kosiborod et al 2008. [26]

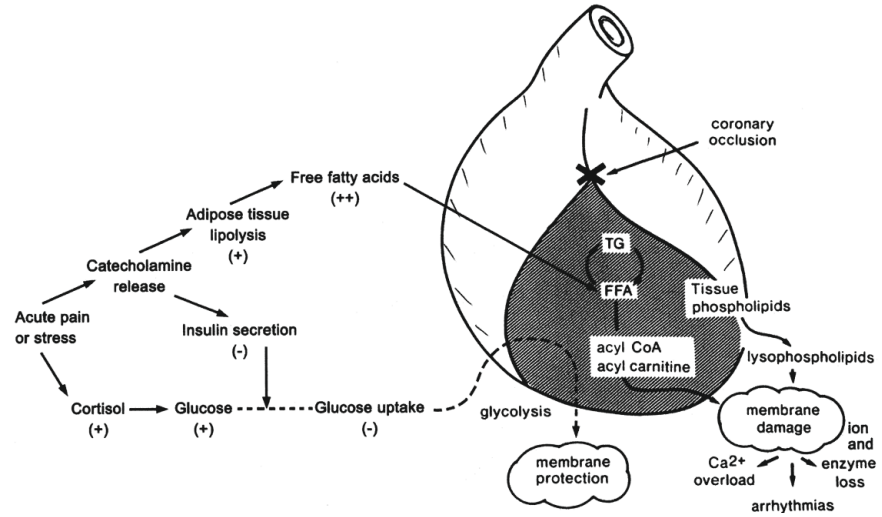
Glucose and myocardial injury: mechanism of disease

Under normal (aerobic) circumstances myocardial metabolism is mostly based on the oxidative phosphorylation of free fatty acids (FFA) and only for a minor part (≈15%) on glucose via glycolysis. The oxidation of glucose is suppressed by the formed citrate and adenosine tri phosphate (ATP). However, under anaerobic circumstances (e.g. ischemia), citrate and ATP levels fall due to a decreased oxygen supply and glycolysis is accelerated. Glycolysis is an anaerobe process, and therefore it does not require oxygen. Oxygen is only required when the formed pyruvate is further metabolized via the citric acid (Krebs) cycle. Furthermore, there is an increase in gluconeogenesis and

in the activity of the insulin sensitive GLUcose Transporter 4 (GLUT-4).[18] This results in increased glucose transport into the cardiomyocyte for glycolysis. An efficient mechanism as this uses less oxygen compared with the oxidative phosphorylation of FFA.

Following this theory, it is conceivable that insulin resistance hampers glucose transport into the cardiomyocyte, which in turn results in higher plasma glucose levels. This lack of intracellular glucose forces the cell to use more FFA. As a consequence more oxygen is used, leading to further hypoxemia under ischemic circumstances which in its turn leads to increased myocardial necrosis, figure 5. Next, the elevated extra cellular (plasma) glucose levels increase platelet aggregation, oxidative stress, inflammation and micro vascular dysfunction, which results in larger myocardial damage.[19-21] This process provides therapeutic opportunities, as the described deleterious effects might potentially be opposed with insulin and glycemic control.[22-24] This hypothesis is evaluated in the current thesis.

Figure 5 Changes in myocardial metabolism during ischemia



The main changes that occur in peripheral and myocardial metabolism during the development of acute myocardial ischemia. CoA = coenzyme A; FFA = free fatty acid; TG = triglyceride.
From: Oliver 2002 [27]

Research questions

This thesis aims to answer three clinically relevant research questions.

First, the role of APG in patient outcome and outcome prediction is investigated. What exactly is the predictive value of elevated AGP for adverse cardiac events now that treatment and outcomes of ACS patients have improved? And what is the relevance of elevated APG in relation to other determinants of risk?

The second question that is addressed in this thesis relates to the management of ACS patients with elevated APG. Which diagnostic tools are applied in Dutch clinical cardiology settings to identify these subjects? What treatment is installed during hospitalization and long-term follow-up? And how do these treatment policies relate to international treatment guidelines?

Finally, and most importantly, this thesis addresses the relation between (modulation of) the glucose metabolism and final myocardial infarct size. Can infarct size be limited by a treatment policy that aims to normalize APG levels?

A variety of study designs and statistical techniques were applied to answer these research questions. We used observational outcome data of 46,064 ACS patients that were collected in a broad range of European cardiology practices. We developed and validated outcome prediction models with and without information on admission glucose levels. We organized a structured interview among 94 Dutch cardiologists to obtain information on treatment preferences. We designed an intensive glucose regulation strategy, and evaluated its effects in a randomized clinical trial that enrolled 294 patients. We used laboratory tests (cardiac troponin), invasive imaging (myocardial perfusion scintigraphy) and information on mortality and morbidity to evaluate treatment effects.

THESIS OUTLINE

PART 1: Outcome prediction

In **Chapter 2** we investigated what information could be used to develop a risk model to predict in hospital mortality after PCI. In addition to clinical parameters, information from various imaging modalities can also be used to predict outcomes. In **Chapter 3 & 4** we describe our experience with single photon emission computed tomography using ^{99m}Tc-sestamibi as a perfusion tracer (MIBI spect). We used this technique to evaluate whether off-site PCI (i.e. in a centre without on-site cardiothoracic surgery as backup) in MI patients would result in a reduced infarct size compared with transferral to a more remote on-site interventional center. Subsequently we investigated the predictive value of MIBI spect parameters on 5 year clinical outcome.

However, a risk model is only an approach of reality and leaves room for improvement. In **Chapter 5** we subsequently studied whether a readily available biomarker such as admission glucose can improve the predictive performance of a well validated risk model that is used in clinical practice, the GRACE risk score.

PART 2: Glucose (regulation) effects

In **Chapter 6** we assess the effect of hyperglycemia on mortality in MI patients in the current invasive era of PCI and compare this to the thrombolysis era. Next, in **Chapter 7 – 9** we assess what amount of MI patients (without known diabetes) have a disturbed glucose metabolism with different diagnostic methods and investigate the awareness for unrecognized DM among Dutch cardiologists.

Chapter 10 describes our experience with the introduction of a new intensive glucose regulation protocol on the coronary care unit. We aim to provide clinicians a step by step tool to implement this protocol on their own coronary care unit.

The most important question is whether this extra attention for, and regulation of, elevated glucose levels will lead to better patient outcomes. In order to thoroughly investigate this, we designed the BIOMArCS 2 glucose trial, as described in **Chapter 11**. This randomized clinical trial investigates whether an intensive glucose regulation strategy limits infarct size in hyperglycemic MI patients, as compared to an expectative strategy. The results are presented in **Chapter 12**.

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PART 1

CHAPTER 2

EuroHeart score for the evaluation of in-hospital mortality in patients undergoing percutaneous coronary intervention

Maarten de Mulder, Anselm Gitt, Ron van Domburg, Matthias Hochadel, Ricardo Seabra-Gomes, Patrick W. Serruys, Sigmund Silber, Franz Weidinger, William Wijns, Uwe Zeymer, Christian Hamm, Eric Boersma

European Heart Journal. 2011;32:1398-1408

ABSTRACT

Background and Aim: The applicability of currently available risk prediction models for patients undergoing percutaneous coronary interventions (PCI) is limited. We aimed to develop a model for the prediction of in-hospital mortality after PCI that is based on contemporary and representative data from a European perspective.

Methods and Results: Our analyses are based on the Euro Heart Survey of PCI (EHS-PCI), which contains information on 46,064 consecutive patients who underwent PCI for different indications in 176 participating European centers during 2005-8. Patients were randomly divided into a training (N=23,032) and validation (N=23,032) set with similar characteristics. In these sets 339 (1.5%) and 305 (1.3%) patients died during hospitalization, respectively. Based on the training set, a logistic model was constructed that related 16 independent patient or lesion characteristics with mortality, including PCI indication, advanced age, hemodynamic instability, multivessel disease and proximal LAD disease. In both the training and validation data sets the model had a good performance in terms of discrimination (C-index 0.91 and 0.90 respectively) and calibration (Hosmer-Lemeshow [H-L] p-value 0.39 and 0.18 respectively).

Conclusion: In-hospital mortality in PCI patients was well predicted by a risk score that contains 16 factors. The score has strong applicability for European practices.

INTRODUCTION

Since its introduction by the late Andreas Grüntzig in 1979, percutaneous coronary interventions (PCIs) have been applied to the benefit of millions of patients across the globe. Over the years this procedure has evolved from elective balloon angioplasty in selected centers to widely available emergency PCI with stent placement. As technology, pharmacology and operators' experience with PCI grows, the procedure associated risks decreases.[1] However, this intervention is still related with mortality, which varies between different groups of patients.

To identify high risk patient groups, risk models are developed that relate patient and lesion characteristics to major complications after PCI.[2-8] Especially in situations where it is difficult to select the most appropriate treatment strategy they can be of extra value. Risk models can then be used to systematically estimate the patient's risk of adverse events. Such estimate might then be used to help the physician decide on further patient management, as high-risk patients might be treated differently than low-risk patients.

It is broadly accepted that currently available risk prediction models for PCI patients have limited applicability, mainly because of heavy selection of the patients that form the model-development dataset. They were either single centre studies,[3 5 8] a selected study cohort [2 9] or studies from an era without techniques such as drug eluting stents; or new anti platelet medications.[2 4 6 7] These limitations were overcome by Peterson et al, who developed a model based on 588.398 procedures from the American NCDR CathPCI registry database.[10] However, as this analysis was performed in a geographically different population, it's use might be limited for a European population.[11] Additionally, the actual use of risk prediction models in routine clinical practice may be an issue. In general, one might expect that models that are based on data that are experienced as 'close' will have a good chance of being implemented. In that respect, models based on European data might more easily penetrate European practices than models based on US data.

Furthermore, several risk models did not have separate training and validation cohorts.[2 7 8 12] Without such separate cohorts, the training data cannot not be formally validated. As a consequence, their reliability remains uncertain.

The Euro Heart Survey of Percutaneous Coronary Interventions (EHS-PCI) was developed to obtain quantitative information on the adherence to guidelines and outcomes in European patients undergoing PCI for different indications. The survey was undertaken during 2005-2008, and includes data on 46,064 patients from European hospitals. Thus, the EHS-PCI provides a unique opportunity to develop

(and validate) a model for the prediction of patient prognosis after PCI, that reflects modern clinical practice. In view of the large number and large variety of hospitals that participated in EHS-PCI, the results of this analysis will potentially be applicable to a broad variety of European practices.

METHODS

PCI Registry within the Euro Heart Survey Programme

The Euro Heart Survey (EHS) programme of the European Society of Cardiology (ESC) was originally designed as a series of surveys, to obtain information on the application of clinical practice guidelines [13] in the ESC member countries, covering the broad spectrum of cardiology practice, [14] an extensive descriptive paper is currently composed.

Typically, patient enrolment in EHS surveys was scheduled for short-term periods of 3 to 6 months, thus taking the risk of being influenced by accidental, or just structural, season-bound variations in patient management or events. In contrast, patient enrolment in the EHS-PCI Registry lasted for a period of three years, from May 2005 to April 2008. That period is long enough to level off accidental situations, as well as structural differences in patient management between participating hospitals, which makes it greatly suitable for our purpose.

Patients and procedures

A total of 176 centers with PCI facilities from 33 ESC member countries participated in the EHS-PCI Registry. The sample of hospitals consisted of a mixture of tertiary referral university hospitals (48%), hospitals that could be considered satellites of university hospitals (15%), district or regional hospitals (13%), specialist cardiology centers (11%), community hospitals (8%), and private hospitals (5%).

Local investigators were asked to continuously enroll all consecutive patients undergoing emergent, urgent or elective PCI, irrespective of any other condition. Patients who participated in (randomized) trials or other registries were eligible for inclusion. Investigators who could not warrant enrolment of each and every patient throughout the entire study period were allowed to participate if consecutive patients could be realized from day 1 to 7 of every calendar month. We had no system installed to verify if the principle of consecutive patient enrolment was satisfied.

Data were collected on a broad range of patient characteristics, including the clinical indication for PCI, cardiovascular risk factors, history of cardiovascular diseases and co-morbidities. PCI-related data were collected as well, including the number and

location of significant lesions, and the ACC-AHA lesion classification [15 16]. An electronic case record form (eCRF) was used for data capture, which was programmed on the basis of the Cardiology Audit and Registration Data Standards (CARDS) for PCI.[17;18] The eCRF was accessible via the internet for data entry and editing. Data were securely stored on a computer mainframe that was physically located in the European Heart House, Nice, France. Automated edit checks were performed to search for missing data, contradictory data entries, as well as for values that are out of the specified normal range. Additionally, manual edit checks were performed by the data management staff of the European Heart House. Final editing of the data, as well as data analyses was performed at the Institut für Herzinfarktforschung Ludwigshafen an der Universitaet Heidelberg (IHF), Ludwigshafen, Germany. Any issues that appeared during this process were resolved in cooperation with the local investigators.

The protocol of the EHS-PCI Registry was approved by each local ethical committee when required. All patients provided informed consent for processing their data anonymously.

Primary objective

The EHS-PCI Registry was designed to evaluate the application of PCI-related treatment guidelines in routine clinical practice. With respect to patient outcome, the current study focuses on mortality. In this manner endpoints that are vulnerable for observer bias, such as re-myocardial infarction, are avoided and adjudication of such events is not required. All cause mortality was reported by the local investigators, and not adjudicated by a Clinical Event Committee / Data Safety Monitoring Board.

Statistical analysis

When patient characteristics were incomplete data were imputed. Otherwise the missing patient data might lead to biased estimates. Since occasionally not all data can be collected in patients who die early, patients with incomplete data often have a higher mortality. Missing values were imputed with the expected value according to gender, age and PCI indication. We also performed a sensitivity analysis using multiple imputation methods. We found that all variables except prior renal failure (RF) and prior MI were of influence in all models. These 2 variables were included in some models but not in others (RF included in 6/20 models, prior MI included in 11/20 models). As with regression imputation the best goodness of fit was achieved, this strategy was chosen.

The percentage of missing data in variables that were significant in multivariate analyses were: 9.1% for bifurcation lesion; 8.7 % for hemodynamic instability; 5.3% for valvular heart disease, 3.9% for TIMI flow; 3.4% for body mass index (BMI) and 3.2%

for smoking status, other variables had fewer than 2% missing data. Discharge status, gender, age and PCI indication were known in all patients.

The database was randomly divided into two equal parts by using a specific application of the statistical analysis program. The first part was used to develop the mortality risk score ('training dataset'). The second part was used to validate the score ('validation dataset').

Univariate logistic regression analyses were applied on the training dataset to study the association between a broad range of clinical and procedural characteristics (which are listed in table 1) and the incidence of the primary objective. Variables that were associated with in-hospital death with a significance level of $p<0.5$ entered the multivariate stage. $P<0.5$ was chosen in order not to miss any potential variables in the multivariate model. The final multivariable regression model was then constructed using backward elimination of the least significant variables, until all variables had a significance level of $p<0.15$. Subsequently, a mortality risk score was determined that included all variables that composed the final regression model. The contribution of these variables to the risk score were weighed according to the corresponding regression coefficient in the logistic model (i.e. the natural logarithm of the corresponding odds ratio). The performance of the mortality risk score was finally studied with respect to discrimination (c-index) and calibration (Hosmer-Lemeshow goodness-of-fit test) in the training and in the validation dataset.

All analyses were repeated for the cohort of patients who presented with ST-elevation Myocardial Infarction (STEMI). The analyses were performed with SAS 9.1 software.

RESULTS

Patient characteristics

The EHS-PCI registry enrolled a total of 46,064 PCI patients. The median age of the study cohort was 64 years and 74% were men. Fifty-one percent of patients underwent PCI for (stabilized) acute coronary syndromes (ACS), and 49% had an elective procedure. In 94% of patients a stent was implanted, 46% of these stents were drug eluding. In 84% of patients percutaneous access was via the femoral and in 15% via the radial approach. Patients in the training and validation dataset had similar clinical and angiographic characteristics (table 1). Patients were discharged after 2 days (IQR 1 – 4), 85.7% went home, 12.8% was transferred to another hospital and 1.5% to a rehabilitation centre.

Table 1 Baseline characteristics of the study patients

	Training cohort	Validation cohort	P-value
Number of patients	23.032	23.032	
Age, years	64 (55, 72)	64 (56, 72)	0.85
Men	74	74	0.81
Indication for PCI			
Admission with STEMI	18	17	0.14
Admission with Non STEMI	13	13	0.73
Stabilised ACS	21	21	0.56
Elective procedure	49	49	0.37
Body Mass Index	27 (25, 30)	27 (25, 30)	0.63
Hypertension	69	70	0.53
Hypercholesterolemia	64	65	0.21
Diabetes mellitus	25	25	0.81
Current smoker	27	27	0.25
Ever smoker	52	52	0.53
Prior PCI	24	25	0.36
Prior CABG	6.2	6.3	0.78
Prior myocardial infarction	34	34	0.64
Congestive heart failure	11	11	0.71
Peripheral vascular disease	6.0	6.0	0.83
Prior stroke	4.1	4.1	0.74
Chronic renal insufficiency	3.5	3.5	0.89
Valvular heart disease	2.1	2.3	0.22
Number of diseased vessels			
1	47	47	0.11
2	31	32	0.02
3	21	21	0.45
Left main	4.5	4.6	0.53
Proximal LAD diseased	34	34	0.53
Bifurcation lesion	16	16	0.47
Type-C lesion	28	28	0.41
Haemodynamic instability (at presentation)	2.7	2.7	0.71
Transferred from other hospital	23	23	0.57
Left ventricular function *			
EF >50%	69	69	0.88
EF 41 – 50%	19	19	0.65
EF 31 – 40%	8.9	8.6	0.37
EF < 30%	4.1	4.0	0.79

Continuous data are presented as median values (25^{th}-75^{th} percentile); dichotomous data are presented as percentages

** Based on 32.267 patients, EF = Ejection Fraction*

Determinants of in-hospital mortality in the training dataset

In the training cohort a total of 339 patients (1.5%) died during hospitalization. In univariable analysis advanced age, particularly age above 80 years (OR 6.8; 95% CI 4.2 – 11), hemodynamic instability (i.e. cardiac shock at admission or resuscitation

prior to PCI) (OR 52; 95% CI 41 – 66), left ventricular function (LVF) ≤30% (OR 28; 95% CI 19 - 40) and STEMI (OR 24; 95% CI 16 – 35) were strongly associated with increased mortality risk (table 2). The presence of 3-vessel disease (OR 3.5; 95% CI 2.7 – 4.6) and the presence of left main disease (OR 4.2; 95% CI 3.1 – 5.7) were the most relevant angiographic characteristics for in-hospital death.

Mortality risk score

A total of 16 variables remained in the multivariable model for the prediction of in-hospital death (table 2), among which hemodynamic instability at admission, STEMI and age ≥ 80 years were most dominant. Ten variables were patient-related and could be obtained prior to the PCI procedure. Six factors were derived during angiography. The multivariable model translated in the scoring system that is presented in figure 1. There is a direct relation between the number of risk points and the estimated and observed mortality. For example, a 72 year old (3 points) woman (2 points) with a prior stroke (2 points) but no known heart disease (thus no prior CABG, 4 points) who presents with STEMI (8 points) and left main disease (3 points) has a total risk score of 22 points. The observed in-hospital mortality risk among the patients with 22 risk points was 5.3 % (20 of 376 patients), and the predicted risk (based on the model) was 3.8%.

As demonstrated in figure 2 and 3, the majority of patients (≈ 90%) have a low mortality risk, i.e. a score ≤ 20 corresponding with a mortality < 2%. A score of 21 – 26 (2 – 8.4% mortality) is present in approximately 7.5 % of patients and the remaining 2.5% of patients is a high risk population with in-hospital mortality over 7.5%, i.e. a score of ≥27.

Table 2 Association between baseline characteristics and in hospital mortality in the training cohort

	In –hospital death	Crude odds ratio and 95% CI	Multivariable adjusted odds ratio 95% CI
Age, years (median)	71 / 64	1.05 (1.04 – 1.06)	
Age categorised, years			
<50	0.73	1	---
≥50 – 60	0.83	1.1 (0.69 – 1.9)	---
≥60 – 70	1.2	1.7 (1.03 – 2.7)	1.7 (1.2 – 2.5)
≥70 – 80	2.0	2.7 (1.7 – 4.3)	2.4 (1.7 – 3.4)
≥80	4.7	6.8 (4.2 – 11)	4.2 (2.8 – 6.5)
Female	2.2 / 1.2	1.8 (1.5 – 2.3)	1.6 (1.2 – 2.1)
Body mass index < 25	2.2 / 1.1	2.0 (1.6 – 2.5)	1.8 (1.4 – 2.3)
Hypertension	1.3 / 1.4	0.93 (0.74 – 1.2)	---
Hypercholesterolemia	0.94 / 1.8	0.57 (0.46 – 0.71)	---
Diabetes mellitus	2.1 / 1.1	1.8 (1.4 – 2.2)	1.9 (1.5 – 2.5)
Ever smoker	1.2 / 1.3	0.94 (0.76 – 1.2)	1.4 (1.04 – 1.9)
Prior PCI	0.77 / 1.6	0.52 (0.38 – 0.71)	---
Prior CABG	0.85 / 1.4	0.63 (0.36 – 1.09)	0.35 (0.18 – 0.69)
Prior myocardial infarction	1.3 / 1.4	0.92 (0.73 – 1.2)	---
Congestive heart failure	1.5 / 1.4	1.1 (0.79 – 1.5)	---
Peripheral vascular disease	2.4 / 1.3	1.8 (1.3 – 2.6)	---
Prior stroke	3.2 / 1.3	2.4 (1.7 – 3.5)	1.8 (1.2 – 2.8)
Chronic renal insufficiency	3.1 / 1.3	2.3 (1.5 – 3.5)	---
Valvular heart disease	2.6 / 1.3	1.9 (1.1 – 3.4)	1.7 (0.83 – 3.4)
Number of diseased vessels.			
1	0.85	1	---
2	1.4	1.7 (1.3 – 2.2)	---
3	2.9	3.5 (2.7 – 4.6)	1.4 (1.1 – 1.9)
Left main	5.3 / 1.3	4.2 (3.1 – 5.7)	2.2 (1.5 – 3.3)
Proximal LAD diseased	2.4 / 1.0	2.4 (1.9 – 3.0)	1.6 (1.2 – 2.0)
Bifurcation lesion	2.1 / 1.5	1.5 (1.1 – 1.9)	1.6 (1.1 – 2.1)
Type – C lesion	2.6 / 1.0	2.6 (2.1 – 3.2)	1.5 (1.2 – 1.9)
TIMI flow 0/1 before PCI.	3.4 / 0.71	4.9 (3.9 – 6.2)	1.5 (1.2 – 2.1)
Indication for PCI.			
Elective procedure	0.24	1	---
Stabilised after ACS	0.86	3.6 (2.1 – 6.2)	2.6 (1.5 – 4.4)
Admission with Non STEMI	2.1	9.1 (5.9 – 14)	5.0 (3.2 – 7.8)
Admission with STEMI	5.4	24 (16 – 35)	7.8 (5.1 – 12)
Haemodynamic Instability	29 / 0.83	52 (41 – 66)	17 (13 – 23)
Left ventricular function.*			
Class I (>50%)	0.46	1	---
Class II (31 – 50%)	2.1	4.6 (3.2 – 6.4)	---
Class III (≤ 30%)	11.5	28 (19 – 40)	---

Continuous data (age) are presented as median values; dichotomous data are presented as percentages.
For in hospital mortality: data represent mortality when variable is present (first number) or absent (second number).
LV function was not used for multivariate analysis as in 30% of patients this value was missing.

Figure 1 EuroHeart PCI score

Characteristic	Points
PCI indication	
Ongoing STE-ACS	8
Ongoing NSTE-ACS	6
Stabilised after ACS	4
Age	
≥60 - 70	2
≥70 - 80	3
≥80	6
Hemodynamic Instability	11
Ever smoker	1
Diabetes mellitus	3
Female gender	2
Prior stroke	2
No prior CABG	4
Valvular heart disease	2
BMI < 25 kg/m2	2
TIMI flow 0/1 before PCI	2
3-vessel disease	1
Left main disease	3
Proximal LAD disease	2
Bifurcation lesion	2
Type C lesion	2

EuroHeart PCI Score

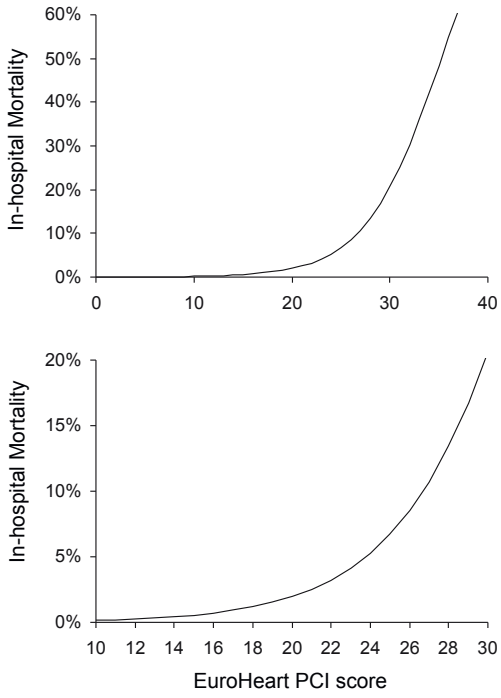


Figure 2 Distribution of assigned scores over the validation cohort

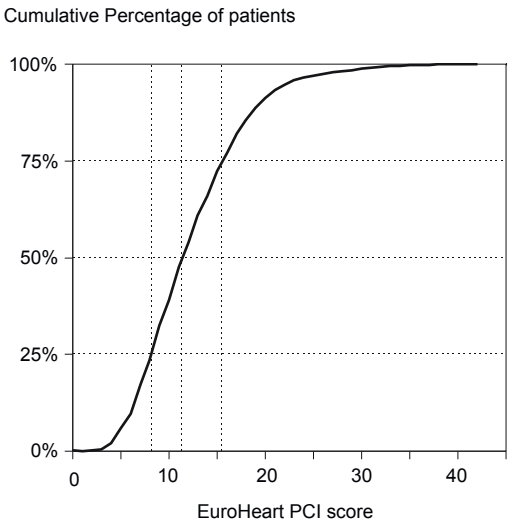
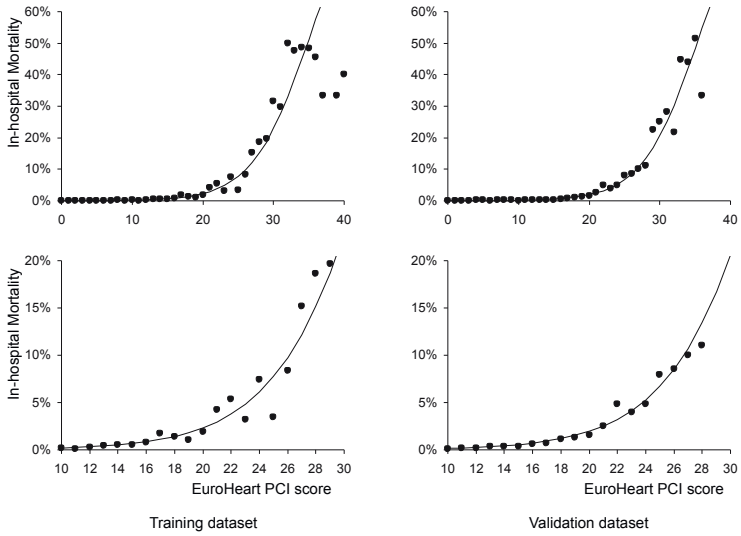
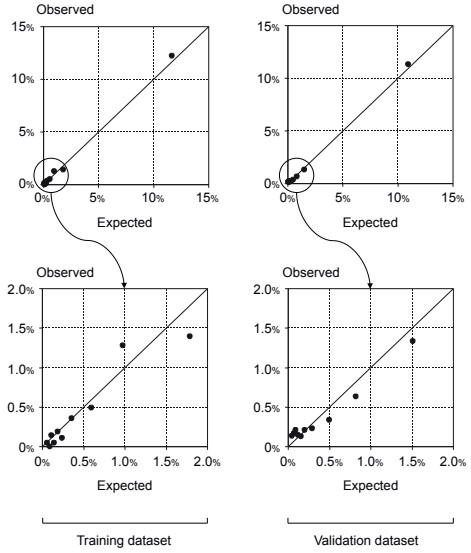


Figure 3 The EuroHeart PCI score model and observed in-hospital mortality



Top left: Score in the Training cohort. Top right: Score in the Validation cohort. Bottom: Enlargement of patients with an intermediate score (10 – 30 points) in the training (left) and validation cohort (right) to better illustrate the transition point from low to intermediate risk. Score >40 is not illustrated as these score groups contain few (≤6) patients), which makes accurate prediction more difficult.
Data points correspond to the observed mortality (y-axis) for patients with a particular score (x-axis), line represents predicted mortality.

Figure 4 Expected versus observed in-hospital mortality



Top left: Training cohort. Top right: Validation cohort. Bottom: Enlargement of both cohorts
Rates were calculated with the Hosmer-Lemeshow goodness of fit test.

Model Performance

The multivariate training model has an excellent performance in terms of discrimination (C-index 0.91) and calibration (Hosmer-Lemeshow [H-L] p-value 0.93). When subsequently the risk score is created and applied to the training set, the C-index is 0.91 and H-L p value 0.39. In the validation set, similar discrimination (C-index 0.90) and adequate calibration (H-L p-value 0.18) was observed, figure 4.
We also investigated the model performance in different subgroups, table 3 and compared the performance of the current model with others, table 4.

Table 3 Subgroup validation in validation cohort

Validated Subgroup	Sample / mortality (n)	C index	H-L p value
Male	17112 / 180	0.90	0.008
Female	5920 / 125	0.90	0.94
Age ≥70 yrs	7433 / 191	0.88	0.36
Age<70 yrs	15599 / 114	0.89	0.003
Diabetes	5772 / 119	0.90	0.80
No diabetes	17084 / 192	0.91	0.67
Patient in shock	574 / 157	0.74	0.85
Patient not in shock	22458 / 148	0.82	0.21
PCI in ACS patient	11710 / 279	0.91	0.85
PCI in Elective patient	11291 / 25	0.57	0.81
STEMI	3969 / 203	0.89	0.57
No STEMI	19063 / 102	0.81	0.37

Although the H-L p value is significant in men and patients <70, the maximum difference of observed and expected mortality per tentile is only 4 deaths, this was observed in the high risk group (tentile 9 /10 for both subgroups). H-L = Hosmer Lemeshow; STEMI = ST elevation Myocardial Infarction;

Patients presenting with STEMI

We performed a separate analysis of the 8060 patients who presented with ST Elevation-ACS to have a valid model for this high risk population, since only a small proportion of the original data consists of high risk patients.

From the original training and validation cohorts, the STEMI patients were selected, i.e. 4091 and 3969 respectively. In the training cohort a total of 220 out of 4091 patients (5.4%) and in the validation cohort 203 out of 3969 (5.1%) died during hospitalization.

With multivariate analysis nineteen variables remained of significant influence. Particularly hemodynamic instability at admission (OR 14; 95% CI 10 – 20), age ≥ 80 (OR 4.6; 95% CI 2.7 – 7.9) and left main disease (OR 2.1; 95% CI 1.2 – 3.7) were associated with a high in-hospital mortality risk, table 5.

Table 4 Different risk models for PCI outcomes

Author and year of publication	AUC (c –index)	Predicted endpoint	Multi centre	DES used?	Remarks
This study	0.91	In-hospital mortality	Yes	Yes	Based on European population, contemporary practice
Peterson[10] (2010)	0.93	In-hospital mortality	Yes	Yes	Based on North American population, contemporary practice
Singh[8] (2008)	0.78 0.75	In-hospital MACE In-hospital mortality	No	N/A	Expansion of MCRS model with CAD specific index
Madan[3] (2008)	0.70	MACE at 30 days	No	Yes	Adding morbidity may have lowered discriminatory ability
Negassa[4] (2007)	0.82	In-hospital mortality	Yes	N/A	3 factors in risk model
Halkin[2] (2005)	0.83 0.79	30 day mortality 1 year mortality	Yes	No	Patients in shock or with complex coronary anatomy were excluded
Addala[9] (2004)	0.78	6 month mortality	Yes	No	STEMI patients form various PAMI trials
Qureshi[5] (2003)	0.87	In-hospital mortality	No	No	LVF and lesion characteristics not included
Shaw[7] (2002)	0.89	In-hospital mortality	Yes	No	No systematic data auditing across participating centres Large dataset (>100.000 PCI's)
Moscucci[6] (2001)	0.90	In-hospital mortality	Yes	No	Little high risk procedures Designed as bedside tool with only clinical parameters
Rihal[12] (2000)	0.86	Death after PCI*	No	No	45% of procedures only balloon angioplasty

AUC = Area under ROC Curve; DES = Drug Eluting Stent; MACE = Major Adverse Cardiac Event; N/A = Not Available; MCRS = Mayo Clinic Risk Score; CAD specific index was developed to determine prognostic influence of co-morbid conditions

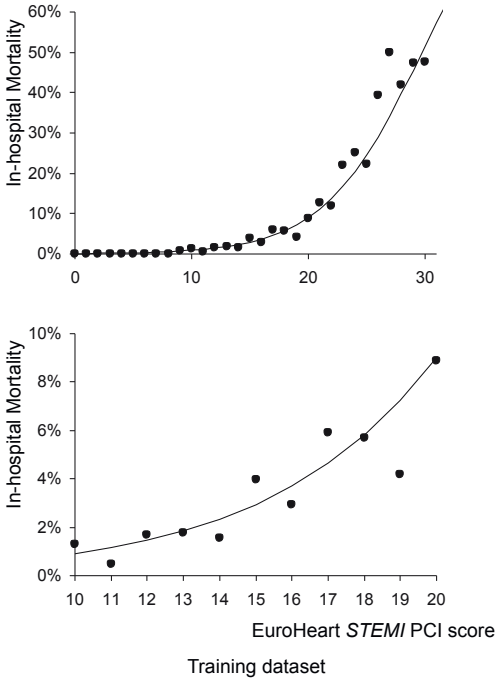
** No specific timeframe specified*

In this subpopulation, the area under the ROC curve was 0.86 with a Hosmer-Lemeshow p value of 0.42, indicating a good discriminatory value in this high risk subpopulation. Subsequently we again created a simplified scoring model which was then tested in the training and validation dataset, the score ranged from 2 – 37 points, figure 5.

In the training STEMI data this simplified model demonstrated an area under the ROC curve of 0.86 with a Hosmer-Lemeshow p-value of 0.75, In the STEMI validation data, similar discrimination (C-index 0.89) and calibration (H-L p-value 0.70) was observed. This acknowledges the validity of the separate STEMI model.

Figure 5 EuroHeart STEMI PCI score

Characteristic	Points
Age	
≥60 - 70	3
≥70 - 80	4
≥80	6
Haemodynamic Instability	11
Ever smoker	2
Diabetes mellitus	2
Female gender	2
Prior Stroke	2
No prior CABG	5
Ischaemic time ≥ 12 hr	**1**
BMI <25	2
TIMI flow 0/1 before PCI	2
2-vessel disease	1
3-vessel disease	2
Proximal LAD diseased	1
LAD target vessel	1
Bifurcation lesion treated	1
Type C lesion treated	2
Left main disease	3
	+
EuroHeart STEMI *PCI Score*	



Assigned integer scores.
Score until 31 points, score 32 to 37 are left out as these contained only few patients (≤ 13)

Table 5 Association between baseline characteristics and in hospital mortality in the STE ACS training cohort

	In-hospital death* (%)	Crude odds ratio and 95% CI	Multi-variable adjusted odds ratio 95% CI
Age, years	71 / 62	1.04 (1.03 – 1.06)	---
Age categorised, years			
<50	2.4	1	---
≥50 – 60	3.1	1.3 (0.72 – 2.3)	---
≥60 – 70	5.4	2.3 (1.3 – 3.9)	1.9 (1.2 – 3.0)
≥70 – 80	7.9	3.4 (2.0 – 5.8)	2.8 (1.8 – 4.3)
≥80	11.9	5.4 (3.1 – 9.6)	4.6 (2.7 – 7.9)
Female	7.6 / 4.6	1.7 (1.3 – 2.3)	1.5 (1.06 – 2.2)
Body mass index	27 / 26	0.97 (0.94 – 1.01)	---
Body mass index <25	7.4 / 4.2	1.8 (1.3 – 2.4)	1.8 (1.3 – 2.5)
Hypertension	5.4 / 3.9	1.4 (1.04 – 1.9)	---
Hypercholesterolemia	4.2 / 4.8	0.89 (0.67 – 1.2)	---
Diabetes mellitus	7.9 / 4.1	1.9 (1.4 – 2.6)	1.7 (1.2 – 2.4)
Ever smoker	4.3 / 4.6	0.88 (0.66 – 1.2)	1.8 (1.2 – 2.7)
Prior PCI	4.8 / 4.9	0.98 (0.62 – 1.6)	---
Prior CABG	4.9 / 5.2	1.06 (0.40 – 2.8)	0.30 (0.10 – 0.94)
Prior myocardial infarction	7.7 / 4.4	1.8 (1.3 – 2.4)	---
Congestive heart failure	8.8 / 4.7	1.9 (1.1 – 3.1)	---
Peripheral vascular disease	12.7 / 4.6	2.8 (1.7 – 4.6)	---
Prior stroke	11.3 / 4.7	2.5 (1.5 – 4.2)	1.6 (0.85 – 3.0)
Chronic renal insufficiency	10.7 / 4.8	2.3 (1.1 – 4.5)	---
Valvular heart disease	12.5 / 4.8	2.7 (1.07 – 6.9)	---
Number of diseased vessels			
1	3.3	1	---
2	5.6	1.7 (1.2 – 2.5)	1.4 (0.92 – 2.0)
3	9.1	2.9 (2.1 – 4.1)	1.5 (1.01 – 2.3)
Left main	20.4 / 4.8	5.1 (3.4 – 7.7)	2.1 (1.2 – 3.7)
Proximal LAD diseased	8.0 / 3.9	2.1 (1.6 – 2.8)	1.4 (1.01 – 2.0)
LAD is target vessel	6.3 / 4.7	1.4 (1.04 – 1.8)	1.4 (0.96 – 1.9)
Bifurcation lesion	8.7 / 5.3	1.7 (1.2 – 2.5)	1.4 (0.93 – 2.2)
Type-C lesion	8.1 / 3.9	2.2 (1.6 – 2.9)	1.5 (1.08 – 2.0)
PCI indication			
Primary PCI (<24 hrs)	5.3	1	---
Rescue PCI	7.0	1.35 (0.83 – 2.2)	---
Facilitated PCI	4.1	0.75 (0.33 – 1.7)	---
TIMI flow 0/1 before PCI	6.3 / 3.5	1.9 (1.3 – 2.6)	1.5 (1.05 – 2.3)
Haemodynamic Instability	30.4 / 2.7	17 (13 – 23)	14 (10 – 20)
*Left ventricular function***			
Class I (>50%)	1.9	1	---
Class II (31 – 50%)	4.0	2.2 (1.3 – 3.6)	---
Class III (≤ 30%)	26.8	19 (11 – 32)	---
Ischemic time			
0 – 3 hours	4.7	1	---
3 – 6 hours	4.8	1.03 (0.71 – 1.5)	---
6 – 12 hours	5.1	1.09 (0.71 – 1.7)	---
>12 hours	6.4	1.4 (0.90 – 2.1)	1.4 (0.92 – 2.1)

Continuous data (age, BMI) are presented as median values; dichotomous data are presented as percentages

** For in-hospital mortality: data represent mortality when variable is present (first number) or absent (second number) Qualitative estimated based on 4091 patients;*

*** LVF was not included in the MV analyses as 36% of patients had missing data*

DISCUSSION

We developed a risk score for in-hospital mortality after PCI based on clinical and angiographic data from the EHS–PCI database, with a high discriminatory value and demonstrated its value in contemporary practice. Strong points of our model are the large sample size, pan-European multi centre approach and the use of recent data from everyday clinical practice.

Previous work in patients undergoing coronary artery bypass grafting (CABG) resulted in the EUROSCORE, a tool designed to assess the peri-operative risk for heart surgery.[19] Recently this model was also tested in PCI and demonstrated a good discriminatory value.[20] However, the EUROSCORE includes various operation related factors that per definition do not apply to PCI. Thus, for PCI patients not all items that compose the score can be filled, which, again per definition, results in inappropriate risk estimation.

These limitations were overcome by the recent NCDR model. [10] To avoid unnecessary risk models, we tried to validate this model on our data, there are some limitations however. The focus in data collection in the EHS PCI survey was different from the NCDR data. As a result we did not have information on 3 (out of 8) variables, i.e. GFR, NYHA class and chronic lung disease. Furthermore the NCDR classification of the indication for PCI was different. With these limitations we found a c-statistic of 0.89 with a Hosmer Lemeshow p value of 0.05. Thus discrimination is good, but calibration is poor.

Our model overcomes these limitations and may therefore be a good first step to create a specific European risk score to assess the peri-procedural risk of PCI. Next, it might be used as a benchmark tool to compare different hospitals. However, additional testing in a separate clinical cohort with new data may be considered beforehand.

Subgroup analysis revealed that our model is less useful to predict mortality in patients who undergo an elective procedure, i.e. not ACS related. Apparently, it is difficult to predict events in this group as the mortality risk is very low (25 events in 11,291 patients = 0.22%). Perhaps we have to accept that mortality risk in elective procedures cannot be predicted with classical risk factors, but might be more dependent on other factors such as operator experience or (contrast)allergies.

Another point of interest is that the tentile of patients with the highest risk has a mortality of approximately 10%. Perhaps that further stratification of this sub-cohort may improve the calibration.

Major determinants in our risk model are hemodynamic instability, STEMI, age

≥ 80 and 3 vessel disease. Singh et al gave an overview of variables used in different risk scores.[21] The main factors they described are also included in our model. However, additional factors from their analysis such as renal failure and peripheral artery disease did not contribute significantly in our multivariate analysis. Possibly this is a consequence of the limitations of a survey in which these data might not have been collected as precisely as in a clinical trial. Indeed, non collection of variables is a problem for any risk model, particularly when it is externally validated.

It appeared that prior CABG has a protective effect in our score model. Interestingly, out of 2857 patients with prior CABG, 2042 (72%) had the intervention only in their native vessels. Therefore we might speculate that these interventions were done under the protection of patent bypass grafts, resulting in better outcomes.

The protocol did not mandate serial electrocardiograms, or blood sampling for determination of cardiac enzymes. As, per design, it was the intention to minimize the impact of the protocol on routine procedures. Since we realize that registry designs are susceptible to observer bias, especially with regard to "soft" parameters, we chose the incidence of all-cause mortality during hospitalization as the primary endpoint of this study. Particularly as this is the clinically most relevant endpoint for patients.

The predictive value of future risk models might be further enhanced when they are also fitted with serum markers such as admission glucose, [22] CRP[23] and NT pro BNP.[24]

It is important to recognize that interventional cardiology is under continuous development and new techniques arise which will require adaptation of existing predictive models. However it might be sufficient to re-validate a powerful existing model instead of developing a complete new one.

Limitations

Our analysis has several limitations that should be mentioned. Since our model predicts in-hospital mortality this can be influenced with different discharge policies. For example: referral centers where patients quickly after PCI are transported to a nearby hospital for further recovery may have low mortality figures as patients spend only several hours in that particular referral centre (this was applicable to 12.8% of patients). The same might be relevant for centers without on-site surgical backup when emergency CABG as a result of the PCI is required. However, only in 49 patients (0.1%) emergency CABG was performed.

Another matter is selection bias as to who receives angiography. It is conceivable that clinicians decide not to perform angiography as they consider that as a result of the advanced age, particularly over 80, PCI risk is already too high. Knowledge of

the coronary anatomy would not change their therapy. Consequently, PCI risk in frail octogenarians may actually be underestimated

Our model uses only patient related factors; therefore we are not informed on operator experience and procedure volumes, which also affect outcomes. In small hospitals for example, experience may be lower due to small sample size. When these are taken into account, the predictive value (as expressed by the c-index) of future models might further increase. However, then the model is not suitable for benchmarking purposes. Additional parameters, such as heart rate or novel biomarkers might give an even better discriminatory power, but were regrettably not available.

CONCLUSION

We have developed a risk score to predict in-hospital mortality in PCI patients. This model is based on a large patient sample, pan-European multi centre approach and recent data from everyday clinical practice, which strengthens its applicability. As it uses clinical and angiographic data, it is easy to implement in clinical practice to estimate the in-hospital mortality risk after PCI.

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Chapter 3

Infarct Size in Primary Angioplasty without On-Site Cardiac Surgical Backup versus Transferal to a Tertiary Center: a single photon emission computed tomography study

Paul Knaapen, Maarten de Mulder, Friso M. van der Zant, Hans O. Peels, Jos W.R. Twisk, Albert C. van Rossum, Jan H. Cornel, Victor A.W.M. Umans

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ABSTRACT

Background: Primary percutaneous coronary intervention (PCI) performed in large community hospitals without cardiac surgery back-up facilities (off-site) reduces door-to-balloon time compared with emergency transferal to tertiary interventional centers (on-site). The present study was performed to explore whether off-site PCI for acute myocardial infarction results in reduced infarct size.

Methods and Results: 128 patients with acute ST-segment elevation myocardial infarction were randomly assigned to undergo primary PCI at the off-site center (n=68) or to transferal to an on-site center (n=60). Three days after PCI, ^{99m}Tc-sestamibi SPECT was performed to estimate infarct size. Off-site PCI significantly reduced door-to-balloon time compared with on-site PCI (94±54 versus 125±59 min, respectively, p<0.01), although symptoms-to-treatment time was only insignificantly reduced (257±211 versus 286±146 min, respectively, p=0.39). Infarct size was comparable between treatment centers (16±15 versus 14±12%, respectively p=0.35). Multivariate analysis revealed that TIMI 0/1 flow grade at initial coronary angiography (OR 3.125, 95% CI 1.17–8.33, p=0.023), anterior wall localization of the myocardial infarction (OR 3.44, 95% CI 1.38–8.55, p<0.01), and development of pathological Q-waves (OR 5.07, 95% CI 2.10–12.25, p<0.01) were independent predictors of an infarct size > 12%.

Conclusion: Off-site PCI reduces door-to-balloon time compared with transferal to a remote on-site interventional center but does not reduce infarct size. Instead, pre-PCI TIMI 0/1 flow, anterior wall infarct localization, and development of Q-waves are more important predictors of infarct size.

INTRODUCTION

Primary percutaneous coronary intervention (PCI) is widely accepted as the preferred reperfusion strategy to reduce infarct size in patients with an acute ST-segment elevation myocardial infarction (STEMI). [1] It has shown to be superior to fibrinolytic therapy in terms of major adverse clinical events,[2] even when additional transfer to an interventional center is required with concomitant treatment delay.[3-5] Unfortunately, only a minor ty of eligible patients receives this form of reperfusion therapy predominantly owing to the lack of available nearby tertiary interventional centers with on-site cardiac surgical backup facilities.[2] The latter constraint has led to the conduction of trials comparing the safety and efficacy of primary PCI in STEMI patients presented to large community hospitals without on-site cardiac surgical backup (off-site) versus transferal to a remote tertiary interventional center (on-site).[6-8] These recent trials have clearly demonstrated that off-site PCI is feasible and suggest that clinical outcome is comparable, although these pilot trials have not been adequately powered to draw definite conclusions. Treatment in off-site centers does however result in a significant reduction in time-to-treatment, which could potentially lead to a reduction in infarct size by more timely salvage of acutely jeopardized ischemic myocardium. [9-11] In that respect, off-site PCI without transfer delay in STEMI patients might even prove to be superior in limiting infarct size. [12 13] Comparative studies evaluating infarct size and LV function between on and off-site PCI centers are, however, lacking.

Therefore, the objective of the present study was to evaluate whether off-site PCI in STEMI patients results in a reduced infarct size compared with transferal to a more remote on-site interventional center. Single-photon emission computed tomography (SPECT) using ^{99m}Tc-sestamibi as a perfusion tracer was used to estimate the extent of irreversible damage after reperfusion. [14]

METHODS

Patients

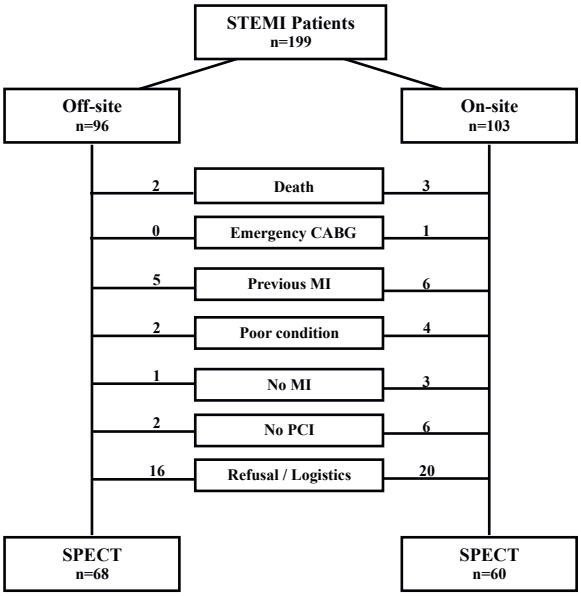
In the context of a previously described study, 199 consecutive STEMI patients were randomly assigned to primary PCI at the center of presentation in a community hospital (off-site, n=96) or to transferal to a remote tertiary center (~ 25 miles) with surgical backup facilities (on-site, n=103).[6] Patients with symptoms of an acute

myocardial infarction persisting >30 minutes, accompanied by a ST-segment elevation > 1 mm (0.1 mV) in at least two contiguous electrocardiographical (ECG) leads, and presenting within 6 hours after the onset of symptoms were included. Patients younger than 18 years of age, unable to give informed consent, with congenital heart disease, or requiring ventilatory assistance were excluded. Cardiogenic shock or patients requiring an intra-aortic balloon pump for hemodynamic support were not excluded. Upon arrival at the cardiac care unit and prior to randomization, all patients were immediately treated with heparin, aspirin, nitroglycerin, and abciximab unless contraindicated. Patients were subsequently randomized to primary PCI at the local off-site center or to be treated at the more distant on-site surgery center. Standard treatment after the PCI procedure included clopidogrel, beta-blockers, aspirin, ace-inhibitors, and statins unless contraindicated. The protocol was approved by the review board or ethical committee of each hospital.

Of this original patient population (n=199), a number of 128 patients consented in undergoing ^{99m}Tc-sestamibi SPECT imaging three days after the cardiac event and are described in the current analysis. None of these patients developed any additional cardiac events within the period of the PCI and SPECT imaging. Figure 1 displays a patient flow chart, including the reasons for not pursuing SPECT.

Exact time lines were generated from the onset of symptoms to hospital admission (symptoms-to-admission) and from admission to PCI (door-to-balloon). Angiographic analysis was blinded and included initial and final Thrombolysis In Myocardial Infarction (TIMI) flow grade of the culprit vessel by consensus of two experienced interventional cardiologists.[15] Enzymatic infarct size was estimated by assessment of the peak CK-MB release. The definition of a pathological Q-wave, i.e. > 30 ms in two or more contiguous ECG leads, was as described previously.[16] Q-waves reported in this study were determined at the time of hospital discharge.

Figure 1



Flow chart of the originally included acute myocardial infarction patients described in the study by Peels et al. who were randomized to primary PCI in either the on or off-site center. Reasons for not performing SPECT 3 days after myocardial infarction are given. STEMI ST-elevation myocardial infarction, CABG coronary artery bypass grafting, MI myocardial infarction, PCI primary angioplasty, SPECT single photon emission computed tomography

Scintigraphic Study

Rest gated myocardial perfusion images were acquired approximately one hour after an intravenous injection of 700 MBq ^{99m}Tc-sestamibi using SPECT. A dual-head camera system, equipped with low-energy high-resolution collimators was used for myocardial imaging (Millennium VG; GE Healthcare). Images were acquired in a 64 x 64 matrix with an acquisition time of 30 s per image. The SPECT images were gated with 8 frames per cardiac cycle, the RR time acceptance was set at 20%. Transaxial slices were reconstructed via backprojection with a ramp filter, followed by a butterworth filter. Using commercially available software, polar maps were created of the relative distribution of tracer uptake throughout the entire left ventricle (LV). Each polar map was normalized to its individual maximum and the defect size was defined as < 50% uptake area of the polar map and was subsequently expressed as a percentage of the LV. From the gated images, end-diastolic (LVEDV) and end-systolic volumes (LVESV) are given, including the ejection fraction (LVEF).

Statistical Analysis

Data were expressed as mean ± SD. Frequencies were compared using the exact Fisher exact test, continuous variables were compared using the independent t test. Comparison of multiple data sets was performed using ANOVA, and specific differences were identified by a Student's t test corrected for multiple comparisons with the Bonferroni adjustment. Linear regression was used to analyze the relationship between continuous variables. Logistic regression analysis with a step-wise backward exclusion procedure was performed to identify independent predictors for scintigraphic infarct size > 12%. Odd ratios (OR) with 95% confidence intervals (CI) were calculated. All analyses were performed using SPSS 12 (SPSS Inc., Chicago, Illinois). A p value < 0.05 was considered significant.

RESULTS

Of the 128 analyzed patients, 60 were randomized to on-site and 68 to off-site PCI. Patient characteristics are listed in Table 1. The groups were comparable in terms of age, sex, and clinical risk profile.

Table 1 Patient characteristics

	On-Site (n=60)	Off-Site (n=68)	*p*
Age (yrs)	64 ± 11	61 ± 12	0.62
Men	44 (73%)	49 (72%)	0.87
Diabetes mellitus	4 (7%)	2 (3%)	0.32
Smoker	24 (40%)	33 (49%)	0.59
Hypertension	15 (25%)	20 (29%)	0.58
Anterior myocardial infarction	23 (38%)	26 (38%)	0.99
Previous PCI	2 (3%)	2 (3%)	0.90
Previous CABG	3 (5%)	2 (3%)	0.55
TIMI flow before PCI < 2	41 (68%)	51 (75%)	0.40
TIMI flow after PCI < 2	4 (7%)	2 (3%)	0.32
Multi (> 1) vessel disease	23 (38%)	28 (41%)	0.74
Killip class > 1	1 (1%)	1 (2%)	0.92
Summed ST deviation (mm)	15 ± 12	17 ± 9	0.27
Q-wave at discharge	32 (53%)	42 (62%)	0.24
Symptoms-to-admission (min)	158 ± 131	163 ± 201	0.87
Door-to-balloon (min)	125 ± 59	94 ± 54	<0.01
Time-to-treatment (min)	286 ± 146	257 ± 211	0.39

PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; TIMI = thrombolysis in myocardial infarction

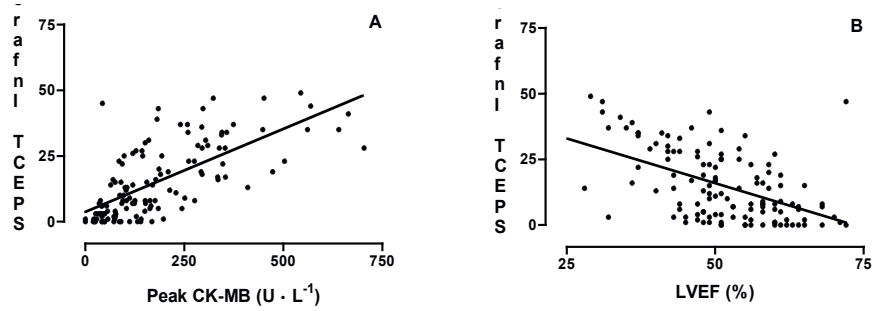
Time-to-Treatment

The time lines revealed no difference in mean time from onset of symptoms to presentation at the clinic between groups. However, the door-to-balloon time was significantly, i.e. 31 minutes, shorter in the off-site center, although this reduction did not result in a significant reduction in time-to-treatment (Table 1). A total of 13 out of 128 patients (10%) were treated within two hours after the onset of symptoms, of whom 10 were assigned to the off-site center (p=NS).

Scintigraphic and Enzymatic infarct Size Data

Table 2 shows the SPECT derived LV volumes and function as well as the scintigraphic and enzymatic estimated infarct size. Average mean scintigraphic infarct size for all patients was 15 ± 14% of the myocardium and was comparable for the on versus off-site PCI groups. Biochemical release of CK-MB was also comparable between groups. As depicted in Figure 2, linear regression analysis demonstrated a good correlation between the scintigraphic and enzymatic estimated infarct size (r=0.69, p<0.001). Furthermore, LVEF was related to scintigraphic infarct size (r=-0.51, p<0.001).

Figure 2



Scatter plots showing the correlation between the SPECT estimated infarct size and peak CK-MB release (r = 0.69, p < 0.01) as well as LVEF (r = -0.51, p <0.01).

Table 2 SPECT data and biochemical enzyme release

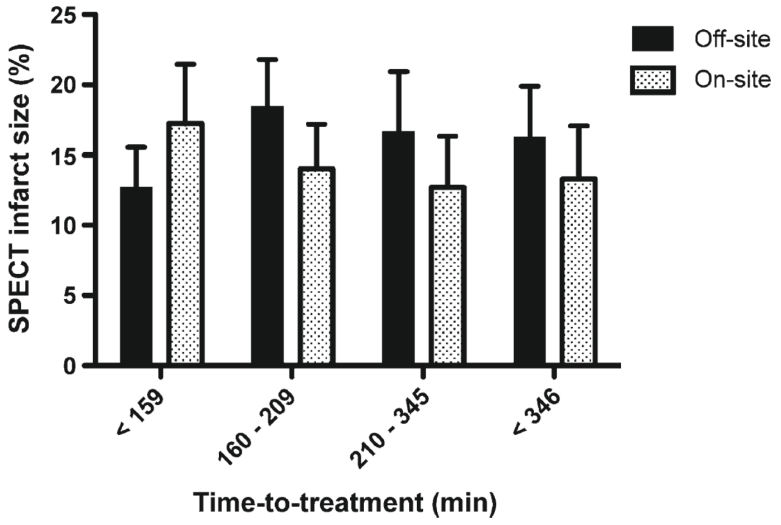
	On-Site (n=60)	Off-Site (n=68)	*p*
LVESV (mL)	58 ± 26	65 ± 31	0.17
LVEDV (mL)	118 ± 36	124 ± 38	0.34
LVEF (%)	52 ± 12	50 ± 11	0.12
Scintigraphic infarct size (%)	14 ± 12	16 ± 15	0.35
Peak CK-MB release (U · L^{-1})	161 ± 136	204 ± 160	0.11

SPECT = single photon emission computed tomography; LVESV = left ventricular end-systolic volume; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction

Determinants of Scintigraphic Infarct Size

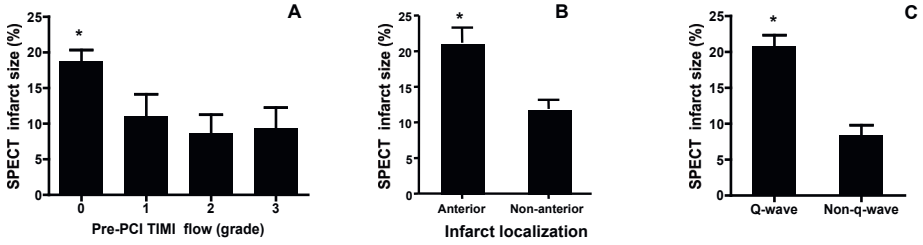
As continuous variables, time-to-treatment and scintigraphic infarct size did not show a significant correlation (r=-0.02, p=0.87), nor were time-to-admission (r=0.02, p=0.83) or door-to-balloon time (r=-0.11, p=0.22) related to infarct size. This lack of agreement is further illustrated in Figure 3, where infarct sizes for quartiles of time-to-treatment per treatment arm did not differ. Table 3 lists the variables included in the multivariate analyses. After step-wise backward exclusion of the non-significant variables, multivariate logistic regression analysis indicated that an infarct size > 12% could independently be predicted by TIMI 0/1 flow grade at initial coronary angiography before PCI (OR 3.125, 95% CI 1.17–8.33, p=0.023), anterior wall localization of the myocardial infarction (OR 3.44, 95% CI 1.38–8.55, p<0.01), and the development of pathological Q-waves (OR 5.07, 95% CI 2.10–12.25, p<0.01). Accordingly, as displayed in Figure 4, infarct size was significantly larger in patients with TIMI 0 flow before PCI (18±14%) compared with higher flow grades (TIMI 1-3 = 11±11, 9±13, and 9±10%, respectively, p <0.01 versus TIMI 0) anterior wall localization (21±15 versus 12±12%, p<0.01), and in those patients who developed an electrographical Q-wave pattern in the infarct area (21±14 versus 8±10%, P<0.01).

Figure 3



Quartiles of time-to-treatment in relation to SPECT estimated infarct size for both the on and off-site treated patients. There were no differences in infarct size between the four timeframes of treatment in both treatment arms. Bar chart represents mean values plus standard error of the mean.

Figure 4



SPECT estimated infarct size is significantly (p < 0.01) larger for pre-PCI TIMI 0 flow compared with higher flow grades, anterior wall infarct localization, and the development of pathological Q-waves. Bar charts represent mean values plus standard error of the mean.

Table 3 Multivariate logistic regression analysis of the predictors of infarct size > 12% measured with SPECT.

	OR	95% CI	*p*
Off-site center	0.49	0.19 – 1.28	0.14
Age (per 10 years)	0.97	0.57 – 1.66	0.91
Female sex	1.73	0.52 – 5.76	0.37
Current smoking	1.53	0.56 – 4.15	0.41
Hypertension	0.55	0.18 – 1.66	0.29
Diabetes mellitus	1.31	0.16 – 10.82	0.80
Anterior myocardial infarction	3.45	1.23 – 9.09	0.02
Summed ST deviation (per 10 mm)	1.31	0.73 – 2.32	0.37
Multi (>1) vessel disease	0.94	0.34 – 2.64	0.91
TIMI flow before PCI < 2	3.70	1.23 – 11.11	0.02
Q-wave at discharge	6.84	2.50 – 18.67	<0.01
Symptoms-to-admission (per 30 minutes)	1.04	0.62 – 1.72	0.89
Door-to-balloon (per 30 minutes)	1.01	0.57 – 1.80	0.97
Time-to-treatment (per 30 minutes)	0.96	0.56 – 1.67	0.89

SPECT = single photon emission computed tomography, OR = odds ratio, CI = confidence interval

DISCUSSION

The present study was conducted to test the hypothesis that a more timely achieved mechanical reperfusion in STEMI patients, by performing a primary PCI at the center of presentation versus deferral to a nearby tertiary center, could limit infarct size. The results indicate that despite a reduction of door-to-balloon time of approximately 30 minutes, infarct size and left ventricular volumes and function are not appreciably affected. Instead, a poor TIMI flow grade of the infarct related artery at initial

angiography and anterior infarction appeared to be more significant determinants of infarct size. Furthermore, the development of pathological Q-waves also proved to be an independent predictor of more extensive myocardial necrosis.

Time-to-treatment

The relationship between the duration of coronary artery occlusion and the extent of myocardial necrosis has been well defined in animal models.[17] Cell death begins as early as 20 minutes after coronary occlusion and infarct size expands for up to six hours according to the wave-front phenomenon. Accordingly, a clear link between infarct size and timing of reperfusion therapy with thrombolytic agents has been established.[18] Conversely, the impact of treatment delay on prognosis and infarct size in patients undergoing primary angioplasty has shown to be less straightforward and results from different studies have been conflicting.[9 11 19 20] As in our study, in which a relationship between timing of reperfusion and infarct size could not be established, sample size probably plays a pivotal role in revealing such a link. In fact, predominantly large clinical trials and meta-analyses have been able to demonstrate that time to treatment is indeed important in salvaging acutely jeopardized myocardium when performing a primary PCI.[9 20]

Off-site versus on-site primary PCI

As previously reported for this cohort of patients by Peels et al,[6] door-to-balloon time was significantly reduced by performing the intervention at the community hospital of patient presentation as opposed to emergency transferal to a tertiary center with on-site cardiac surgical facilities. As already mentioned, this more timely delivery of mechanical reperfusion did not result in a reduction of SPECT estimated infarct size. The reduction in door-to-balloon of 30 minutes, however, was relatively short, particularly given the average time-to-treatment of 4.5 hours, which may have obscured a potential benefit. Moreover, myocardial salvage is particularly pronounced within the first two hours of infarction and levels off in the ensuing hours, [21] partly explaining the lack of differences in infarct sizes between treatment centers in the current study, as very few patients (10%) were treated within this early timeframe. It is of interest to note that 10 of these 13 patients were assigned to the off-site center.

Pre-PCI TIMI flow grade

(Partial) restored antegrade flow of the infarct related artery prior to coronary intervention was associated with limited myocardial damage compared with complete coronary occlusion. This observation underscores the notion that early pre-PCI reperfusion has salutary effects, and is in line with previous reports demonstrating

improved clinical outcome and reduced infarct size in patients with sufficient coronary flow at initial angiography before primary angioplasty.[10 22 23] It appears that reperfusion before primary PCI is of more importance than timing of the intervention itself. Although in the current study there was no distinction in myocardial salvage with increasing TIMI flow grades from 1 to 3 (Figure 3), pooled analysis from clinical trials indicate that there is most likely a gradual benefit with increasing TIMI flow grade. [22 24] Comparable with other reports, approximately 30% of patients displayed TIMI 2 or 3 flow at initial angiography.[22] An obvious treatment goal would therefore be to increase this rate of early reperfusion in the setting of a primary PCI. Accordingly, so called facilitated PCI, i.e. administration of thrombolytic agents, anticoagulants, and / or anti-platelets before PCI, could prove to be beneficial. However, clinical trials thus far have yielded conflicting results using this strategy. [25-27]

Infarct localization and Q-wave infarction

Anterior localization of acute myocardial infarction has long been recognized as a predictor of a relative large infarct size with a concomitant poorer prognosis. [28 29] In fact, in a recent publication including close to 1200 patients undergoing primary PCI, left anterior descending artery as the infarct related artery was one of the strongest determinates of the extent of myocardial scarring estimated by SPECT.[24] Consequently, infarct localization has been taken up in well validated risk stratification algorithms for STEMI patients.[30] Our data therefore further confirm the importance of infarct localization in predicting infarct size.

Likewise, the relationship between the development of pathological Q-waves has been linked to larger myocardial infarctions before, although an unfavorable outcome compared with non-q-wave infarction has not been established. [28 29] As recently demonstrated by Moon et al. in a contrast enhanced cardiovascular magnetic resonance imaging (CMR) study, the occurrence of post-myocardial Q-waves is indeed indicative of increased total scar burden, rather than the extent of transmurality.[31]

Limitations

The number of investigated patients was relatively small and may explain why the impact of time on infarct size was not apparent. The same argument holds true for previously demonstrated gender related correlates of scar size.[24]

In addition, irreversible damage was assessed using SPECT, which is characterized by relatively low spatial resolution. More sensitive imaging techniques, such as contrast enhanced CMR, may have yielded different results.[10] Furthermore, SPECT imaging was performed three days after infarction whereas it is known that scintigraphic infarct size regresses in the ensuing months of follow-up and final infarct size may therefore have

been overestimated.[14] On the other hand, this effect occurs equally in both treatment arms, making the comparison between patients groups still valid. Furthermore, the extent of infarction was similar to a recently published post infarction SPECT analysis where scintigraphy was performed 30 days after the event.[24]

Finally, selection of patients who participated in the current study was biased in terms of clinical condition, i.e. those patients who were in a poor clinical condition were unable to undergo SPECT imaging. As a consequence, the study population constituted low-risk STEMI patients with a relatively uncomplicated clinical course.

Practical Implications

Off-site primary PCI appears to be a feasible alternative to emergency transferal to an on-site emergency intervention center.[6 7] In addition, performing primary PCI at off-site centers increases the availability of this preferred treatment in patients with acute myocardial infarction and adds to a number of strategies to more rapidly achieve reperfusion.[32] This could especially benefit patients inhabiting regions where tertiary interventional centers are geographically remote and / or for those patients who are hemodynamically compromised and consequently most likely to benefit from early intervention.[12] Nonetheless, some determinants of infarct size, such as infarct localization, are not amendable to change and pharmacologically induced pre-PCI reperfusion as well as reduction in time-to-treatment strategies are reaching their current limits. Future studies will therefore likely shift towards preventing reperfusion injury in an effort to minimize the extent of myocardial necrosis after PCI.[33]

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Chapter 4

Long term clinical outcome and MIBI SPECT parameters in off-site percutaneous coronary interventions

Maarten de Mulder; Friso M. van der Zant; Paul Knaapen;
Jan H. Cornel; Victor A. Umans

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ABSTRACT

Background and aim: Primary percutaneous coronary intervention (PCI) is the preferred treatment option for acute myocardial infarction (MI). Off-site PCI reduces time-to-treatment, which could potentially lead to enhanced clinical outcomes. Therefore, we investigated whether off-site PCI improves 5-year clinical outcomes compared to on-site PCI and whether this is related with in hospital MIBI spect parameters.

Methods: We describe the 5 year follow up for a combined endpoint of death or re-infarction in 128 patients with acute MI who were randomly assigned to undergo primary PCI at the off-site centre (n=68) or to transfer to an on-site centre (n=60). Three days after PCI, ^{99m}Tc-sestamibi SPECT was performed to estimate infarct size. A multivariate Cox regression model was created to study the relation between MIBI spect parameters and long term clinical outcomes.

Results: After a mean follow up of 5.8 ± 1.1 years, 25 events occurred. Off-site PCI significantly reduced door-to-balloon time compared to on-site PCI (94 ±54 versus 125 ±59 min, p= 0.003). However, infarct size (17 ±15 versus 14 ±12%, p=0.34) and 5 year death or infarct rate (21% versus 18%, p = 0.75) were comparable between treatment centers. With multivariate analysis only Killip class ≥2 and Q wave MI, but not scintigraphic data, predicted long term clinical outcomes.

Conclusion: Off site PCI reduced door-to-balloon time with a comparable 5 year death or infarct rate. Parameters from resting MIBI spect on day 3 after MI did not predict long term clinical outcomes.

INTRODUCTION

Primary percutaneous coronary intervention (PCI) is widely accepted as the preferred reperfusion strategy to reduce infarct size in patients with acute ST-segment elevation myocardial infarction (STEMI).[1] Trials comparing PCI in STEMI patients presented to large community hospitals without on-site cardiac surgical backup (off-site) versus PCI in a tertiary interventional centre (on-site) have demonstrated that off-site PCI is feasible and results in comparable short term clinical outcome.[2,3] Treatment in off-site centers results in a significant reduction in time-to-treatment, which could potentially lead to a reduction in infarct size by more timely salvage of acutely jeopardized ischemic myocardium.[4-6] In that respect, off-site PCI without transfer delay in STEMI patients might even prove to be superior in limiting infarct size.[7,8]

We extended our earlier findings [9] and investigated whether off-site PCI improves 5-year clinical outcomes compared to on-site PCI and if this is related with in hospital ^{99m}Tc-sestamibi SPECT parameters.

METHODS

Patients

This study describes the 5 year follow up of STEMI patients who in a previous study were randomly assigned to primary PCI at the centre of presentation in a community hospital (off-site, n=103) or to transfer to a remote tertiary centre with surgical backup facilities (on-site, n=96).[6] The in hospital outcomes in relation to ^{99m}Tc-sestamibi SPECT parameters in 128 patients were described previously.[9] STEMI patients who presented within 6 hours after the onset of symptoms, who were able to give informed consent and did not require mechanical ventilatory assistance, were eligible for randomization. Upon arrival at the cardiac care unit and prior to randomization, all patients were immediately treated with heparin, aspirin, nitroglycerin, and abciximab unless contraindicated. Standard treatment after the PCI procedure included clopidogrel, beta-blockers, aspirin, ace-inhibitors, and statins unless contraindicated. The protocol was approved by the review board or ethical committee of each hospital.

Of the original consecutive patient population (n=199), 128 patients consented in undergoing ^{99m}Tc-sestamibi SPECT imaging three days after the cardiac event. Failure to undergo ^{99m}Tc-sestamibi SPECT was due to early death (5), emergency CABG (1), previous MI (11), unable or unwilling to provide consent (42), no PCI was performed and the absence of MI (4).

Scintigraphy

Rest gated myocardial perfusion images were acquired approximately one hour after an intravenous injection of 700 MBq ^{99m}Tc-sestamibi using SPECT. A dual-head camera system, equipped with low-energy high-resolution collimators was used for myocardial imaging (Millennium VG; GE Healthcare). Images were acquired in a 64×64matrix with an acquisition time of 30 s per image. The SPECT images were gated with 8 frames per cardiac cycle, the RR time acceptance was set at 20%. Transaxial slices were reconstructed via backprojection with a ramp filter, followed by a butterworth filter. Using commercially available software, polar maps were created of the relative distribution of tracer uptake throughout the entire left ventricle (LV). Each polar map was normalized to its individual maximum and the defect size was defined as < 50% uptake area of the polar map and was subsequently expressed as a percentage of the LV.

Follow up

Information on survival status was obtained in all patients in June 2009. Digital hospital records were reviewed for all cause mortality and enzymatically confirmed myocardial re infarction (re-MI), i.e. typical chest pain plus CKMB or troponin I above the upper limit of normal, i.e. >16 U/l and >0,45 ug/l respectively.

Statistical Analysis

Data are expressed as mean ± standard deviation (SD). Frequencies were compared using Fisher exact test and Students T test, continuous variables were compared using the independent t test. Comparison of multiple data sets was performed using ANOVA, and specific differences were identified by a Student's t test corrected for multiple comparisons with the Bonferroni adjustment.

The incidence of the combined endpoint over time was evaluated according to the method of Kaplan-Meier (KM) and differences between groups of patients were analyzed with the log rank test. Univariate analysis of the combined endpoint over time for baseline and ^{99m}Tc-sestamibi SPECT parameters was performed using Cox proportional hazard regression. Variables with a p-value <0.5 in univariate analysis were included in the multivariable model, so that no (measured) confounders were missed, using the enter method. All analyses were performed using SPSS 14 (SPSS Inc., Chicago, Illinois). A p value < 0.05 was considered significant.

RESULTS

The study cohort consisted of 128 patients, 93 (73%) were men and the mean age was 62 ± 12 SD years. Baseline characteristics and risk profile were comparable between the 60 patients randomized to on-site and 68 patients randomized to off-site PCI, see table 1. Mean follow up was 5.8 years ± 1.1 SD. In this time frame, 15 re-MIs were documented and 10 patients died. Kaplan Meier analysis demonstrated that there was no difference in long term outcomes and centre of randomization, log rank 0.715, figure 1.

Table 1 Patient characteristics

	On-Site (n=60)	Off-Site (n=68)	*p*
Age (yrs)	64 ± 11	61 ± 12	0.62
Men	44 (73%)	49 (72%)	0.87
Diabetes mellitus	4 (7%)	2 (3%)	0.32
Smoker	24 (40%)	33 (49%)	0.59
Hypertension	15 (25%)	20 (29%)	0.58
Family history of CVD	27 (45%)	28 (41%)	0.66
Previous PCI	2 (3%)	2 (3%)	0.90
Previous CABG	3 (5%)	2 (3%)	0.55
Killip class > 1	1 (1%)	1 (2%)	0.92
Summed ST deviation (mm)	15 ± 12	17 ± 9	0.27
Anterior myocardial infarction	23 (38%)	26 (38%)	0.99
Q-wave	32 (53%)	42 (62%)	0.24
Multi (> 1) vessel disease	23 (38%)	28 (41%)	0.74
TIMI flow *pre* PCI <2	38 (67%)	51 (75%)	0.31
TIMI flow *post* PCI <2	1 (2%)	2 (3%)	0.67
Symptoms-to-admission (min)	158 ± 131	163 ± 201	0.87
Symptoms – balloon (min)	286 ± 146	257 ± 211	0.38
Symptoms – arrival (min)	158 ± 131	163 ± 201	0.87
Door -to-balloon (min)	125 ± 59	94 ± 54	0.003
Time-to-treatment (min)	286 ± 146	257 ± 211	0.39

CVD = cardiovascular disease; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; TIMI = thrombolysis in myocardial infarction

Figure 1 Difference in long term follow up between centres for the combined endpoint of either death or reinfarction. Log rank 0.715

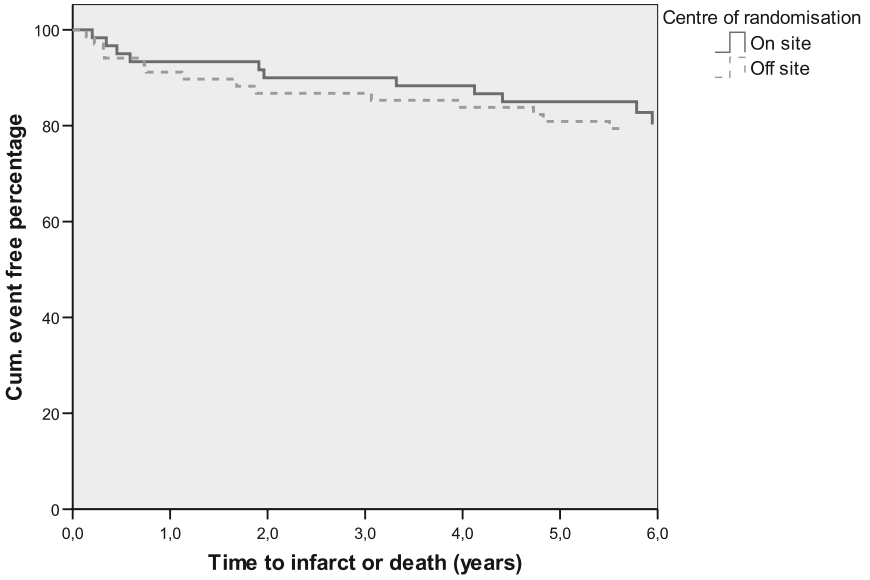

Table 2 Comparison of centres regarding MIBI spect data and 5 year clinical outcomes

	On-Site (n=60)	Off-Site (n=68)	p
Death or infarct	11 (18%)	14 (21%)	0.75
LVESV (mL)	58 ± 26	65 ± 31	0.17
LVEDV (mL)	118 ± 36	124 ± 38	0.34
LVEF (%)	52 ± 12	50 ± 11	0.06
Infarct extent (%)	14 ± 12	17 ± 15	0.34
SRS	11 ± 9.6	12 ± 12	0.33
SMS	19 ± 13	24 ± 20	0.06
STS	14 ± 12	17 ± 15	0.028
Peak CK	1611 ± 1838	1894 ±1609	0.35
Peak CK-MB (U/L)	161 ± 136	204 ± 160	0.11

Continuous data are presented as mean values ± standard deviation. Dichotomous data are presented as numbers and percentages

SPECT = single photon emission computed tomography; LVESV = left ventricular end-systolic volume; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; SRS = Summed rest Score; SMS = Summed Motion Score; STS = Summed Thickening Score; CK= Creatin Kinase

Table 3 Uni & Multivariate analysis for the long term combined endpoint (death / re-MI)

	Crude Hazard Ratio and 95% CI	Multivariate adjusted Hazard Ratio and 95% CI	P value
Off site centre	1.2 (0.53 – 2.6)	1.3 (0.56 – 3.2)	0.51
Age (yrs)	1.03 (0.99 – 1.06)	1.03 (0.99 – 1.1)	0.14
Men	1.0 (0.42 – 2.4)	---	
Diabetes mellitus	3.2 (0.97 – 11)	2.5 (0.63 – 9.7)	0.20
Smoker	1.3 (0.72 – 2.2)	1.3 (0.74 – 2.3)	0.36
Hypertension	1.3 (0.54 – 2.9)	---	
Family history of CVD	0.60 (0.26 – 1.4)	0.76 (0.31 – 1.8)	0.54
Previous PCI	0.05 (0 – 600)	---	
Previous CABG	1.1 (0.15 – 8.3)	---	
Killip class > 1	2.8 (0.38 – 21)	25.1 (2.0 – 315)	0.013
Summed ST deviation (mm)	1.03 (0.72 – 1.5)	---	
Anterior myocardial infarction	1.3 (0.60 – 2.9)	1.4 (0.49 – 4.0)	0.54
Q-wave	3.1 (1.2 – 8.4)	3.4 (1.02 – 11.2)	0.046
Multi (> 1) vessel disease	1.1 (0.49 – 2.4)	---	
TIMI flow *pre* PCI <2	1.2 (0.51 – 2.8)	---	
TIMI flow *post* PCI <2	0.46 (0.06 – 3.4)	0.75 (0.08 – 7.3)	0.80
Symptoms-to-admission (hrs)	1.06 (0.96 – 1.16)	0.94 (0.61 – 1.5)	0.79
Door-to-balloon (hrs)	1.01 (0.68 – 1.5)	---	
Time-to-treatment (hrs)	1.05 (0.96 – 1.15)	1.09 (0.71 – 1.7)	0.69
LVESV (10 mL)	1.02 (0.90 – 1.2)	---	
LVEDV (10 mL)	1.01 (0.91 – 1.1)	---	
LVEF (%)	1.0 (0.97 – 1.03)	---	
Infarct extent (%)	1.02 (0.99 – 1.04)	1.0 (0.82 – 1.2)	0.97
SRS	1.02 (0.99 – 1.05)	1.03 (0.80 – 1.3)	0.83
SMS	1.01 (0.99 – 1.03)	1.03 (0.95 – 1.1)	0.50
STS	1.01 (0.99 – 1.03)	0.95 (0.86 – 1.1)	0.35

Variables with a p-value <0.5 in univariate analysis and all scintigraphic variables were included in the multivariable model.
MI = Myocardial Infarction; LVESV = left ventricular end-systolic volume; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; SRS = Summed rest Score; SMS = Summed Motion Score; STS = Summed Thickening Score

Time to treatment and centre of randomization

The time lines revealed no difference in mean time from onset of symptoms to presentation at the clinic between groups. However, the door-to-balloon time was with 31 minutes significantly, shorter in the off-site centre, although this reduction did not result in a significant reduction in pain-onset time-to-treatment. Neither did this reduction of door-to-balloon time result in an enzymatically smaller infarct size in off-site treated patients, peak CKMB 204 vs. 161 U/l, *p* value 0.11, table 2. In uni- & multivariate analysis this was further confirmed as none of the time line variables had a significant relation with long term clinical outcomes.

Scintigraphic data and centre of randomization

Various scintigraphic variables were analyzed, but most were comparable between on and off-site PCI. However, the summed thickening score (STS) was smaller in patients randomized to on-site treatment, 14 ±12 versus 17 ±15 SD, *p* value 0.028, see table 2.

Scintigraphic data and 5 year clinical outcome

We investigated if parameters from a ^{99m}Tc-sestamibi SPECT on day 3 were related to the combined endpoint of death or re-MI at 5 years follow up. However, in uni- and multivariate Cox regression analysis none of the assessed scintigraphic parameters was related to this combined endpoint. Only a higher Killip class and Q wave infarction were related, table 3.

DISCUSSION

The results indicate that despite a 31 minutes reduction of door-to-balloon time, scintigraphic parameters and 5 year clinical outcome are not considerably affected by performing off site PCI. Additionally, in our series, off site PCI is equally safe compared to on site PCI. However, the reduction in door to balloon time did not result in improved 5 year clinical outcomes with off site PCI.

Scintigraphic data and long term clinical outcome

Scintigraphic parameters did not predict 5 year clinical outcomes. This is in contrast to the results of Spinelli et al who found that dysfunctional but viable myocardium with preserved systolic thickening was the strongest predictor of cardiovascular risk.[10] However, the infarct size in their study was quite small, while larger infarcts, i.e. > 12 % of LV myocardial mass correlate to mortality.[11] Clinical factors that independently predicted 5 year clinical outcomes in our series were a higher Killip class and Q-wave myocardial infarction.

On site versus off site PCI; influence on clinical and scintigraphic parameters

In spite of a reduced door-to-balloon time, off site PCI did not result in a significantly different infarct size or long term clinical outcomes, although the STS was smaller in on site PCI. However, the reduction in door-to-balloon time with 31 minutes in off site PCI was relatively short. Myocardial salvage is particularly pronounced within the first two hours of infarction and levels off in the ensuing hours.[12] Given the average time-to-treatment of 4.5 hours, this may have obscured a potential benefit.

Particularly as few patients (10%) were treated within this early timeframe.

Door to balloon time; influence on clinical and scintigraphic parameters

Earlier large studies demonstrated that time to treatment is important in salvaging acutely jeopardized myocardium when performing a primary PCI.[5 13] However, in our study a relationship between timing of reperfusion and infarct size or 5 year clinical outcome could not be established. This is similar to results from smaller studies that provided conflicting results with the larger studies.[6 14]

Limitations

The number of investigated patients was relatively small and may explain why the impact of time on infarct size or long term clinical outcome was not apparent. In addition, this study was performed in an area with a good infrastructure and relatively small inter-hospital transfer distances. In a more remote area, differences might actually become apparent.

The ^{99m}Tc-sestamibi SPECT might have been to early, since early cardiac remodeling after the acute phase takes several weeks before a final equilibrium has been reached.[15] Therefore it might have been more appropriate to perform this scan at a later stage, e.g. 6 weeks after the event.

CONCLUSION

After a mean follow up of 5.8 years, long term clinical outcomes and scintigraphic parameters were not affected by performing off site PCI, despite a 31 minutes reduction of door-to-balloon time. Parameters from rest gated ^{99m}Tc-sestamibi SPECT on day 3 after MI did not predict long term clinical outcomes.

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Supplement:
Test questions for the CVOI (Netherlands Institute for Continuing Cardiovascular Education)

With:
De Mulder et al *Long term clinical outcome and MIBI SPECT parameters in percutaneous coronary interventions* Neth Heart J (2011) 19:68–72

Correct Answer	**Q 1**	What is an effective strategy to shorten door to balloon time?
	A	Increase awareness of heart attack symptoms among healthy individuals
X	**B**	Shorten transport time by using off-site PCI facilities
	C	Shorten transport time by using air transport as standard
	D	Decrease the distance from patient to hospital by building more hospitals

Correct Answer	**Q 2**	What MIBI spect parameter predicted 5 year clinical outcomes in this study?
	A	Left ventricular ejection fraction
	B	Infarct extent
	C	Summed thickening score
X	**D**	None of the above

Correct Answer	**Q 3**	Which statement is true? In the current study 5 year clinical outcomes are predicted by:
X	**A**	Killip class and presence of Q waves
	B	Door to balloon time and Killip class
	C	TIMI 2 flow post PCI and door to balloon time
	D	Age and off site PCI

Correct Answer	**Q 4**	The authors mention a limitation of the MIBI SPECT scan, which one and why?
	A	The scan is performed too early. Stress hormones released during the infarction still influence proper distribution of ^{99m} Technetium.
	B	The scan is performed too late. It should be performed prior to PCI in order to get a proper estimate of the area at risk.
	C	They only performed a rest scintigraphy. When additional stress images were collected, LVEF could be better estimated.
X	**D**	The scan is performed too early. Cardiac remodelling has not yet completed while it is known that scintigraphic infarct size regresses in the ensuing months.

Correct Answer	Q 5	Regarding radiation safety, what statements are true or false? 1) The recommended dose of ^{99m} Technetium for MIBI scinitgraphy is 350 Bq. When using a double dose, the radiation exposure of 2,7 mSv also doubles 2) When Thallium is used instead of ^{99m} Technetium, radiation exposure decreases 3) Cardiac CT angiography provides both information on cardiac anatomy and function with less radiation as compared to conventional coronary angiography.
	A	Statement 1 & 2 are true, statement 3 is false
	B	Statement 1 & 3 are true, statement 2 is false
X	**C**	Statement 1 is true, statement 2 & 3 are false
	D	Statement 2 is true, statement 1& 3 are false
	E	Statement 3 is true, statement 1& 2 are false

Correct Answer	Q 6	Time is muscle. However, despite a reduction of 31 minutes with off site PCI, this did not lead to a reduction of infarct size. What is probably the most important explanation for this phenomenon?
X	**A**	Ninety percent of patients in this study did not arrive within the first 2 golden hours. Consequently, most potential benefit is lost and a reduction of half an hour becomes less relevant.
	B	The 31 minutes difference between off site and on site treatment was statistically not significant
	C	Timing of the MIBI SPECT was inappropriate, therefore infarct size can not be compared between off site and on site treatment
	D	No proper explanation can be given

Correct Answer	Q 7	What trial design would be the best to investigate the influence of door to balloon time on clinical outcomes from a methodological point of view?
X	**A**	A large randomised clinical trial (RCT) where patients with suspected acute MI are randomised to either immediate presentation by the ambulance at the cath lab or at the emergency room allowing patient evaluation by a physician.
	B	Prospective cohort study where patients are either taken to an on site or off site PCI centre, depending on traffic conditions at the discretion of the ambulance personnel.
	C	Retrospective cohort study where the outcomes of patients treated within 2 hours are compared with those treated after 2 hours.
	D	A meta analysis of small RCT's comparing on site and off site PCI

Correct Answer	Q 8	Which statement regarding off site PCI is true? Off site PCI:
	A	Can be performed everywhere, given that an experienced interventional cardiologist is present.
X	**B**	Requires a close cooperation between the off site centre and the supporting cardiothoracic centre. Only then off site PCI is safe and feasible.
	C	Is superfluous as the capacity of centres with on site cardiac surgery facilities to perform extra PCI's is sufficient
	D	Is preferred over on site PCI when this implies that patients are closer to their family

Correct Answer	Q 9	When the diagnosis ST elevation MI has been established in the ambulance, where should the patient be admitted
	A	Nearest hospital with ICU/CCU
	B	Nearest emergency room
	C	Nearest hospital with PCI and cardiothoracic surgery facilities
X	**D**	Nearest CATH lab with PCI facilities, either with or without cardiothoracic surgery facilities

Correct Answer	Q 10	How many PCI centres are currently operational in the Netherlands and how many are working with off-site cardiothoracic surgery back-up?
	A	21 PCI centres, 15 with on site surgery and 6 with off site surgery
	B	22 PCI centres, 17 with on site surgery and 5 with off site surgery
X	**C**	21 PCI centres, 16 with on site surgery and 5 with off site surgery
	D	22 PCI centres, 18 with on site surgery and 4 with off site surgery

PART 2

CHAPTER 5

Admission glucose does not improve GRACE score at 6 months and 5 years after myocardial infarction

Maarten de Mulder; Tjeerd van der Ploeg; Guus A de Waard;
Eric Boersma; Victor A Umans

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ABSTRACT

Objective: Admission plasma glucose (APG) is a biomarker that predicts mortality in myocardial infarction (MI) patients. Therefore, APG may improve risk stratification based on the GRACE risk score.

Methods: We collected data on baseline characteristics and long-term (median 55 months) outcome of 550 MI patients who entered our hospital in 2003 and 2006. We determined the GRACE risk score at admission for each patient, which was entered in a logistic regression model, together with APG, to evaluate their prognostic value for 6-month and 5-year mortality.

Results: Patients with APG ≥7.8 mmol/l had higher mortality than those with APG levels <7.8 mmol/l, 6-months: 13.7% vs. 3.6%, *p*-value < 0.001; 5-years: 20.4% vs. 11.1%, *p*-value 0.003. After adjustment for the GRACE risk score variables, APG appeared a significant predictor of 6-month and 5 year mortality, adjusted OR 1.17 (1.06 – 1.29) and 1.12 (1.03 – 1.22). The combination of the GRACE risk score and APG increased the models' performance, (discrimination C-index 0.87 vs. 0.85), although the difference was not significant, *p*-value 0.095. Combining the GRACE risk score and APG reclassified 12.9% of patients, but net reclassification improvement (NRI) was non significant, *p*-value 0.146.

Conclusion: APG is a predictor of 6-month and 5-year mortality, each mmol/l increase in APG was associated with a mortality increase of 17% and 12% respectively, independent of the GRACE risk score. However, adding APG to the GRACE model did not result in significantly improved clinical risk stratification.

BACKGROUND

In medicine, risk models are usually applied to assess a patients' risk for events in order to guide clinicians towards the best treatment strategy to prevent these events. For patients admitted with (suspected) myocardial infarction (MI) the risk model developed by the Global Registry of Acute Coronary Events (GRACE) investigators is well established and can be used to predict in-hospital and 6-month mortality. [1 2] Although the validity and clinical usefulness of this model has been demonstrated, there still is room for improvement, as the discriminative capacity expressed by the C-statistic of the 6-month mortality model was 0.81.

Biomarkers might be of additional value to risk models as they can provide information on various pathological processes, better so than most clinical features. Before a novel biomarker can be implemented into daily practice, several phases of evaluation should be completed. After proof of concept and prospective validation, the incremental value and clinical utility of a biomarker should be assessed according to Hlatky et al.[3]

Admission plasma glucose (APG) is a marker that has been extensively investigated. Elevated APG levels are very common in patients admitted with MI and are associated with a higher incidence of adverse clinical outcomes.[4-7] Much is known about the pathophysiology of elevated glucose levels: they affect several pathophysiological mechanisms involved in MI that can influence clinical outcome. Patients with elevated glucose levels have increased platelet aggregation and circulating clotting factors, more markers of oxidative stress and apoptosis and more endothelial dysfunction leading to impaired myocardial perfusion. [8-10] However, the intrinsic prognostic value of APG in MI patients has so far been underrepresented. The GRACE investigators found in 13,526 patients that fasting glucose (but not admission glucose) was an independent predictor for mortality in ACS patients. However, they did not investigate its added value on top of the GRACE model.[11]

Given the clinical importance of the GRACE model and APG as outcome parameters, we performed an exploratory study in 550 patients to investigate the incremental value of APG to the GRACE mortality risk score in a cohort of ST Elevation MI (STEMI) and non-STEMI patients at short- and long-term follow-up.

METHODS

Patients

In 2003 and 2006 we collected baseline characteristics in 550 patients who were admitted to the coronary care unit (CCU) of the Medical Centre Alkmaar and who had a final diagnosis of MI.[7]

The diagnosis of MI was based on the following criteria: typical ischemic chest pain for at least 15 minutes and either ECG changes indicative of MI and/or elevated markers of myocardial necrosis (i.e. Troponin I and/or CK-MB above the upper limit of normal, i.e. >0.45 µg/l and 16 U/l respectively) within 24 hours after the onset of chest pain. An MI was regarded as STEMI if new ST elevation >1 mm was present in two or more contiguous leads.

Admission glucose

In all patients blood was drawn at admission and APG was determined by the hospital lab, as determined by the MI treatment protocol. Patients were divided into 3 APG classes based on WHO criteria for impaired glucose tolerance and diabetes; <7.8mmol/l, 7.8 – 11.0 mmol/l and ≥ 11.1mmol/l.[12]

Patients were defined as having known diabetes when they were using either oral hypoglycemic agents or insulin treatment at admission. Patients with an APG >12 mmol/l were treated with intravenous insulin in the acute phase unless the attending physician decided otherwise.

Follow-up

Survival data were obtained of all patients in December 2010. Digital hospital records were reviewed using a computerized search to obtain mortality data. We report all cause mortality.

Estimates of determinant-outcome relations might become instable and imprecise if based on low numbers of patients at risk. Therefore, we decided to present mortality data until 60 months (5 years) follow up.

GRACE mortality risk score

Complete details of the design and methods of the GRACE risk score were published earlier.[1,2] The model uses 8 admission variables to predict mortality in acute coronary syndrome (ACS, i.e. STEMI, non STEMI and unstable angina) patients from admission to 6 months follow up: age, heart rate, systolic blood pressure, creatinine levels, Killip classification, the presence of cardiac arrest, ST segment deviation on the ECG and the presence of elevated cardiac enzymes.

Statistical analysis

Missing patient characteristics might lead to biased estimates as in patients who die early it is often difficult to obtain complete data. Therefore GRACE score variables were imputed, when incomplete, based on the mean (dichotomized) value of other patients where this variable was present. A regression imputation model was rejected due to a bad correlation between observed and predicted values. Heart rate and systolic blood pressure had 2.4 and 2.9 % missing data, the other variables had <1% missing data.

Categorical data are presented as numbers and proportions, and continuous data are presented as median values with 25th and 75th percentiles. Differences in baseline characteristics in relation to APG class were evaluated by chi-square tests (categorical data), or analysis of variance (ANOVA), using Scheffe for multiple comparisons.

The incidence of mortality over time was evaluated using Kaplan-Meier analysis (KM) and differences between APG classes were analyzed using the log rank test.
We used logistic regression modeling (enter method) for univariate and multivariate analysis with respect to the 8 GRACE-score variables, APG and mortality. We report crude and adjusted odds ratios (OR) together with their 95% confidence interval (CI). To correct for diabetic state, we repeated the multivariate analysis by adding the known diabetic state and the interaction term between known diabetes and APG to the model with GRACE variables and APG.

All statistical tests were 2-sided, and a *p*-value <0.05 was considered statistically significant. The analyses were performed using SPSS 14 (SPSS Inc., Chicago, IL, USA).

Predictive performance

First we tested the predictive value of the GRACE ACS risk model at admission (GRACE score) in our population at 6 months. Additionally we tested the model at 5-year follow up in order to investigate its' predictive value for long term follow up. For this purpose the GRACE model score points were calculated for every patient using formulas from the "*Fox model for death between hospital admission and 6 months later*" as presented by the GRACE investigators.[13] This formula assigns points to age, heart rate, systolic blood pressure, creatinine, Killip class, cardiac arrest, elevated cardiac enzymes and ST segment change, all measured at admission.

Subsequently, a logistic regression model was created using these score points to calculate the predicted probability of death for each patient with and without glucose. In order to investigate whether adding APG to the GRACE score (GRACE-glucose) increased the models predictive performance, we compared the C-index for the GRACE and GRACE-glucose model; both at 6-month and 5-year follow up. The C-index (or: area under the ROC curve, AUC) is a measure of discrimination which

determines the probability of accurately identifying a patient as a case or not and thus is the probability assigned by a model that a patient will have the event or not. A value of 0.5 reflects an even change and 1.0 is the optimal value.

To compare these C-indices we used the technique as described by DeLong et al [14] in MedCalc 11.5.1 (MedCalc software, Mariakerke, Belgium).

The apparent AUC-values were corrected for optimism using 10-fold cross validation.

Reclassification

To investigate the reclassification capacity of APG we divided the entire cohort using quartiles of the predicted probabilities of the logistic regression model for 6-month mortality. Patients belonging to the first quartile were labeled as 'low risk', those who belong to the second or third quartile as 'intermediate risk' and those belonging to the fourth quartile as 'high risk'. The same cut-off values were used to classify patients into these 3 risk groups using quartiles of the predicted probabilities of the logistic regression model for the GRACE-glucose model. Next, the number of patients that changed risk groups was assessed.

In order to investigate whether the number of reclassified patients is a significant improvement of the ´old´ model, we assessed the Net Reclassification Improvement (NRI) as described by Pencina et al.[15] In brief, the NRI method focuses on the number of patients who change from one risk group into another (e.g. from intermediate into high) by adding a new variable to an existing risk model. It reflects the number of patients with and without events that are correctly reclassified, i.e. upwards for patients with events and downwards for those without events. It is calculated as follows: NRI = [(# events reclassified higher risk - # events reclassified lower risk) / # events] - [(# non-events reclassified higher risk - # non-events reclassified lower risk) / # non-events]

The NRI and associated *p*-values were calculated using R 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria) A *p*-value <0.05 demonstrates that with the new model more events are predicted correctly compared to the old model and thus the new model is an improved version of the old model.

RESULTS

Patient characteristics

After a median follow up of 55 months (IQR 49; 86 months) 97 (17.6%) patients had died of which 86 (15.6%) died within 5 years and 47 (8.5%) died within 6 months.

A total of 193 patients (35%) had an APG between 7.8 and 11.1 mmol/l, whereas 77 (14%) an APG ≥ 11.1mmol/l. Patients with elevated APG levels had a different clinical profile than those with normal levels, as they were older, more often women, more often had a history of diabetes, more often were admitted with STEMI, were in a poorer clinical condition as expressed by a higher Killip class and less often underwent percutaneous coronary interventions (PCI's), table 1.

Table 1 Baseline Characteristics per admission glucose group

	Total N = 550	<7.8 mmol/l N = 280	7.8 -11 mmol/l N = 193	>11 mmol/l N = 77	*P* value
Age (yrs)	66 (57; 76)	63 (55; 73)	68 (58; 77)	73 (61; 81)	<0.001
Men	400 (73)	230 (82)	125 (65)	45 (58)	<0.001
Hypertension	203 (38)	93 (34)	81 (43)	29 (41)	0.096
Hypercholesterolemia	309 (58)	169 (61)	98 (52)	42 (60)	0.144
Diabetes	56 (10)	14 (5.0)	18 (9.5)	24 (34)	<0.001
Smoking	240 (45)	134 (48)	77 (41)	29 (41)	0.237
Previous MI	63 (12)	33 (12)	21 (11)	9 (13)	0.941
Previous CABG	29 (5.4)	16 (5.7)	6 (3.2)	7 (9.7)	0.101
Family history of MI	223 (42)	121 (44)	82 (44)	20 (29)	0.061
Admitted with STEMI	409 (74)	188 (67)	158 (82)	63 (82)	<0.001
Multi vessel disease	253 (50)	125 (48)	93 (52)	35 (56)	0.488
CAG performed	504 (92)	261 (94)	180 (93)	63 (85)	0.045
PCI performed	424 (77)	212 (76)	161 (83)	51 (66)	0.007
Heart rate *	75 (61; 88)	75 (63; 85)	75 (60; 88)	80 (68; 97)	0.066
Systolic BP *	135 (117; 150)	135 (120; 150)	130 (115; 150)	130 (114; 150)	0.325
Creatinine (mg/dL) *	1.04 (0.89; 1.21)	1.02 (0.88;1.17)	1.04 (0.88; 1.21)	1.18 (1.00; 1.48)	0.035
Killip class ≥2 *	112 (20)	36 (13)	41 (21)	35 (46)	<0.001
Cardiac arrest †	37 (6.8)	14 (5.0)	9 (4.7)	14 (18)	<0.001
ST segment deviation *	452 (82)	216 (77)	169 (88)	67 (87)	0.007
Elevated cardiac Enzymes *	236 (43)	129 (46)	63 (33)	44 (57)	<0.001

Continuous data are presented as median values (25th; 75th percentile), Dichotomous data are presented as numbers and percentages.
CABG = Coronary artery bypass graft surgery; CAG = Coronary angiography; PCI = Percutaneous coronary intervention; STEMI = ST Elevation MI.To convert glucose in mmol/l to mg/dL multiply by 18.
** At admission † In the ambulance or at admission*

Admission plasma glucose and mortality

Mortality increased with increasing APG. Six month mortality in patients with APG <7.8 mmol/l, 7.8-11.0, and ≥11.1 was 3.6%, 10.9% and 20.8% respectively, log rank *p*-value <0.001. At 5-year follow up mortality for these glucose groups were 11.1%, 16.1% and 31.2% respectively, log rank *p*-value <0.001, figure 1.

Unadjusted regression analyses demonstrated a significant relation between APG

and 6-month mortality: each mmol/l increase in APG was associated with a 25% mortality increase, OR 1.25 (1.16 – 1.35), *p*-value <0.001. When adjusted for the 8 variables from the GRACE score, APG remained significantly associated with death, OR 1.17 (1.06 – 1.29), *p*-value 0.002, table 2. Also after 5 years follow up elevated APG predicted mortality, unadjusted OR 1.19 (1.11 – 1.26), *p* <0.001 and when adjusted for the GRACE score variables OR 1.12 (1.03 – 1.22) *p*-value 0.007.

In order to investigate whether APG also is an independent predictor of mortality when corrected for diabetic state, we repeated the multivariate analysis by adding the diabetic state and the interaction term between diabetes and APG to the 6-month model with GRACE variables and APG. It appeared that the interaction term and diabetes had no significant contribution. APG however, still remained significantly associated with death, OR 1.20 (1.04 – 1.38), *p*-value 0.01. Hence, there is no evidence for heterogeneity in the relation between APG and outcome for patients with and without diabetes.

Table 2 Odds ratios for 6 month mortality for GRACE score variables and glucose

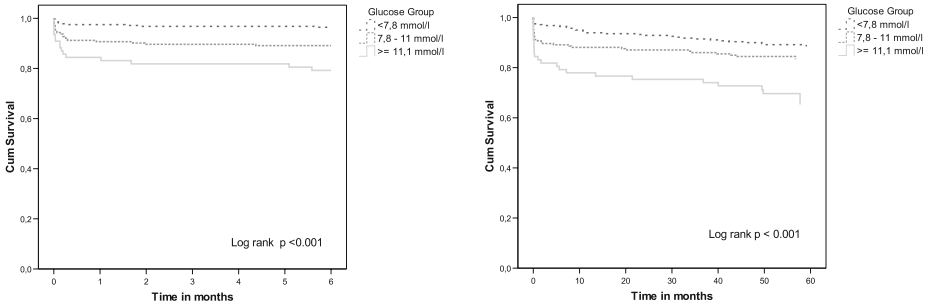
	Crude OR (95% CI)	Adjusted OR (95% CI)	*p* value
Age (per 10 yrs increase)	2.39 (1.77 – 3.23)	1.86 (1.32 – 2.61)	<0.001
Heart rate (per 30 bpm increase)	1.33 (0.92 – 1.94)	1.19 (0.75 – 1.87)	0.459
Systolic BP (per 20mmHg decrease)	1.10 (0.89 – 1.37)	1.02 (0.79 – 1.30)	0.897
Creatinine (per 1mg/dL increase)	6.46 (3.61 – 11.6)	2.86 (1.53 – 5.34)	0.001
Killip class (per increase in class)	2.56 (2.96 – 3.35)	1.78 (1.20 – 2.66)	0.005
Cardiac arrest *	1.75 (0.65 – 4.73)	0.89 (0.21 – 3.73)	0.878
ST segment deviation	2.47 (0.87 – 7.05)	3.14 (0.93 – 10.5)	0.065
Elevated cardiac enzymes	2.82 (1.50 – 5.28)	1.68 (0.79 – 3.58)	0.178
Glucose (per mmol/l increase)	1.25 (1.16 – 1.35)	1.17 (1.06 – 1.29)	0.002

All variables measured at admission, CI = Confidence Interval
** in the ambulance or at hospital arrival*

Incremental value of admission plasma glucose to the GRACE score

The calculated AUC for the 6-month GRACE model was 0.85 (95% CI 0.80 – 0.90), when APG was added the AUC increased to 0.87 (95% CI 0.83 – 0.92), *p*-value 0.095 for AUC difference. For the cross validated AUC-values, see table 3. At 5-year follow up the AUC was 0.81 (95% CI 0.76 – 0.86) for the GRACE model and 0.82 (95% CI 0.77 – 0.87), *p*-value 0.295 for AUC difference, for the GRACE glucose model, figure 2.

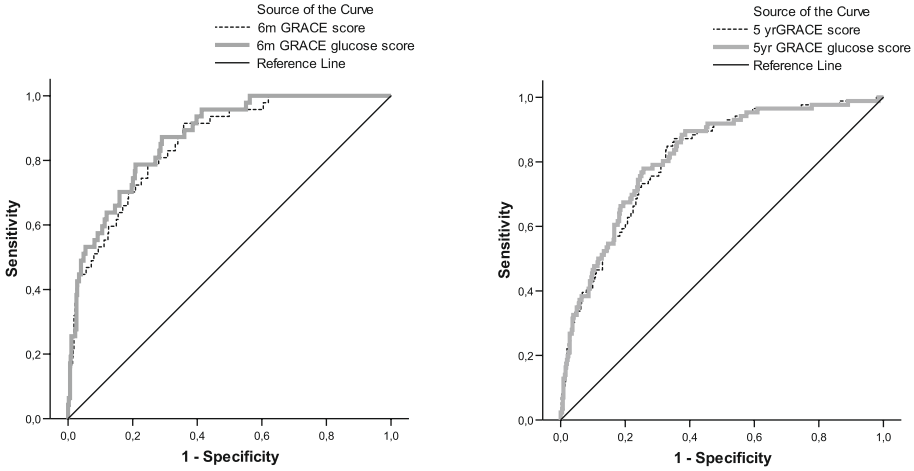
Figure 1 Kaplan Meier survival curves per glucose group



left panel: 6-month survival
right panel: 60-month (5 year) survival
Group I = APG <7.8 mmol/l; Group II = APG 7.8 – 11 mmol/l; Group III = APG ≥ 11.1 mmol/l
APG = Admission Plasma Glucose

7.8 mmol/l = 140 mg/dl; 11.1 mmol/l = 200 mg/dl

Figure 2 ROC curves for GRACE score with or without APG



left panel: 6-month GRACE model with and without glucose, AUC 0.87 vs 0.85, p-value 0.095
right panel: 5-year GRACE model with and without glucose, AUC 0.82 vs 0.81, p-value 0.295

Reclassification

We created a reclassification table which demonstrated that with the 6-month GRACE glucose model 46 patients were properly classified into a lower risk category as they survived and 2 patients were incorrectly classified into a lower risk category as they died. Three patients were properly classified into a higher risk group as they died and 20 were incorrectly classified into a higher risk group as they survived, table 4.

These figures were used to calculate the NRI and assess whether adding APG to the GRACE model improved event and non event classification. For the overall model the NRI was 0.073 (95% CI -0.026 – 0.171) and the *p*-value was 0.146.

We also used alternative cut off values. For this purpose we divided patients into tertiles and used cut-offs as proposed by the GRACE investigators for STEMI.[16] The NRI was 0.062 (95% CI -0.046 – 0.169), *p*-value: 0.263 and NRI 0.015 (95% CI -0.101 – 0.130), *p*-value: 0.805 respectively.

Table 3 Cross validated (10x) AUC-values

	Apparent AUC	Mean training	Mean testing	Optimism	Cross validated AUC
Model without APG	0,854	0,854	0,853	0,001	0,853
Model with APG	0,871	0,871	0,863	0,008	0,863

AUC for 6-month models

Table 4 Reclassification of patients when APG is added to the GRACE score

	GRACE glucose low risk	GRACE glucose intermediate risk	GRACE glucose high risk	Total
Alive at 6 month FU				
GRACE low risk	130	7	0	137
GRACE intermediate risk	28	220	13	261
GRACE high risk	0	18	87	105
Nr of patients alive	158	245	100	503
Deceased at 6 month FU				
GRACE low risk	0	0	0	0
GRACE intermediate risk	0	11	3	14
GRACE high risk	0	2	31	33
Nr of patients deceased	0	13	34	47

DISCUSSION

We investigated whether adding the serum biomarker admission plasma glucose (APG) to the GRACE ACS risk model at admission improved the predictive value of this well validated risk model. Our findings in this exploratory study of 550 patients are twofold; we demonstrate that adding APG to the GRACE score did not provide a more accurate risk group classification as expressed by the NRI, nor an improved discrimination as expressed by the C-index. On the other hand, we acknowledge APG as an independent predictor of short and long term mortality. This ambiguous importance of APG mandates further analysis in upcoming ACS studies. Furthermore the value of the GRACE model at admission to predict 5-year mortality was confirmed.

How could APG improve the GRACE score?

There are different ways to investigate whether a new marker can improve an existing model: the C-index, reclassification tables and the NRI. The most common method is expressing the discriminative capacity, i.e. the ability of a model to distinguish between those who have the event and those who survive without it, by the C-index or area under the ROC curve (AUC). Since the increase in C-index is often very small, as in our study, confidence intervals are overlapping and the increase proves to be non significant.

Therefore a second method was developed, reclassification tables. They provide further insight into the effect of adding a new marker to an existing model. By adding a new variable, the ratio between the old variables changes, which makes them extra or less important for the new model and patients may change risk group. It demonstrates whether patients can be classified into a higher or lower risk group. E.g. Ridker et al used this method to investigate the value of adding CRP to a cardiovascular risk model for women and found that up to 40% could be reclassified into another risk group.[17]

In order to determine whether this change in risk group is significant, Pencina et al proposed a third method, the net reclassification improvement (NRI).[15] With this method, we demonstrated that reclassification into low, intermediate or high risk groups did not improve significantly when APG was added to the 6-month GRACE model.

To solidify our NRI findings, we also used alternative cut off values, since it is conceivable that with different cut offs the reclassification of patients might turn out to be different. Both provided a non significant *p*-value and thus acknowledged our findings.

There are only few studies investigating the added value of glucose to the GRACE score. Correia et al performed an analysis similar to ours and found that APG in NSTEMI patients did not have additive value on top of the admission GRACE model for in hospital cardiovascular events.[18] Aronson et al did find incremental value of APG and particularly fasting glucose on top of the post discharge GRACE score for non diabetic patients, but not in patients with known diabetes two years after an acute MI.[19] This is conceivable as patients with APG levels that remain elevated have a worse prognosis. [20] These divergent results may be caused by the fact that we used the admission GRACE model and Aronson et al used the post discharge GRACE model which uses different variables.

Other studies also investigated whether the GRACE score could be improved by adding a biomarker. The biomarkers GDF-15, cystatin C, IL-6 and NT-proBNP were all independently found to improve the GRACE score. [21-23] However, the GRACE score is based on routinely used clinical and serum parameters. GDF-15, cystatin C, IL-6 and NT-proBNP are not used in routine clinical practice, while APG levels are routinely measured. Therefore APG would be a more practical parameter.

GRACE score and long term mortality

With our 5-year results we further extend the validity of the "GRACE model at admission" to predict long term clinical outcomes in the era of invasive treatment of MI. Earlier work already acknowledged the value of the "post discharge GRACE model" in ACS patients after up to 4 years follow up. [24] However this study was performed from 2000 – 2002, an era dominated by thrombolysis and consequently only 21% of patients underwent PCI.

Limitations

Several limitations need to be addressed. We only explored STEMI and NSTEMI patients; as a result we are not informed whether APG improves the GRACE model for patients with unstable angina. Furthermore, part of our data were collected retrospectively, therefore some data (less then 3%) were incomplete and needed to be imputed. Next the NRI uses logistic regression and thus does not take the time-to-event into account as does Cox regression.

Being an exploratory study, with the inherent limitation of sample size, the magnitude of the values for change in C-index and NRI may be clinically important. The *p*-values for these changes are not significant, because there are too few events although APG is a strong predictive outcome measure. Ultimately, future large prospective clinical trials are essential and should include APG in order to demonstrate the added value of APG to the GRACE score or to confirm our findings.

Implications

Although adding APG to the GRACE score did not improve risk stratification, it was a predictor of mortality independent of the GRACE score variables. A proper interpretation of these two different matters is challenging. Our exploratory sample is by virtue of study design relatively small but allows a more accurate calculation of power of upcoming prospective clinical trials which are mandated given the ambiguous outcome of our study.

We conclude that the GRACE score is a good tool for risk stratification at admission and APG did not increase its predictive value in our population. However, as the relation of elevated APG with increased mortality was reconfirmed, we feel that clinicians should be aware of the possible implications of hyperglycemia and timely recognition is important. The proper treatment strategy of elevated APG is still subject of further research.[25]

Furthermore, it should be realized that elevated APG can also be a sign of hitherto unrecognized diabetes mellitus. In fact, one in three patients with CVD appears to have previously unrecognized diabetes.[26] [27] Therefore guidelines from the ESC/EASD recommend to perform an oral glucose tolerance test in all patients with known cardiovascular disease but without known diabetes.[28]

CONCLUSION

We demonstrated a significant relation between APG and both 6-month and 5-year mortality. Each mmol/l increase in APG was associated with a significant mortality increase of 17% and 12% respectively, also when adjusted for GRACE score variables. However, adding APG to the "GRACE ACS risk model at admission" did not provide a more accurate risk group classification. Finally, the GRACE score at admission accurately predicts 5-year mortality in real-world NSTEMI and STEMI patients.

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Chapter 6

Elevated admission glucose is associated with increased long term mortality in myocardial infarction patients, irrespective of the initially applied reperfusion strategy

Maarten de Mulder; Jan H Cornel; Tjeerd van der Ploeg;
Eric Boersma; Victor A Umans

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ABSTRACT

Background: It is uncertain if elevated admission plasma glucose (APG) remains an independent determinant of longer-term mortality in myocardial infarction (MI) patients with early restoration of coronary reperfusion by primary percutaneous coronary intervention (PCI).

Objective: To describe the relation between elevated APG and long term mortality in MI patients undergoing invasive management.

Methods: We studied 1185 consecutive MI patients treated in the Medical Center Alkmaar in the separate years 1996, 1999 (pre-invasive era), and 2003, 2006 (invasive era). In both eras APG was derived according to a standard protocol. A multivariate Cox regression model was created to study the relation between APG, reperfusion era and 5-year mortality.

Results: During a median follow-up of 63 months, 261 patients had died. Mortality was lower in the invasive (19%) than in the pre-invasive era (28%). Increased APG was associated with increased mortality, irrespective of the initial reperfusion strategy, although the relation was more pronounced in the pre-invasive era (p-value for heterogeneity of effects < 0.001. Each mmol/l APG increase corresponded with 7% increased mortality (adjusted hazard ratio [HR] 1.07 and 95% confidence interval [CI] 1.04 to 1.10). Patients with an APG > 11 mmol/l had nearly 2-fold higher mortality (HR 1.9 and 95% CI 1.3 to 2.7) than those with lower values.

Conclusion: Elevated APG remains a determinant of long term mortality in MI patients, irrespective of the advances that have been made in reperfusion therapy.

INTRODUCTION

Elevated glucose levels are associated with adverse prognosis in patients with myocardial infarction (MI). Several investigators have demonstrated that elevated admission plasma glucose (APG) is associated with increased mortality in patients who are admitted for MI, even if these glucose levels remain below the diagnostic threshold for diabetes mellitus (DM), i.e. 11 mmol/l.[1-3] We realize that most of these studies were undertaken in patients receiving fibrinolytic (FL) therapy as initial reperfusion strategy. Nowadays, a more invasive approach has become the standard of care for MI treatment, based on early coronary angiography (CAG), and followed by percutaneous coronary intervention (PCI) if indicated. Regional networks are constructed, which allow rapid pre-hospital triage, with subsequent transportation to dedicated hospitals with adequate PCI facilities and experienced operators.[4 5] In view of these developments, it is uncertain if elevated admission glucose remains an independent determinant of longer-term mortality, particularly in patients without previously diagnosed DM.

We aimed to describe the relation between APG and long-term (5-year) mortality in MI patients undergoing early CAG and subsequent PCI. We were also interested to learn if the APG-outcome relation has changed along with the change in the initial treatment strategy.

Our analyses are based on a single center registry of consecutive MI patients. This design implies an important advantage over earlier reports, which were based on more stringent patient selection, such as patients undergoing particular treatment (e.g. fibrinolysis or primary PCI), elderly, or patients with previously diagnosed diabetes mellitus.

METHODS

Regional situation

The Medical Center Alkmaar (MCA) is a large teaching hospital with an adherence region of approximately 350.000 inhabitants, mainly Caucasian. Since 2002 off site PCI service is offered 24 hours per day and 7 days per week by 3 experienced interventional cardiologists. Surgical backup is provided by a nearby (45 km) university hospital. Currently, all patients with (suspected) MI in the larger Alkmaar area are transported to our hospital by the ambulance service to undergo immediate CAG and subsequent PCI. Two community hospitals in the region (21 km and 46 km distance) also refer patients to our hospital for (primary) PCI, when appropriate.

Patients and treatment

For quality control purposes, in the separate years 1996, 1999, 2003 and 2006 we prospectively registered all consecutive patients who were admitted to our hospital, and who had a final diagnosis of MI. For the current study, we considered the patients who were admitted in 1996 or 1999 (pre-invasive era) and the patients admitted in 2003 or 2006 (invasive era) as two distinct cohorts. For patients who appeared more than once in the sample, only the first admission record was included as an independent observation.

Reperfusion therapy in the pre-invasive era was a tailored approach that is described earlier. [6 7] In brief: a structured treatment-decision model was applied to estimate the myocardial area at risk for necrosis without reperfusion therapy, based on clinical and electrocardiographical determinants at admission. Subsequently, the potential benefits and hazards of reperfusion therapy were estimated, and the appropriate treatment intensity (FL or PCI) selected. In this era, most patients received FL, according to the so-called 'accelerated' alteplase regimen. [8]

In the era of invasive treatment, early CAG and subsequent PCI was performed according to the decision-algorithm that is described by Peels et al.[5] In brief: ambulance personnel derived a 12-lead ECG in patients with suspected acute MI (i.e. within 6h after symptom onset), which was then used for pre-hospital triage. Patients with confirmed MI were immediately transported to the MCA for CAG and primary PCI. Otherwise, patients were transported to one of the two regional community hospitals for further management. If myocardial ischemia remained, PCI could still be applied within 6 to 48 h after onset of symptoms.

According to the MI treatment protocol, APG was obtained in all patients. In both treatment eras, patients with an APG >12 mmol/l were treated with intravenous insulin in the acute phase.

Definitions

In both eras, the diagnosis of MI was based on the following criteria: typical ischemic chest pain for at least 15 minutes and either ECG changes indicative of MI and/or elevated markers of myocardial necrosis (i.e. CK-MB above the upper limit of normal) within 24 hours after the onset of chest pain. An MI was regarded as ST Elevation MI (STEMI) if new ST elevation > 1mm was present in two or more contiguous leads. Enzymatic infarct size was estimated by measurement of the peak CK-MB value within 5 days of admission.

Patients were defined as having diabetes mellitus (DM) when they were using either oral hypoglycemic agents or insulin treatment at admission. For our analysis, we categorized patients according to their APG as normal, mild impaired or profound

impaired glucose metabolism (APG < 7.8, 7.8 -11 or >11 mmol/l, respectively), based on WHO criteria [9]. APG was obtained at admission, and therefore non-fasting. An APG ≥7.8 mmol/l was considered as hyperglycemia.

Follow-up

Information on survival status was obtained in all patients in February 2009. Digital hospital records were reviewed using a computerized search to obtain mortality data. When insufficient information was available, general practitioners were contacted by telephone for additional data on survival status.

The median overall follow up was 63 months (1st; 3rd Quartile: 28; 115 months). To have a more homogenous follow up for mortality analysis between the two eras, we decided to present mortality data until 60 months (5 years) follow up.

Statistical analysis

Categorical data are presented as numbers and proportions, and continuous data are presented as mean values ± one standard deviation (SD). Differences in baseline characteristics in relation to APG and in relation to reperfusion era (pre-invasive versus invasive) were evaluated by chi-square or Fisher's exact tests (dichotomous data), or one-way analysis of variance (ANOVA), Kruskall Wallis and Student's T-tests, while applying Scheffe's correction for inflation of the type I error with multiple testing (continuous data), as appropriate.

The incidence of mortality over time was evaluated according to the method of Kaplan-Meier (KM) and differences between groups of patients were analyzed with the log rank test. We applied Cox proportional hazard (CPH) regression analyses to study the relation between APG, reperfusion era and long-term mortality, as follows. First, crude hazard ratios (HR) were determined based on the single fixed effect CPH model, including APG as continuous variable. These analyses were then repeated with adjustment for a broad range of potential confounders, as described in table 2. Subsequently, CPH models were fitted that included APG, reperfusion era and their interaction. If the interaction term has a significant ($p<0.05$) contribution to the model, then there is sufficient evidence to accept heterogeneity in the APG-outcome relation between patients who are treated in the invasive era versus those who are treated in the pre-invasive era. All variables with a p-value <0.5 in univariable analysis were included in the multivariable model, so that no (measured) confounders were missed. Analyses were also conducted with APG as dichotomous variable. A CPH model with APG, diabetes history and the interaction term between these variables was created to study the relation between APG, diabetes and mortality in more detail. We report crude and adjusted HRs together with their 95% confidence interval (CI).

Table 1 Baseline Characteristics per glucose group

	Pre-invasive era, 1996 & 1999 N= 612				
	<7.8 mmol/l n (%)	7.8 -11 mmol/l n (%)	>11 mmol/l n (%)	Total n (%)	P value
Age (yrs)	65 (+/-12)	66 (+/-12)	71 (+/-11)	66 (+/-12)	<0.001 †
CKMB (U/l)	135 (+/-123)	163 (+/-163)	141 (+/- 136)	143 (+/-130)	0.059
Men	284 (76)	100 (69)	42 (44)	426 (70)	<0.001
Hypertension	109(29)	39 (27)	47 (50)	195 (32)	<0.001
Hypercholesterolemia	142 (38)	59 (41)	40 (42)	241 (39)	0.699
Diabetes	11 (3)	21 (15)	48 (51)	80 (13)	<0.001
Smoking	173 (46)	59 (41)	31 (33)	263 (43)	0.046
Previous MI	59 (16)	20 (14)	18 (19)	97 (16)	0.59
Previous CABG	14 (3.8)	8 (5.6)	7 (7.4)	29 (4.7)	0.291
Family history of MI	125 (34)	30 (21)	15 (16)	170 (28)	<0.001
Admitted with STEMI	259 (69)	102 (71)	66 (70)	427 (70)	0.951
Anterolateral infarction	149 (40)	64 (44)	51(54)	264 (43)	0.051
Multi vessel disease §	128 (34)	60 (42)	35 (37)	223 (36)	0.002
CAG performed	224 (60)	77 (54)	47 (50)	348 (57)	0.114
Initial treatment					
Fibrinolysis	204 (55)	86 (60)	38 (40)	328 (54)	0.009
Primary PCI	8 (2.1)	3 (2.1)	2 (2.1)	13 (2.1)	0.99
Emergency CABG	0	0	0	0	-
No intervention	161 (43)	54 (38)	55 (58)	270 (44)	0.007

Continuous data are presented as mean values (+ or – Standard Deviation, Dichotomous data are presented as numbers (percentages)
** No admission glucose available in 8 patients, 4 of these patients died within 3 months;*
† Significant difference glucose > 11 versus other 2 groups;
‡ Significant difference glucose <7.8 versus other 2 groups; § When CAG results available;
For conversion from mmol/l to mg/dL multiply by 18
CABG = Coronary artery bypass graft surgery; CAG = Coronary angiography; PCI = Percutaneous coronary intervention; STEMI = ST Elevation MI

	Invasive era, 2003 & 2006 N= 573 *				
	<7.8 mmol/l n (%)	7.8 -11 mmol/l n (%)	>11 mmol/l n (%)	Total n (%)	P value
	64 (+/-13)	68 (+/-13)	71 (+/-13)	66 (+/-13)	<0.001 ‡
	128 (+/- 128)	156 (+/- 156)	167 (+/- 150)	143 (+/-143)	0.061
	234 (82)	128 (65)	49 (59)	411 (73)	<0.001
	94 (33)	83 (43)	31 (41)	208 (38)	0.086
	172 (61)	100 (52)	47 (62)	319 (58)	0.104
	14 (5)	20 (10)	27 (36)	61 (11)	<0.001
	135 (48)	78 (40)	34 (45)	247 (45)	0.369
	35 (12)	23 (12)	11 (14)	69 (12)	0.877
	17 (6.0)	6 (3.1)	7 (9.0)	30 (5.4)	0.125
	122 (44)	83 (44)	21 (28)	226 (42)	0.044
	189 (66)	161 (82)	64 (77)	414 (73)	0.001
	91 (32)	72 (37)	38 (46)	201 (36)	0.064
	130 (46)	98 (50)	35 (42)	263 (47)	<0.001
	264 (93)	183 (93)	63 (76)	510 (90)	<0.001
	1 (0.4)	0	0	1 (0.2)	0.611
	178 (63)	148 (75)	50 (60)	376 (67)	0.007
	0	2 (1.0)	1 (1.2)	3 (0.5)	0.211
	98 (34)	45 (23)	31 (37)	174 (31)	0.01

All statistical tests were 2-sided, and a p-value <0.05 was considered statistically significant.

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RESULTS

Patient characteristics
The study cohort consisted of 1185 MI patients, with a mean age of 66 ± 11 years. Most patients (72%) were men. There were some differences in baseline characteristics between the 612 patients who were treated in the years 1996 or 1999 (pre-invasive era) and the 573 patients who were treated in 2003 or 2006 (invasive era); table 1. In the invasive era, significantly more patients had known hypertension (38% vs. 32%), hypercholesterolemia (58 vs. 39%), a family history of MI (42% vs. 28%) and multivessel disease (47% vs. 36%). By virtue of the study design, patients in the invasive era more often underwent early CAG with subsequent coronary revascularization than patients treated in the pre-invasive era (90% vs. 57% CAGs; p-value <0.001). The percentage of patients undergoing reperfusion therapy within 12 hours after the onset of symptoms increased from 56% to 69% (p-value <0.001).

The proportion of patients with hyperglycemia increased over time. In the pre-invasive era 39% of patients had an APG ≥ 7.8 mmol/l and this figure was as high as 50% in the invasive era. We observed clinically relevant differences in baseline characteristics in relation to APG, irrespective of treatment era (table 1). Patients with elevated blood glucose were older, were more likely woman than man, more often had a history of DM, and more often had hypertension (pre-invasive era).
In both eras, patients with elevated blood glucose were treated less frequently according to an invasive strategy.

A total of 261 patients were reported dead during 5-year follow-up (KM estimate 24%). Mortality was significantly lower in the invasive era than in the pre-invasive era (KM estimate 19% versus 28%; P<0.001). As the figures 1 and 2 demonstrate, in

both eras elevated APG was associated with increased late mortality. At the other hand, in all glucose groups late mortality was significantly lower in patients treated in the invasive era than in the pre-invasive era (KM estimates 12% vs. 21% if APG <7.8 mmol/l; 18% vs. 27% if APG ≥7.8 and ≤11 mmol/l; and 47% vs. 52% if APG >11 mmol/l). Interestingly, the mortality differences between glucose groups appeared early during follow-up, and were already present after 30 days.

Unadjusted regression analyses demonstrated a significant relation between APG and long term follow-up: each mmol/l increase in APG was associated with a 9% mortality increase (HR 1.09 and 95% CI 1.07 to 1.12; table 2). As compared with patients with an APG <7.8, APG values between 7.8 and 11.0 were associated with a 1.4-fold higher mortality risk, and APG values >11.0 with a 3.5-fold higher risk.
We observed a statistically significant heterogeneity in the relation between APG and late mortality between both treatment eras. In the pre-invasive era each mmol/l increase was associated with a 1.20-fold increased risk (95% CI 1.14 to 1.26), whereas in the invasive era a value of 1.08 (95% CI 1.05 to 1.10) was observed (p-value associated with treatment era * APG interaction < 0.001).

Other statistically significant determinants of late mortality included age, (female) gender, prior MI and DM. After adjustment for a range of (potential) confounders, APG remained significantly associated with death: the adjusted HR for each mmol/l increase was 1.07 (95% CI 1.04 to 1.10). In a multivariable model with APG as a dichotomous value, and compared with APG values <7.8, APG-values between 7.8 and 11 mmol/l were associated with a HR of 1.3 (95% CI 0.92 to 1.8), and APG-values >11 mmol/l with a HR of 1.9 (95% CI 1.3 to 2.7).

Table 2 Association between baseline characteristics and 5yr mortality

	5 yr mortality*	%	Crude Hazard Ratio and 95% CI	Multivariable adjusted Hazard Ratio and 95% CI	P value
Admission glucose			1.09 (1.07 – 1.12)	1.07 (1.04 – 1.10)	<0.001
APG <7.8 mmol/l	107 / 657	16	1	1	
APG 7.8 – 11 mmol/l	72 / 340	21	1.4 (1.1 – 1.9)	1.3 (0.92 – 1.8)	0.14
APG >11 mmol/l	78 / 178	44	3.5 (2.6 – 4.7)	1.9 (1.3 – 2.7)	<0.001
Age			1.09 (1.07 – 1.10)	1.07 (1.06 – 1.09)	<0.001
CK MB †			1.1 (0.99 – 1.2)	1.2 (1.1 – 1.3)	<0.001
Invasive Era	94 / 571	17	0.66 (0.51 – 0.85)	0.66 (0.49 – 0.88)	0.005
Fibrinolysis era	167 / 612	27	1	1	
Initial Reperfusion ‡	116 / 717	16	0.47 (0.36 - 0.60)	0.54 (0.38 – 0.88)	<0.001
No initial reperfusion	145 / 466	31	1	1	
Female	114 / 344	33	2.1 (1.7 – 2.7)	1.2 (0.91 – 1.6)	0.19
Male	147 / 839	18	1	1	
Prior MI	65 / 166	39	2.3 (1.7 – 3.1)	2.0 (1.5 – 2.8)	<0.001
No prior MI	190 / 1007	19	1	1	
Prior CABG	20 /59	22	1.7 (1.1 – 2.7)	0.98 (0.58 – 1.6)	0.94
No prior CABG	235 /1115	21	1	1	
Hypertension	101 / 404	25	1.4 (1.1 – 1.7)	0.97 (0.74 – 1.3)	0.81
No hypertension	150 / 764	20	1	1	
Diabetes mellitus	54 /142	38	2.3 (1.7 – 3.1)	1.1 (0.78 – 1.6)	0.56
No diabetes	197 / 1026	19	1	1	
Hypercholesterolemia	89 / 558	16	0.55 (0.43 – 0.72)	0.87 (0.65 – 1.2)	0.35
No hypercholesterolemia	162 / 610	27	1	1	
Smoker	78 / 512	15	0.53 (0.40 – 0.69)	1.1 (0.78 – 1.4)	0.73
Non smoker	173 / 655	26	1	1	
Family history of MI	44 / 397	11	0.38 (0.27 – 0.53)	0.81 (0.57 – 1.1)	0.23
No family history of MI	201 / 761	26	1	1	
Admitted with STEMI	180 / 842	21	0.88 (0.68 – 1.1)	1.4 (0.99 – 2.0)	0.056
Admitted without STEMI	81 / 341	24	1	1	
Anterolateral infarction	125 / 467	27	1.5 (1.1 – 1.9)	1.1 (0.87 – 1.5)	0.33
No Anterolateral infarction	136 / 716	19	1	1	
Multivessel disease §	83 / 489	19	1.9 (1.3 – 2.8)		
No Multivessel disease	35 / 372	9.4	1		

** 2 patients moved abroad and were lost to follow up*

† HR for CKMB for every 100 units increase

‡ i.e. when initiated within 12 hours of the onset of symptoms.

§ Multivessel disease was not included in the multivariate model as there were to many missing values.

APG = Admission Plasma Glucose; CABG = Coronary Artery Bypass Graft surgery; MI = Myocardial Infarction; STEMI = ST Elevation MI

APG and mortality in patients with documented diabetes mellitus

If APG was included in the multivariable model, previously documented DM did not contribute to the prediction of 5-year death (p-value 0.56). However, if APG was not considered as potential determinant, previous DM became a significant factor

(p-value 0.037). To further study this interesting phenomenon, we fitted a CPH model that included APG, previous DM and their interaction term. It appeared that the interaction term had no significant contribution. In diabetic patients each mmol/l increase was associated with a 1.09 increased risk (95% CI 1.06 to 1.11) and in non diabetic patients a value of 1.09 (95% CI 1.03 to 1.15) was observed, the associated p-value for diabetic state * APG interaction was 0.86. Hence, there is no evidence for heterogeneity in the relation between APG and outcome for patients with and without diabetes.

Figure 1 Kaplan Meier 5 year Survival
Glucose in mmol/l, for conversion to mg/dL multiply by 18

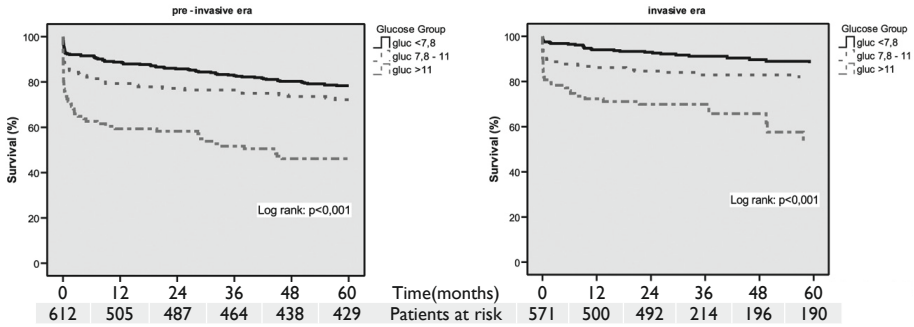
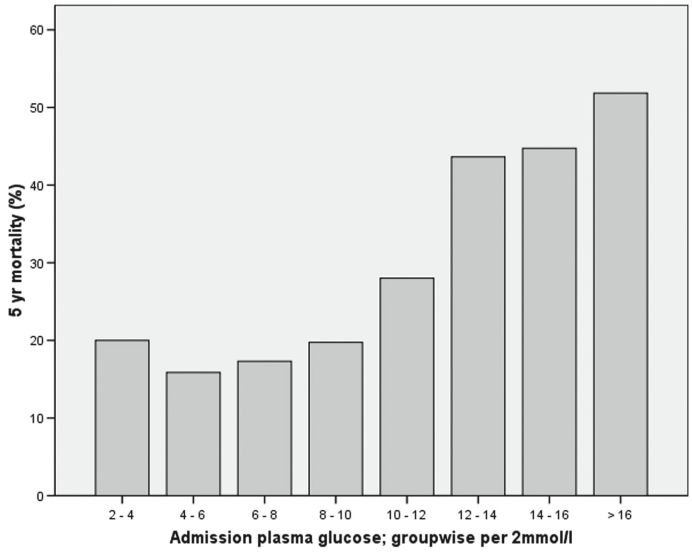


Figure 2 Overall 5 year mortality, per glucose subgroup
Glucose range: 3.2 – 43.5 mmol/l



DISCUSSION

Myocardial infarction patients who were treated during 1996 - 2006 in the MCA -a dedicated regional center for MI treatment -, and who had elevated APG had higher 5-year mortality than their counterparts with normal glucose levels. Interestingly, high blood glucose remained associated with increased mortality in the current era of invasive management. Although at lower mortality risk than those receiving non-PCI -based treatment, apparently, patients are not protected against the negative effects of elevated blood glucose levels by the PCI per se. The second main finding of our analysis is what might be called a 'risk-treatment paradox': patients with elevated blood glucose, who are at high risk of death, were less likely to receive PCI, a therapy that has been demonstrated to effectively reduce death rates.

Pathophysiology

Our results confirm the relevance of hyperglycemia as a determinant of mortality. The current era of invasive treatment of AMI patients is characterized by a rapid diagnosis, and an early, complete and sustained reperfusion. Still, APG remains a factor that influences prognosis.

Various deleterious effects of elevated glucose levels suggest that elevated APG is a mediator in case of metabolic dysregulation. Firstly, hyperglycemic AMI patients have more markers of oxidative stress, inflammation and apoptosis compared to normoglycemic patients. This results in a lower left ventricular ejection fraction.[10] [11] Secondly, hyperglycemia influences coagulation as it is associated with increased platelet aggregation and circulating clotting factors [11] [12] Another mechanism is the no-reflow phenomenon, reflecting microvascular dysfunction,[13] which is more common in hyperglycemic patients.[11] [14] This worse outcome is partly explained by impaired perfusion due to endothelial dysfunction.[12] The aforementioned effects of hyperglycemia are even more pronounced in the pre invasive era, as with FL reperfusion is less successful.

Thus, also with a more invasive approach, there remains a potential for the improvement of patient prognosis, despite the advances in outcome that have been reached by the introduction of (primary) PCI. This might be achieved by regulating elevated glucose levels, although the clinical benefits of glucose control in AMI have not been definitively established and remains to be confirmed in further clinical trials.

Clinical implications

We demonstrated that known DM does not influence the predictive value of APG.

This implicates that APG rather than the diabetic state adds prognostic information on mortality when both are present. Moreover, it is the admission glucose level that is particularly important, irrespective of DM history, as every mmol increase in APG resulted in a 7% higher 5 year mortality. This lack of interaction between APG and DM confirms previous findings of Norhammar et al where 31% of MI patients with APG <11.1 mmol/l had new onset diabetes when tested with an oral glucose tolerance test (OGTT).15 This illustrates the limited use of APG to predict new onset diabetes. This is in contrast however with others who found that hyperglycemic patients without diabetes with fare worse compared to those with diabetes.[2 16 17] The difference between these studies remains to be determined, but could be due to difference in sample size with respect to endpoints, the variance in incidence of diabetes, and the definition of hyperglycemia.

Additionally, in our continuous rather than their dichotomous analysis a similar continuous relationship between APG and mortality for both diabetic and non diabetic patients was found. As APG is a continuous variable it provides more information than a dichotomous variable such as the label "known diabetes". An abnormal APG also recognizes patients with pre diabetes and can trigger physicians to further investigate glucose metabolism and subsequently diagnose new onset diabetes.

Risk treatment paradox

An interesting observation is that although patients with higher APG have a higher mortality risk, this group of patients is treated less frequently with early reperfusion. Despite the fact that this group may benefit the most from rapid reperfusion. This risk-treatment paradox might be due to increased age and higher incidence of diabetes in the higher glucose groups. Perhaps older patients are to easily considered as to fragile for intervention, possibly as with increasing age the risk of the procedure itself increases. [18] In diabetic patients the lack of early reperfusion has been described before, although a satisfying explanation could not be given. [19]

Hyperglycemia, a window of opportunity?

We found an early separation of the Kaplan Meier survival curves, with worst outcome in patients with profound metabolic dysregulation. These findings imply a negative effect of hyperglycemia predominantly in the early phase of the infarct process. This may provide the treating physician a window of opportunity, as well as a tool to further improve prognosis. However at the current stage, these results could not be confirmed in various clinical trials such as DIGAMI [20 21] and HI-5,[22] which may explain the disappointing real world clinical practice in hyperglycemia treatment in the acute phase of MI in non-diabetic patients. [23]

The optimal target range for glucose regulation has yet to be established. However as figure 2 demonstrated that mortality was lowest in our patients with APG 4 – 6 mmol/l, it seems reasonable to aim for (near) normoglycemic values. The American Heart Association finds 5.0 – 7.8 mmol/l a reasonable goal.[24] However, the NICE SUGAR trial demonstrated that intensive glucose regulation in ICU patients might result in increased mortality compared to conventional glucose regulation.[25]

In contrast to hyperglycemia, the issue of hypoglycemia may need further attention as well.

Earlier studies found that both hypo- and hyperglycemia were associated with increased mortality as there was a U- or J-shaped relationship of blood glucose with adverse outcomes among patients with myocardial infarction. [26-28] More recently Kosiborod et al pointed out that particularly spontaneous, not iatrogenic, hypoglycemia is deleterious. [29]

The patients in our analysis had a blood glucose of 3.2 to 43.5 mmol/l, and only 3 (0.25%) had a value <4 mmol/l. Thus, we had too few data to confirm the negative effects of hypoglycemia. Nevertheless, our data should not be used to argue that blood glucose should be reduced as low as technically possible. Treatment strategies that aim to reduce elevated blood glucose should definitely include measures to avoid hypoglycemia.

Furthermore, this observation may be a platform to optimize the adjunctive medical treatment in MI while aiming at improving long-term outcome. It may further shift the focus of attention from diabetic patients to all patients with acute metabolic dysregulation. Early recognition of new onset diabetes and subsequent intensive glucose regulation seems beneficial, as this decreased the risk of microvascular complications in the UKPDS trial. [30]

Limitations

The current results are derived from a single center, so its applicability to other populations is uncertain, although baseline and clinical outcome parameters are comparable to other studies.[1 2 31] However, a single center study does provide the opportunity to compare two eras within the same clinical setting. We studied consecutive, all-comer MI patients, who were treated in two different eras. This design differs from previous studies in which patients were either exclusively treated by FL or primary PCI [31], were selected by age [32] or selected from cohorts without previously documented DM. [33]

It would be of interest to know what proportion of our patients with elevated

APG but without known diabetes would be diagnosed with new onset diabetes. Unfortunately, oral glucose tolerance test data or HbA1c values were not available.
In this study we compared two eras with two different treatment strategies for MI. However, much more has changed in MI treatment strategies over the years. For example: the use of statins, beta blockers and glycoprotein IIb/IIIa inhibitors has increased and contributed to better outcomes. Indeed, not all residual confounding issues could be taken into account and may have influenced our findings necessitating further studies.

CONCLUSION

Elevated APG remains a prognostic predictor of long-term outcome in the era of invasive MI treatment, in patients with or without previously documented DM. Five-year mortality increases by 7% for every mmol/l increase in admission glucose, the excess mortality emerged in the first month after admission. However, controversy on the optimal glucose management strategy still exists.

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Chapter 7

Comparison of Diagnostic Criteria to Detect Undiagnosed Diabetes in Hyperglycemic Acute Coronary Syndrome Patients

Maarten de Mulder; Rohit M Oemrawsingh; Frank Stam;
Eric Boersma:Victor A Umans

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ABSTRACT

Background: Elevated admission plasma glucose (APG) is very common among patients with acute coronary syndromes (ACS) and can be the first indication of diabetes mellitus.

Objective: To provide insight into the prevalence of previously undiagnosed diabetes and to compare different methods of diagnosing diabetes in ACS patients.

Methods: ACS patients with elevated APG who participated in the BIOMArCS 2 glucose trial underwent an oral glucose tolerance test (OGTT) prior to discharge. We included 130 patients who underwent metabolic assessment. Of these, 109 underwent an OGTT and 13 patients had pre-existent diabetes.

Results: OGTT results were categorized as (previously) undiagnosed diabetes in 35% of patients (fasting plasma glucose (FPG) ≥ 7.0 mmol/l or 2-hour post load glucose (PLG) ≥11.1 mmol/l) and impaired glucose metabolism in 44% (FPG 6.1 to 6.9 mmol/l or PLG 7.8 to 11.0 mmol/l), thus only 21% had a normal glucose metabolism. Undiagnosed diabetes could not be adequately predicted with APG, FPG or HbA1c, the area under the ROC curve was 0.61, 0.75 and 0.72 respectively. Patients with abnormal glucose metabolism were significantly older, had higher admission HbA1c values, a higher Killip classification and more often had a prior stroke when compared to patients with normal glucose metabolism.

Conclusion: 79% of hyperglycemic ACS patients were found to have abnormal glucose metabolism. As APG, HbA1c and FPG had a low sensitivity to detect undiagnosed diabetes, an OGTT appears to be the best test to assess the presence of previously undiagnosed diabetes or impaired glucose metabolism in hyperglycemic ACS patients.

INTRODUCTION

Elevated admission plasma glucose levels (APG) are common in patients admitted with acute coronary syndromes (ACS) and are associated with a high incidence of adverse clinical outcomes, particularly when compared to normoglycemic ACS patients. [1-5] Nevertheless hyperglycemia remains unrecognized and untreated in a considerable portion of patients with ACS.[6] This observation can partly be explained by the lack of convincing results of studies that have evaluated the clinical effectiveness of strategies aiming at early and strict plasma glucose regulation. It remains to be established whether hyperglycemia is a marker or therapeutic target and which strategy would be best.[7 8] Consequently, clinical treatment guidelines do not contain strong recommendations in this respect.[9] Furthermore, clinicians may consider an elevated APG as a parameter of the temporary physical stress that is a natural part of – and caused by – the ACS, which will normalize once the coronary event is adequately managed. It should be realized, however, that elevated APG can also be a sign of hitherto unrecognized diabetes mellitus (DM). In this respect, the lack of knowledge of an elevated APG is of concern as the prevalence of undiagnosed diabetes will be underestimated.

Early recognition (and treatment) of diabetes in these high risk patients may be prognostically important for two reasons. First, in the UK Prospective Diabetes Study (UKPDS) early treatment limited microvascular complications.[10] Second, besides new diabetes, impaired glucose metabolism which can be considered a pre diabetic state, is also detected. Early detection allows early measures such as lifestyle interventions or (off label) metformin therapy to prevent deterioration to full diabetes.[11] Physicians in the cardiovascular field should therefore become aware of the various diagnostic tools to detect undiagnosed diabetes and its basic treatment modalities.

The European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) already advocate to investigate glucose metabolism in patients without known diabetes but with established cardiovascular disease (CVD) through an oral glucose tolerance test (OGTT).[12] However, a recent survey in The Netherlands demonstrated that 76% of cardiologists do not routinely measure an HbA1c prior to discharge in patients with ACS.[6] With this in mind it is unlikely that the more labour-intensive OGTT is standard care in daily cardiology practice.

The aim of this report is to identify the occurrence of previously undiagnosed diabetes in ACS patients with hyperglycemia at admission, to compare different diagnostic methods for diabetes in ACS patients and to stress their importance.

METHODS

Patients

The current analysis was part of the BIOMArCS 2 *glucose* study in the Medical Centre Alkmaar, BIOMArCS is an acronym for *BIOMarker study to identify the Acute risk of a Coronary Syndrome*. Briefly, this study investigated the safety and effectiveness of intensive glucose regulation. It included patients with a clinical diagnosis of ACS and an APG 7.8 – 16 mmol/l, who were then randomized to intensive glucose regulation with intravenous insulin or expectative glucose management. Major exclusion criteria were the use of subcutaneous insulin (i.e. insulin dependent diabetes mellitus, IDDM), creatinine >220 mmol/l, left ventricular ejection fraction < 30% and an expected transfer to another hospital within 48 hours.[13] The study was approved by the local ethics committee and all patients provided written informed consent.

Between July 2008 and April 2010 a total of 883 consecutive ACS patients were admitted, 475 (54%) patients presented with an APG of ≥ 7.8 mmol/l, 345 of whom met one or more exclusion criteria, and thus 130 patients were enrolled and form the study group. An OGTT was performed in 109 patients. The test was not performed in 13 patients with established non IDDM, 6 patients who refused the test, and 2 patients who died before the test could be performed, figure 1.

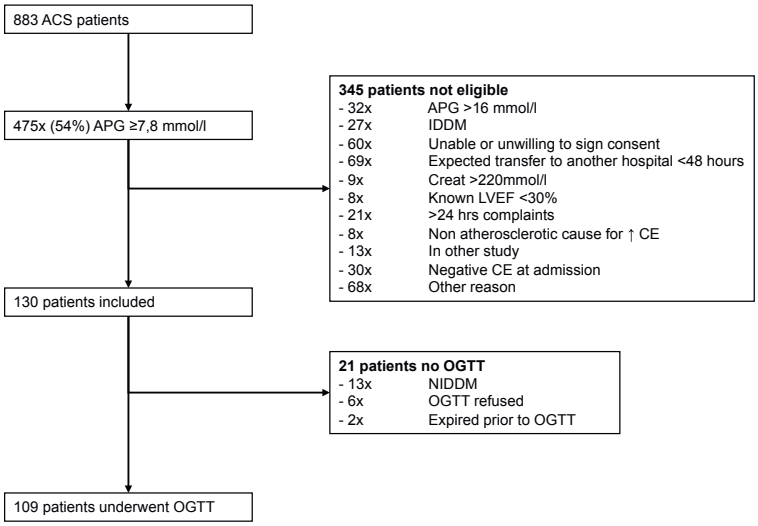
The diagnosis of ACS was based on the following criteria: typical ischemic chest pain for at least 15 minutes and either ST elevation >1mm in two consecutive leads and/or elevated markers of myocardial necrosis, i.e. Troponin I above 0.45 ug/l (Beckman Coulter, Brea, USA) within 24 hours after the onset of chest pain.

Oral glucose tolerance test and undiagnosed diabetes

The OGTT was performed according to a standardized protocol with 75g glucose. The protocol specified that the test be performed prior to discharge, preferably on day 3 of admission. Hitherto undiagnosed diabetes was defined as a fasting plasma glucose (FPG) of ≥ 7.0 mmol/l or a plasma glucose value of ≥11.1 mmol/l 2 hours after loading with 75g glucose (post load glucose (PLG)), according to the American Diabetes Association (ADA) and WHO recommendations.[14 15] Both FPG and PLG values were measured by the central hospital laboratory in venous whole blood, using sodium fluoride tubes. For safety reasons, a PLG was only obtained when FPG was < 7.0 mmol/l. Impaired glucose metabolism was defined as either impaired fasting glucose (FPG 6.1 to 6.9 mmol/l) or impaired glucose tolerance (PLG 7.8 to 11.0 mmol). Patients who did not fall into either of these groups were considered to have normal glucose metabolism.

Admission HbA1c, FPG and APG were compared with the OGTT result as the gold standard in order to compare different diagnostic methods for the detection of diabetes mellitus according to the ADA guidelines.[14] ROC curves and the area under the curve (AUC) were calculated for APG, HbA1c and FPG, in order to investigate an appropriate cut off to detect previously undiagnosed diabetes.

Figure 1 Patient selection



ACS Acute coronary syndrome; APG Admission plasma Glucose; CE Cardiac Enzymes; (N)IDDM (non) Insulin Dependent Diabetes Mellitus; OGTT Oral Glucose Tolerance Test
NIDDM patients were defined as patients currently using oral anti diabetic therapy.

Statistical analysis

Categorical data are presented as numbers and proportions, and continuous data are presented as median values and the interquartile range (IQR). Kolmogorov – Smirnov tests were performed and proved to be non significant, indicating a normal distribution of cases within continuous variables. Differences in baseline characteristics in relation to OGTT results were evaluated by Pearson chi-square test (dichotomous data), or the Kruskall Wallis test (continuous data). Next, variables with a p value <0.05 were further investigated to detect which of the 3 OGTT groups were different from each other. For this, Mann – Whitney and Pearson chi square tests were used as appropriate.

All statistical tests were 2-sided, and a p-value <0.05 was considered statistically significant. The analyses were performed using SPSS 14 (SPSS Inc., Chicago, IL, USA)

RESULTS

One hundred nine non-diabetic ACS patients entered the analysis and underwent an OGTT. The median age was 64 years (IQR 55 - 73), 81% were men and 98% were of Caucasian origin. Patients were discharged after a median of 3.6 days (IQR 2.4 - 4.7). The median APG was 9.2 mmol/l (IQR 8.3 - 10.4). ST-elevation was present in 92 (84%) patients, who had a median APG of 9.4 mmol/l (IQR 8.4 - 10.4), compared with 8.6 mmol/l (IQR 8.3 - 9.6) in patients presenting without ST-elevation (*p* value 0.061). The median FPG was 5.9 mmol/l (IQR 5.5 – 6.3) and the median PLG 9.1 mmol/l (IQR 7.4 – 11.6). Diabetes was newly diagnosed in 38 (35%) patients, impaired glucose metabolism was found in 48 (44%) patients and only 23 (21%) patients had normal glucose metabolism, figure 2. The diagnosis of new diabetes was based on a FPG ≥ 7 mmol/l in 14 patients and in 24 patients on the PLG value of ≥ 11.1 mmol/l. Side effects of the OGTT were limited to mild nausea. Patients with undiagnosed diabetes were significantly older, had higher admission HbA1c values, had more often experienced a stroke, and were in a clinically worse condition as expressed by a higher Killip class, table 1.

With a FPG of ≥ 7.0 mmol/l as diagnostic cut off, 14 out of 38 patients with undiagnosed diabetes were recognized, table 2. With this cut off value sensitivity was 37% and specificity 100%, figure 3, left panel.

With HbA1c ≥ 6.5% (48 mmol/mol) as the diagnostic cut off, only 11 out of 38 (29%) patients with undiagnosed diabetes were detected, table 2. In these 11 patients the OGTT confirmed undiagnosed diabetes. In our series the sensitivity at this HbA1c cut-off value to detect undiagnosed diabetes in ACS patients with elevated APG was only 29%, with a specificity of 100%, figure 3, middle panel.

In patients with undiagnosed diabetes the APG varied between 8.0 mmol/l and 16.0 mmol/l. An APG cut off value with reasonable sensitivity and specificity to predict undiagnosed diabetes could not be determined. The optimal cut-off value at the crossing of sensitivity and specificity curves was an APG value of 9.3 mmol/l; however sensitivity and specificity were only 56%. When the diagnostic cut-off for a random glucose in symptomatic patients was used instead (i.e. ≥ 11.1 mmol/l), sensitivity was 16% and specificity 89%, figure 3 right panel.

The area under the ROC curve was 0.61 for APG, 0.75 for FPG and 0.72 for HbA1c, figure 4. These tests therefore discriminate poorly between patients with a positive and negative OGTT.

Table 1 Baseline characteristics and results of patients who underwent an OGTT

	Total	Normal glucose metabolism	Impaired glucose metabolism	New diagnosed DM	P value
Number of patients	109	23	48	38	
Age (yrs)	64 (55 – 73)	56 (49 – 67)	63 (56 – 72)	71 (59 – 76)	0.003
Men	88 (81)	22 (96)	36 (75)	30 (79)	0.11
Current smoker	41 (38)	11 (48)	18 (38)	12 (32)	0.45
Hypertension	40 (37)	6 (26)	18 (38)	12 (32)	0.45
Hyper-cholesterolemia	27 (25)	5 (22)	14 (29)	8 (21)	0.64
Family history of MI	29 (27)	8 (35)	11 (23)	10 (33)	0.51
Previous MI	9 (8.3)	2 (8.7)	5 (10)	2 (5.3)	0.69
Previous stroke	8 (7.3)	0	2 (4.2)	6 (16)	0.04
Peripheral Artery Disease	8 (7.3)	1 (4.3)	2 (4.2)	5 (13.2)	0.23
Chronic lungdisease	5 (4.6)	1 (4.3)	2 (4.2)	2 (5.3)	0.97
Admission plasma glucose	9.2 (8.3 – 10.4)	9.2 (8.3 – 9.9)	9.2 (8.1 – 10.4)	9.5 (8.8 – 10.5)	0.18
HbA1c (%)	5.8 (5.6 – 6.1)	5.6 (5.4 – 5.7)	5.8 (5.6 – 6.0)	6.1 (5.7 – 6.7)	<0.001
Creatinine (mmol/l)	87 (74 – 105)	91 (73 – 106)	87 (77 – 96)	85 (72 – 108)	0.57
Admission diagnosis STEMI	92 (84)	21 (91)	42 (88)	29 (76)	0.22
Multivessel disease	56 (53)	10 (46)	24 (51)	22 (61)	0.47
Killip class ≥2 at admission	8 (7.4)	0	2 (4.3)	6 (16)	0.04
Waist circumference (cm)	99 (94 – 106)	98 (89 – 103)	100 (96 – 107)	98 (93 – 109)	0.19
Body mass index (kg/m^2)	26 (24 – 28)	26 (24 – 28)	26 (24 – 28)	25 (24 – 29)	0.84
Medication at admission					
Aspirin	18 (17)	2 (8.7)	9 (19)	7 (18)	0.52
B blockers	18 (17)	2 (8.7)	9 (19)	7 (18)	0.51
ACE inhibitors	8 (7.3)	3 (13)	0	5 (13)	0.03
Statins	20 (18)	3 (13)	9 (19)	8 (21)	0.73

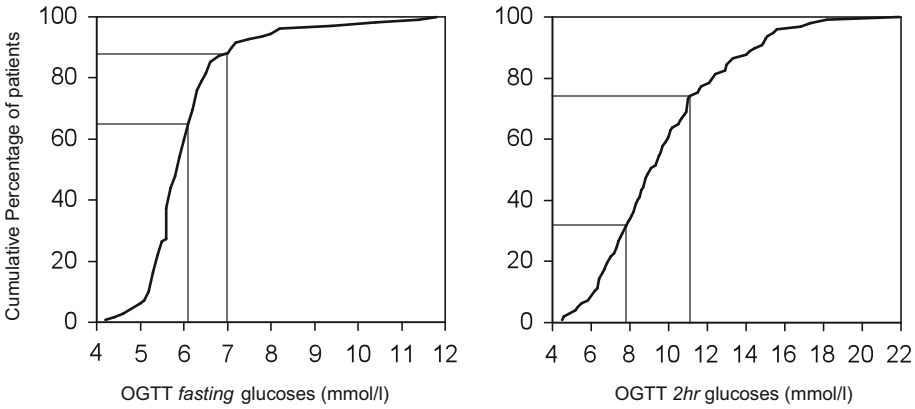
Continuous values are given as median values with first and third quartiles, dichotomous variables are numbers with percentages. MI = Myocardial Infarction, STEMI = ST elevation MI Glucose in mmol/l, for conversion to mg/dL multiply by 18. HbA1c given as %, for conversion to mmol/mol: HbA1c (%) x 10.93 – 23.5

Table 2 Comparison of diagnostic methods for diabetes

	Fasting glucose		HbA1c		Admission glucose		total
	≥ 7.0 mmol/l	< 7.0 mmol/l	≥ 6.5 %	< 6.5%	≥ 11.1 mmol/l	<11.1 mmol/l	
OGTT diabetes	14	24	11	27	6	32	38
OGTT no diabetes	0	71	0	71	8	63	71
total	14	95	11	98	14	95	109

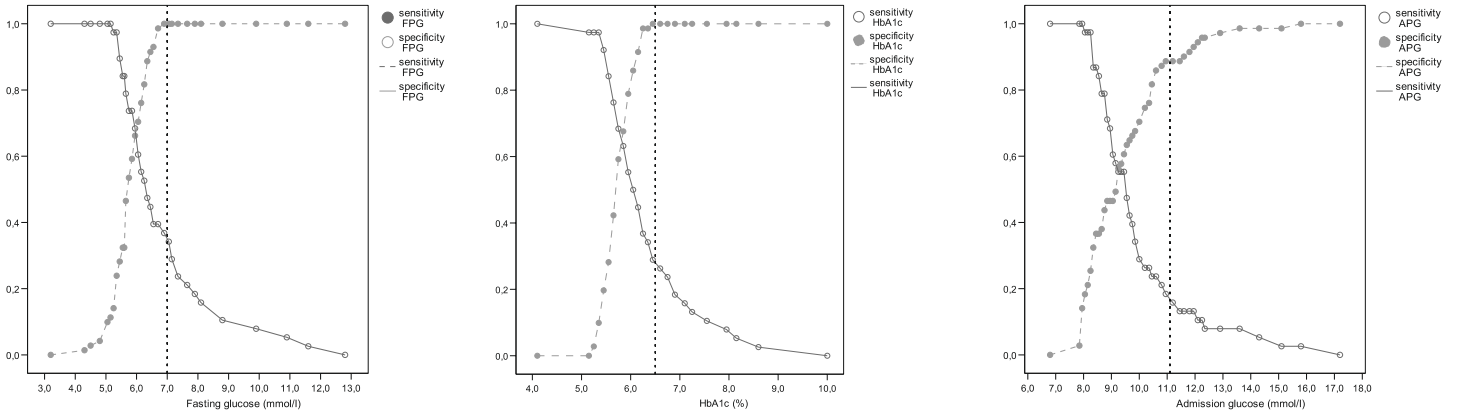
HbA1c 6.5% equals 48 mmol/mol

Figure 2 OGTT results



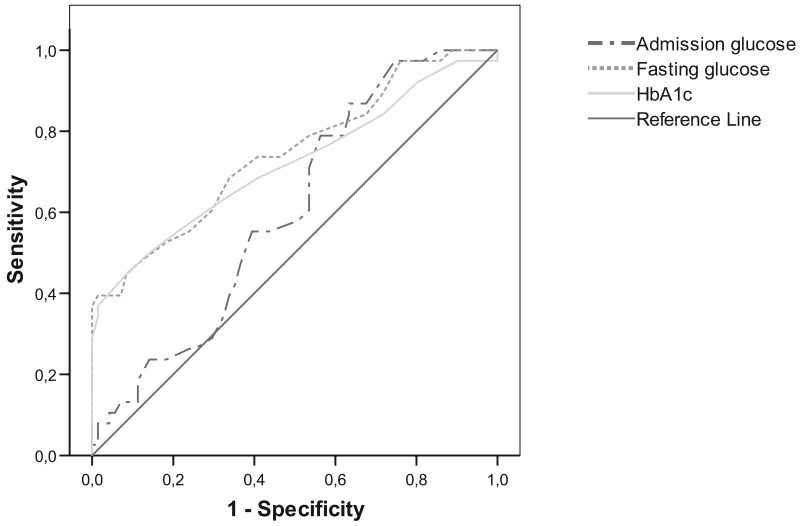
Left panel: Cumulative percentage of fasting OGTT results
Right panel: Cumulative percentage of 2 hour OGTT results
Reference lines represent cut-off values for either impaired glucose metabolism (6.1 and 7.8 mmol/l) or diabetes (7.0 and 11.1 mmol/l).

Figure 3 Sensitivity and specificity curves



Sensitivity and specificity curves for Fasting glucose (FPG, left panel), HbA1c (middle panel) and Admission glucose (APG, right panel) compared to the OGTT as gold standard. Reference lines represent diagnostic cut-off values for diabetes as recommended by the American Diabetes Association. (FPG 7.0 mmol/l; HbA1c 6.5%; and APG 11.1 mmol/l)

Figure 4 ROC curves to compare different diagnostic methods for diabetes



OGTT result used as reference. AUC was 0.61 for APG, 0.75 for FPG and 0.72 for HbA1c.

DISCUSSION

One in three hyperglycemic ACS patients had previously undiagnosed diabetes and 44% were found to have impaired glucose metabolism. The strength of this study is the direct comparison of the four diagnostic methods for diabetes in these high risk patients.

A pre-discharge OGTT was a more sensitive method to detect undiagnosed diabetes and impaired glucose metabolism than APG, FPG and HbA1c. These results confirm the important role of an OGTT in detecting previously undiagnosed diabetes. They also demonstrate that diabetes is a common finding in hyperglycemic ACS patients, with or without ST elevation.

Our results extend the current knowledge of the prevalence of undiagnosed diabetes in hyperglycemic ACS patients in addition to myocardial infarction (MI) patients in the fibrinolysis era, in elective consultations for cardiovascular disease and in patients who underwent an elective percutaneous coronary intervention (PCI), where the prevalence as found with an OGTT was 31%, 22% and 16% respectively.[16-18]

Diagnostic criteria to detect diabetes

Four criteria exist to diagnose diabetes; HbA1c, OGTT, fasting glucose and a random glucose in a patient with classic symptoms of hyperglycemia.[14] Which of these is most appropriate to detect undiagnosed diabetes in the setting of ACS remains to be clearly defined.

With HbA1c ≥ 6.5% (48mmol/mol) as the diagnostic cut-off value, the AUC was 0.72 in our series, indicating it as a suboptimal test to detect diabetes, figure 4. Compared with the OGTT, HbA1c missed 71% of patients with undiagnosed diabetes. In addition to 6.5% as the diagnostic cut-off for diabetes, the ADA recommends the use of an HbA1c of 5.7 – 6.4% (39 – 46 mmol/mol) to identify patients with an increased risk of future diabetes.[14] However, in this latter HbA1c group of 59 patients, the OGTT identified 31% patients as currently having undiagnosed diabetes.

There may be several reasons for the limited sensitivity of HbA1c to detect undiagnosed diabetes. As HbA1c correlates with the mean blood glucose over the previous 8 to 12 weeks, it requires regularly elevated glucose levels to increase. As a consequence HbA1c levels rise above the diagnostic threshold at a later stage than direct glucose level measurement with an OGTT. Furthermore, in spite of standardization, there are biological and patient-specific factors that can influence HbA1c results, such as hemoglobin variants, erythrocyte survival and turnover, and race. [19-21] (see also www.ngsp.org) Therefore a 'normal' HbA1c value may not be the most accurate method to rule out diabetes.

Measurement of FPG is another method frequently used by clinicians to screen for diabetes in patients with an elevated APG. However, the FPG of the OGTT recognized undiagnosed diabetes only in 37% in our series and the AUC was 0.75, figure 4. Thus FPG is insufficient and, in addition, a PLG should be determined (i.e. a complete OGTT) to detect diabetes adequately.

In patients with classic hyperglycemic symptoms, a random glucose level of ≥ 11.1 mmol/l can be used to diagnose diabetes. Elevated admission glucoses in ACS patients are often considered a stress response and although not suitable to diagnose diabetes, it was felt that it may predict the outcome of an OGTT. In this series however, a reasonably sensitive cut off value could not be determined. Although the probability of finding diabetes with an OGTT increased with increasing APG levels, this high specificity could only be obtained at the cost of a low sensitivity, figure 3. APG was therefore not useful to predict diabetes. This is further illustrated by the AUC of only 0.61 when ≥ 11.1 mmol/l was used as cut-off, figure 4.

As with any test, the OGTT has limitations. The timing of the test may be important. It is conceivable that in the days following an MI, although the glucose levels have normalized, the underlying glucose metabolism has not yet fully recovered, resulting

in a false positive test. This matter remains controversial. Some studies question the reproducibility of an OGTT as the disturbances were found to be transient, [22-24] whereas others suggest that an OGTT in the early phase of MI is appropriate.[16 25] A strong correlation between the 2-hr blood glucose values at discharge and at 3 months was found, indicating that raised blood glucose values are not only related to stress induced by the ischemic event. [16]

Possible clinical consequence of abnormal glucose metabolism

The early detection of diabetes in patients with CVD offers the chance to make early lifestyle interventions in this high risk population. Apart from the question whether or not a pre discharge OGTT is the optimal timing to detect diabetes, Høfsten et al found that higher pre discharge OGTT values were associated with increased mortality. [26] Hence, it may be important to recognize all patients at risk and thus to use a test that detects as many patients with (pre)diabetes as possible. The ESC/EASD guidelines therefore recommend that an OGTT should be used to assess glucose metabolism in patients without known diabetes but with established CVD.[12]

With patient risk management we aim to eliminate, or favorably modify, risk factors. Unfortunately, many of these factors such as age cannot be influenced. It is therefore even more important to manage the factors we can influence, including newly diagnosed diabetes. Haffner et al demonstrated that diabetic patients without previous MI have as high a risk of MI as non-diabetic patients with previous MI.[27] This has provided the rationale for treating cardiovascular risk factors in diabetic patients as aggressively as in non-diabetic patients with prior MI. Perhaps the opposite is also valid, and abnormal glucose metabolism in MI patients should be treated as aggressively as in diabetic patients.

Limitations

The number of patients included is relatively small and selected from patients who participated in a single centre randomized clinical trial; therefore the true prevalence of undiagnosed diabetes should be confirmed in a larger cohort of patients from multiple hospitals and countries that represent the broad spectrum of ACS. Particularly the proportion of diabetes and pre diabetes in patients with an APG <7.8 is interesting, as they were not eligible for the current study.

Additionally, it would be of interest to repeat the OGTT in all patients after 1 or 2 years to investigate which patients advanced from impaired glucose metabolism to diabetes and vice versa. This would help to determine whether a pre discharge OGTT is the proper timing.

CONCLUSION

Our results underscore that previously undiagnosed diabetes mellitus in ACS patients with an elevated APG occurs frequently, and only 21% of patients had a normal glucose metabolism. APG, FPG and HbA1c under-diagnosed diabetes compared with an OGTT.

As the OGTT is a straightforward, non-invasive and affordable test that can be performed during clinical recovery we would like to advocate that an OGTT should become standard care in all patients admitted with ACS, at least in those with an elevated APG. This will result in early recognition of diabetes and pre diabetes and subsequently earlier lifestyle and medical interventions.

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Chapter 8

Diagnosing diabetes on admission hyperglycemia

Ayesha C Qureshi, Andrew P Asherson, Ashley B Grossman

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INTRODUCTION

Diabetes mellitus and cardiovascular disease are two closely related diseases. In patients with both stable and unstable coronary artery disease (CAD), there is a high prevalence of diabetes and increased rates of both undiagnosed diabetes and impaired glucose metabolism such as impaired glucose tolerance (IGT) or impaired fasting glucose (IFG).[1 2] Patients with known or newly diagnosed diabetes are at particularly elevated risk for both mortality and adverse cardiac events at 1 year of follow-up.[2] Cardiovascular disease is currently the leading cause of death worldwide.[3] At the same time, there is a worldwide epidemic of diabetes mellitus, with over 280 million (6.4%) of the world's population affected.[4] There is therefore a need for a closer working relationship between diabetologists and cardiologists in order to improve the management of such patients.[5] Thus, if one sees a patient with suspected CAD, it is extremely important to confirm whether or not he or she has diabetes and, in due course, to treat it effectively. This is especially true in the case of an acute coronary syndrome (ACS). One method that has been used is the assessment of admission hyperglycaemia, which has been shown to increase subsequent cardiovascular events.[6] Patients presenting with ACS and documented hyperglycaemia on admission have worse outcomes irrespective of underlying diabetes status.[7-11]

However, a quite different question is whether such admission hyperglycemia can predict longer-term diabetes or IGT. The current American Diabetes Association definition for IFG is a blood glucose level of 5.6 - 6.9 mmol/l after an 8-h fast.[12] This was adopted in order to achieve a better consensus with the WHO criteria for IGT, which is defined as a glucose level of ≥7.8 and <11.1 mmol/l 2 h after a glucose load.[13] The current WHO diagnostic criteria for diabetes are fasting plasma glucose (FPG) ≥7.0 mmol/l or 2 h plasma glucose ≥11.1 mmol/l on oral glucose tolerance testing (OGTT). Although OGTT remains the gold standard test to diagnose diabetes, measuring FPG is often preferred in clinical practice as it is easier to perform, less onerous for the patient and cheaper. Both the WHO and the International Diabetes Federation have recommended the adoption of IFG for primary screening.[14 15] However, measuring only fasting values can lead to false-negative results.[5 16 17] This has led to an International Expert Committee and an independent panel of experts to propose the use of HbA1c as a diagnostic tool. [18 19] Diabetes should be diagnosed when HbA1c is ≥6.5% (48 mmol/l), and this has also been endorsed by the American Diabetes Association.[20]

Can we use admission hyperglycaemia to diagnose diabetes?

Thus, to establish the utility of admission hyperglycemia in the diagnosis of subsequent diabetes, de Mulder et al [21] elegantly compared different diagnostic methods for diabetes in patients with ACS (in press). Participants were enrolled in the single-centre BIOMArCS Study (BIOMarker study to identify the Acute risk of a Coronary Syndrome), which evaluated the safety and effectiveness of intensive glucose regulation. Patients in the sub study (n=130) reported here had a clinical diagnosis of ACS and an admission plasma glucose (APG) between 7.8 and 16 mmol/l. APG was then compared with FPG, HbA1c and OGTT in the diagnosis of diabetes. Receiver operating characteristic (ROC) curves were constructed and the area under curve (AUC) was reported in order to investigate an appropriate cut-off for previously undiagnosed diabetes.

OGTT results were categorised as a new diagnosis of diabetes in 35% of patients and impaired glucose metabolism in 44% of patients therefore, on admission, only 22% of the patients had normal glucose metabolism. Patients with abnormal glucose metabolism were significantly older, had higher HbA1c levels, had a higher Killip class and had a more frequent history of prior stroke. On ROC analysis, the authors concluded that undiagnosed diabetes could not be adequately predicted with APG, FPG or HbA1c as the AUC values were all low at 0.61, 0.75 and 0.72, respectively. The use of ROC curves and logistic regression is well established when testing biomarkers for their relationship with disease status and clinical outcomes.[22] However, there are limitations to this approach, especially when one attempts to use a new biomarker measurement to complement an established diagnostic test.[23] Even biomarkers that can be shown to be an effective, independent predictor of an outcome when logistic regression is used may struggle to show much increase in the AUC or C-statistic of the ROC curve when the AUC for the previously used measurement was already high. In many ways, this is not a surprising result, since a predictive model that performs well will generally be harder to improve upon.[24]

Thus, APG led to the diagnosis of nearly 80% of patients with IGT or diabetes subsequently, although on its own, it is clearly not sufficient to make the diagnosis. It would be extremely useful to ascertain the prevalence of IGT and diabetes in those individuals without an elevated APG.

Another study evaluated the prevalence of abnormal glucose metabolism using an OGTT in patients without diabetes admitted with an ACS.[25 26] OGTT was performed both in-hospital and at 3 months following discharge. In hospital, 35% of patients had IGT and 25% had a new diagnosis of diabetes. These figures were 40% and 25%, respectively, at 3 months. The follow-up of this study showed that in patients without a known history of diabetes, abnormal glucose metabolism was associated

with a significantly increased risk of subsequent adverse cardiovascular events.[27] Data from the Euro Heart Survey showed that patients with both stable and unstable cardiovascular disease and a new diagnosis of diabetes had worse outcomes after 1 year,[28] although this was not observed in patients with either IFG or IGT. This is in contrast to data from the DECODE (Diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe) study, which clearly demonstrated that IGT was a risk factor for cardiovascular events.[29] In patients with a known diagnosis of diabetes, both fasting glucose levels at the time of ACS[30] and long-term glycemic control before and after the ACS episode predict the risk of subsequent cardiovascular events.[31 32]

CONCLUSIONS

Diabetes is an important risk factor for coronary CAD, and admission hyperglycaemia in a patient with ACS mandates further study after the acute episode is over. While admission hyperglycemia is very likely to indicate either diabetes or IGT, a subsequent formal OGTT is required to confirm the diagnosis. The importance of treating admission hyperglycaemia remains unclear[33] but will be established following the full analysis of this study in the future.

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Chapter 9

Current management of hyperglycemia in acute coronary syndromes, a national Dutch survey

Maarten de Mulder; Rohit M Oemrawsingh; Frank Stam;
Eric Boersma; Victor A Umans

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ABSTRACT

Background: Hyperglycemia is common among patients admitted with Acute Coronary Syndromes (ACS) and is associated with less favorable clinical outcomes. Guidelines for the treatment of hyperglycemia in myocardial infarction are confusing, partly due to lack of sufficient evidence. Neither do we know what the everyday practice on hyperglycemia in ACS is. Therefore the aim of our study is to describe current glucose management in ACS patients in The Netherlands.

Methods: We designed a multiple-choice questionnaire that was emailed to all 94 independent cardiology departments of each of the 114 hospitals within The Netherlands. We interviewed cardiologists about their specific hospital setting, the presence, content and actual use of a dedicated hyperglycemia protocol in the setting of ACS.

Results: Ninety-four questionnaires were returned (response rate 100%). Only 32% of the respondents reported to have a routinely applied, dedicated hyperglycemia protocol in the setting of ACS. An admission glucose of 13.0 mmol/l is considered a stress value by 60% of respondents. Treatment of hyperglycemia is postponed until after the acute phase (i.e. after > six hours) in 41% of the cardiology departments and in 76% HbA1c is not routinely measured before discharge.

Conclusion: Only a minority of Dutch cardiology departments have a routinely applied, dedicated hyperglycemia protocol for patients admitted with ACS. Different views exist on the interpretation of admission hyperglycemia in patients without previously diagnosed diabetes. Dedicated protocols with well established treatment goals allow early treatment and are mandatory in order to improve timely metabolic regulation.

INTRODUCTION

In patients admitted with acute coronary syndromes (ACS), hyperglycemia on admission is a common finding. Observational studies have reported a fasting glucose level above 7.8 mmol/l, which is the generally accepted threshold to diagnose hyperglycemia, [1 2] in 40% to 58% of patients.[3 4] Diabetes mellitus (DM), which corresponds to a random glucose level above 11 mmol/l, is diagnosed in 14% to 24% of subjects presenting with ACS. [3 4] Previous studies have provided convincing evidence that hyperglycemia during hospitalization for an acute myocardial infarction (AMI) is a strong and independent predictor of all cause mortality and in-hospital complications. [3-7]

Different treatment strategies regarding glucose metabolism have been studied in ST Elevation -ACS as well as Non ST Elevation –ACS, the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction study (DIGAMI) 1 & 2, [8 9] the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation— Estudios Clinicos Latino America / Organization for the Assessment of Strategies for Ischemic Syndromes-6 (CREATE-ECLA/OASIS-6),[10] the Glucose Insulin Potassium Study (GIPS) 1 & 2 [11 12] and the Hyperglycemia: Intensive Insulin Infusion In Infarction (HI-5)study.[2] Regrettably these studies provided mixed, sometimes even confusing results [1] presumably due to (i) differences in the chosen treatment strategy, which was either driven by glucose-level control [2 8 9] or plain insulin administration, [10] (ii) the selection of treatment, either Glucose-Insulin-Potassium (GIK)[10] or insulin-glucose, [8 9] (iii) the selection of different glucose target values (varying between 4 and 11 mmol/l), (iv) the HI-5 and DIGAMI-2 studies ended up in comparing two different insulin strategies instead of different intensity of glucose control and (v) although most studies intended to improve prognosis after ACS by lowering blood glucose levels, in CREATE-ECLA/OASIS-6 glucose levels were actually higher in the GIK arm than in the placebo arm.

Consequently, guidelines on this matter speak only in general terms [13 14] and the selection of the most appropriate treatment strategy appears to be a great challenge for cardiologists. Therefore it might be essential to know how cardiologists actually treat hyperglycemia in real-world practice, outside the environment of strict study protocols. Or, as put in a recent statement by the American Heart Association (AHA) ,[1] one of the specific areas in need of further investigation is: "to describe current patterns of glucose management among patients hospitalized with ACS". Hence, the aim of this study is to report current practice for hyperglycemia treatment in ACS patients by all cardiology departments in The Netherlands.

METHODS

Design

In March 2008 a questionnaire on hyperglycemia management was designed and emailed to each of the 94 cardiology departments within The Netherlands. From every department we obtained the questionnaire from their representative cardiologist. The questionnaire consisted of nine multiple-choice questions, specifically addressing the adherence to the recent AHA recommendations.[1] Two questions allowed additional written information to be added.

A reminder was emailed to non-responders and if necessary the questions were taken by phone. We asked physicians about their hospital setting, whether their department has implemented a dedicated hyperglycemia protocol in the setting of ACS, what they consider admission hyperglycemia and how they act upon it, see appendix.

Participants

In the Netherlands (16 million inhabitants) there are eight university hospitals and another 106 community hospitals, which largely vary in size, that offer cardiological care. These 114 hospitals are served by 94 independent cardiology groups. Typically, Dutch cardiologists work in departments varying from 4 to 15 cardiologists.

We interviewed a representative / chairman of the cardiology group. In the majority of cases this cardiologist is, in addition to clinical care, also in charge of the research and trial programs. In academic clinics or if such a representative was not available we interviewed a cardiologist who is responsible for the coronary care unit (CCU).

Hospitals may be categorized as academic/tertiary referral centre or community hospitals, all within a single, national healthcare system.

Data analysis

Answers to the multiple-choice questions are presented as numbers and percentages. The answers were related to hospital characteristics, and Mann-Whitney tests or Kruskal-Wallis tests were applied, as appropriate. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

From the 94 independent cardiology departments we received 94 questionnaires. Twelve cardiologists represented a cardiology department of an academic or tertiary referral centre, 14 represented a large (>700 beds in total), 26 a medium sized (400 - 700 beds in total) and 42 a small (<400 beds in total) community hospital.

Protocol

A dedicated protocol for the evaluation and treatment of hyperglycemia in ACS patients is used in 46% of cardiology departments, in 32% of these departments the protocol is used routinely (i.e. a good adherence to the local protocol is reported), while the other 14% seldom applies it.

The cardiology departments that routinely apply a dedicated hyperglycemia protocol use significantly (*p*-value <0.001) lower threshold admission glucose values to start active glucose regulation (table 1). Furthermore, they report to start glucose regulation earlier (*p*-value <0.001) and strive for lower (*p*-value 0.01) glucose target values compared to departments that do not routinely apply such protocol (table 2). Finally, 60% of the departments with a dedicated hyperglycemia protocol consider an admission glucose of 13.0 mmol/l to be diabetes, compared to only 26% of their counterparts without such protocol (*p*-value 0.01).

Hyperglycemia

The relevance of an admission glucose value up to 13.0 mmol/l is considered as a temporary stress-induced hyperglycemia by 60% of the respondents, whereas 37% argued that this value corresponds to (latent) diabetes. Overall, 51% of respondents directly start with treatment of hyperglycemia of 13.0 mmol/l or higher (figure 1). Furthermore, 36% of the cardiology departments report to postpone active glucose management while they await a second glucose value (24%) or a fasting glucose value (12%), table 1 and figure 2.

Assessment of the long-term glucose status by measurement of an HbA1C level is claimed to be performed at admission by 11% and later during hospital stay by 13% of the respondents. However, 76% of respondents stated that they do not routinely measure HbA1c before discharge.

Table 1 Threshold values to start hyperglycemia treatment

Protocol present?	6.1 – 7.7 mmol/l		7.8 – 11 mmol/l		11.1 – 12 mmol/l		12.1 – 14 mmol/l		14.1 – 16 mmol/l		>16 mmol/l		Wait for 2nd value, then start treatment		Wait for fasting glucose, then start treatment		Total present protocols
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
Yes, routinely applied	3	10.0	9	30	11	36.7	1	3.3	0	0	1	3.3	4	13.3	1	3.3	30 (37%)
Yes, seldom applied	1	8.3	1	8.3	2	16.7	4	33.3	2	16.7	0	0	2	16.7	0	0	12 (15%)
No protocol	0	0	6	15.4	5	12.8	2	5.1	2	5.1	2	5.1	13	33.3	9	23.1	39 (48%)
Total	4	5	16	19.8	18	22.2	7	8.6	4	4.9	3	3.7	19	23.5	10	12.3	81

Kruskall Wallis P < 0.001 for distribution differences. Percentages within "protocol present"

Table 2 Time to hyperglycemia treatment in ACS

Protocol present?	<2 hrs		2 - 4 hrs		4 - 6 hrs		6 - 9 hrs		9 - 12 hrs		>12 hrs		Total Present protocols
	n	%	n	%	n	%	n	%	n	%	n	%	
Yes, routinely applied	16	53.3	8	26.7	3	10.0	0	0	2	6.7	1	3.3	30(32%)
Yes, seldom applied	2	16.7	5	41.7	1	16.7	2	16.7	1	8.3	1	8.3	12(14%)
No	8	17.0	6	12.8	4	12.8	6	12.8	8	17.0	15	31.9	47(54%)
Total	26	29.2	19	21.3	8	9.0	8	9.0	11	12.4	17	19.1	89

Kruskall Wallis P < 0.001 for distribution differences. Percentages within "protocol present"

Table 3 Time to hyperglycemia treatment, according to unit of admission in the 79 community hospitals.

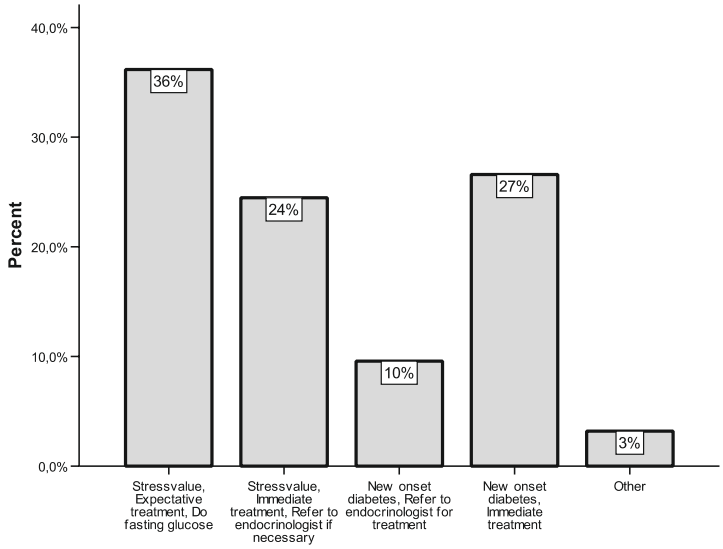
Place of admission	<2 hrs		2 - 4 hrs		4 - 6 hrs		6 - 9 hrs		9 - 12 hrs		>12 hrs		Total
	n	%	n	%	n	%	n	%	n	%	n	%	
CCU*	9	17.3	13	25	6	11.5	6	11.5	8	15.4	10	19.2	52(66%)
ICU/CCU†	12	44.4	5	18.5	2	7.4	0	0	2	7.4	6	22.2	27(34%)
Total	21	26.6	18	22.8	8	10.1	6	7.6	10	12.7	16	20.3	79

Mann Whitney p value = 0.086 for distribution differences. Percentages within place of admission

** CCU is a separate coronary care unit*

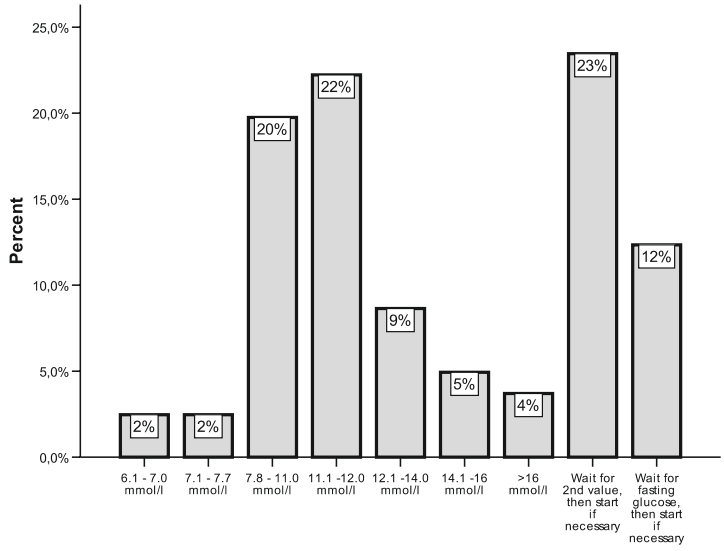
† ICU/CCU is a combined intensive care and coronary care unit.

Figure 1 Hyperglycemia interpretation.



The interpretation of an admission glucose of 13.0 mmol/L in ACS patients without a history of diabetes

Figure 2 Threshold values.



The threshold admission glucose value to start treatment of hyperglycemia in the setting of an ACS.

Timing of treatment

Twenty-nine percent of all respondents stated that they start hyperglycemia treatment within 2 hours after admission for ACS, 21% within 2 to 4 hours and 9% within 4 to 6 hours. Late starts were also reported; 9%, 12% and 19% start in 6 to 9 hours, 9 to 12 hours or over 12 hours respectively.

The start of treatment is significantly influenced by the presence of a dedicated protocol, as cardiology departments with a dedicated hyperglycemia protocol in place claim earlier commencement of treatment than departments without such a protocol (p-value <0.001). The unit of admission, either combined intensive/coronary care units (ICU/CCU) or separate CCU, seems related with the timing of the onset of treatment (table 3).

Cardiology departments in community hospitals with combined units report to start within two hours after admission in 44% of cases, and within four hours in 63%. In cardiology departments with separate CCUs these percentages were 17% (within two hours) and 42% (within four hours), respectively.

In our survey we found that hospitals where hyperglycemic treatment is started within 6 hours after admission, 70% administer intravenous (IV) insulin. The remaining hospitals use subcutaneous insulin (21%), GIK (7%) or oral medication (2%).

DISCUSSION

This nationwide survey shows the lack of a univocal treatment strategy for hyperglycemia in ACS patients among cardiologists, especially in patients without a history of diabetes.

Hyperglycemia in ACS: Temporary stress value or diabetes?

Less than half of the Dutch cardiology departments consider an admission glucose of 13.0 mmol/l diagnostic for diabetes, in spite of the WHO criteria for diabetes, [15] in which a 2-hour post glucose tolerance test plasma glucose value of ≥11.1 mmol/l is considered diabetes. One could argue that these values are not valid in situations with extreme physical stress, like a myocardial infarction. However, it could also be argued that an otherwise well functioning body metabolism should be able to compensate various (hormonal and physical) stressors and maintain a near euglycemic status. [16] Given this metabolic regulatory mechanism, an admission glucose of 13.0 mmol/l in the setting of ACS should not too easily be considered as a stress value. Norhammar et al indeed found an incidence of 31% of new onset diabetes in ACS patients with moderate hyperglycemia at admission. [17]

The national North American "Cooperative Cardiovascular Project" [4] found that only 21% of non diabetic ACS patients admitted with a glucose >13,3 mmol/l received insulin treatment. This suggests a low awareness of the importance of hyperglycemia in the setting of ACS among cardiologists, just as we demonstrate in our study.

The diverse opinions on the management of hyperglycemia in ACS can partly be explained by the lack of clear guidelines for this matter, which in turn can be explained by the lack of univocal study results. As a consequence it is hard to develop evidence based local hospital protocols for management of hyperglycemia in ACS. We believe many more colleagues should become aware of the importance of such hyperglycemia and we may have to call on endocrinologists to jointly develop dedicated protocols to improve metabolic regulation.

The importance of treatment timing and clinical setting

Whether the impact of varying treatment regimes or the delayed start of hyperglycemia treatment may result in poorer outcomes has not been fully elucidated. However, Jonassen et al.[18] observed in rat models that a "metabolic cocktail" (Glucose-Insulin-Potassium (GIK)) administered at myocardial reperfusion reduced infarct size by 45% compared to controls. But when given 15 minutes into reperfusion this effect was nullified. In a clinical setting Goyal et al.[19] found that lowering glucose levels in the first 24 hours was associated with improved 30-day survival. They, however, could not distinguish spontaneous from insulin mediated glucose lowering. With this in mind, it seems reasonable to suggest that early hyperglycemia treatment may lead to an improved clinical outcome, although further prospective clinical research is required. Even though this swift therapy start is proposed earlier,[1] only a small portion of Dutch cardiologists recognize its importance.

This strategy seems to be implemented in small community and academic/tertiary referral hospitals. A possible explanation for this observation could be that in smaller Dutch hospitals ACS patients are often admitted to a combined ICU/CCU with intensive care staff on ward, whereas larger hospitals more often have a coronary care unit (CCU) with cardiology staff on ward. In general, ICU protocols tend to pay more attention to hyperglycemia, as there is some evidence for improved outcome after aggressive glucose management in various patient populations within the surgical ICU setting. However this effect is less pronounced in the medical ICU setting and has not been firmly established yet in the CCU setting. This line of reasoning is supported by the significant earlier start of hyperglycemia treatment in community hospitals where a patient is admitted to a combined ICU/CCU.

Choice of therapy

The majority of cardiology departments reported to use IV insulin in order to treat hyperglycemia in the acute phase of an ACS, as recommended by the AHA.[1]

Insulin seems to be beneficial, [20-22] and might be administered preferably intravenously,[2 22] though unclarity exists on the preferred method of administration. It is not clear either if insulin administration should be performed with or without a regime of strict glucose control and what target glucose values should be strived for. [2 23 24]

An important caveat of insulin therapy is the occurrence of hypoglycemia. There is a U- or J-shaped relationship between glucose levels and cardiovascular outcomes [24-26] and both hypo- and hyperglycemia during hospitalization of ACS patients are independently associated with higher mortality.

With the aforementioned limitations, the AHA recommended to consider intensive glucose level control, targeting 5 – 7.8mmol/l (61% of our respondents) when levels exceed 10mmol/l (25% of our respondents start when levels exceed 11mmol/l), regardless of prior diabetes, while avoiding hypoglycemia.

HbA1c measurement

We also addressed the use of HbA1c as a metabolic biomarker. HbA1c is considered the gold standard for assessing glycemic control in diabetic patients. Green Conaway et al. [27] studied 235 ACS patients with a documented history of diabetes and found that almost one third did not have HbA1c assessment during admission; particularly older patients and those not evaluated by an endocrinologist were at risk of not having a HbA1c level measured.

In our questionnaire we found that 76% of cardiology departments do not routinely measure HbA1c during hospitalization. To routinely perform an HbA1c in hyperglycemic patients seems logical as this value is a good starting point to monitor the effect of further diabetes management and is therefore advocated by the AHA. This would apply to approximately 14 – 25% of patients admitted with ACS, as their admission glucose is ≥ 11.1 mmol/l, which could be considered as newly diagnosed diabetes.

Limitations

This survey represents the general vision among Dutch cardiologists and their departments, but by the nature of the study, survey responders could not be anonymous.

Although respondents were asked to report on their local environment in which ACS patients with hyperglycemia are admitted, it is possible that their personal

opinion was given instead of the instructions in the local protocol. The personal nature of answers is unsurprisingly always the case when no protocol was present.

An important limitation is that we are only informed on the perception of the clinicians, but by virtue of the study not on the actual outcome of the initiated treatment nor on its effect on survival or infarct size. Furthermore, different countries have different healthcare systems and different views on certain aspects of medicine. In this view a larger survey among different countries may be required.

CONCLUSION

This nationwide survey on the treatment of hyperglycemia in ACS revealed a limited use of dedicated hyperglycemia protocols for such patients among cardiology departments in The Netherlands. This survey taught us that the routine use of such a protocol permits cardiologists to initiate hyperglycemic treatment earlier and aim for stricter glucose levels. This particular attention for hyperglycemia may lead to an earlier correction of metabolic dysregulation in ACS patients. Finally, large randomized clinical trials of glucose control in hospitalized ACS patients are warranted.

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Appendix; The questionnaire

What type of hospital do you represent?	
Academic/tertiary referral centre	12
Large community hospital (>700 beds)	14
Medium community hospital (400 – 700 beds)	26
Small community hospital (< 400beds)	42
How do you consider an admission glucose of 13.0mmol/l in AMI* without prior diabetes?	
Stress value, no immediate treatment required, repeat fasting glucose	34
Stress value, start immediate treatment, refer to endocrinologist if necessary	23
Diabetes de novo, no immediate treatment required, refer to endocrinologist	9
Diabetes de novo, start immediate treatment, refer to endocrinologist	25
Other	3
Do you have a dedicated protocol for hyperglycemia treatment in ACS† patients?	
Yes, it is routinely applied in clinical practice	30
Yes, but seldom applied in clinical practice	13
No	51
What is the threshold admission glucose value to start treatment? Either in your protocol or, when none available, in your professional opinion.	
6.1 – 7.0 mmol/l	2
7.1 – 7.7 mmol/l	2
7.8 – 11.0 mmol/l	16
11.1 – 12.0 mmol/l	18
12.1 – 14.0 mmol/l	7
14.1 – 16.0 mmol/l	4
>16.0 mmol/l	3
Wait for a 2nd value before treatment starts	19
Wait for a fasting glucose before treatment starts	10
Missing answer	13
Whenever you start treating hyperglycemia, within what time span after admission for ACS is this on average?	
<2 hours	26
2 – 4 hours	19
4 – 6 hours	8
6 – 9 hours	8
9 – 12 hours	11
>12 hours	17
Missing answer	5

What target glucose values are strived for, once treatment has started?	
4.7 – 6.1 mmol/l	20
4.7 – 7.7 mmol/l	37
7.0 – 10.0 mmol/l	22
Other	6
Missing answer	9
Whenever treatment is started within 6 hours after admission, in what form is this?	
Subcutaneous Insulin	11
Intravenous Insulin	37
GIK ‡	4
Oral anti diabetic medication	1
Start > 6 hours after admission / Missing answer	41
Is HbA1c routinely measured before discharge?	
Yes, at admission	10
Yes, after the acute phase	12
No	68
Missing answer	4
For community hospitals, in what clinical setting is an AMI patient admitted?	
Combined ICU/CCU §	28
Separate CCU	53
Missing answer or Academic/tertiary centre	13

Questions and answers of the 94 independent cardiology departments. Numbers represent the number of responders with a particular answer. For conversion from mmol/l to mg/dl multiply by 18.

** ACS = Acute Coronary Syndrome; † AMI = Acute Myocardial Infarction; ‡ GIK = Glucose-Insulin-Potassium; § ICU = Intensive care Unit / CCU = Coronary Care Unit.*

Chapter 10

How to implement a clinical pathway for intensive glucose regulation in acute coronary syndromes

Maarten de Mulder, Esther G Zwaan, Yvonne M Wielinga,
Frank Stam, Victor A Umans

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ABSTRACT

Background: Hyperglycemia upon admission of myocardial infarction patients predicts inferior clinical outcomes. Current strategies investigating hyperglycemia correction mostly use glucose driven protocols. Implementation of these often labor intensive protocols might be facilitated with the approach of a clinical pathway. Therefore we evaluated the implementation of our glucose driven protocol.

Methods: We adapted a protocol for use in our coronary care unit (CCU) which was implemented according to the steps of a clinical pathway. To compensate for carbohydrates in meals we additionally developed a regime of subcutaneous insulin. Protocol adherence was facilitated with a web based insulin calculator. All hyperglycemic patients admitted to the CCU were eligible for treatment according to this protocol.

Results: In a four month period 643 glucose measurements were obtained in hyperglycemic patients admitted to our CCU. Patients were treated intensively with IV insulin for 35 hours and had 23 glucose measurements in this time span on average. This regimen achieved a median glucose of 6.2 mmol/l. Severe hypoglycemia occurred in only 1.1% of measurements and was without severe clinical side effects.

Conclusion: Introduction of a new intensive insulin protocol according to the steps of a clinical pathway is safe and feasible. The presence of a clinical pathway coordinator and sound communication are important conditions for successful introduction, which can be further aided with a computerized calculator.

INTRODUCTION

Patients with or without a history of diabetes may present with hyperglycemia during acute myocardial infarction (AMI). Several studies have demonstrated a relationship between hyperglycemia upon admission and increased adverse events such as left ventricular failure, cardiogenic shock and death.[1-4] Subsequent intervention trials showed mixed results with regard to clinical as well as metabolic results. In particular, the experience from the Leuven group[5] in intensive care unit (ICU) patients and DIGAMI 1[6] in AMI patients were favorable, however other groups could not demonstrate such convincing results. Nor has direct hyperglycemic interventions through GIK therapy [7] been favorable in the setting of an acute coronary syndrome (ACS). New efforts direct to use a glucose driven protocol (in contrast to insulin driven protocols) of intensive insulin therapy in the setting of acute myocardial infarction.

A clinical pathway may become a tool to facilitate the implementation of such new strategies and may even facilitate adherence to the guidelines.[8] It may indeed be an important methodology to implement a multidisciplinary protocol such as intensive insulin therapy in ACS patients. This methodology requires the input of a team of physician and nursing experts and the skills of a dedicated clinical pathway coordinator. The availability of such a coordinator may be of critical importance to achieve an optimal metabolic and clinical outcome for patients.

Computers can assist in providing guidelines, protocols and optimizing patient outcome. With a bedside electronic medical record, there is the possibility of linking patient data with these aids. Ideally, electronic protocols should be flexible enough to accommodate the complex work patterns of clinical practice, without compromising the goal of appropriate care. Such techniques may prevent variations in a care protocol that are dependent on who is using the protocol in what part of the institution. Clinician compliance may be further improved when protocols are customized into a clinical pathway [9], where appropriate.

We describe the implementation of a clinical pathway for intensive glucose regulation in acute coronary syndromes on the coronary care unit (CCU) of a teaching hospital.

METHODS

Setting and design

The Medical Center Alkmaar (MCA) is a large (900 beds) teaching hospital. The CCU consists of 12 beds with a nurse to patient ratio of 1 to 2.5.

Clinical pathway organization

A knowledge center for clinical pathways was created previously in our hospital. Initially, expertise was gained within the cardiology department. The knowledge center's structure allows for a steering committee, working groups and an advisory board.

The steering committee is co-chaired by a cardiologist and managing nursing director and consists further of the clinical pathway coordinator and ICT programmer. The members of the steering committee will govern the entire clinical pathway program and initiate new pathways. The working groups are chaired by the clinical pathway coordinator and consist of 2 cardiologists, 2 ward nurses and a secretary. Typically these members will act as ambassadors of this particular pathway. The coordinator will act as an intermediary to the departments of radiology and chemistry. The advisory board consists of the co-chairs of the steering group members, a representative of the board of directors, chief ICT, chief pharmacist and a representative of the department of nursing quality. Typically these members provide input from the entire hospital organization and may advise on future projects.

The steering group members are asked to propose areas for improvement on an organizational level. The working group members do this on a medical content level. The introduction of a new insulin protocol was approached as a clinical pathway.

This clinical pathway was designed using a bottom-up approach, starting at the departmental rather than the staff level. An intensive insulin treatment strategy demands a multidisciplinary approach in which the clinical pathway coordinator functions as a spin-doctor to enable good interdisciplinary communication. The coordinator remains part of the team on the CCU and is a first *in-the-field* contact. Furthermore he worked closely with 2 selected cardiologists, an internist and diabetes nurse in developing the intensive insulin protocol. The rationale for this approach was the team's desire to make full use of nurse specialist expertise when developing the clinical pathway.

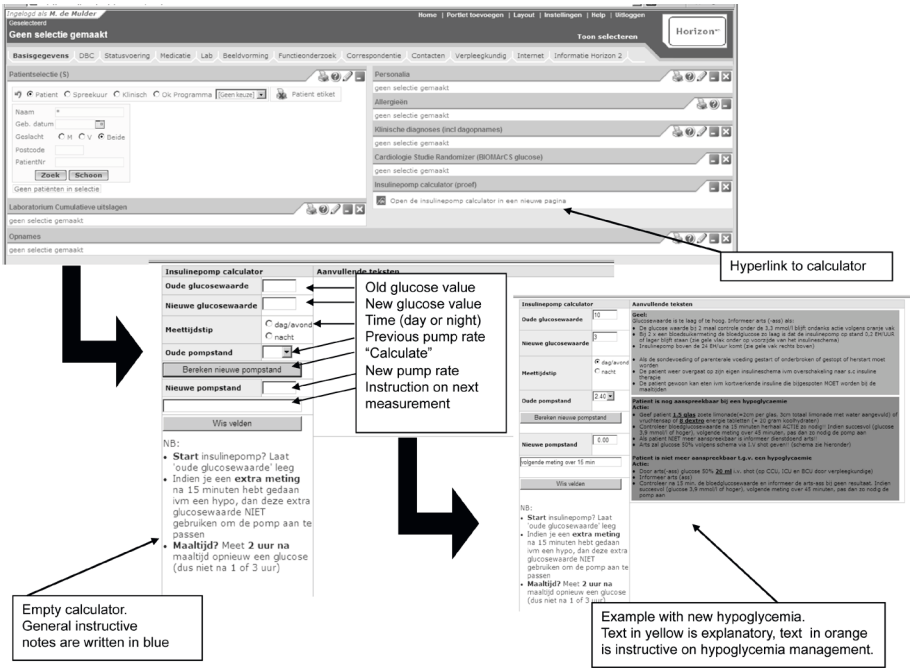
Implementation

The subsequent introduction in clinical practice demanded three important steps:

Firstly, all nurses (45) were trained in small groups by the coordinator. During this 1.5 hour training the importance of good glucose regulation with a new protocol was pointed out and the decision rules of the new protocol were reviewed stepwise. Secondly, we used the protocol decision rules to develop a computerized calculator to facilitate adherence to the protocol.This calculator is integrated within our hospital computer environment (*Horizon*, by McKesson), is web-based and can be easily accessed from any computer by all staff working in the CCU, figure 1. Additionally, this calculator can be modified in hospital without external expertise. Particularly during the introduction phase the latter is helpful.

Thirdly, in the first month the clinical pathway coordinator visited the CCU daily to assist with everyday practice and to give 1-to-1 tuition to nurses where necessary, after this he was accessible for any further questions.

Figure 1 Integration of calculator within hospital management system



The protocol

Our nurse driven protocol is a further modified version of a protocol developed in Aalst, Belgium [10,11] which is based on the ideas of Bode et al.[12]

Table 1 Protocol decision rules

Start insulin perfusor		
Infusion solution		50 Units Novorapid in 49.5 ml NaCl 0.9%
History of diabetes?		Stop all current diabetes medication
Start level of perfusor		Dependent on admission glucose See column 2 (fig 2)
Glucose measurement?		Use *bedside* glucose meter with venous whole blood. (Value displayed is a plasma value)
Target glucose values		Daytime: 4.7 – 6.1 mmol/l At night: 4.7 – 7.7 mmol/l
Adjusting insulin perfusion rate		
Stable glucose: (within target range*, 4.7 – 6.1 mmol/l)		Measure glucose *every 3 hours.* Adjust perfusor rate by changing row *in the same* column (see fig 2)
Unstable glucose (outside target range)		Measure glucose *hourly* (preferably on the hour e.g. 13^{00} hr, 14^{00} hr etc) Adjust perfusor rate dependent on glucose level. When hypoglycemia occurs give patient lemonade/glucose when necessary
Glucose *(white area)*	Has lowered	Move rows down within same column according to glucose level
Glucose *(white area)*	In same range	Move 1 column to the right within same row
Glucose *(white area)*	Has risen	Move 1 column to the right AND move rows up
Glucose *(green area)*	Within target range	Move rows up or down 1 within same column
Glucose *(pink area)*	Under 4.7	Move 1 column left AND move up or down
Solving hypoglycemia		
Glucose value	*Patient is conscious †*	*Patient is unconscious †*
3.4 – 3.8 mmol/l	Give 1 glass ‡ of lemonade ¶	Administer 15ml glucose 50% IV
2.8 – 3.3 mmol/l	Give 1.5 glasses of lemonade	Administer 20ml glucose 50% IV
<2.8 mmol/l	Give 2 glasses of lemonade	Administer 25ml glucose 50% IV
Around meals		
1	Measure glucose directly before meal	
2	Adjust perfusor rate if necessary	
3	Give Novorapid 6EH s.c., adjust if necessary (table 2, step 1)	
4	Measure glucose again 2 hours after a meal and adjust perfusor infusion rate	
5	Adjust dose for next meal according to difference in postprandial and pre meal glucose value (table 2, step 2)	
6	Subsequently measure every hour/three hours again (dependent on glucose level).	
Stop Perfusor		
Stop perfusor when in the preceding 6 hours glucose levels were stable or by order of the attending physician.		
Note: Oral Glucose Tolerance Test before discharge if no history of diabetes. Refer to internist dependent on outcome.		

* At night target range is 4.7 – 7.7 mmol/l

† Check glucose value after 15minutes, repeat action if glucose is still < 3.9 mmol/l

‡.1 glass = 150 ml = approx. 15g carbohydrates

¶ Lemonade = apple juice, orange juice etc

The protocol aims to reach normoglycemic values (4.7 – 6.1 mmol/l), whilst avoiding hypoglycemia. In the target range glucose measurement are done every three hours, outside this range every hour. During the night the target range is slightly wider (4.7 – 7.7 mmol/l) to decrease the amount of measurements and allow patients some sleep.

Perfusor adjustments are done according to decision rules described in table 1, these rules guide you across a table (figure 2) with insulin perfusor rates.
A new perfusor rate is calculated based on the previous glucose value, current glucose value and previous insulin infusion rate. To simplify its clinical use, these rules are integrated within an insulin rate calculator, figure 1.

Figure 2 Perfusor adjustment scheme

Glucose value (mmol/l)	column 1 U/hr	column 2 U/hr START	column 3 U/hr	column 4 U/hr	column 5 U/hr	column 6 U/hr	column 7 U/hr	column 8 U/hr	column 9 U/hr	column 10 U/hr
> 25	4.4	8.8	13.2	17.6	22.0	26.4	30.8	35.2	39.6	44.0
21.4 - 25.0	3.6	7.2	10.8	14.4	18.0	21.6	25.2	28.8	32.4	36.0
18.5 - 21.3	3,0	6.0	9.0	12.0	15.0	18.0	21.0	24.0	27.0	30.0
16.1 - 18.4	2.5	5.0	7.5	10.0	12.5	15.0	17.5	20.0	22.5	25.0
13.9 - 16.0	2.1	4.2	6.3	8.4	10.5	12.6	14.7	16.8	18.9	21.0
12.1 - 13.8	1.7	3.4	5.1	7.2	8.5	10.2	11.9	13.6	15.3	17.0
10.4 - 12.0	1.4	2.8	4.2	5.6	7.0	8.4	9.8	11.2	12.6	14.0
9.1 - 10.3	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0
8.4 - 9.0	1,0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0	10.0
7.8 - 8.3	0.9	1.8	2.7	3.6	4.5	5.4	6.3	7.2	8.1	9.0
7.3 - 7.7	0.8	1.6	2.4	3.2	4.0	4.8	5.6	6.4	7.2	8.0
6.7 - 7.2	0.7	1.4	2.1	2.8	3.5	4.2	4.9	5.8	6.3	7.0
6.2 - 6.6	0.6	1.2	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0
5.9 - 6.1	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
5.6 - 5.8	0.4	0.9	1.3	1.8	2.2	2.7	3.1	3.6	4.0	4.5
5.3 - 5.5	0.4	0.8	1.2	1.6	2.0	2.4	2.8	3.2	3.6	4.0
5.0 - 5.2	0.3	0.7	1.0	1.4	1.7	2.1	2.4	2.8	3.2	3.5
4.7 - 4.9	0.3	0.6	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3.0
4.4 - 4.6	0.2	0.5	0.7	1.0	1.2	1.5	1.7	2.0	2.3	2.5
4.2 - 4.3	0.2	0.4	0.6	0.8	1.0	1.2	1.4	1.6	1.8	2.0
3.9 - 4.1	0.1	0.3	0.4	0.6	0.7	0.9	1.0	1.2	1.3	1.5
3.3 - 3.8	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
< 3.3	0	0	0	0	0	0	0	0	0	0

i.v. insulin perfusor (50 EH novorapid in 49.5 ml NaCl=50 ml =1 ml:1 EH)
START in column 2!
Adjust perfusor rate based on glucosevalues

When glucosevalue has lowered (within white area):
Move down within the same column and adjust perfusor rate according to glucose value

When glucosevalue is within the same range (within white area):
Move 1 column to the right within same row and adjust perfusor rate

When glucosevalue has risen (within white area):
Move 1 column to the right AND move up rows according to glucosevalue

At night: 6.2 - 7.7 mmol/l to be interpreted as green area
Daytime: 6.2 - 7.7 mmol/l to be interpreted as white area

When glucosevalue remains between 4.7 - 6.1 mmol/l:
Move up or down rows according to glucosevalue within same column.

When glucosevalue is under 4.7 mmol/l:
Move 1 column left AND move rows up or down according to glucosevalue
Treat *hypoglycaemia* when a glucosevalue is under 3.9 mmol/l

Contact attending physician if glucose remains <3.3mmol twice or perfusor rate exceeds 24U/hr

To eat or not to eat

The carbohydrate bolus in these meals has to be neutralized with extra subcutaneous insulin. Therefore, we developed a standard regime that mandates an additional insulin bolus of 6 units subcutaneous Insulin aspart (Novorapid®, Novo Nordisk; Copenhagen, Denmark) for the first meal. According to the glucose level immediately before every meal, this standard dose was modified when necessary (step 1 table 2). Two hours after the meal a new glucose level is measured. The difference between the pre- and post-prandial glucose is used to calculate a new standard dose for the next meal (step 2, table 2). In this manner we both corrected for actual glucose levels and additionally for a patient's personal insulin sensitivity.

Table 2 Adjustment of subcutaneous (s.c.) insulin around meals.

Step 1	
Pre prandial glucose	**Adjust current standard dose of s.c. insulin for *this* meal with:**
< 4.0 mmol/l	- 2 IU
4.1 – 6.5 mmol/l	- 1 IU
6.6 – 9.0 mmol/l	Planned amount of insulin
9.1 – 13.0 mmol/l	+ 1 IU
13.1 – 17.0 mmol/l	+ 2 IU
17.1 – 20.0 mmol/l	+ 3 IU
>20.1 mmol/l	Contact attending physician

Step 2	
Difference between glucose value 2 hour *post* prandial and *pre* prandial glucose	**Adjust current standard dose of s.c. insulin for *next* meal with:**
≥ 6 mmol lower etc	- 3 IU etc
≥ 4 mmol/l lower	- 2 IU
≥ 2 mmol/l lower	- 1 IU
Difference less then 2mmol/l	Standard dose Unchanged
≥ 2 mmol/l higher	+ 1 IU
≥ 4 mmol/l higher	+ 2 IU
≥ 6 mmol/l higher	+ 3 IU etc

Standard dose for the first meal is 6 IU Novorapid

Glucose measurements

Blood glucose values were measured at the bedside with the Accu-Chek inform device (Roche Diagnostics). This device uses a drop of venous whole blood to calculate a plasma-like glucose value in 20- 30 seconds. This value is displayed and subsequently send to the central laboratory system.

All nurses received a single 20 minute training in operating this device, either by a senior CCU nurse or central laboratory staff. To describe the protocol outcomes, continuous data are presented as means +/- standard deviation (SD) and the hyperglycemic index (HGI) was calculated as described before. [13]

Eligible patients

All patients admitted to the CCU with an acute myocardial infarction (AMI) and an admission glucose ≥12mmol/l (no history of diabetes) or ≥11 mmol/l (history of diabetes) are eligible for intensive glucose regulation. Furthermore AMI patients within a research setting are eligible if their admission glucose exceeds 7.7 mmol/l. Other patients in the CCU are regulated with this protocol if deemed necessary by the attending physician.

RESULTS

In a 4 month period we obtained 643 glucose measurements in 28 patients (table 3). Patients on average were treated with IV insulin for 35 hours, had 23 glucose measurements in this time span, and reached a median glucose of 6.2 mmol/l, table 4. The median time until the first glucose value was in the target range (4.7 – 6.1mmol/l) was 4.4 hours. The percentage of measurements within target range increased from 26.6% in the first 12 hours to 55.2% after 48 hours, figure 3. We reached a mean HGI of 1.59 (+/- 1.49 SD).

Severe hypoglycemia was rare and occurred in only 1.1% of measurements. All of these cases were without severe clinical side effects.

Table 3 Patient characteristics

Mean Age (yrs)	71 (+/- 12 SD)
Sex male/female	15/13
Mean admission glucose	13.2 mmol/l (+/- 3.9 SD)
Diabetes history	
No diabetes	8
New onset diabetes (diagnosed during current admission)	8
Non IDDM	8
IDDM	4
Admission diagnosis	
STEMI / NSTEMI / UA / HF	16 / 8 / 3 / 1

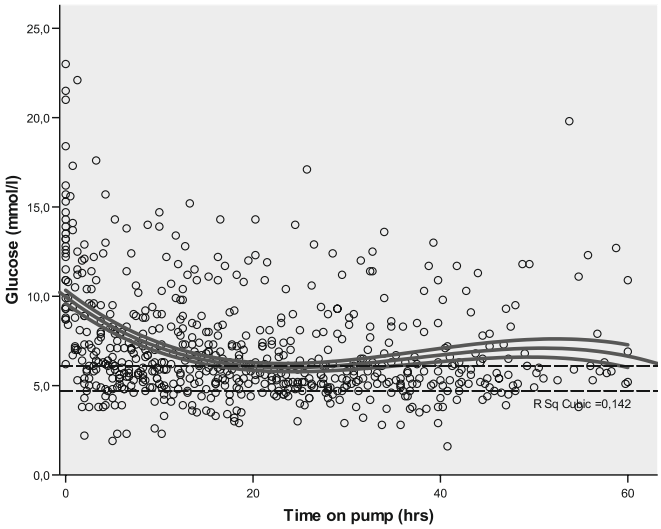
IDDM= Insulin Dependent Diabetes Mellitus, (N)STEMI = (non) ST elevation Myocardial Infarction, UA = Unstable Angina, HF = acute Heart Failure

Table 4 Glucose measurements in 28 CCU patients.

Total number of glucose measurements (average/patient)	643 (23)
Mean glucose level (range 1.6 – 23 mmol/l)	7.14 mmol/l (+/- 3.1 SD)
Median glucose level	6.20 mmol/l
Mean Time on pump (range 8.25 – 60 hours)	35.45 hrs (+/- 16.4 SD)
Median time to first glucose value in target range	4.4 hrs
Mean HGI	1.59 (+/- 1.49 SD)
Nr of glucose measurements 3.9 – 4.6 mmol/l	49 (7.6%)
Nr of glucose measurements in target range (4.7 – 6.1 mmol/l)	230 (35.8%)
Nr of glucose measurements 6.2 – 7.7 mmol/l	130 (20.2%)
Nr of glucose measurements 7.8 – 10 mmol/l	95 (14.7%)
Nr of glucose measurements >10 mmol/l	101 (15.7%)
Mild hypoglycemia (Glucose 3.4 – 3.8 mmol/l)	20 (3.1%)
Moderate hypoglycemia (Glucose 2.8 – 3.4 mmol/l)	11 (1.8%)
Severe hypoglycemia (Glucose <2.8 mmol/l)	7 (1.1%)

For conversion from mmol/l to mg/dl multiply by 18.
HGI = Hyperglycemic index; i.e. area under the curve above target value (6.1mmol/l) divided by time on insulin pump

Figure 3 Glucose measurements over time



Fit curve is cubic with mean 95% CI
Straight lines represent target values (4.7 – 6.1 mmol/l)

DISCUSSION

This intensive insulin treatment strategy for hyperglycemia in ACS patients has been successfully introduced while complying with the rules of a clinical pathway. The results show normalization within 4.4 hours of the metabolic disorder while avoiding moderate to severe hypoglycemia. The success factors for this achievement relate to the embedded clinical pathway coordinator, the use of computer technology and integration of medical and nursing charts.

Clinical pathways as a tool to improve protocol adherence

There are many practical thresholds to implementing an intensive insulin treatment strategy in the coronary care unit. These are mainly related to the experienced increased working load of nurses and the fear of hypoglycemia induced by this scheme. Successful studies have shown the importance of a dedicated nurse who is attached to the ICU team and solely responsible for the insulin management. [5] In contrast; others who failed to have such a nurse did report a less successful outcome.[14] Our study demonstrates the success of applying the methodology of clinical pathways while

implementing this demanding protocol. We achieved a successful implementation by the CCU nursing team of 45 members with a clinical pathway coordinator on stand-by. This implies that the regimen can safely be applied by the entire nursing team in stead of one nurse. We have therefore changed this therapy from nurse-oriented to team-oriented. Protocol adherence is further improved by using computer technology. The use of the dedicated calculator prevents inappropriate dosing changes and direct reference to guidelines and recent publications can be incorporated in our digital pathway documents.

Rationale and pitfalls of intensive insulin therapy

Hyperglycemia is common among patients admitted with ACS and is associated with inferior clinical outcomes. Clear guidelines on treatment of hyperglycemia in myocardial infarction have not been developed yet, partly due to lack of sufficient univocal evidence.

Several studies found a benefit for glucose regulation [5 6 15] while others could not confirm this.[14 16 17] This can partly be explained by the fact that some could not acquire sufficient difference in glucose levels between treatment groups.[14 16] Our results demonstrate that rapid correction of hyperglycemia towards normoglycemic values is possible. However, maintaining these target values is another challenge, furthermore there seems to be a certain rebound effect after approximately 24 hours, figure 3. This in spite of stricter target values compared to others.[18]

Meals are an important difficulty for glucose regulation. In the intensive care unit (ICU) patients are mostly fed continuously through a feeding tube, this in contrast to our CCU where patients mostly have regular meals. These extra carbohydrates have to be counterbalanced.

Another important caveat is hypoglycemia as there is a U- or J-shaped relationship between glucose levels and cardiovascular outcomes. [17 19 20] This possibly diminishes the beneficial effect of glucose regulation.

In a 2005 review [21] 24 studies with glucose regulation were evaluated and the occurrence of hypoglycemia was described. The definition and frequency varied widely, e.g. hypoglycemia occurred in 0.2% (<3.3mmol/l) in a cardiothoracic ICU population [22] , 5.1% (<2.2 mmol/l) in the Leuven study [5] and 17% (<3.0mmol/l) in the DIGAMI study.[23]

With our protocol, aided with a calculator, only 1.1% of measurements was a severe hypoglycemia (<2.8mmol/l), see table 4. So when applied in a larger clinical study hypoglycemia will probably contribute little to harmful effects.

Success factors for successful implementation

In our view several conditions apply for the successful introduction of a new critical care pathway such as a new insulin protocol in the CCU. Cannon and Ornato [24] described several important steps for the preparation phase; we feel these can be extended.

Firstly a small team has to be established. This team has a clinical pathway coordinator to monitor the introduction and encourage all staff members. Furthermore the necessary department opinion leaders such as a cardiologist, cardiology ward nurse, internist and computer programmer need to be involved. Together they have to create a vision and local strategy for implementation, including important landmarks in time and recognize possible pitfalls, e.g. the fear of nurses that new insulin protocols will result in frequent hypoglycemia. In this manner all involved personnel feel they have influence on the process, it is *their* protocol.

As a second step both nurses and cardiologists need to become aware of the urge to implement a new pathway in order to create sufficient support for change. This can be achieved by showing studies in favor of intensive glucose regulation, compare these new protocols to the old situation and demonstrate the advantages. Change? Yes we can!

The next step is a critical one. Communication. Use all available means to communicate the content of the protocol and available tools such as a calculator, e.g. with frequent training sessions. Ensure that the protocol coordinator is very easily accessible for questions, especially as a coach for the workers in the field, the nurses. Also keep your coworkers up-to-date about the results. Communicate small successes swiftly and directly coach the staff on a one-to-one basis when protocol violations are made.

A fourth aspect is to evaluate the protocol more in depth when the protocol is in use for a certain time (e.g. 4 months). Search for any structural steps that can be improved. See if the predicted pitfalls (step one) were successfully avoided and, if not, how this can be improved in the near future. As a final step ensure that the new protocol is firmly rooted in daily practice and give periodical updates on further progress.

Limitations

Although our study has a substantial amount of glucose measurements, the number of patients is only small. Future analysis will tell us if the present results can be maintained and if tight glucose regulation has additional benefits for CCU patients. Furthermore the optimal target value has yet to be defined, we used 4.7 – 6.1 mmol/l but maybe a wider range, e.g. 4.5 – 7.5 mmol/l, might be more suitable in clinical

practice. Even though we made a first attempt to compensate for fluctuations in glucose levels around meals, more research is needed to come across a suitable approach for this problem. This might particularly be the case for patients who are on IV insulin for prolonged times, as there seems to occur a rebound in glucose levels after 24 hours.

Frequent measurements in this protocol implicate extra workload for nurses. This is feasible in high care units but might be a bridge too far on regular wards. To make this extra workload accepted more easily, a calculator can give nurses the feeling of support. It is important however that they understand the concept of the protocol and consider the calculator solely as a tool.

CONCLUSION

We investigated the introduction of a new intensive insulin protocol in the CCU.

This protocol is feasible with severe hypoglycemia occurring in only 1.1% of the measurements. For successful introduction it is important to make the right preparations according to a proper action plan, such as a clinical pathway. During the implementation; stress the need for change, give continuous feedback to all contributing staff to ensure their involvement and facilitate the introduction and the avoidance of protocol violations with an easy-to-use computer calculator.

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Chapter 11

Intensive Management of Hyperglycemia in Acute Coronary Syndromes
Study design and rationale of the BIOMArCS 2 glucose trial

Maarten de Mulder, Victor A Umans, Frank Stam, Jan H Cornel, Rohit M Oemrawsingh, Eric Boersma

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ABSTRACT

Background: Elevated admission plasma glucose (APG) is associated with increased mortality in patients who are admitted with an acute coronary syndrome (ACS). This may be mediated by increased inflammation, apoptosis and coagulation, and by a disturbed endothelial function that can be found in hyperglycemic patients. Insulin has several characteristics that may potentially counteract these mechanisms.

Methods: The BIOMArCS program is a multi-centre initiative and currently consists of three different studies. The effects of ACS on acute biomarkers washout are studied in the BIOMArCS pilot and the value of biomarkers in predicting upcoming ACS events is studied in BIOMArCS 1.

The third study (BIOMArCS 2 glucose),which will be presented here, investigates the effectiveness and safety of intensive glucose level control compared to conventional glucose management in patients with ACS and an APG 7.8 – 16 mmol/l.
In BIOMArCS 2 glucose a total of 300 patients without insulin treated diabetes mellitus (ITDM) will be randomized in a 1:1 ratio to either intensive or conventional glucose management on top of standard medical care.

The primary endpoint is infarct size as expressed by the cardiac Troponin T level 72 hours after admission. To study the metabolic effects of insulin administration, we will investigate biomarker wash out patterns of various metabolic mechanisms up to 7 days after admission. These markers will address inflammation, oxidative stress, hyper-coagulability, endothelial activation and vasodilatation.

Implications: Current ACS guidelines lack a clear strategy for hyperglycemia treatment. This study will extend our knowledge on this matter as it may clarify mechanisms and generate hypotheses if and how myocardial infarct size may be limited by glucose management at admission.

BACKGROUND

The prognosis of patients with an acute coronary syndrome (ACS) is worse in the presence of abnormal glucose metabolism. Several investigators demonstrated that elevated admission plasma glucose (APG) is associated with increased mortality in patients who are admitted for myocardial infarction (MI), even if these glucose levels remain below 11 mmol/l, the diagnostic threshold for diabetes mellitus (DM).[1-4] Although the introduction of percutaneous coronary interventions (PCI) lowered mortality significantly, elevated APG remains a determinant of long term mortality, [5] patients with persistently elevated levels fare worst of all.[6]

In the setting of acute MI, the DIGAMI 1 study was the first trial to demonstrate the benefit of glucose regulation in acute MI patients with established diabetes or APG ≥ 11 mmol/l. A relative mortality risk reduction of 29% was observed with intravenous (IV) insulin-glucose infusion followed by a multi-dose insulin regimen. One year mortality was 18.6% in the infusion group and 26.1% in the control group, p = 0.027. [7] However, these results could not be confirmed in the DIGAMI 2 and HI-5 trials,[8 9] although the latter trial did reduce the re-infarction rate and cardiac failure significantly. This lack of benefit for survival may be attributable to the fact that similar levels of mean 24 hour glucose were achieved in both the treatment and control arms of these trials. Hence these trials compared 2 different glucose lowering strategies, of which IV insulin was one, rather than the intended 2 different *intensities* of glucose control.

Nevertheless, these results might imply that glucose control rather than insulin administration per se is important in patients with MI. This is further illustrated by the results of the CREATE ECLA and OASIS 6 study.[10] In this work, Diaz et al found a higher mortality in patients treated with infusion of glucose insulin potassium (GIK) than in the control group. They proposed that this might partly be due to the tendency of GIK to increase glucose levels.

Work by Marfella et al focused on the molecular side of glucose regulation in MI. They concluded that tight glycemic control might reduce remodeling and apoptosis in peri-infarcted areas in AMI patients by reducing oxidative stress and inflammation.[11] In the intensive care unit (ICU) setting a landmark trial by Van den Berghe et al called attention to intensive glucose regulation with an in-hospital mortality reduction of 34% in a surgical ICU. In this single centre study the majority of patients (63%) were admitted after cardiac surgery. The mortality in the conventional group was 8% vs. 4.6% in the intensive insulin group, *p*-value 0.04. [12] However, other trials could not confirm these results. The NICE SUGAR trial was a multi-centre study where patients who were expected to require ICU treatment for 3 or more consecutive days were included. This trial demonstrated that intensive glucose regulation in ICU

patients might actually result in increased mortality compared with conventional glucose regulation. The underlying mechanism remains to be clarified. [13]

Based on these and other mixed study results, an optimal evidence based treatment strategy of elevated APG in ACS patients remains unclear. Nevertheless, recent guidelines suggest that is reasonable to consider glucose control in patients with significant hyperglycemia regardless of prior diabetes history, although what glucose level to aim for has not yet been defined precisely.[4] Consequently, different views exist on the importance of hyperglycemia in ACS patients and therefore half of the patients remain untreated during the acute phase. [14] This is a cause for concern as 40 – 58% of ACS patients have an elevated APG. [3 15]

In this article we introduce the study design to evaluate intensive glucose regulation in ACS and we discuss the rationale for this approach, which might become a new strategy. We designed a study to further investigate the safety and efficacy of intensive glucose regulation and tried to overcome the limitations of prior studies. Specific points of attention were: (1) obtaining a clear difference in glucose levels between treatment arms by using an intensive insulin protocol whilst avoiding hypoglycemia, (2) using a glucose driven approach rather than an insulin driven approach and (3) ensuring a timely start of insulin therapy.

METHODS

Objective

BIOMArCS is an acronym for "BIOMarker study to identify the Acute risk of a Coronary Syndrome". The BIOMArCS program is a multi-centre initiative which currently consists of three different studies. The BIOMArCS pilot investigates the effects of ACS on acute biomarkers washout. BIOMArCS 1 studies the value of biomarkers in predicting upcoming ACS events. The third study, BIOMArCS 2 glucose, will be presented here.

The BIOMArCS 2 glucose trial primarily investigates the effectiveness and safety of intensive glucose level control compared with conventional glucose management in patients presenting with ACS and hyperglycemia. As secondary objectives, this trial will study differences in biomarker wash out patterns in patients allocated to intensive or conventional glucose management; to determine whether modification of glucose levels relate to improved prognosis; and to evaluate if the effects of intensive glucose level control are modified by treatment delay.

This trial is registered in the Netherlands Trial Register (www.trialregister.nl); trial ID NTR1205 and has been approved by the local Medical Ethics Committee.

Design

BIOMArCS 2 glucose is designed as a single centre prospective randomized open-label clinical trial to evaluate our hypotheses systematically. In total, 300 ACS patients with an elevated APG will be included. They will be randomized by means of a computer program in a 1:1 ratio to either intensive or conventional glucose management on top of standard medical care.

Study population

Patients admitted with an ACS and an APG between 7.8 – 16 mmol/l are eligible if they fulfill the in- and exclusion criteria, table 1. ACS is defined as typical ischemic chest pain lasting 10 minutes or more, with the onset of symptoms within the preceding 24 hours, with either new persistent or non-persistent ST-segment elevation >1.0 mm in two or more contiguous electrocardiogram (ECG) leads or elevated biomarkers of myocardial necrosis, i.e. creatine kinase (CK)-MB >1 times the upper limit of normal (>16 U/L), or Troponin-I > 0.45 ng/ml. Patients with an APG > 16 mmol/l and patients with insulin treated diabetes (ITDM) patients are excluded for safety reasons. Patients will be asked to participate as soon as the APG and diagnosis of ACS have been established, preferably within 2 hours after the diagnosis.

Table 1 Inclusion and exclusion criteria for BIOMArCS 2 glucose

Inclusion criteria
• Age > 18 years
• Clinical diagnosis of ACS diagnosed by:
- Typical ischemic chest pain, lasting 10 minutes or more, with onset of symptoms within the preceding 24 hours, *and either*
- ECG changes indicative of myocardial infarction, i.e. ECG showing new persistent or non-persistent ST-segment *elevation* >1.0 mm in two or more contiguous leads
or
- Elevated biomarkers of myocardial necrosis, i.e. CK-MB >1 times the upper limit of normal of the laboratory (>16 U/L), or Troponin-I > 0.45 ng/ml.
• Admission plasma glucose 7.8 – 16.0 mmol/L
Exclusion criteria
• Patient currently using insulin, i.e. ITDM (note that Non-ITDM patients can be included)
• Myocardial ischemia precipitated by a condition other than atherosclerotic coronary artery disease (e.g. arrhythmia, severe anemia, hypoxia, thyrotoxicosis, cocaine, severe valvular disease, and hypotension).
• Known severely-impaired left ventricular function (ejection fraction < 30%)
• Severe chronic kidney disease (creatinine > 220 umol/l)
• Co-existent condition associated with a life-expectancy <6 weeks.
• Patient is expected to be transferred to another hospital within 48 hours
• Pregnancy
• Refusal to sign informed consent
ACS = Acute coronary syndrome; ITDM = Insulin treated diabetes mellitus; for conversion from mmol/L to mg/dL multiply by 18

Hospital setting

The Medical Centre Alkmaar (MCA) is a large teaching hospital with an adherence region of approximately 350.000 inhabitants, mainly Caucasian. Currently, all patients in the greater Alkmaar area with suspected acute MI are transported to our hospital by ambulance service to undergo immediate coronary angiography and subsequent PCI.

Allocated treatment

Following consent, study patients will be randomly allocated either to a strategy of intensive glucose level control for 48 hours or to conventional glucose management. Patients in the intensive glucose control arm will receive insulin (insulin aspart (Novorapid ®) NovoNordisk, Bagsvaerd, Denmark), preferably within two hours after they were diagnosed with ACS.

Intensive glucose level control

In patients randomized to intensive glucose level control, glucose levels will be regulated according to a nurse driven insulin protocol. Our (IV) insulin protocol is a further modified version of a protocol developed in Aalst, Belgium [16] who based their protocol on the ideas of Bode et al. [17]

Venous whole blood samples will be collected via an IV line at one-hour intervals (+/- 15 minutes), followed by three-hour intervals when values have stabilized in the target range.

The protocol aims to reach normoglycemic values (4.7 – 6.1 mmol/l during the day and 4.7 – 7.7 at night, i.e. 23:00 – 6:00 hours), whilst avoiding hypoglycemia.

Glucose levels will be measured with a Point-Of-Care (P-O-C) glucometer (Accu-Chek inform device, Roche Diagnostics, Basel, Switzerland); values displayed are plasma values (whole blood is converted by the P-O-C glucometer to a plasma value). Based on this plasma value the insulin infusion rate will then be adapted every hour or every three hours according to the protocol. Perfusor adjustments are done according to decision rules as we described earlier [18]. A new perfusor rate is calculated based on the previous glucose value, current glucose value and previous glucose infusion rate. To simplify its clinical use, these rules are integrated within an insulin rate calculator.

Meals are a challenge for glucose regulation. In the intensive care unit (ICU) patients are mostly fed continuously via a feeding tube, in contrast to a coronary care unit (CCU), where patients mostly have regular meals. The carbohydrate bolus in these meals has to be neutralized with extra subcutaneous insulin. Therefore, we developed a standard regime which mandates an additional insulin bolus of 6 units

subcutaneous insulin for the first meal. Depending on the glucose level immediately before every meal, this standard dose is modified when necessary. Two hours after the meal, the glucose level is measured again. The difference between the pre- and post-prandial glucose is used to calculate a new standard dose for the next meal. In this manner we correct for both actual glucose levels and for a patient's personal insulin sensitivity.

In patients who were previously diagnosed with type 2 diabetes, but who were not treated with insulin at admission (non-ITDM), oral diabetes treatment will be ceased as long as intravenous insulin is administered. Insulin infusion will continue for at least 48 hours and can be stopped if glucose values have stabilized in the target range (4.7 - 6.1 mmol/l) within the previous 6 hours. If patients fail to obtain stable values, infusion will be continued until a stable situation has been achieved for a duration of 6 hours. The infusion will always be terminated 96 hours after the start of insulin, regardless of glucose values. To prevent low serum potassium levels, a daily potassium sample will be obtained during IV insulin infusion and low levels will be corrected if necessary.

A fasting standard 75 g Oral Glucose Tolerance Test (OGTT) will be performed (i.e. no food or beverage consumption for at least 8 hours) before discharge (given that insulin infusion has been stopped for >8 hours). Patients will be referred to an endocrinologist for further intensive glucose management if the OGTT is positive, i.e. fasting plasma glucose ≥7.0 mmol/l and/or 2 hours after glucose ingestion ≥ 11.1 mmol/l. In that case, follow-up management consists of subcutaneous insulin with an HbA1c target value of <7.0% (53 mmol/mol). Approximately six weeks after discharge patients will visit the endocrinologist again for further diabetes management according to diabetic state and prevailing guidelines irrespective of the treatment arm.

If the OGTT is negative, i.e. fasting glucose is <7.0 mmol/l and plasma glucose 2 hours after glucose ingestion <11.1 mmol/l, follow up will be expectative and patients are advised to consult their family doctor after approximately 12 months to repeat a fasting glucose measurement.

Conventional glucose management

In patients randomized to conventional glucose management, glucose levels will be obtained at 6, 12, 24, 36, and 72 hours after onset of symptoms. Patients with previously diagnosed non-ITDM will continue their oral treatment. Glucose levels up to 16 mmol/l will not be treated with insulin. Patients will crossover to intensive glucose level control if a single glucose level >16 mmol/l appears at any of these time points.

A fasting standard 75 g OGTT will be performed before discharge. Patients will

be referred to an endocrinologist for further conventional glucose management if the OGTT is positive, i.e. fasting plasma glucose ≥7.0 mmol/l and/or 2 hours after glucose ingestion ≥ 11.1 mmol/l. In that case, follow-up management is at the discretion of the endocrinologist, but usually consists of oral treatment. If the OGTT is negative, i.e. fasting glucose is <7.0 mmol/l and plasma glucose 2 hours after glucose ingestion <11.1 mmol/l, follow up will be expectative, and patients are advised to consult their family doctor after approximately 12 months to repeat a fasting glucose measurement.

General patient management

Treatment for this study will be confined to managing glucose levels and will not interfere with other treatment strategies, which will be applied according to international guidelines for ACS management at the discretion of the attending physician. [19 20] We expect this will include (primary) PCI for the majority of patients. Furthermore, patients may not be included in another randomized trial.

Clinical data collection

Clinical data will be collected at baseline and at a 6 weeks follow-up visit, applying the CARDS-ACS data definitions. [2122] These data include cardiovascular risk factors, medical history, medication use, and ECG. Information on the incidence of clinical complications will be obtained at the follow up visit.

Clinical data will be collected on a digital Case Report Form (CRF) and entered into a database. The database will allow electronic checks for internal consistency of data-elements. Data sets for each subject will be identified by number. Study data will only be accessible to authorized personnel. In all cases, caution will be exercised to assure the patient's confidentiality.

Blood sampling

During hospitalization biomarker blood samples will be collected at admission, 24 hours (+/- 4 hours), 48 hours (+/- 4 hours), 72 hours (+/- 4 hours) after admission and when admitted ≥ 96 hours at discharge to evaluate biomarker patterns. At the follow-up visit, six weeks (+/- 1 week) after the initial event an additional biomarker sample will be collected. To determine the course of cardiac enzymes and glucose levels, additional samples are drawn at admission and 6, 12, 24, 36 and 72 hours after the onset of symptoms.

Myocardial perfusion scintigraphy

Six weeks (+/- 1week) after the index event, a rest gated myocardial perfusion scintigraphy SPECT will be performed to assess left ventricular (LV) ejection fraction

and infarct size. Rest gated myocardial perfusion images are acquired approximately one hour after an intravenous injection of 700 MBq ^{99m}Tc-myoview using SPECT. A dual-head camera system equipped with low-energy high-resolution collimators is used for myocardial imaging (CCAM; Siemens, Erlangen, Germany). Images are acquired in a 64×64matrix with an acquisition time of 30 s per image. The SPECT images are gated with 16 frames per cardiac cycle, the RR time acceptance is set at 60%. Transaxial slices are reconstructed via backprojection with a ramp filter, followed by a butterworth filter. Using commercially available software, polar maps are created of the relative distribution of tracer uptake throughout the entire left ventricle (LV). Each polar map will be normalized to its individual maximum and the defect size is defined as < 50% uptake area of the polar map and will subsequently be expressed as a percentage of the LV.

End points

The primary endpoint of this study is infarct size as expressed by the cardiac Troponin T level 72 hours after admission.

Secondary study endpoints include

- Extent of myocardial damage as expressed by area under the CKMB curve. The CKMB curve will consist of serial measurements of CKMB, the area under the curve will be calculated by linear interpolation.
- Left Ventricle Ejection Fraction (LVEF) and infarct size using a ^{99m}Tc-sestamibi SPECT 6 weeks (±1 week) after randomization (patients with atrial fibrillation are excluded from this analysis).
- ST segment resolution (change) at 6 hours after randomization. Single ST segment resolution will be measured as described by Zeymer et al. [23]
- Serum NTpro BNP 72 hours and 6 weeks after randomization.
- All-cause death, cardiovascular death and non fatal myocardial reinfarction (reinfarction ≥72hr after initial event) at 6 weeks after randomization.
- Biomarkers of (vascular) inflammation, hypercoagulability or neurohumoral activation (not yet specified) at 24, 48 and 72 hours and 6 weeks after randomization.
- HbA1C values at 6 weeks after randomization.

Selection of biomarkers

To appreciate differences in biomarker patterns between treatment groups various markers will be selected. We will distinguish various metabolic mechanisms which have their own specific biomarkers. These markers will address inflammation, oxidative stress, hypercoagulability, endothelial activation and vasodilatation. However, as biomarker research in cardiovascular disease is rapidly evolving, a definite choice of

the analysis-panel and of the most promising mix per system has not yet been made.

The following markers will at least be considered: C-reactive protein (CRP), interleukin (IL)-6, IL -8, IL-10, matrix metalloproteinase (MMP)-2, MMP-9, pregnancy-associated plasma protein-A (PAPP-A), placental growth factor (PlGF - systemic and vascular inflammation); soluble CD40 Ligand (sCD-40L – hypercoagulability, pro-inflammatory); cardiac Troponin-T (cTnT - necrosis); N terminal pro brain-natriuretic peptide (NT-ProBNP - neurohumoral activation).

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Statistical considerations

Power calculation

Based on the study of Steen et al, [24] the mean Troponin T level at 72 hours (primary endpoint) in patients allocated to conventional glucose management is estimated to be 1.2 to 1.4 µg/l, with a standard deviation around 0.7 to 1.2 µg/l. We suspect that intensive glucose management may reduce this value by 20% to 30%, resulting in Troponin T levels at 72 hours between 0.84 to 1.12µg/L. In order to declare these differences statistically significant (α=0.05, 2-sided test) with a power of 80% (β=0.2) a total of 2*135=270 patients are needed. We assume a dropout rate of maximal 10%. Hence, a total of 300 patients will be randomized.

Data analysis

All analyses will be performed according to the intention to treat principle. Homogeneity in treatment effects will be studied in relation to the following patient characteristics: non-insulin treated diabetes; ACS diagnosis (ST segment Elevation- versus Non ST segment Elevation-ACS); time from onset of symptoms to randomization; APG level (> or < 10 mmol/l [4]).

An independent endpoint committee, whose members are unaware of the allocated treatment regimen, will assess clinical endpoints.

A data safety monitoring board (DSMB) was installed to conduct an interim safety analysis after 100 patients have completed the study protocol. As insulin is a widely used drug with limited side effects under close monitoring, the task of the DSMB is limited to safety monitoring only. They will assess the incidence of death, re MI and revascularization. In addition they will evaluate the incidence of hypoglycemia in the

treatment arm and advise whether this is an acceptable rate compared to other clinical trials.

DISCUSSION

The primary aim of this study is to evaluate the effect of acute intensive glucose regulation on infarct size. There are several reasons to assume that this will limit infarct size.

Hyperglycemia, marker or mediator?

It remains unclear whether hyperglycemia is an 'innocent bystander', induced by stress hormones released during MI (such as catecholamine and cortisol), which may create a state of temporary insulin resistance resulting in higher glucose levels. When these stress hormone levels return to baseline, glucose levels will follow. In that case an elevated APG might be considered only as a marker of the severity of disease.

Hyperglycemia may also be appreciated as a mediator and therefore it is of interest to look further into the disturbed cardiac metabolism during ischemia. Under normal (aerobic) circumstances myocardial metabolism is mostly based on the oxidative phosphorylation of free fatty acids (FFA) and only for a minor part (≈15%) on glucose via glycolysis. The oxidation of glucose is suppressed by the formed citrate and ATP. However, under anaerobic circumstances (e.g. ischemia), citrate and ATP levels fall due to a decreased oxygen supply and glycolysis is accelerated. Glycolysis is an anaerobe process, and therefore it does not require oxygen. Oxygen is only required when the formed pyruvate is further metabolized via the citric acid (Krebs) cycle.
Furthermore, there is an increase in gluconeogenesis and in the activity of the insulin sensitive GLUcose Transporter 4 (GLUT-4).[25] This results in increased glucose transport into the cardiomyocyte for glycolysis. An efficient mechanism as this uses less oxygen compared with the oxidative phosphorylation of FFA.

Following this line of reasoning, it is conceivable how insulin resistance results in less glucose transport into the cardiomyocyte, which in turn results in higher plasma glucose levels. This lack of intracellular glucose forces the cell to use more FFA. As a consequence more oxygen is used, leading to further hypoxemia under ischemic circumstances which in its turn leads to increased myocardial necrosis.

Consequences of hyperglycemia

Elevated glucose levels have detrimental effects via several mechanisms.
Glucose can induce reactive oxygen species (ROS) generation through the activation

and induction of NADPH oxidase based mechanisms in healthy subjects. [26] In hyperglycemic AMI patients this increased oxidative stress, combined with increased inflammation and apoptosis, this results in a lower left ventricular ejection fraction. [11 27]

Secondly, hyperglycemia influences coagulation as it is associated with increased platelet aggregation, circulating clotting factors and tissue factor. [27 28] The latter is an activator of thrombotic mechanisms and matrix metallo-proteinases which destabilize the atherosclerotic plaque and mediate its rupture.

Another mechanism is the no-reflow phenomenon, reflecting micro vascular dysfunction, which is more common in hyperglycemic patients. [27 29] This dysfunction is partly explained by impaired perfusion due to endothelial dysfunction. [28]

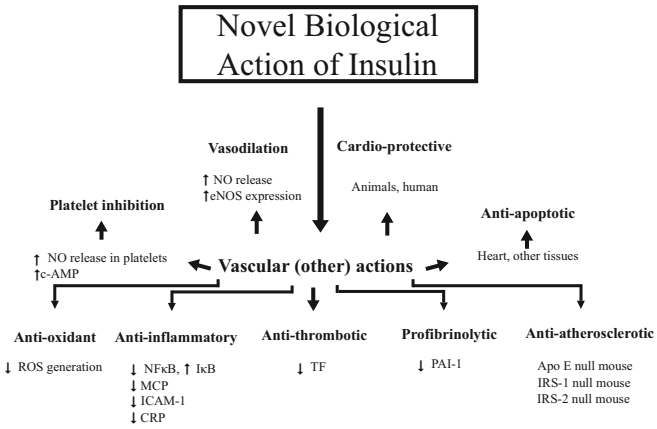
Insulin effects in myocardial infarction

Insulin has several interesting characteristics that may (potentially) counteract the harmful effects of hyperglycemia. In particular its anti-inflammatory, anti-apoptotic, vasodilating and platelet inhibiting effects are features of interest, as summarized by Dandona et al.[28] and as shown in figure 1.

The relation between hyperglycemia and myocardial injury may provide therapeutic opportunities as these deleterious effects can be opposed with insulin and glycemic control. [11 27 28 30] As an illustration, in the setting of ST elevation MI and fibrinolytic therapy the activity of plasminogen activator inhibitor-1 (PAI-1, an inhibitor of fibrinolysis), was suppressed by insulin.[30] Furthermore, insulin attenuated the increase in FFA, which is important since an elevation of FFAs can be pro-inflammatory and can induce oxidative stress. [31] For ACS patients, what appears to be important is the regulation of the glucose metabolism, i.e. a glucose driven approach, rather than the plain administration of insulin, although this remains to be established. [4 32]

When these ideas were tested in a clinical setting, one of the difficulties was that studies like the DIGAMI 2 and HI 5 trials, could not reach their target glucose range. [8 9] As a result these trials compared two different glucose lowering strategies, of which IV insulin was one rather than a different intensity of glucose control. They used a relatively conservative target range in their treatment arms, i.e. 7.0 – 10 mmol/l and 4 – 10 mmol/l respectively. We assume that stricter glucose targets may help to overcome this difficulty and we therefore selected a nearly normoglycemic target range, 4.7 – 6.1 mmol/l. Naturally, caution is required to avoid hypoglycemic episodes as there is a U- or J-shaped relationship between glucose levels and cardiovascular outcomes, i.e. both hypo- and hyperglycemia are associated with increased mortality. [33 34]

Figure 1



Novel biological effects of insulin, targeted at endothelial cells, platelets, and leukocytes resulting in vasodilation, antiaggregatory effects on platelets, anti-inflammatory effects, and other related effects.
Reproduced from Dandona et al.[28]

Timing of therapy

It has not been fully clarified whether the timing of hyperglycemia treatment influences clinical outcomes. However, in rat models Jonassen et al. observed that a metabolic cocktail containing insulin reduced infarct size by 45% compared with controls when administered at myocardial reperfusion. When given 15 minutes into reperfusion however, this effect was nullified. [35] In a clinical setting, lowering glucose levels in the first 24 hours was associated with improved 30-day survival.[6] With this in mind, it seems reasonable to suggest that early hyperglycemia treatment may lead to an improved clinical outcome.

In conclusion, we postulate that an elevated APG in ACS patients has a detrimental effect on infarct size and left ventricular function which may be reduced with intensive glucose regulation using intravenous insulin. We assume that the beneficial effects of this strategy are influenced negatively by treatment delay (i.e. early treatment results in better outcomes), especially in STE-ACS patients. On a molecular level the effects of intensive glucose regulation will be reflected by a more favorable biomarker wash-out pattern.

Whether or not we will find an effect on infarct size, still both positive and negative study results will provide more insight into the effect of insulin and elevated glucose levels on important pathophysiologic mechanisms involved in myocardial infarction. This will further help to answer the question whether hyperglycemia is a marker or mediator in myocardial infarction and to develop future treatment strategies in hyperglycemic ACS patients.

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Chapter 12

Intensive Glucose Regulation in Hyperglycemic Acute Coronary Syndromes: Results of the Randomized BIOMArCS-2 Glucose Trial

Maarten de Mulder, Victor A Umans, Jan H Cornel,
Friso M van der Zant, Frank Stam, Rohit M Oemrawsingh,
K Martijn Akkerhuis, Eric Boersma

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ABSTRACT

Importance

Elevated admission plasma glucose in acute coronary syndrome (ACS) patients is associated with increased mortality. Clinical trials of glucose regulation have provided inconsistent results with respect to cardiovascular outcomes perhaps because target glucose levels have been suboptimal.

Objective

To study the effectiveness and safety of intensive glucose management in ACS patients with hyperglycemia, aiming at strict blood glucose normalization.

Design & Setting

BIOMArCS-2 Glucose is a single-centre, prospective, open-label, randomized clinical trial in a large teaching hospital. Patients were enrolled from July 2008 until February 2012.

Participants

ACS patients with an admission plasma glucose of 7.8-16.0mmol/l (140-288 mg/dL) were eligible for inclusion, patients with insulin dependent diabetes mellitus were excluded. Informed consent was obtained in 294 patients who were then randomized. 94% of patients received percutaneous coronary intervention (PCI).

Intervention

Patients were randomized to an intensive glucose management strategy, aiming at a plasma glucose of 4.7-6.1 mmol/l (85-110 mg/dL) by using intravenous insulin, or conventional expectative glucose management.

Main outcomes

Endpoints were assessed according to the intention to treat principle. The primary endpoint was high sensitivity Troponin T 72 hours after admission (hsTropT72). Secondary endpoints were the area under the curve (AUC) of CKMB release, and myocardial perfusion scintigraphy (MPS) parameters at 6 weeks of follow-up.

Results

In the intensive arm hsTropT72 was 1197 ng/L (541-2296) vs. 1354 ng/L (530-3057) in the conventional arm, p-value 0.41. Median AUC-CKMB was 2372 U/L (1242-

5004) vs. 3171 U/L (1620-5337), p-value 0.18. The difference in median extent of myocardial injury measured by MPS was not significant (2% vs. 4%, p value 0.071). Severe hypoglycemia (<2.8 mmol/l / 50mg/dL)) was rare and occurred in 13 patients. Before discharge, death or spontaneous recurrent MI occurred in 8 (5.7%) vs. 1 patients, p-value 0.036

Conclusion

Intensive glucose regulation did not reduce infarct size in hyperglycemic ACS patients treated with PCI, and was associated with harm.

BACKGROUND

Elevated admission plasma glucose levels are common among patients admitted with an acute coronary syndrome (ACS). Well over 40% of myocardial infarction (MI) patients have an admission plasma glucose ≥7.8mmol/l(140mg/dL),[1-3] the clinically relevant threshold of impaired glucose tolerance.[4] Admission plasma glucose has been recognized as an independent determinant of adverse outcomes in patients with and without established diabetes mellitus(DM), both in the thrombolytic and PCI era.[2 3 5-8] In MI patients, elevated glucose results in a pro-thrombotic state, modulates the inflammatory response and oxidative stress, and leads to microvascular dysfunction and no reflow.[9-11] These mechanisms may explain the association between elevated plasma glucose and adverse reactions in MI patients. Still, it is unclear, if elevated plasma glucose contributes to myocardial injury and infarction, or is a marker of disease severity.

Earlier studies attempted to regulate hyperglycemia in MI patients through a metabolic approach at a cellular level, using a combined insulin-glucose infusion. In the landmark DIGAMI-1 trial, which studied MI patients with DM) or hyperglycemia, lower 1-year mortality was observed after IG infusion compared with control treatment (18.6% versus 26.1% deaths). This finding was not confirmed in the DIGAMI-2, CREATE-ECLA/OASIS-6, GIPS and IMMEDIATE trials,[12-15] perhaps because of inadequate plasma glucose level reduction and extensive fluid overload. The recent HI-5 trial explored a strategy that directly influenced plasma glucose levels with insulin-dextrose infusion.[16] The incidence of reMI and heart failure was reduced by active treatment, but mortality was not. Importantly, 24 h glucose levels were similar in both trial arms, and exceeded the normal range. The potential effects of insulin were also investigated in an outpatient setting. The recent ORIGIN trial tested if the provision of sufficient basal insulin could reduce cardiovascular events, but failed to demonstrate such a relation after 6 year follow up. [17]

We designed the BIOMArCS-2 Glucose trial to study the hypothesis that treatment of hyperglycemia aiming at strict glucose control within normal levels will limit infarct size in patients presenting with MI/ACS (acute coronary syndromes). In patients allocated to intensive glucose management we aimed to obtain a rapid reduction of blood glucose to normoglycemic levels by using an intensive insulin protocol, whilst avoiding hypoglycemia.

METHODS

BIOMArCS-2 Glucose

BIOMArCS-2 Glucose was designed as a single centre (Medical Center Alkmaar) open-label randomized controlled clinical trial to investigate the effectiveness and safety of intensive glucose level control and regulation in patients presenting with ACS and hyperglycemia.

We have published the design of the BIOMArCS-2 glucose trial and additional details are given in the online supplement. [18] Briefly, ACS patients presenting with an admission plasma glucose between 7.8 and 16.0mmol/l (140-288mg/dL) were eligible for inclusion. ACS was defined as typical ischemic chest pain with either ST-segment elevation, or elevated biomarkers of myocardial necrosis (CK-MB > 16U/L or cardiac troponin I >0.45 µg/ml, the upper limit of normal in our centre). The main exclusion criteria were the use of subcutaneous insulin, creatinine >220µmol/l(2.5mg/dL), and a known left ventricular ejection fraction (LVEF) <30%. Eligible patients were randomized to a strategy of intensive glucose level control for 48h with intravenous (IV) insulin, or to conventional glucose management.

Treatment

Patients were treated in accordance with the guidelines of the European Society of Cardiology (ESC). [19 20]

Intensive glucose level control and regulation

Patients were randomized by means of a computer program in a 1:1 ratio to either intensive or conventional glucose management on top of standard medical care. In patients randomized to the strategy of intensive glucose level control, glucose levels were regulated according to a nurse driven protocol using IV insulin (insulin aspart, Novorapid®, NovoNordisk, Bagsvaerd, Denmark). Details of the protocol were published earlier.[21] Perfusor adjustments were made to reach normoglycemic values, whilst avoiding hypoglycemia. We targeted at glucose level between 4.7-6.1mmol/l (85-110mg/dL) during daytime (6:00am-23:00pm) and 4.7-7.7mmol/l (85-139mg/dL) at night (23:00pm-6:00am). Measurements were repeated every hour, and perfusor adjustments were performed until glucose levels appeared in the target range. Then, glucose levels were measured every 3 hours. Additional subcutaneous (s.c.) insulin (standard dose of 6 IU, or additional if required) was given around meals. Two hours after the meal a new glucose level was measured. We refer to the Online Supplement for more details.

Conventional glucose management

In patients randomized to conventional, expectative glucose management, glucose levels were obtained at 6, 12, 24, 36 and 72 h after onset of symptoms. Patients with previously diagnosed non-IDDM continued their oral hypoglycemic drugs. Insulin treatment was not started if glucose levels remained below 16.0mmol/l(288mg/dL) at all time points. Patients crossed over to intensive glucose regulation as soon as a single glucose level exceeded 16.0mmol/l.

Infarct size measurements

Final infarct size was estimated by 3 methods. First, high sensitivity troponin T values were determined 72 h after admission (hsTropT72), which was defined as the sample closest to 72 h within the 48-96 h time window after admission.

Secondly, the area under the CKMB curve (AUC-CKMB) was calculated by the linear-trapezoidal method. Blood samples were obtained at admission and 6, 12, 24, 36 and 72 h after the onset of symptoms. Missing baseline and 72h CKMB values were set to 0. The log normal function was used to estimate CKMB values in case of missing values at intermediate time points.[22] The AUC-CKMB was not determined in case of≥2 missing intermediate samples (29 patients).

The third method was based on rest gated myocardial perfusion scintigraphy (MPS) using 99mTc-myoview single photon emission computed tomography (SPECT). MPS-SPECT imaging took place at 6±1 weeks after the index event. Technical details have been described previously.[18] We determined the extent of myocardial injury, as well as LVEF. We realize that MPS-SPECT measurements might also reflect previous myocardial damage since patients with previous MI, were not excluded. Still, because BIOMArCS-2 Glucose is a randomized trial, we can assume that the two groups are similar with regard to prior injury at entry into the study.

Endpoints

We chose hsTropT72 as the primary endpoint of our trial (i.e. the sample closest to 72h within 48-96h after admission, see above). Previous studies in ACS patients have demonstrated that the accumulation of cardiac Troponin reaches a plateau in this time window, whereas a single measurement window correlated well with final infarct size as determined by cardiac MRI. [23-26]

Secondary endpoints include AUC-CKMB during the first 72h; LVEF and infarct size as determined by MPS-SPECT at 6 weeks; all-cause death, non-fatal repeat MI (reMI) and their composite, at discharge. ReMI was defined as a repeat elevation of Troponin or CKMB above the upper limit of normal, and/or ECG showing new ST-

segment elevation >1.0mm. Clinical endpoints were adjudicated by two independent cardiologists who were blinded to treatment strategies. A decision was made by a third cardiologist in case of disagreement.

Statistical methods of data analysis

An independent statistician, who was blinded for the allocated treatment, performed all data analyses. We refer to the Statistical Analysis Plan for details on the analyses.[27] The plan was published before the primary endpoint was determined.

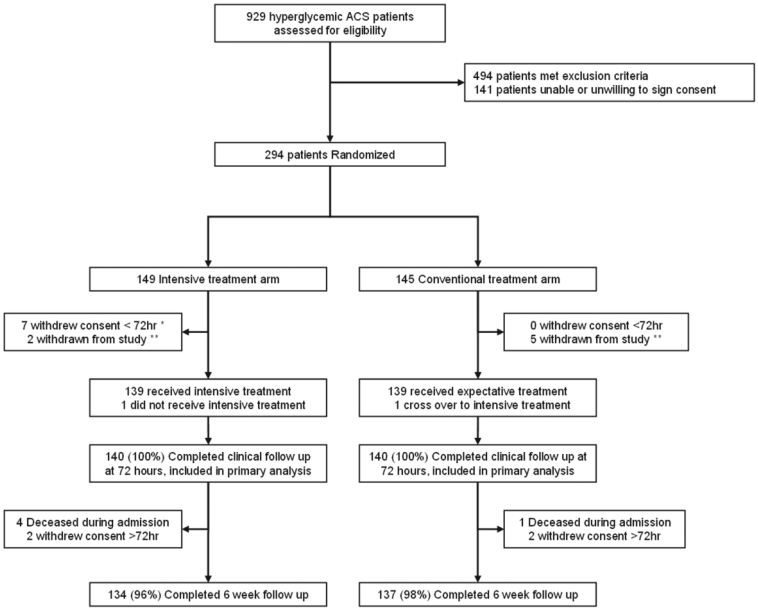
Categorical data are presented as numbers and proportions, and continuous data are presented as median values with the 25th and 75th percentiles of the distribution or mean values ± one SD. Chi-square or Fisher's exact tests were used to study differences in categorical data, as appropriate. The distribution of continuous data was tested with the Kolmogorov-Smirnov test. Subsequently, Student's t or Mann-Whitney tests were applied to study between-sample differences.

All 294 randomized patients were analyzed according to the allocated treatment strategy. However, 14 patients had to be excluded from the analysis of the primary endpoint because of incomplete data (figure 1). The main analyses of treatment effect are based on a comparison of medians (hsTropT72, AUC-CKMB and MPS-SPECT-based endpoints). Secondary analyses utilized comparisons of frequencies (binary classification of patients according to their hsTropT72: below or above the median; clinical endpoints) and linear regression models (to adjust for baseline data, in order to increase precision of effect estimates).

Stratified analyses are presented according to sex, age, Killip class, infarct localization, diabetic state, admission glucose and infarct type.

All statistical tests used a two sided significance level of α=0.05. The analyses were performed using SPSS 20) and R statistical software 2.14.

Figure 1 Flowchart



** Patient withdrew consent after randomization, prior to further study procedures*
*** These patients were withdrawn from the study by the investigators within one hour because of absence of Acute Coronary Syndrome (ACS) (N=6) or immediate transfer to another hospital. No data were obtained in these subjects.*

RESULTS

Patients

Between July 2008 and February 2012 a total of 1773 ACS patients were admitted. admission plasma glucose exceeded 7.8mmol/l in 929 (52%) patients, who were then assessed for eligibility. Agreement to participate, signed informed consent and randomization was achieved in 294 patients. Seven patients were withdrawn from the study by the investigators within one hour because of absence of ACS (N=6) or immediate transfer to another hospital. No data were obtained in these subjects. Another 7 patients withdrew consent within 72h after randomization. Thus, a total of 280 patients are available for analysis, 140 were randomized to intensive glucose management (figure 1). 250 Patients underwent MPS-SPECT imaging. No patients were lost for the follow-up of clinical endpoints.

At baseline, patients in the control group were more likely to have a history of having a PC I (p=.01), a prior MI (p=05), and tended to be more likely to have

Table 1 Baseline Characteristics

	Conventional N = 140	Intensive N = 140	*P* value
Age (yrs)	64 (57 – 73)	66 (56 – 75)	0.89
Male gender	113 (81%)	105 (75%)	0.25
Cardiovascular risk factors			
Diabetes mellitus *	14 (10%)	13 (9.4%)	0.86
Hypertension	46 (33%)	55 (40%)	0.24
Hypercholesterolemia	43 (30%)	29 (21%)	0.07
Family history of CAD †	38 (28%)	35 (27%)	0.82
Current Smoker	58 (41%)	49 (35%)	0.27
Cardiovascular disease history			
Myocardial infarction	20 (14%)	10 (7.1%)	0.053
PCI	18 (13%)	6 (4.3%)	0.01
CABG	8 (5.7%)	4 (2.9%)	0.24
Stroke	10 (7.1%)	11 (7.9%)	0.82
PAD	7 (5.0%)	13 (9.3%)	0.16
Admission diagnosis			
STEMI	119 (85%)	110 (79%)	0.16
NSTEMI	21 (15%)	30 (21%)	0.16
Infarct localization			
Anterior	59 (42)	56 (40)	0.72
Non anterior	81 (58)	84 (60)	0.72
Laboratory parameters ‡			
Admission glucose (mmol/l)	9.2 (8.5 – 10.5)	9.0 (8.3 – 10.1)	0.13
HbA1c (%)	5.8 (5.6 – 6.2)	5.8 (5.6 – 6.2)	0.62
Creatinine (µmol/l)	88 (76 – 102)	83 (70 – 100)	0.15
CRP (mg/l)	2.8 (1.5 – 5.3)	3.0 (1.7 – 8.0)	0.07
Total cholesterol (mmol/l)	5.1 (4.5 – 6.1)	5.5 (4.6 – 6.1)	0.17
HDL cholesterol (mmol/l)	1.1 (0.9 – 1.3)	1.1 (0.9 – 1.4)	0.19
Baseline hsTropT (ng/L)	487 (210 – 1879)	588 (262 – 2501)	0.35
Physical examination §			
Waist circumference (cm)	100 (94 – 107)	100 (95 – 108)	0.82
Body mass index (kg/m^2)	26 (24 – 29)	26 (24 – 28)	0.36
Heart rate (bpm)	74 (65 – 83)	73 (62 – 86)	0.85
Systolic blood pressure (mm/Hg)	130 (114 – 145)	133 (116 – 150)	0.18
Diastolic blood pressure (mm/Hg)	80 (70 – 90)	80 (69 – 90)	0.99
Killip class ≥2 at admission	10 (6.1%)	15 (11%)	0.29
Medication use prior to admission			
Aspirin	32 (23%)	27 (19%)	0.46
Beta blockers	33 (24%)	29 (21%)	0.59
ACE inhibitors	20 (14%)	13 (9.3%)	0.19
Statins	34 (24%)	27 (19%)	0.31

Continuous data are presented as median values (25th – 75th percentile), Dichotomous data are presented as numbers and percentages.

CABG = Coronary artery bypass graft surgery; CAD = Coronary artery disease; CAG = Coronary angiography; CRP = C-reactive protein; hsTropT = High sensitivity troponin T; MI = Myocardial infarction; PAD = Peripheral artery disease; PCI = Percutaneous coronary intervention

** i.e. only non Insulin dependent diabetes mellitus (non IDDM) patients, as IDDM patients were excluded*

† Angina, MI or sudden death without obvious cause in a first degree blood relative < 55 years

‡ Measured at admission, thus non fasting.

§ First measurement in stable cardiac rhythm, for STEMI patients generally after primary PCI

hypercholesterolemia (p=.07). Characteristics of the two groups were otherwise similar (table 1). There were 218 (78%) men and 62 (22%) women; the median age was 65 (56-74) years. Two hundred and twenty-nine patients (82%) were admitted with ST-elevation MI (STEMI) of whom 45% had an anterior MI. Admission plasma glucose was 7.8-10mmol/l(140-180 mg/dL) in 188 (67%) and ≥10-16.0 mmol/l(≥180-288 mg/dL) in 92 (33%) patients, the median APG was 9.2 (8.4-10.4)mmol/l(166 mg/dL (151 – 187)) and 27 (9.6%) patients had previously diagnosed non-IDDM.

General initial treatment

Treatment characteristics were similar in both treatment arms (table 2). During admission 227 (99%) STEMI patients underwent (primary) PCI. The time from symptom onset to admission was 120 (75-195)min in the patients randomized to intensive glucose management and 105 (75-180)min in those randomized to conventional management. The time from admission to the first balloon inflation was 35 (25-50)min and 30 (20-50)min, respectively. In the non-STEMI patients, in the intensive and conventional treatment group, respectively 26 (87%) and 21 (100%) subjects underwent catheterization during admission, 16 (62%) and 14 (67%) of which were performed within 48h, and PCI was performed in 69% of NSTEMI patients. Overall, 262 (94%) of patients in the sample had a PCI performed during admission, 253 of which were within 72 hours after admission.

Insulin effects

The 140 patients in the intensive treatment arm received IV insulin for a median period of 47 (43-48)h. They had 29 (25-32) glucose measurements. A median glucose level of 6.2 (5.4-7.2)mmol/l (112mg/dL (97-130)) was reached at 24 h. Severe hypoglycemia was rare and occurred in 16 (0.41%) measurements in 13 patients. All hypoglycemias could be corrected with oral glucose.

A severe hypoglycemia occurred in 1 of the patients with an in-hospital re MI.

The time from symptom onset to the start of insulin was 5.0 h (3.9-7.7), while the admission-to-insulin time was 2.4 (1.8-3.5)h. In STEMI patients insulin was started earlier than in non-STEMI patients: 2.3 (1.7-3.0) versus 4.3 (2.5-8.2) h after admission. Six hours after symptom onset 40% of glucose levels were in the target range; this percentage had increased to 60% at 24 h. Median glucose values in the patients randomized to intensive glucose management were significantly lower than in those randomized to conventional management (figure 2). However, neither the change in glucose levels nor the time to normalization was related to the hsTropT level at 72 hrs, regardless of allocated therapy, eTable1.

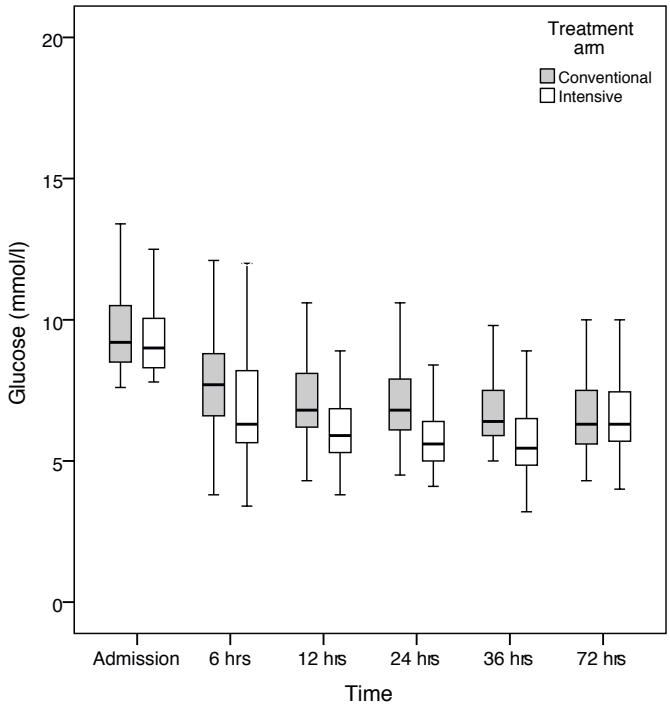
Table 2 General treatment characteristics

	Conventional	Intensive	*P* value
STEMI patients (n = 229)			
CAG	119 (100)	110 (100)	-
Primary PCI / elective PCI	116 (98) / 1 (0.8)	108 (98) / 2 (1.8)	0.72
Emergency CABG	0	0	-
Medical therapy	2 (1.7%)	0	0.17
Symptoms to balloon time (min) *	140 (105 – 215)	153 (110 – 235)	0.97
Door to balloon time (min) †	30 (20 – 50)	35 (25 – 50)	0.67
NSTEMI patients (n = 51)			
CAG	21 (100)	26 (87)	0.08
PCI	14 (67)	21 (70)	0.80
Emergency CABG	0	0	-
Medical therapy	7 (33)	9 (30)	0.80
Symptoms to balloon time (hr) *	28 (7.6 – 77)	16 (9.6 – 82)	0.42
Door to balloon time (hr) †	24 (5.7 – 66)	13 (3.4 – 80)	0.98
All patients			
Time to admission (hr) ‡	1.9 (1.3 – 3.0)	2.2 (1.4 – 4.0)	0.10
Time from admission to randomization (hr)	1.7 (1.1 – 2.7)	1.9 (1.3 – 2.8)	0.04
Vessel disease §			
No visible CAD	1 (0.7)	0	
1 vessel	67 (49)	65 (46)	0.80
2 vessels	37 (26)	37 (26)	
3 vessels	35 (25)	34 (24)	
IABP used	6 (4.3)	8 (5.7)	0.58
Medication at discharge			
Aspirin	137 (98)	132 (96)	0.45
Clopidogrel	104 (74)	97 (69)	0.35
Prasugrel ||	29 (21)	32 (23)	0.66
ACE inhibitors	110 (79)	95 (69)	0.08
Angiotensin 2 receptor blockers	14 (10)	15 (11)	0.80
Beta blockers	138 (99)	135 (99)	0.98
Statins	139 (99)	133 (98)	0.30

CAD = Coronary Artery Disease; CAG = Coronary angiography; IABP = intra aortic balloon pump; (N)STEMI = (non) ST Elevation Myocardial Infarction; PCI = Percutaneous Coronary intervention

** Time from pain onset to balloon inflation*
† Time from hospital admission to balloon inflation
‡ Time from pain onset to admission
§ >50% narrowing was considered significant
|| In use since December 2010 for patients admitted with STEMI, instead of Clopidogrel

Figure 2 Median glucose values per treatment arm



Median glucose values per time point after admission. At 6, 12, 24 and 36 hours there is a significant difference between treatment arms, all p values <0.001.
To convert from mmol/l to mg/dL multiply by 18.

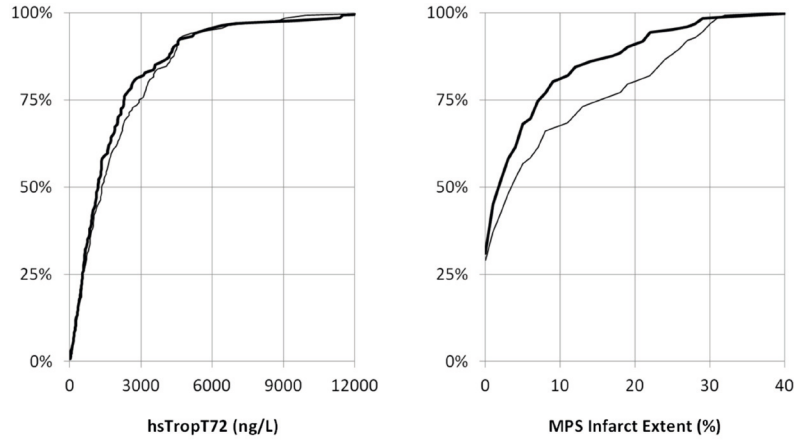
Primary endpoint,

There were no significant differences in enzymatic infarct size between the 2 treatment groups (Figure 3 en 4). Patients randomized to intensive glucose management had a median hsTropT72 of 1197 ng/L (541-2296) compared with 1354 ng/L (530-3057) in patients treated conventionally (p-value 0.41).

We observed no difference between the 2 randomized groups in the percentage of patients with an hsTropT72 below the overall median value (1302 ng/L). Analysis of prespecified subgroups did not reveal differences either, figure 5.

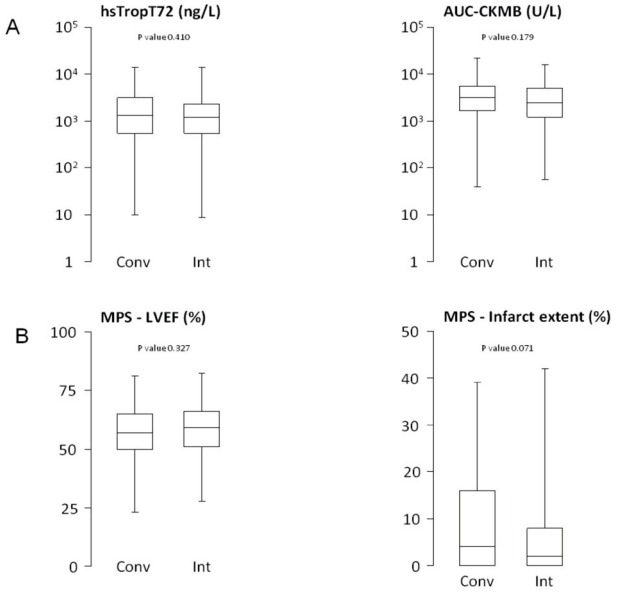
Finally, we applied linear regression with admission hsTropT and randomly allocated treatment as determinants of hsTropT72. Also in this analysis hsTropT72 was not influenced by allocated treatment (p-value 0.70). Further adjustment by adding age and sex as endpoint determinants confirmed these findings.

Figure 3 Cumulative infarct size



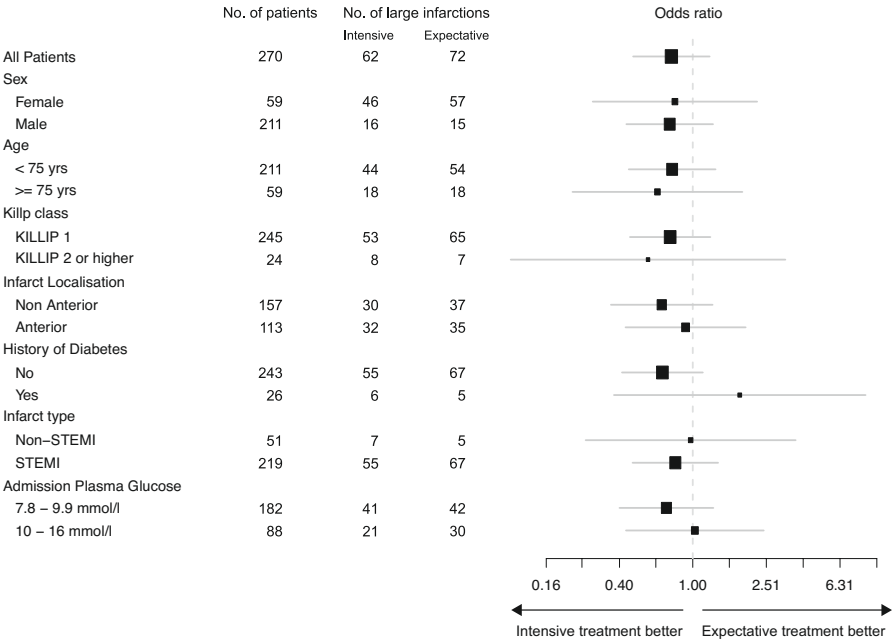
Distribution of infarct size per treatment arm for hsTropT72 and infarct extent from myocardial perfusion scintigraphy (MPS). Thick line: Conventional arm. Thin line: Intensive arm

Figure 4 Treatment effects



A : Effect on enzymatic infarct size for high sensitivity Troponin T 72 hours after admission (left panel) and area under the CKMB curve (right panel), logarithmic scale.
B : Effect on myocardial perfusion scintigraphy (MPS) parameters 6 weeks after the index event; left ventricular ejection fraction (LVEF) (left panel) and infarct extent (right panel)
All values are medians. Conv = conventional treatment arm; Int = intensive treatment arm

Figure 5 Treatment effect for different pre-specified subgroups.



Infarct size was dichotomized by dividing patients above (large infarction) or under (small infarction) the median hsTropT72hr value. In 10 patients hsTropT72 was missing and therefore they were not included in this analysis.

Secondary endpoints

The median AUC-CKMB during the first 72h was 2372 U/L (1242-5004) and 3171 U/L (1620-5337), respectively (p-value 0.18).

The difference in median extent of MPS-SPECT myocardial injury at 6 weeks (2% vs. 4%; p-value 0.071) and the left ventricular function (LVEF 59% vs. 57%; p-value 0.33) were similar in both trial arms. Despite randomization, there were relevant differences in the prevalence of prior PCI and MI between both study arms, this may have influenced the measurements of myocardial injury as measured by MPS-SPECT. Therefore we applied linear regression with prior MI, prior PCI, randomly allocated treatment arm, age and sex as determinants of myocardial injury. There was still no significant difference in MPS-SPECT infarct extent between treatment arms.

Clinical endpoints

Patients were admitted for 3.6 (2.9-4.9) days. During this period 4 (2.9%) patients who were randomized to intensive glucose management died, compared with 1 (0.7%) patient in the conventional arm (p-value 0.37). Spontaneous re MI occurred in 5 (3.6%) vs. 0 patients (p-value 0.060). The composite endpoint of death or spontaneous re MI occurred in 8 (5.7%) vs. 1 patients respectively (p-value 0.036).

DISCUSSION

In the BIOMArCS-2 Glucose trial a fast and (near) normalization of blood glucose levels was achieved in hyperglycemic ACS patients by applying an early intensive glucose management strategy. The well-controlled glucose levels, however, were not accompanied by a reduction in enzymatic or scintigraphic infarct size, whereas the incidence of the composite of death or myocardial reinfarction was increased.

Optimal ACS management has been achieved

ACS management has undergone several important changes in recent decades. In particular, primary PCI is now considered the first treatment option in STEMI patients, whereas early coronary angiography and subsequent PCI is also applied in the majority of non-STEMI patients. Also antiplatelet strategies have evolved, and dual antiplatelet therapy is common practice.

Furthermore, out of hospital networks have been developed to start medical therapy by paramedics, while transporting patients directly to the interventional clinics, thereby reducing symptom-onset-to-balloon times. Such expeditious acute ACS management has been achieved in the current trial, which should be considered when interpreting the presented data.

The BIOMArCS-2 Glucose trial was successful in enrolling high risk hyperglycemic patients presenting with STEMI (82%) or NSTEMI (18%) infarctions, with 50% having multivessel coronary artery disease. Coronary angiography was performed in 100% vs. 92% of cases, and primary PCI was accomplished in almost all STEMI patients after a median of 30 minutes following presentation. The favorable outcome of this infarction-limiting concept of optimal ACS care has been reported in recent literature,[28 29] and may explain why our intervention designed to normalize glucose did not achieve any further benefits.

Effective treatment of hyperglycemia has been reached

The BIOMArCS-2 Glucose trial achieved a rapid normalization of plasma glucose levels in the insulin treated patients. Glucose levels were significantly lower in the patients receiving intensive treatment than in controls at all measured time points between 6 and 72h. This illustrates the effectiveness of glucose management in our study: compared to other studies aiming at strict blood glucose control, lower mean blood glucose level were reached with even less hypoglycemic episodes.[12 16] However, this treatment effect was not be translated to a smaller enzymatic infarct size.

Glucose level control and infarct size, why did it not work?

There are several possible reasons why rapid and adequate glucose level control was not accompanied with a reduction in enzymatic infarct size First, the timing of insulin therapy might have been suboptimal. Intensive glucose management was often delayed until after the (primary) PCI was conducted. As a result of this early reperfusion, part of the metabolic stress of the earlier occlusion is resolved and several patients might have had a near normal glucose level at the start of the insulin infusion. It is conceivable that the effect of insulin is dependent on the 'reperfusion induced' glucose regulation, and those with persistently elevated glucose levels post-PCI might still benefit.

Second, patients were enrolled at a median of 4.1 (3.0-6.5)h after symptom onset. Their evolving infarction was terminated as a result of the early PCI. Consequently, the post-PCI evolvement of the infarction might have been too small (at least enzymatically) to be influenced by the intensive glucose regulation that was started after the procedure. Pre-procedural (i.e. during transportation to the intervention center) reduction of glucose levels may have greater impact.

Third, given the wide variation in glucose levels that we observed until 6 hours after presentation, glucose levels appear to remain unstable early after MI/ACS onset. Furthermore, patients with persistently elevated glucose levels had somewhat larger infarct size than those who obtained normal values, irrespective of the allocated treatment. Therefore glucose lowering and stabilization may be more important early after symptom onset.[30].

Finally, it is possible that elevated plasma glucose is a marker of severity of injury and does not have a causal role in extent of myocardial infarction.

We opted for hsTropT72 as the primary endpoint, and sought supportive evidence by the 'classical' AUC-CKMB and MPS-SPECT as secondary endpoints. One might question if hsTropT72 was sensitive and specific enough to quantify final MI size. We chose this endpoint, since prior studies demonstrated that Troponin levels within 48-96 h correlate well with final infarct size determined by cardiac MRI.[23-26 31] Still, an in-depth analysis of the evolvement of cardiac troponin during the first 72h (and their relation with infarct size as determined by MPS-SPECT) is warranted. As a result of the expedited management, the infarct extent in our ACS/PCI patients was relatively small. Future trials in similar populations might consider PET or MRI in stead of cardiac enzymes and SPECT to study infarct size. The better spatial resolution of MRI, compared to MPS, may be more appropriate to detect small differences.

Safety and clinical perspective

Hypoglycemia as a result of too strict glucose regulation bears an important risk as has been demonstrated by a J shaped relation between glucose level and outcome.[32]

Furthermore, in the NICE SUGAR trial, intensive care patients receiving intensive glucose regulation had increased mortality compared to those receiving conventional glucose regulation. This increased mortality has been attributed to hypoglycemia.[33] Although the incidence of severe hypoglycemia in the current trial was low (0.4% vs. 6.8% in NICE SUGAR), the incidence of the composite endpoint of death or spontaneous reMI was significantly increased in the patients randomized to intensive glucose management. The mechanism underlying this increased risk needs to be studied. In the mean time, this observation emphasizes that the potential benefit of intensive glucose regulation needs to be carefully weighed against the demonstrated patient risk.

Limitations

BIOMArCS-2 Glucose is a single center study, which might limit the generalisability of its results. Furthermore, we excluded patients with insulin dependent diabetes and patients who required mechanical ventilation. Also, the outcome of glucose management in the current BIOMArCS 2 glucose trial and in the IMMEDIATE trial should be considered in the context of the delivered PCI in a timely fashion at an experienced intervention center. The short symptom to balloon times and urgent PCI as appropriate in non-STEMI patients may have contributed to limited infarct sizes.

CONCLUSION AND FUTURE PERSPECTIVE

The BIOMArCS-2 glucose trial failed to demonstrate that intensive glucose regulation is associated with a reduction in enzymatic or scintigraphic infarct size in hyperglycemic, troponin positive ACS patients undergoing PCI. In fact, we found evidence that intensive glucose regulation is associated with harm. Thus, based on our data, intensive insulin therapy is not a recommended practice.

Fifty percent of ACS patients present with elevated blood glucose, which is related with adverse clinical outcomes during longer term follow-up, even after initial successful PCI treatment. Therefore, further research in this field is warranted. We believe, future studies should focus on ACS patients with persistently elevated blood glucose after PCI, and should evaluate alternative strategies for optimizing glycemia. Also, in view of the results of our trial, the relation between (intensive) blood glucose management by i.v. insulin in the first hours after ACS onset and the increased risk of early myocardial reinfarction needs further exploration. In the mean time, a strategy of 'strict, but not too strict' glucose control, as suggested by the ESC guidelines,[20] seems to be the best practical approach.

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ONLINE SUPPLEMENT

This supplement provides additional information on the methods and results of the BIOMArCS 2 glucose trial. BIOMArCS is an acronym for *BIOMarker study to identify the Acute risk of a Coronary Syndrome*.

Treatment

After the pre hospital diagnosis of acute coronary syndrome (ACS), using ACS-ECG software for ambulance ECGs, was established, patients were, if indicated, transported directly to the catheterization laboratory of the Medical Center Alkmaar for coronary angiography and subsequent (primary) percutaneous coronary intervention (PCI). Treatment with aspirin, heparin and clopidogrel was started prior to the PCI procedure, usually in the pre hospital phase.

Glucose measurements in the intensive treatment arm

Venous whole blood samples were collected via an IV line at one-hour intervals, followed by three-hour intervals when values were stabilized in the target range. Blood glucose values were measured at the bedside with a Point-Of-Care testing (POCT) glucometer (Accu-Chek inform device, Roche Diagnostics, Basel, Switzerland). This device uses a drop of venous whole blood to calculate a plasma-like glucose value in 20 to 30 seconds. In rare cases, blood could not be collected from the IV line, and glucose measurements were obtained from finger pricks.

Intensive insulin protocol decision rules

Perfusor adjustments were performed according to decision rules that were implemented in a bedside chart and online calculator. A new infusion rate was based upon the difference between the previous and current glucose value and the corresponding previous infusion rate. When glucose levels were outside the target range, they were measured every hour, when they were within target range, glucose levels were measured every 3 hours.

Around meals:

To compensate for the carbohydrate bolus in meals, additional subcutaneous (s.c.) insulin was given around meals. Patients started with a standard dose of 6 units s.c. insulin. According to the glucose level immediately before every meal, this standard dose was modified when necessary. Two hours after the meal a new glucose level was measured. The difference between the pre- and postprandial glucose is used to calculate a new standard dose for the next meal. In this manner, we both corrected

for actual glucose levels and additionally for a patient's personal insulin sensitivity.

In case of a hypoglycemia, the protocol specified the administration of concentrated lemonade (or IV 50% glucose if the patient was unconscious) and adjustment of insulin dose. Hypoglycemia was defined as mild (3.4 – 3.8 mmol/l / 61 – 68 mg/dL), moderate (2.8 – 3.3 mmol/l / 50 – 60 mg/dL) or severe (<2.8mmol/l / < 50 mg/dL).

Long-term patient management

Prior to discharge, patients without previously diagnosed diabetes mellitus (DM) underwent an oral glucose tolerance test (OGTT) to evaluate glucose metabolism. Patients were classified into 3 groups: new onset DM (fasting plasma glucose (FPG) ≥7.0 mmol/l or 2 h post load glucose (PLG) ≥11.1 mmol/l), impaired glucose metabolism (FPG between 6.1-6.9 mmol/l or PLG between 7.8-11.0 mmol/l), or normal glucose metabolism (FPG <6.1 mmol/l and PLG between <7.8 mmol/l).

When new onset DM was diagnosed, further management depended upon randomization group. Patients in the intensive arm were referred to an internist for further intensive glucose management with subcutaneous insulin aiming at an HbA1c level <7.0% (53 mmol/mol). Patients in the conventional arm were treated at the discretion of the internist, which usually consisted of oral treatment. Approximately 6 weeks after discharge, patients visited the internist again for further diabetes management according to diabetic state and prevailing guidelines, irrespective of the treatment arm.

Blood sample handling

We collected multiple blood samples during hospitalization. Blood samples for the primary endpoint, hsTropT72, were drawn in sodium heparin tubes (Vacutainer SST II Advance, BD and Company, Franklin Lakes, New Jersey, USA), centrifuged and subsequently the plasma was stored at -70° Celsius using 1.1 ml polypropylene test tubes (Micronics BV, Lelystad, The Netherlands). We aimed to complete the process from blood withdrawal to freezing within 2 h in order to minimize pre-analytic variability. Samples were stored until batch analysis took place in the central laboratory (Erasmus MC) in July 2012. For this purpose we used the Elecsys Troponin T hs assay on a Cobas 6000 analyzer (both: Roche Diagnostics, Mannheim, Germany).

Sample size

The mean 72 h troponin T value in patients randomized to conventional glucose management was estimated at 1.2-1.4 ug/l, with a standard deviation (SD) of 0.7-1.2 ug/l.[1] We hypothesized that intensive glucose management may reduce this value by

20-30%, resulting in troponin T values between 0.84-1.12 ug/l. In order to declare these differences statistically significant ($\alpha = 0.05$, 2-sided test) with a power of 80% ($\beta = 0.2$), a total of 2x 135 = 270 patients are needed. We assumed a dropout rate of maximal 10%. Hence, the sample size was determined at a total of 300 patients.

Data quality

Several measures were taken to ensure optimal data quality. Prior to entry into the electronic case report form (CRF) data were checked for logic and consistency on an individual basis. When patient enrolment was complete, an independent monitor verified whether data from the electronic CRF, paper CRF and hospital records of 29 (10%) randomly selected patients were aligned. Any issues that appeared during this process were resolved in cooperation with the investigators, no systematic errors were found. Prior to analysis further manual edit checks were performed by the investigators to search for missing data, contradictory data entries, as well as for values that were out of the specified normal range.

Definitions

Re-MI was defined as a Troponin or CKMB > Upper normal limit and/or ECG showing new persistent or non-persistent ST-segment elevation >1.0 mm in two or more contiguous leads.

Given that previous values have stabilized (= Stable or decreasing values on 2 samples and 20% increase 3 to 6 hours after second sample). MI subtypes (type 1 – type 5) were recognized according to the universal definition of MI. [2]

End point adjudication

Clinical end points were adjudicated prior to analysis by two independent cardiologists who were blinded for the treatment arm. In case of disagreement a third cardiologist was asked to review the event.

Medical ethics

The design of BIOMArCS-2 Glucose was approved by the Medical Ethics Committee Noord Holland. The trial was registered in the Netherlands trial register (www.trialregister.nl): NTR 1205. All trial participants provided written informed consent. A Data Safety Monitoring Board (DSMB) conducted an interim safety analysis after the first 100 patients had completed the study protocol. The DSMB reported no safety concerns and approved the continuation of the trial.

eTable 1a Glucose change and outcome by randomization arm

	Conventional	Intensive	*P* value
6hr glucose <7.8 mmol/l			
hsTropT72	1335 (445 – 2795)	1176 (573 – 2148)	0.754
6hr glucose ≥7.8 mmol/l			
hsTropT72	1724 (837 – 3238)	1344 (655 – 2646)	0.661
24hr glucose <7.8 mmol/l			
hsTropT72	1156 (531 – 2795)	1216 (598 – 2396)	0.763
24hr glucose ≥7.8 mmol/l			
hsTropT72	2218 (966 – 3700)	565 (262 – 1451)	0.062

eTable 1b Infarct size in patients with or without persistently elevated glucose levels (≥ 7.8 mmol/l) 6 hours after symptom onset:

	6hr glucose ≥ 7.8 mmol/l	6hr glucose < 7.8 mmol/l	*P* value
HsTropT72			
All patients	1522 (779 - 3183)	1205 (517 - 2313)	p 0.089
Conventional arm	1724 (837 - 3238)	1335 (445 - 2795)	p 0.225
Intensive arm	1344 (655 - 2646)	1176 (573 - 2148)	p 0.325

eTable 1c Association between glucose (change) in patients with or without a clinical event (death or re myocardial infarction)

	Event (Death or re MI)	No Event (No death or re MI)	*P* value
Median APG (mmol/l)	9.5 (8.0 - 10.0)	9.2 (8.4 – 10.4)	0.49
Median glucose *change* in the first 6 hours after admission (mmol/l)	- 0.3 (-1.7 – 0.23)	- 2.3 (-3.6 – -0.7)	0.014
Median glucose *change* in the first 12 hours after admission (mmol/l)	– 2.2 (-3.5 – -1.9)	- 2.9 (-4.1 – -1.7)	0.622

APG = admission plasma glucose; hsTropT72 = High sensitive troponin T 72 hours after admission; MI = Myocardial infarction
To convert glucose from mmol/l to mg/dL: multiply by 18

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Chapter 13

Summary & discussion
Nederlandse samenvatting

SUMMARY AND DISCUSSION

The central theme of this thesis is the relevance of admission plasma glucose (APG) in the setting of acute coronary syndromes (ACS) The thesis consists of two main sections. In the first section, APG is studied as determinant of patient outcome. Several outcome prediction models for ACS patients are developed and validated, with and without information on APG. In the second section, APG is studied as treatment target. We conducted a randomized trial in myocardial infarction (MI) patients with elevated APG. We studied the effects of intensive insulin treatment (aiming at a rapid reduction of APG levels) on final infarct size.

Outcome prediction in ACS

In Chapter 2 we used Euro Heart Survey data on patients who underwent a percutaneous coronary intervention (PCI) for different indications to develop a risk model to predict in hospital mortality. In both the training (N=23,032 patients) and validation (N=23,032 patients) data sets the model had a good performance in terms of discrimination and calibration using 16 different patient and angiographic factors. Models such as these can particularly be of value in situations where it is difficult to select the most appropriate treatment strategy. They can help to estimate the patient's risk of adverse events. This estimate might then be used to help the physician decide on further patient management, while addressing the question if the expected benefits of a particular intervention outweigh the associated risks.

Imaging characteristics can serve as a marker to assess patient outcomes. In Chapter 3 & 4 we investigate the value of single photon emission computed tomography (SPECT) using 99mTc-sestamibi as perfusion tracer in MI patients. We studied 128 patients with ST elevation MI (STEMI) who were randomized to receive PCI in a center without local cardiothoracic surgery backup (off site) or who were transferred to a more remote center that has such local backup (on site). A 99mTc-sestamibi SPECT scan was performed 3 days after PCI to estimate infarct size. With off site PCI door to balloon time was significantly reduced compared to onsite PCI. However, this did not result in a significantly reduced time from symptom onset to treatment or reduced infarct size as determined with 99mTc-sestamibi SPECT. In a follow up study we examined whether the 99mTc-sestamibi SPECT parameters in these patients could be used to predict 5 year clinical outcomes, i.e. death or re MI. With multivariate Cox regression we found that only Killip class and the presence of Q-waves, but not scintigraphic data, predicted long term clinical outcomes.

Does admission glucose improve outcome prediction?

In Chapter 5 we investigated whether we could improve the predictive power of a risk model by adding a readily available biomarker: admission plasma glucose (APG). For this purpose we used the risk score developed by the Global Registry of Acute Coronary Events (GRACE) investigators, a widely applied risk model to predict mortality in patients with an MI. We calculated the GRACE score with and without APG for 550 MI patients from the Medical Center Alkmaar and found that although the models' performance improved, this change was not significant. In addition we divided patients into 3 different risk groups and used the net reclassification index (NRI) to investigate whether adding APG would provide more accurate risk groups. This change was also non significant however. Nevertheless, APG proved to be a predictor of 6 month and 5 year mortality independent from the GRACE score.

Many studies that explored the value of APG as outcome predictor were performed in the thrombolytic era rather than the current invasive era of PCI. The era of invasive treatment of MI patients is characterized by a rapid diagnosis, and an early, complete and sustained reperfusion. Therefore we compared the relation between APG and 5 year mortality in both eras in Chapter 6. The incidence of hyperglycemia increased from 39% in the thrombolytic era to 50% in the invasive era. With improved reperfusion techniques five year mortality decreased, however increased APG was still associated with increased mortality in both eras. Each mmol/l APG increase corresponded with a 7% increase in mortality.

Thus also in the current invasive era of urgent reperfusion with PCI, APG remains an independent predictor of mortality for MI patients. However, we could not demonstrate an added predictive effect on top of the GRACE score variables.

Detection of diabetes in clinical practice

In Chapter 7 we compare different methods to detect diabetes mellitus (DM). The American Diabetes Association describes 4 methods to diagnose DM: random glucose (in this study APG was used instead), HbA1c, fasting glucose and oral glucose tolerance test (OGTT). We compared the amount of newly detected DM as determined by APG, HbA1c, fasting glucose and OGTT. Newly detected DM was found in 35% of acute coronary syndrome (ACS) patients who were admitted with an APG 7.8 – 16.0 mmol/l and only 20% of patients had a normal glucose metabolism. The OGTT proved most sensitive to detect this. The accompanying editorial is provided in Chapter 8, and underscores the importance of a timely and proper diagnosis of DM in patients with cardiovascular disease.

Considering the importance of DM and implications of elevated APG, it is of interest to explore how (Dutch) cardiologists use trial data such as this to treat

their hyperglycemic MI patients in daily practice, Chapter 9. Only one third of Dutch cardiology departments reported to have a routinely applied protocol for the treatment of hyperglycemia in the setting of ACS. An APG of 13.0 mmol/l in a patient without known diabetes was considered a stress value by 60% and as new onset diabetes by 37%. As in 76% of the departments HbA1c is not routinely measured before discharge, it seems unlikely that the focus lies on longer term glucose management rather than short term management.

In summary, we demonstrated that hyperglycemia occurs in up to 50% of ACS patients. The OGTT proved the most sensitive method to diagnose hitherto undetected DM which was found in one third of hyperglycemic MI patients. However, as only a minority of clinicians routinely investigate glucose metabolism, they appear to be to be unfamiliar with the implications of hyperglycemia in ACS. Their awareness of undetected DM should improve. When hyperglycemia is present in high risk patients, such as those with an ACS, it should be considered as a trigger to further investigate glucose metabolism. National cardiology societies could play an important role in this matter.

Glucose regulation in ACS, how to start?

We found that only a minority of Dutch cardiology practices have a routinely applied protocol for hyperglycemic ACS patients. In Chapter 10 we present our experience with the implementation of such a protocol on the coronary care unit (CCU) in a stepwise approach, as is common in a clinical pathway. In cooperation with an internist we developed a protocol that uses subsequent glucose values to adapt the amount of insulin administered, i.e. a glucose driven approach. The protocol aims at near normoglycemic values; 4.7 – 6.1 mmol/l. For this purpose it uses both continuous intravenous (IV) insulin and additional boluses of subcutaneous insulin around meals.

There are several important aspects. Firstly, the protocol provides the CCU nurse all necessary 'rules' to independently modify the amount of insulin. Furthermore a computer tool was developed and integrated in the hospital management system to support protocol adherence and, thirdly, a clinical pathway coordinator was readily available, particularly in the start up phase, to help with any problems encountered. The introduction of a new intensive insulin protocol on the CCU according to the steps of a clinical pathway appeared safe and feasible.

Effect of glucose regulation in ACS

Given the observation that hyperglycemia remains a predictor of mortality today (Chapter 6), the key question is whether lowering elevated glucose values with an intensive glucose lowering strategy will lead to better outcomes. For this purpose

we designed the BIOMArCS 2 *glucose* trial, its rationale and design are given in Chapter 11. BIOMArCS is an acronym for "BIOMarker study to identify the Acute risk of a Coronary Syndrome". BIOMArCS 2 *glucose* is a single-centre, prospective, open-label, randomized clinical trial that investigated the effectiveness and safety of intensive glucose level control with IV insulin (target plasma glucose 4.7 – 6.1 mmol/l) compared to conventional glucose management in patients admitted with an ACS and an APG 7.8 – 16 mmol/l, patients with insulin dependent DM were excluded. Endpoints were high sensitivity Troponin T 72 hours after admission (hsTropT72) (primary), the area under the curve (AUC) of CKMB release, and myocardial perfusion scintigraphy (MPS) parameters at 6 weeks follow-up.

The results are presented in Chapter 12. We included 294 hyperglycemic ACS patients. However, intensive glucose regulation did not reduce enzymatic or scintigraphic infarct size in troponin positive ACS patients treated with PCI, as compared to the conventional expectative strategy. Severe hypoglycemia (<2.8 mmol/l) was rare, but death or spontaneous recurrent MI before discharge, occurred more often.

Earlier studies in both animals and humans provided sufficient evidence to hypothesize that hyperglycemia is a mediator of disease, i.e. it has an active role in MI, and results in a larger infarct size through different metabolic pathways. BIOMArCS 2 *glucose* was designed to answer this hypothesis. However, we did not find evidence that intensive glucose regulation on top of standard care, including urgent PCI, reduced infarct size in hyperglycemic MI patients.

FUTURE PERSPECTIVES & RECOMMENDATIONS

APG remains an independent predictor of mortality in the current era of PCI and is a first sign of hitherto unrecognized DM. Remarkably, however, the awareness among Dutch cardiologists for disturbed glucose metabolism is low. Early detection allows lifestyle interventions to prevent the progression of impaired glucose metabolism to full diabetes. This is one of the reasons that the European Society of Cardiology (ESC) already advocates to investigate glucose metabolism in all ACS patients. Given the observed results among Dutch cardiologists, further work should address effective methods to stimulate clinicians to implement this recommendation in their daily practice.

Elevated APG levels upon admission occur in up to 50% of ACS patients and are related with adverse clinical outcomes. Therefore it appeared as a promising target to further improve patient outcomes. The reasons why we could not demonstrate an added benefit of intensive glucose regulation in our BIOMArCS 2 glucose study are as yet uncertain, but are most likely multifactorial. In our trial, initial blood glucose levels were measured around the PCI procedure, whereas intensive glucose management was often delayed until after the PCI was conducted. As a result, several patients might have had a near normal glucose level at the start of the insulin infusion. Furthermore, it is conceivable that a possible additive effect of insulin is dependent on the extent of 'reperfusion induced' glucose regulation. Hence, those with persistently elevated glucose levels post-PCI might still benefit, particularly patients with persistent glucose levels above 10 mmol/l. Future studies might focus on these patients. Until the results of such research become available, clinicians should follow the strategy of 'strict, but not too strict' glucose control as recommended by the European guidelines.

NEDERLANDSE SAMENVATTING

Het centrale onderwerp van dit proefschrift is de waarde van opnameglucose (OG) bij acuut coronaire syndromen (ACS) en bestaat uit 2 delen. In het eerste deel wordt de waarde van OG als determinant van patiënt uitkomsten onderzocht. Verschillende risicomodellen voor ACS patiënten werden ontwikkeld, met en zonder OG.

In het tweede deel wordt OG als behandeldoel onderzocht. We voerden een gerandomiseerde studie uit bij patiënten met een myocard infarct (MI, of: hartinfarct), en een hyperglycemie (verhoogde bloedsuikerwaarde) bij opname. Hierin onderzochten we het effect van intensieve glucose regulatie middels insuline op de uiteindelijke infarct grootte.

Uitkomsten voorspellen bij ACS

In hoofdstuk 2 worden de data van 46,064 patiënten die een percutane coronair interventie (PCI, of: dotterprocedure) ondergingen gebruikt, die zijn verzameld in het kader van de Euro Heart Survey. Hiermee werd een risicomodel gemaakt om de ziekenhuis sterfte te voorspellen na een dergelijke ingreep. Met 16 verschillende patiënt gebonden en angiografische factoren werd een model ontworpen en getest. Het model bleek zowel in de training als validatie dataset een goed onderscheid te kunnen maken tussen patiënten die overleden of overleefden. Een dergelijk model kan het risico op bijwerkingen van een ingreep schatten en zo de behandelend arts helpen een goede afweging te maken of de voordelen opwegen tegen de nadelen van de ingreep, voor zowel hoog als laag risico patiënten.

Gegevens verkregen met beeldvorming van het hart kunnen ook worden gebruikt om uitkomsten te voorspellen. In Hoofdstuk 3 en 4 worden hiervoor de data gebruikt die zijn verkregen bij 128 patiënten die 3 dagen na hun hartinfarct een 99mTc-sestamibi single photon emission computed tomography (mibi SPECT) ondergingen om de infarctgrootte in te schatten. Deze patiënten werden gerandomiseerd om een PCI te ondergaan in een verder weg gelegen ziekenhuis met lokale cardio-chirurgische ondersteuning ('on site' PCI) of naar een dichtbij gelegen ziekenhuis dat deze ondersteuning echter op afstand heeft ('off site' PCI). Middels 'off site' PCI werd de tijd van ziekenhuisopname tot het opblazen van de dotterballon significant korter vergeleken met 'on site' PCI. Dit resulteerde echter niet in een kortere duur van het begin van de klachten tot balloninflatie of een kleinere infarctgrootte gemeten met mibi SPECT.

In een vervolgstudie onderzochten we middels Cox regressie analyse of mibi

SPECT karakteristieken konden worden gebruikt om langere termijnuitkomsten te voorspellen. Patiënten werden 5 jaar vervolgd en we onderzochten of hiermee een nieuw hartinfarct of overlijden kon worden voorspeld. Het bleek dat alleen de Killip classificatie bij opname (een maat voor de ernst van een hartinfarct) en de aanwezigheid van Q golven op het ECG dit konden voorspellen, mibi SPECT gegevens echter niet.

Kan opnameglucose uitkomstvoorspelling verbeteren?

In Hoofdstuk 5 onderzoeken we of de voorspellende waarde van een veelgebruikt risicomodel kan worden verbeterd door een eenvoudig te bepalen biomarker als OG toe te voegen. Hiervoor gebruikten we een veelgebruikt risico model dat de sterfte na een hartinfarct voorspelt, zoals ontwikkeld door de Global Registry of Acute Coronary Events (GRACE) onderzoekers. Van 550 patiënten die in het Medisch Centrum Alkmaar werden opgenomen met een hartinfarct, werd de GRACE score berekend met en zonder OG. De voorspellende waarde verbeterde, maar deze verbetering was niet significant. Desondanks bleek het OG onafhankelijk van de GRACE score een voorspeller van sterfte 6 maanden en 5 jaar na opname.

Veel onderzoek naar de voorspellende waarde van OG is gedaan in het thrombolyse tijdperk, terwijl de moderne behandeling van het hartinfarct een meer invasieve benadering kent middels PCI. Deze wordt gekenmerkt door het vroeg diagnosticeren van een MI en vervolgens snel verkrijgen van een betere en blijvende doorgankelijkheid van de aangedane kransslagader. Derhalve wordt in Hoofdstuk 6 de waarde van OG om de sterfte na 5 jaar te voorspellen in beide tijdperken vergeleken. Het vóórkomen van een verhoogde glucose waarde bij MI patiënten neemt toe van 39% in het thrombolyse tijdperk tot 50% in het invasieve PCI tijdperk. Tegelijkertijd daalde de 5-jaars sterfte, desondanks was een verhoogde OG in beide tijdperken gerelateerd aan een hogere sterfte, gemiddeld gaf elke mmol/l verhoging in OG een 7% hogere sterfte na 5 jaar.

Dus ook in het huidige tijdperk van een snelle, invasieve behandeling van het hartinfarct, blijft OG een onafhankelijke voorspeller van sterfte. Echter, OG had geen toegevoegde waarde bovenop de variabelen van de GRACE score.

Opsporen van diabetes mellitus in de praktijk

In Hoofdstuk 7 vergelijken we verschillende methodes om diabetes mellitus (DM, of: suikerziekte) op te sporen. Volgens de American Diabetes Association zijn hiervoor 4 methoden: een willekeurige glucose meting (in deze studie werd hiervoor OG gebruikt), de HbA1c waarde, nuchtere glucose waarde en een orale glucose tolerantie test (OGTT).

Bij hartinfarct patiënten met een OG van 7.8 – 16.0 mmol/l werd bij 35% niet eerder ontdekte diabetes vastgesteld en slechts 20% had een normaal glucose metabolisme. De OGTT was de meest gevoelige methode om dit op te sporen. Hoofdstuk 8 is het begeleidende redactionele artikel dat het belang van tijdige en adequate opsporing van diabetes bij patiënten met hart en vaatziekten onderschrijft.

Uit het voorgaande blijkt wel dat ook vandaag de dag een ontregeld glucose metabolisme van belang is bij patiënten met een hartinfarct. Om te kijken in hoeverre cardiologen zich hier in de dagelijkse praktijk van bewust zijn, hielden we een enquête onder de 94 Nederlandse cardiologische vakgroepen. Hoofdstuk 9 laat zien dat slechts een derde van hen een routinematig toegepast protocol heeft voor de behandeling van hyperglycemie bij patiënten met een hartinfarct. Gezien het feit dat 76% van de vakgroepen *geen* HbA1c (een maat voor de gemiddelde glucose waarde in de voorafgaande 2 maanden) meet tijdens opname, lijkt het onwaarschijnlijk dat de focus op de lange, in plaats van korte, termijn effecten ligt.

Hieruit blijkt wel dat in de dagelijkse praktijk de gevolgen van een hyperglycemie onbekend of onzeker zijn.

Samengevat hebben we verschillende dingen aangetoond. Allereerst heeft tot 50% van de hartinfarct patiënten een hyperglycemie bij opname. De OGTT was de meest gevoelige methode om nog niet eerder ontdekte DM op te sporen, bij een derde van de hartinfarct patiënten met een hyperglycemie bleek dit aanwezig te zijn. Desondanks onderzoekt slechts een minderheid van de clinici het glucosemetabolisme van deze patiënten. Zodoende lijkt hun bewustzijn voor tot dan toe nog niet herkende DM ruimte te laten voor verbetering. Als een hyperglycemie aanwezig is bij hoog risico patiënten, zoals hartinfarct patiënten, dan zou dit een trigger moeten zijn om het glucose metabolisme verder te onderzoeken. Nationale cardiologische verengingen zouden hierin een belangrijke rol kunnen vervullen.

Glucose regulatie bij ACS, hoe te beginnen?

We hebben aangetoond dat slechts een minderheid van de Nederlandse cardiologen een routinematig gebruikt protocol heeft voor de behandeling van een hyperglycemie bij patiënten met een ACS.

In Hoofdstuk 10 delen we stapsgewijs onze ervaring om een dergelijk protocol te implementeren op de hartbewaking. In samenwerking met een internist werd een protocol ontwikkeld dat achtereenvolgende glucosewaardes gebruikt om de hoeveelheid toegediende insuline optimaal op de individuele patiënt in te stellen. Er werd gestreefd naar glucose waardes van 4.7 – 6.1 mmol/l middels zowel continue intraveneuze toediening als met extra subcutane bolus injecties insuline bij maaltijden.

Met dit protocol kan de verpleegkundige zelfstandig de dosering titreren, geholpen door een computerprogramma binnen de bestaande ziekenhuis ICT structuur. Dit stappenplan volgde de lijn van een klinisch pad, hiermee was de introductie op de hartbewaking veilig en haalbaar.

Het effect van glucose regulatie bij ACS

Met de bevindingen van hoofdstuk 5 in het achterhoofd is de sleutelvraag of het verlagen van verhoogde OG waardes met een intensief behandel protocol leidt tot betere uitkomsten. Met dit doel werd het BIOMArCS 2 glucose onderzoek ontworpen, de studieopzet en achtergrond worden gegeven in Hoofdstuk 11. Het is een prospectieve, gerandomiseerde klinische studie in het Medisch Centrum Alkmaar die de effecten van intensieve glucose regulatie middels intraveneuze insuline (glucose streefwaarde 4.7 – 6.1 mmol/l) vergelijkt met conventionele, meer afwachtende, glucose regulatie bij patiënten opgenomen met een hartinfarct en een OG van 7.8 – 16.0 mmol/l, insuline afhankelijke DM patiënten werden geexcludeerd. Eindpunten zijn o.a. het high sensitive Troponine T 72 uur na opname (hsTropT72), oppervlakte onder de CKMB curve (AUC CKMB) en myocardial perfusion scintigraphy (MPS) parameters 6 weken na opname.

De studieresultaten worden gepresenteerd in Hoofdstuk 12. Er werden 294 hyperglycemische hartinfarct patiënten geincludeerd. Echter, we konden niet aantonen dat intensieve glucose regulatie de infarctgrootte kon beperken bij patiënten die voor hun hartinfarct een PCI ondergingen. Ernstige hypoglycemieen kwamen weinig voor, maar dood of spontane reinfarcering traden vaker op.

Eerdere studies gaven aanleiding om te stellen dat een verhoogde glucosewaarde via verschillende metabole processen een actieve rol speelt in de ontwikkeling van een hartinfarct en leidt tot grotere infarcten. De BIOMArCS 2 glucose studie werd ontworpen om deze hypothese te onderzoeken. Er werd echter geen bewijs gevonden dat beïnvloeding met intensieve glucose regulatie, bovenop de reguliere zorg, leidt tot kleinere infarcten bij hyperglycemische hartinfarct patiënten.

TOEKOMSTPERSPECTIEF

Opnameglucose blijft ook in het huidige invasieve behandeltijdperk een onafhankelijke voorspeller van mortaliteit en is een eerste teken van niet eerder herkende DM. Het is daarom opvallend dat Nederlandse cardiologen zich weinig bewust zijn van (de implicaties van) een verstoord glucose metabolisme. Terwijl vroege opsporing de kans biedt om progressie van een verstoord glucose metabolisme naar diabetes tegen te gaan met leefstijladviezen. Daarom adviseert de European Society of Cardiology ook om bij alle ACS patiënten het glucose metabolisme te onderzoeken. Gezien de resultaten bij Nederlandse cardiologen, lijkt toekomstig onderzoek zich ook te moeten richten op manieren om clinici te motiveren om deze aanbeveling ook in de praktijk te brengen.

In het licht van het frequente vóórkomen (tot 50%) van een hyperglycemie bij opname van een hartinfarct patiënt en de relatie met slechtere uitkomsten, leken verhoogde glucose waarden een veelbelovend doel om de behandeling van hartinfarct patiënten verder te verbeteren. Het is nog onduidelijk waarom we dit in de BIOMArCS 2 glucose studie met intensieve glucose regulatie niet konden aantonen, waarschijnlijk zijn de oorzaken divers.

In de acute fase werd voorrang gegeven aan de PCI en werd insuline toediening meestal pas hierna gestart. Hierdoor hadden verscheidene patiënten een vrijwel normale glucose waarde op het moment dat de insuline daadwerkelijk werd gestart, de timing van toedienen van insuline laat dus nog ruimte voor verbetering. Verder is het voorstelbaar dat de waarde van insuline toediening mede wordt bepaald door de mate van ´spontane´ glucose regulatie verkregen met reperfusie bij PCI. Mogelijk zijn de patiënten die desondanks na de PCI nog verhoogde glucose waardes houden, in het bijzonder > 10mmol/l, de meest geschikte kandidaten voor additionele glucose regulatie middels insuline. Verder onderzoek kan deze vragen wellicht helpen beantwoorden. Tot die tijd zouden clinici de huidige Europese richtlijnen moeten volgen die stellen dat er ´strikte, maar niet te strikte´ glucose regulatie moet worden toegepast bij hyperglycemische hartinfarct patiënten.

Chapter 14

Dankwoord & CV

DANKWOORD

Promoveren is vaak een kwestie van stug volhouden, van alsmaar anderen (en jezelf) blijven motiveren om mee te blijven doen en onderweg niet vergeten te genieten van het feit dat je kapitein bent van "jouw" project. Maar promoveren is vooral ook sport, teamsport. Daarom zijn er een aantal mensen die ik graag extra wil bedanken.

Allereerst mijn promotor, Prof.dr.ir. H Boersma. Beste Eric, ik vond de samenwerking erg prettig. Je bent heel benaderbaar en meestal razendsnel met het opbouwende commentaar op onze stukken. Hierdoor was de fysieke afstand Alkmaar – Rotterdam nauwelijks een belemmering. Het was eigenlijk pas in het najaar van 2011 dat ik me met Sanneke realiseerde dat een van ons de eerste is die bij jouw als professor gaat promoveren. Wat mij betreft een aanrader.

En natuurlijk mijn co promotor, Dr. VA Umans. Beste Victor, ik was eigenlijk nog een broekie op zaal toen je me strikte voor dit onderzoek. Prachtig om samen een dergelijk project op te bouwen in een wat ongebruikelijke constructie met universitaire ondersteuning op afstand.

Je introduceerde wielrennen: het Peter Post concept met een wisselende kopman, iets wat met name het laatste jaar vorm kreeg met nog een promovendus en wetenschappelijke stage studenten.

De leden van de leescommissie, de heren Prof.dr. F Zijlstra, Prof.dr. JGP Tijssen en Prof.dr. EJG. Sijbrands wil ik danken voor hun bereidheid om dit manuscript door te nemen.

Op de afdeling cardiologie allereerst alle (interventie) cardiologen en arts assistenten die, ook in de diensturen, hebben geholpen met includeren. Jan Hein, voor jou was een korte blik op een tekst vaak genoeg om te zien waar de valkuilen nog lagen die omzeild moesten worden, dank voor het meedenken.

Annet Bos-Schaap en later Nick van Boven, dank voor het waarnemen tijdens mijn vakanties en het zo nodig uitvoeren van glucose tolerantie testen. En natuurlijk jullie hulp bij het includeren van de laatste paar studiepatiënten.

Uiteraard ook alle CCU verpleegkundigen die zich hebben ingezet om het insulineprotocol goed te laten draaien, in het bijzonder Yvonne Wielinga. Dank voor het vele sleutelen aan pompstanden, afnemen van studiemateriaal etc.

Verder natuurlijk de researchverpleegkundigen voor tips & diverse onderzoeks hand en spandiensten, met name in het begin. Op de poli alle assistentes die aan mijn

spreekuren konden sleutelen.

Collega's uit het Erasmus, allereerst Rohit "BIOMArCS" Oemrawsingh & Sanneke "elke 4 weken een manuscript lukt best" de Boer. Rohit, vooral in de beginfase veel gespard om het protocol goed uit te werken en op te zetten. Jouw voorwerk voor het opzetten van de logistiek voor de labbuizen was erg waardevol. Inmiddels begonnen in de kliniek en aan het wachten totdat jouw BIOMArCS tak voldoende patiënten heeft, het gaat nooit snel genoeg. En natuurlijk was het leuk om samen met jullie diverse congressen te bezoeken.

Collega onderzoekers in het MCA, mn Josje "staat er goeie wind" Altenburg, Dominic "leuk zo'n NRI" Snijders, Mireille "TAUP" van Steijn, Joery, Jeroen, Manon, en alle anderen.

Henk Jan Prins & Nick v Boven; rocket science wordt steeds gezelliger, en binnenkort moeten we dan toch echt werken aan de 1e editie van "*Amazing Medicine*". En natuurlijk Tjeerd van der Ploeg, dank voor je statistiek hulp, je uitleg was altijd vol enthousiasme en werd met leuke voorbeelden makkelijker te onthouden.

Ook ondersteuning van andere disciplines was zeer waardevol om dit onderzoek tot een goed einde te brengen. Allereerst bij de interne geneeskunde, Frank Stam en Regina Westra. Frank, dank voor het meedenken over insuline protocollen en glucose tolerantie testen, je inbreng was zeer welkom. Inmiddels ben ik me nog verder in jouw vak aan het verdiepen tijdens mijn vooropleiding cardiologie. Veel dank ook voor het zoeken naar mogelijkheden om tijd te vinden om opleiding en het afronden van onderzoek te combineren. Regina, dank voor het zien & voorlichten van alle diabetes patiënten die we opspoorden.

Verder Esmeralda van Weelen, dank voor je hulp bij het implementeren van het nieuwe studie insulineprotocol, veel plezier nog in Zuid Afrika. En ook jullie andere collega's zoals Timo, Leon & Tineke.

Ook de afdeling nucleaire moet natuurlijk genoemd worden. Friso, dank voor het bekijken van de vele MIBI (of nee: MPS) scans en het meedenken over de invulling van beeldvorming. Daarnaast natuurlijk alle laboranten, Sonja in het bijzonder, die zorgden voor goede scans en extra labafnames.

Veel dank ook voor alle labmedewerkers die de samples tot in de kleine uurtjes hebben bewerkt, met name Jasper Sjoerdsma en Ina van der Hulst.

Lieve ouders & zus, bedankt voor jullie morele steun wanneer dat nodig was.

Lieve Alice, met jou erbij is het leven een stuk leuker! Dank voor de ruimte om mijn onderzoek te kunnen afronden, thuissupport is top. Zeker met Pien erbij was dat extra fijn. Alkmaar verlaten voor Rotterdam is een hele opgave, maar ook daar gaan we er met elkaar iets moois van maken. Plus 1!

CURRICULUM VITAE

Maarten de Mulder werd op 1 juni 1980 geboren te Amsterdam. Nadat hij in 1998 zijn VWO diploma haalde aan de Schoter Scholengemeenschap in Haarlem, heeft hij een aantal maanden als zeilinstructeur gewerkt en door Australië gereisd. In 1999 begon hij met de studie geneeskunde aan de Universiteit van Amsterdam, dit werd enthousiast gecombineerd met commissie en bestuurswerk voor zeilvereniging Waterland. In 2003 vertrok hij opnieuw naar Australië, deze keer voor zijn wetenschappelijke stage aan de Universiteit van Melbourne.

In augustus 2006 behaalde hij zijn artsenbul waarna hij begon als arts assistent cardiologie in het Medisch Centrum Alkmaar. Het vak beviel zo goed dat hij in januari 2008 startte met zijn promotieonderzoek. Hiertoe werd een succesvolle samenwerking tussen de Erasmus Universiteit en het Medisch Centrum Alkmaar tot stand gebracht. Hierbij vonden de dagelijkse werkzaamheden in Alkmaar plaats en was de academische ondersteuning vanuit het thoraxcentrum in Rotterdam in handen van Prof.dr.ir. Eric Boersma. Sinds 1 december 2011 is hij in opleiding tot cardioloog (opleider Dr. F.J. ten Cate), momenteel doet hij de vooropleiding interne geneeskunde in het Medisch Centrum Alkmaar.

SUPPLEMENT

Publications

PUBLICATIONS

1. **de Mulder M**, Oemrawsingh RM, Stam F, Boersma E, Umans VA. Comparison of diagnostic criteria to detect undiagnosed diabetes in hyperglycaemic patients with acute coronary syndrome. *Heart* 2012;**98**:37-41.
2. de Waard GA, Jansen EK, **de Mulder M**, Vonk AB, Umans VA. Long-term outcomes of isolated aortic valve replacement and concomitant AVR and coronary artery bypass grafting. *Neth.Heart J* 2012;**20**:110-7.
3. **de Mulder M**, van der PT, de Waard GA, Boersma E, Umans VA. Admission glucose does not improve GRACE score at 6 months and 5 years after myocardial infarction. *Cardiology* 2011;**120**:227-34.
4. **de Mulder M**, Umans VA, Stam F, Cornel JH, Oemrawsingh RM, Boersma E. Intensive management of hyperglycaemia in acute coronary syndromes. Study design and rationale of the BIOMArCS 2 glucose trial. *Diabet.Med* 2011;**28**:1168-75.
5. **de Mulder M,** van der Zant FM, Knaapen P, Cornel JH, Umans VA. Long-term Clinical Outcome and MIBI SPECT Parameters in Percutaneous Coronary Interventions. *Neth.Heart J* 2011;**19**:68-72.
6. **de Mulder M**, Gitt A, van Domburg R, Hochadel M, Seabra-Gomes R, Serruys PW *et al*. EuroHeart score for the evaluation of in-hospital mortality in patients undergoing percutaneous coronary intervention. *Eur Heart J* 2011;**32**:1398-408.
7. **de Mulder M**, Cornel JH, van der PT, Boersma E, Umans VA. Elevated admission glucose is associated with increased long-term mortality in myocardial infarction patients, irrespective of the initially applied reperfusion strategy. *Am Heart J* 2010;**160**:412-9.
8. Wit MA, **de Mulder M**, Jansen EK, Umans VA. Diabetes mellitus and its impact on long-term outcomes after coronary artery bypass graft surgery. *Acta Diabetol.* Published online 21 September 2010.
9. **de Mulder M,** Broers CJ, Jansen EK, de Swart HB, Peels HO, Lieuw AFM *et al*. Arterial end-to-side grafting in coronary artery bypass grafting: the Tector procedure. *Neth.Heart J* 2010;**18**:7-11.
10. Knaapen P, **de Mulder M,** van der Zant FM, Peels HO, Twisk JW, van Rossum AC *et al*. Infarct size in primary angioplasty without on-site cardiac surgical backup versus transferal to a tertiary center: a single photon emission computed tomography study. *Eur J Nucl Med Mol.Imaging* 2009;**36**:237-43.

11. **de Mulder M**, Zwaan E, Wielinga Y, Stam F, Umans VA. How to implement a clinical pathway for intensive glucose regulation in acute coronary syndromes. *Crit Pathw.Cardiol* 2009;**8**:72-8.
12. **de Mulder M**, Oemrawsingh RM, Stam F, Boersma E, Umans VA. Current management of hyperglycemia in acute coronary syndromes: a national Dutch survey. *Crit Pathw.Cardiol* 2009;**8**:66-70.
13. **de Mulder M**, Umans VA. Response to 'Insulin therapy in acute coronary syndromes'. *Diab.Vasc Dis Res* 2009;**6**:139.

PhD portfolio

PHD PORTFOLIO

Courses

	Year	ECTS
COEUR		
Pathophysiology of cardiac aging	2008	0.4
Cardiovascular imaging and diagnostics	2008	1.5
Clinical cardiovascular epidemiology	2008	1.5
Neurovascular and peripheral vascular diseases	2008	1.5
Pathophysiology of ischemic heart disease	2009	1.0
Arrhythmia research methodology	2009	1.5
Intensive care research	2009	1.5
Nederlandse Hart Stichting		
Thrombosis and Haemostasis	2008	2.0
Vascular Biology	2009	2.0
NIHES		
Regression analysis for clinicians (EWP 23)	2011	1.9
Other		
Cursus Patiëntgebonden Onderzoek	2008	0.3
Basiscursus SPSS & Statistiek	2008	0.3
Vervolgcursus SPSS	2008	0.3
ICH Good Clinical Practice	2008	0.6
NWO Talentendag	2008	0.3
Presentatie cursus	2008	0.6
Wetenschappelijk Engels schrijven	2009	0.6
ICH Good Clinical Practice Update	2009	0.1
Kritisch lezen workshop	2009	0.1

Oral presentations

	Year	ECTS
Minisymposium Hyperglycaemie bij ACS, Groningen *Hyperglyceamie & ACS, wat doen we eraan in Nederland*	2008	0.3
NVVC najaarscongres, Amsterdam *Sugar ain't sweet, but what do you do?*	2008	0.6
COEUR research seminar, Rotterdam *Biomarkers for risk prediction*	2010	0.8
XXIII Annual Scientific WCN Congress, Amsterdam *Trial design BIOMArCS 2 glucose*	2010	0.3

Poster presentations

	Year	ECTS
NVVC voorjaarscongres, Amsterdam *A Dutch experience with arterial end-to-side grafting in CABG; the Tector procedure*	2008	0.6
American College of Cardiology '10, Atlanta, USA *Increased admission glucose relates with increased 5yr mortality in MI patients, irrespective of the initially applied reperfusion strategy.*	2010	0.9
European Society of Cardiology '10, Stockholm, Sweden *1) Undiagnosed diabetes in patients with MI and admission hyperglycemia* *2) EuroHeart Score for the Evaluation of In-hospital Mortality in Patients Undergoing Percutaneous Coronary Intervention*	2010	1.2
European Society of Cardiology '11, Paris, France *Admission glucose does not improve GRACE score at 6 months and 5 years after myocardial infarction*	2011	1.5

Teaching

	Year	ECTS
Training for coronary care unit nurses (MCA) *Interpretatie labuitslagen*	2008	0.3
Training for coronary care unit nurses (MCA) *Risicostratificatie bij acuut coronair syndroom & antistolling*	2010	0.3
Training for cardiology ward nurses (MCA) *Acuut coronair syndroom & diabetes*	2010	0.2
Initiator to and informal chairman of research meetings for PhD students in the Medical Center Alkmaar	2008 - 2011	3.0
Co-supervisor scientific training of medical student	2011	0.6
Chairman "Vereniging arts Assistenten Alkmaar"	2011 - 2012	1.0

Symposia & Congresses

	Year	ECTS
First Dutch symposium on off-site PCI	2007	0.3
Symposium: *Cardiologie, vasculaire geneeskunde en lichamelijke belasting*	2008	0.2
Regiomeeting Noord-Hollandse cardiologen *Ablatie*	2009	0.1
Regiomeeting Noord-Hollandse cardiologen *Cardiale MRI*	2009	0.1
NVVC voorjaarscongres	2009	0.6
NVVC Juniorkamerdag	2010	0.3
CVOI ACS symposium	2010	0.3
NVVC najaarscongres	2010	0.3
Symposium: *Acute MI, the next decade*	2010	0.3
NVVC voorjaarscongres	2011	0.3
NVVC Juniorkamerdag	2011	0.3

Awards

	Year	ECTS
Winner Pieter van Foreest poster prize 2009	2010	0.2
Shared winner Pieter van Foreest poster prize 2010	2011	0.2

Co - authors

CO - AUTHORS

Martijn Akkerhuis
Eric Boersma
Jan-Hein Cornel
Ron van Domburg
Anselm Gitt
Christian Hamm
Matthias Hochadel
Paul Knaapen
Rohit M.Oemrawsingh
Hans-Otto Peels
Tjeerd van der Ploeg
Albert C. van Rossum
Ricardo Seabra-Gomes
Patrick W. Serruys
Sigmund Silber
Frank Stam
Jos W. Twisk
Victor A. Umans
Guus de Waard
Franz Weidinger
Yvonne M Wielinga
William Wijns
Friso M. van der Zant
Uwe Zeymer
Esther G Zwaan

Used Databases

USED DATABASES

Chapter 2	European society of cardiology PCI registry 2005 - 2008
Chapter 3	Infarct data MCA (2002)
Chapter 4	Infarct data MCA (2002)
Chapter 5	Infarct data MCA (2003, 2006)
Chapter 6	Infarct data MCA (1996, 1999, 2003, 2006)
Chapter 7	BIOMArCS 2 glucose data (first 109 patients without prior diabetes)
Chapter 8	---
Chapter 9	Dutch cardiologists survey data
Chapter 10	Insulin/glucose protocol analysis data
Chapter 11	---
Chapter 12	BIOMArCS 2 glucose data (all patients)