Type 2 Diabetes Mellitus in the Acute Coronary Syndrome

Diagnosis, effect on atherosclerotic burden and prognosis

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Thesis for the Degree of Philosophiae Doctor

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Ágrip

Sykursýki 2 (SS2) og forstig SS2 eru þekktir áhættuþættir æðakölkunar og alvarlegra fylgikvilla hjarta- og æðasjúkdóma. Skimun sjúklinga með brátt kransæðaheilkenni (BKH) með sykurþolsprófi hefur gefið til kynna hátt algengi ógreindrar SS2 og forstigs SS2. Hins vegar er ekki ljóst hvernig truflun á sykurefnaskiptum verður best greind hjá sjúklingum með BKH. Að auki hefur magn æðakölkunar eða áhætta á fylgikvillum hjarta- og æðasjúkdóma ekki verið metin hjá sjúklingum með BKH sem greindir hafa verið með truflun á sykurefnaskiptum á grundvelli leiðbeininga Alþjóðaheilbrigðisstofnunarinnar (WHO) og Bandarísku sykursýkis–samtakanna (ADA). Markmið þessarar ritgerðar var þríþætt. Í fyrsta lagi að finna áreiðanlega aðferð til að greina SS2 og forstig SS2 hjá sjúklingum með BKH. Í öðru lagi að meta áhrif truflaðara sykurefnaskipta á magn æðakölkunar hjá sjúklingum með BKH. Að lokum að meta aukna áhættu á fylgikvillum hjarta- og kransæðasjúkdóma hjá sjúklingum með BKH og truflað sykurefnaskipti.

Sjúklingum sem lagðir voru inn á hjartadeild Landspítalans með BKH á sautján mánaða tímabili var boðið að taka þátt í rannsókninni. Sykurefnaskipti voru metin hjá sjúklingum án fyrri sögu um sykursýki með mælingum á HbA1c og fastandi glúkósa í plasma (FPG) ásamt tveggja klukkustunda stöðluðu sykurþolsprófi. Þessar mælingar voru framkvæmdar í sjúkrahúslegu og endurteknar að þremur mánuðum liðnum. Til að greina nýja SS2 (nSS2) þurfti að minnsta kosti tvær mælingar sem voru yfir greiningarþröskuldi fyrir sykursýki. Ein mæling með niðurstöðu yfir greiningarþröskuldi fyrir sykursýki eða fyrir forstig SS2 var skilmerki til greiningar á forstigi SS2. Sjúklingar með allar sex mælingar innan eðlilegra marka töldust hafa eðlileg sykurefnaskipti. Sjúklingar með þekkta SS2 (þSS2) voru flokkaðir sem slíkir. Æðakölkun í hálsslagæðum var metin hjá sjúklingum með áður ógreinda sykursýki með staðlaðri hálsæðaómunum þar sem sjúklingar voru flokkaðir eftir því hvort æðakölkun var til staðar eða ekki og heildarflatarmál æðakölkunar reiknað. Þá var sjúklingum fylgt eftir og kannað hvort þeir þróuðu með sér alvarlega fylgikvilla hjarta- og æðasjúkdóma.

Af þeim 372 sjúklingum með BKH sem tóku þátt voru 20,7% með eðlileg sykurefnaskipti, 46,5% með forstig SS2, 6,2% með nSS2 og 26,6% með þSS2. Næmi til að greina nSS2 hjá sjúklingum með áður óþekkta sykursýki var 33,3%, 61,1% og 77,8% eftir því hvort notað var HbA1c, FPG og 2hPG í sjúkralegu. Þremur mánuðum seinna voru samsvarandi gildi 27,8%, 61,1% og 72,2%. Jákvætt forspárgildi (PPV) til að greina SS2 var 100%, 91,7% og

51,9% með því að nota HbA1c, FPG eða 2hPG í legu. Samsvarandi gildi þremur mánuðum seinna voru 71,4%, 91,7% og 65,0%. Þegar HbA1c og FPG mælingar í legu og þremur mánuðum seinna eru teknar saman var næmi 88,9% og PPV 80,0%. Með því að nota samsetningar með sykurþolsprófi var næmið til að greina SS2 100% en PPV á bilinu 44,2% til 66,7%.

Í sjúklingum með áður ógreinda sykursýki sást æðakölkun í hálsslagæðum hjá 48,5% þeirra sem höfðu eðlileg sykurefnaskipti, 66,9% sem höfðu forstig SS2 og 72,2% sjúklinga með nSS2. Hjá sjúklingum með nýgreint forstig SS2 eða nSS2 var 25,5% og 35,9% aukning á heildarflatarmáli æðakölkunar miðað við sjúklinga með eðlileg sykurefnaskipti (p=0,04). Gerð var fjölþátta aðhvarfsgreiningu þar sem leiðrétt var fyrir hefðbundnum áhættuþáttum æðakölkunarsjúkdóms. Gagnlíkindahlutfall (OR) hjá sjúklingum með nýgreint forstig SS2 eða nSS2 var 2,17 (95% CI 1,15-4,15) að hafa æðakölkun í hálsslagæðum, samanborið við sjúklinga með eðlileg sykurefnaskipti. Þegar einnig var leiðrétt fyrir blóðglúkósa-gildi tveimur klst eftir inntöku glúkósa var OR 1,77 (95% CI 0,83-3,84).

Áhættuhlutfall var 10,9 (95% CI 1,2 – 98,3) fyrir sjúklinga með nSS2 fyrir dauða eða hjartadrep og 2,9 (95% CI 1,0 – 8,0) fyrir alvarlega fylgikvilla hjarta- og æðasjúkdóma eftir 2,9 ár, samanborið við sjúklinga með eðlileg sykurefnaskipti. Hjá sjúklingum með þSS2 var áhættuhlutfallið 14,9 (95% CI 2,0 – 113,7) fyrir dauða eða hjartadrep og 3,3 (95% CI 1,5 – 7,6) fyrir alvarlega fylgikvilla hjarta- og æðasjúkdóma eftir 2,9 ár, samanborið við sjúklinga með eðlileg sykurefnaskipti. Dauðsföll og hjartadrep voru marktækt fleiri hjá sjúklingum með skert sykurþol (IGT), samanborið við sjúklinga með hækkaðan fastandi blóðsykursstjórn (IFG) eða hækkað HbA1c.

Við ályktum að unnt sé að greina með öryggi SS2 hjá sjúklingum með BKH með endurteknum mælingum á HbA1c og FPG þar sem greining SS2 eykst ekki að marki með viðbót sykurþolsprófs. Einnig höfum við sýnt fram á að nýgreint forstig SS2 og SS2 hjá sjúklingum með BKH eru sjálfstæðir áhættuþættir fyrir æðakölkun í hálsslagæðum þar sem hækkað blóðglúkósa-gildi tveim klukkustundum eftir inntöku glúkósa hefur sterk tengsl við aukna æðakölkun. Að lokum, sjúklingar með nSS2 og þSS2 eru í aukinni dánar- og hjartadrepsáhættu sem og aukinni hættu á alvarlegum fylgikvillum hjarta- og æðasjúkdóma, samanborið við BKH sjúklinga með eðlileg sykurefnaskipti.

Lykilorð: brátt kransæðaheilkenni, sykursýki 2, forstig sykursýki, æðakölkun, hjartadrep.

Abstract

Type 2 diabetes mellitus (T2DM) and prediabetes are established risk factors for atherosclerosis and major adverse cardiac events (MACE) in the general population. Screening by oral glucose tolerance test (OGTT) shows high prevalence of undiagnosed dysglycemia among patients with acute coronary syndrome. However, the optimal method to diagnose T2DM and prediabetes in patients with acute coronary syndromes (ACS) has yet to be determined. Furthermore, atherosclerotic burden and risk of future cardiac events among patients with ACS and T2DM or prediabetes as defned by World Health Organization (WHO) and American Diabetes Association (ADA) criteria have not been evaluated. The aim of this thesis is to identify the most reliable method to diagnose T2DM and prediabetes in patients with ACS. In addition, we evaluate atherosclerotic burden and risk of future adverse cardiac events among patients with ACS with different glucose metabolic perturbations according to current WHO and ADA criteria.

Patients diagnosed with ACS and admitted to the coronary care unit were consecutively included in the study. Patients without a previous history of diabetes underwent evaluation of their glucose metabolism by HbA1c, fasting plasma glucose (FPG) and 2-hour plasma glucose (2hPG) with standard OGTT, during hospital admission and at 3-month follow-up. Patients were classified into various categories of glucose metabolism: at least two measurements with results above the diabetes cut-off point, according to WHO and ADA critera, were required to diagnose new T2DM (nT2DM). Subjects with one measurement above the cut-off point for diabetes or prediabetes fulfilled the criteria for prediabetes while patients with all measurements within normal range were classified as having normal glucose metabolism (NGM). Patients with previously known T2DM (kT2DM) were classified as such. Patients without a previous history of T2DM underwent standardized ultrasound examination of their carotid arteries to evalute presence of significant plaques and to measure the total plaque area (TPA). Finally, patients were followed for significant clinical outcome parameters, including all-cause death or myocardial infarction (MI) and major adverse cardiac events (MACE).

Among the 372 ACS patients included in the study, 20.7%, 46.5%, 6.2% and 26.6% were diagnosed with NGM, prediabetes, nT2DM and kT2DM,

respectively. Glucometabolic measurements from patients without a previous diagnosis of T2DM indicated that elevated 2hPG has the highest sensitivity for diagnosing T2DM: 77.8% during hospital admission and 72.2% at follow-up, compared to HbA1c with 33.3% and 27.8%, respectively, and FPG with 61.1% at admission and follow-up. However, the positive predictive values (PPVs) for diagnosing T2DM were 100%, 91.7% and 51.9% during admission and 71.4%, 91.7% and 65.0% at follow-up for HbA1c, FPG and 2hPG, respectively. By combining HbA1c and FPG measurements during admission and follow-up, the sensitivity to diagnose T2DM was 8.9% and PPV was 80.0%, while combinations of FPG and HbA1c with OGTT had 100% sensitivity and a PPV ranging from 44.2% to 66.7%.

Among patients without a previous history of diabetes, a significant atherosclerotic plaque was detected in 48.5%, 66.9% and 72.2% of patients with NGM, prediabetes and nT2DM, respectively. An incremental increase in TPA was found from NGM to prediabetes and nT2DM (p=0.04). Patients with newly diagnosed dysglycemia were found to be at increased risk of having significant atherosclerotic plaque in the carotid arteries, when adjusted for conventional cardiovascular risk factors, with OR of 2.17 (95% CI 1.15-4.15) compared to patients with NGM. When also adjusted for 2hPG, the OR attenuated to 1.77 (95% CI 0.83-3.84).

After a mean follow-up period of 2.9 years, compared to patients with NGM, patients with nT2DM and kT2DM had HR 10.9 (95% CI 1.2 – 98.3) and 14.9 (95% CI 2.0 – 113.7), respectively, for death/MI and 2.9 (95% CI 1.0 – 8.0) and 3.3 (95% CI 1.5 – 7.6), respectively, for a composite of MACE. Patients with prediabetes had increased near future risk for death/MI but this did not reach statistical significance. Patients with impaired glucose tolerance suffered significantly more events of death or MI compared to patients with impaired fasting glucose or elevated Hb1Ac.

In conclusion, T2DM can be diagnosed with reasonable certainty using repeated measurements of HbA1c and FPG in ACS patients, with limited added value of OGTT. Furthermore, newly detected dysglycemia is an independent predictor of atherosclerotic plaque formation in the carotid arteries with OGTT as the major determinant of risk of carotid plaque burden. Finally, patients with nT2DM and kT2DM were found to have an increased risk of death or MI and MACE compared to ACS patients with NGM.

Keywords: acute coronary syndrome, type 2 diabetes, prediabetes, atherosclerosis, myocardial infarction.

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Contents

List of abbreviations

2hPG	2-hour Postload Glucose
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
ACS	Acute Coronary Syndrome
apoB-LP	Apolipoprotein B-containing Lipoprotein
AUC	Area Under the Curve
BMI	Body Mass Index
BIF	Carotid Bifurcation
BPL	Blood Pressure Lowering
CABG	Coronary Artery Bypass Graft
CAC	Coronary Artery Calcium
CAD	Coronary Artery Disease
CCA	Common Carotid Artery
CI	Confidence Interval
cIMT	Carotid Intima-Media Thickness
CT	Computer Tomography
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DDP-4	Dipeptidyl Peptidase-4
DIGAMI	Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction
ER	Endoplasmic-reticulum
ESC	European Society of Cardiology
FPG	Fasting Plasma Glucose

GLP-1	Glucagon-like Peptide-1
HbA1c	Glycated Hemoglobin
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HR	Hazard Ratio
hS-CRP	High-Sensitive C-Reactive Protein
ICA	Internal Carotid Artery
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IQR	Interquartile Range
kT2DM	Known Type 2 Diabetes Mellitus
MACE	Major Adverse Cardiac Events
MI	Myocardial Infarction
NGM	Normal Glucose Metabolism
NPV	Negative Predictive Value
NSTEMI	Non-ST Elevation Myocardial Infarction
nT2DM	New Type 2 Diabetes Mellitus
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
ORIGIN	Outcome Reduction with Initial Glargine Intervention
PCI	Percutaneous Coronary Intervention
PPV	Positive Predictive Value
ROC	Receiver Operating Characteristics
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SGLT-2	Sodium-Glucose Transport Protein 2
STEMI	ST Elevation Myocardial Infarction
T2DM	Type 2 Diabetes Mellitus

TPA	Total Plaque Area
TZD	Thiazolidinediones
UAP	Unstable Angina Pectoris
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Administration Diabetes Trail
VSN	Vísindasiðanefnd (e. Icelandic Bioethics Committee)
WHO	World Health Organization
WHR	Waist-to-Hip Ratio

List of figures

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List of original papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals.

I. **Bjarnason TA, Kristinsdottir LB, Oskarsdottir ES, Hafthorsson SO, Olafsson I, Lund SH, Andersen K.** Editor´s Choice – Diagnosis of type 2 diabetes and prediabetes among patients with acute coronary syndrome. *Eur Heart J Acute Cardiovasc Care 2017 Dec;6(8):744-749.*

II. **Bjarnason TA, Hafthorsson SO, Kristinsdottir LB, Oskarsdottir ES, Aspelund T, Sigudsson S, Gudnason V, Andersen K.** Oral glucose tolerance test predicts increased carotid plaque burden in patients with acute coronary syndrome. *PLoS One 2017 Aug 30;12(8):e0183839.*

III. **Bjarnson TA, Hafthorsson SO, Kristinsdottir LB, Oskarsdottir ES, Johnsen A, Andersen K.** Prognostic effect of known and newly detected Type 2 diabetes in patients with acute coronary syndrome. *Eur Heart J Acute Cardiovasc Care 2019 May 20:2048872619849925. DOI: 10.1177/2048872619849925.*

Declaration of contribution

The doctoral candidate, Þórarinn Árni Bjarnason, participated in developing the scientific questions and planning of the research protocol with Karl Andersen. The doctoral candidate´s contribution was as follows.

- Recruited majority of patients in the Coronary Care Unit at Landspitali into the study
- Explained the reason for the study, potential harm and obtained consent from patients
- Ordered glucose metabolic measurements during admission and at follow-up
- Scheduled follow-up for repeat glucose metabolism measurements and carotid ultrasound examination
- Performed majority of OGTTs and phlebotomies during follow-up
- Informed patients of their results and referred to appropriate health care provider if indicated
- Collected patient's data, maintained the database and performed statistical analysis
- Drew conclusions and interpretation of the results
- Wrote manuscript for the three papers that this thesis is based on in addition to numerous abstracts generated by this scientific work

1 Introduction

Atherosclerotic plaque is the end-product of a process during which the arterial intima expands with cells, lipids and extracellular matrix over several years or decades. Atherosclerosis tends to form where blood flow is turbulent instead of laminar, particularly at arterial branching points and bifurcations. A key initial step in atherogenesis is subendothelial accumulation of apolipoprotein B-containing lipoproteins (apoB-LPs) that subsequently provokes inflammatory response. Subsequently monocytes are recruited into the subendothelial space, prompting further inflammatory response (Moore & Tabas, 2011). These monocytes then become macrophages and start to ingest and process apoB-LPs, leading to cholesterol accumulation in the cell. The macrophage transforms into a foam cell that then further re-esterificates the cholesterol in the endoplasmic reticulum (ER) to form cholesteryl fatty acid esters (Brown, Ho, & Goldstein, 1980). With chronic inflammation localized in the atherosclerotic plaque, monocytes continue to enter the plaque, differentiating into macrophages and later foam cells. Finally, foam cells undergo apoptosis resulting in extracellular build-up of cholesterol and fibrotic tissue that causes progression and expansion of the atherosclerotic plaque (Moore & Tabas, 2011). Atherosclerotic plaque can be categorized into vulnerable plaques and stable plaques. Vulnerable plaques have a lipid-rich core and a thin fibrous cap with increased plaque inflammation, neovascularization of vasa-vasorum and intra-plaque hemorrhage compared to stable plaques with lipid-poor plaques and thick fibrous cap (Moreno, 2010; Virmani, Burke, Kolodgie, & Farb, 2002). Vulnerable plaques are more likely than stable plaques to result in plaque rupture with subsequent thrombus formation at the site of injury. Plaque erosion is a different process, an abrasion of the endothelium without plaque rupture thought to occur due to apoptosis of endothelial cells, but with formation of thrombus at the injury site (Lafont, 2003; Virmani, Burke, & Farb, 1999). In coronary arteries, atherosclerotic plaque can, in time, restrict blood flow, causing stable coronary artery disease (CAD) or acute coronary syndrome (ACS) in the setting of plaque rupture or erosion with subsequent luminal thrombosis.

1.1 Risk Factors for Atherosclerosis

There are several risk factors known to contribute to formation and expansion of atherosclerotic plaque causing increased risk for cardiovascular disease

(CVD). These include age, male gender, hypercholesterolemia, hypertension, diabetes, smoking, obesity and sedentary lifestyle (K. M. Anderson, Castelli, & Levy, 1987; Berlin & Colditz, 1990; Doyle, Dawber, Kannel, Heslin, & Kahn, 1962; Go et al., 2014; Hubert, Feinleib, McNamara, & Castelli, 1983; Mellbin, Anselmino, & Ryden, 2010; Stamler, Stamler, & Neaton, 1993; Stamler, Wentworth, & Neaton, 1986). Family history, representing genetic susceptibility, is also a contributing factor in the process of atherosclerotic plaque formation and increased risk of CVD. However, although numerous genetic variants have been identified, so far they only account for a small percentage of risk for CVD (Abi-Younes et al., 2000; Andresdottir, Sigurdsson, Sigvaldason, & Gudnason, 2002; Lloyd-Jones et al., 2004; Lotta, 2010; Mehta et al., 2011; Moore & Tabas, 2011; Tregouet et al., 2009). As genetic research and knowledge continues to grow, our understanding of how genetics affect atherosclerotic formation and progression will improve, possibly leading to better risk stratification and targeted therapy (Inouye et al., 2018).

Over the last several decades significant progress has been made to reduce mortality from CAD. In the United States, age-adjusted death rates from CAD decreased from 543 to 267 deaths per 100.000 among men and from 263 to 134 per 100.000 in women from 1980 through 2000 (Ford et al., 2007). Similar results have been observed in Iceland over the last several decades. Mortality from CAD in Iceland has decreased by 80% from 1981 through 2006 and incidence of myocardial infarction (MI) decrease by 66% during the same time period (Andersen et al., 2017; Aspelund et al., 2010). This has been attributed to more favourable risk factor trends with reduction in cholesterol, lower systolic blood pressure, decreased smoking prevalence and increased physical activity as well as therapies including initial treatment in ACS, secondary prevention after MI, revascularization and heart failure treatment. In Iceland, approximately 73% of the observed CAD mortality decrease was attributable to risk factor reductions (Aspelund et al., 2010). However, increasing obesity and prevalence of diabetes have partially offset the reduction of CAD mortality. CVD remains the most common cause of death worldwide, with the 2013 Global Burden of disease estimated to be 17.3 million deaths globally (Roth et al., 2015).

1.2 Type 2 Diabetes Mellitus

The prevalence of type 2 diabetes mellitus (T2DM) has been increasing in recent years, especially in the Western world, and it was estimated by the World Health Organization (WHO) that worldwide prevalence of diabetes

rose from 108 million in 1980 to 422 million in 2014 with a global prevalence of diabetes among adults over the age of 18 being 8.5% (WHO, 2017). The prevalence is expected to further grow over the coming decades (Boyle, Thompson, Gregg, Barker, & Williamson, 2010; Whiting, Guariguata, Weil, & Shaw, 2011). T2DM is primarily caused by a high-energy diet with high sugar and fat content and low physical activity that contributes to obesity as well as being genetically exposed to develop T2Dm. With increased weight, muscles become insulin-resistant, requiring more insulin to be produced by the islet β cells in the pancreas. Initially the islet β cells are able to produce more insulin, causing hyperinsulinemia in order to respond to the increased glucose load. Postprandial hyperglycemia is often thought to be the first sign of glucose derangement when patients are severely insulin-resistant, where the muscles and liver require more insulin for adequate glucose uptake and suppress hepatic glucose production, respectively (DeFronzo, Gunnarsson, Bjorkman, Olsson, & Wahren, 1985; Ferrannini et al., 1988). As the islet β cells increase their insulin production and secretion, with subsequent hyperinsulinemia, the fasting glucose remains within normal limits. However, eventually the islet β cells of susceptible individuals start to fail and are unable to meet the increasing demand for insulin production with associated hyperglycemia, leading to overt T2DM and associated complications, most notably retinopathy, neuropathy, nephropathy and atheroscleotic disease (DeFronzo & Abdul-Ghani, 2011; Nolan, Damm, & Prentki, 2011).

1.3 Diagnosis of Type 2 Diabetes Mellitus

Currently, there are two main diagnostic criteria for dysglycemia, the WHO criteria and the American Diabetes Association (ADA) criteria (ADA, 2012a; WHO, 2006, 2011). Both of these criteria concur on the diagnosis of T2DM in asymptomatic patients, using fasting plasma glucose (FPG), standardized 2-hour oral glucose tolerance test (OGTT) and glycated hemoglobin (HbA1c) with at least two measurements required above the diagnostic cut-point for the diagnosis of diabetes (Alberti & Zimmet, 1998; ADA, 2012a; WHO, 2006, 2011). These guidelines apply diagnostic criteria that are based on the glucose levels that lead to retinopathy according to three epidemiologic studies from the general population (ADA, 2012a). These studies showed glycemic levels with low prevalence of microvascular disease, like retinopathy, nephropathy and neuropathy, above which the prevalence started to increase in apparently linear fashion. Therefore, both the ADA and WHO define diabetes as 2-hour postload glucose (2hPG) ≥11.1 mmol/l (200 mg/dL), FPG ≥7.0 mmol/l (126 mg/dL) or HbA1c ≥6.5% (48 mmol/mol) with at

least two measurements required to fulfill the criteria for diabetes in asymptomatic patients (table 1). However, more recent studies have indicated an increased risk of macrovascular complications, like CVD, in individuals with dysglycemic levels that are lower than the current diagnostic cut-point for diabetes (Coutinho, Gerstein, Wang, & Yusuf, 1999; Sinnaeve et al., 2009).

Table 1. Diagnostic criteria for T2DM and prediabetes according to WHO and ADA

	WHO	ADA
Diabetes		
- FPG	≧ 7.0 mmol/l	≧ 7.0 mmol/l
- 2hPG	≧ 11.1 mmol/l	≧ 11.1 mmol/l
- HbA1c	≧ 6.5%	≧ 6.5%
Prediabetes		
- FPG	6.1 – 6.9 mmol/l	5.6 – 6.9 mmol/l
- 2hPG	7.8 – 11.0 mmol/l	7.8 – 11.0 mmol/l
- HbA1c	-	5.7 – 6.4%
NGM		
- FPG	≦ 6.0 mmol/l	≦ 5.5 mmol/l
- 2hPG	≦ 7.7 mmol/l	≦ 7.7 mmol/l
- HbA1c	-	≦ 5.6%

WHO: World Health Organization, ADA: American Diabetes Association, FPG: fasting plasma glucose, 2hPG: 2-hour plasma glucose

Individuals with slightly elevated blood glucose levels not meeting the criteria of diabetes are considered to have prediabetes. These individuals have impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and/or abnormal elevation of HbA1c and are considered to represent an intermediate stage between normal glucose metabolism (NGM) and diabetes. These individuals are at high risk of developing diabetes in the future, with 5-10% of patients with prediabetes becoming diabetic annually, as well as developing CVD (ADA, 2012a; Forouhi, Luan, Hennings, & Wareham, 2007; Nathan et al., 2007). Contrary to the diagnosis of diabetes, the WHO and ADA do not agree on the diagnostic criteria for prediabetes. Both criteria agree on a 2hPG range of 7.8 – 11.0 mmol/l (140 – 199 mg/dl) to identify IGT but the ADA has a lower cut-off point for FPG of 5.6 – 6.9 mmol/l (100 – 125 mg/dL), while the WHO proposes 6.1 – 6.9 mmol/l (110 – 125 mg/dL) to diagnose IFG. The reason the ADA applies a lower cut-off point to define IFG is to ensure similar prevalence of IFG and IGT. And while the ADA criteria defines HbA1c of 5.7 – 6.4% as prediabetes, the WHO has not incorporated HbA1c to identify prediabetes. The ADA included elevated HbA1c to identify prediabetes as studies have shown a continuous increaseing risk of developing diabetes with higher HbA1c, reportedly three to ten times higher risk compared to lower levels (Edelman, Olsen, Dudley, Harris, & Oddone, 2004; Pradhan, Rifai, Buring, & Ridker, 2007; Sato et al., 2009; Shimazaki, Kadowaki, Ohyama, Ohe, & Kubota, 2007). Also, the HbA1c level that most accurately identifies

individuals with IFG and IGT falls between 5.5 – 6.0% with FPG of 6.1 mmol/l and 5.6 mmol/l in the nondiabetic adult population to correspond to HbA1c of 5.6% and 5.4%, respectively (ADA, 2012a). Finally, data from the Diabetes Prevention Program where the mean HbA1c was 5.9% demonstrated that preventive interventions were effective in participants below and above 5.9%, indicating that preventive interventions were likely to have significant effect with HbA1c somewhere in the 5.5 – 6.0% range (Knowler et al., 2002). For these reasons the ADA set the lower threshold of prediabetes for HbA1c at 5.6%.

1.4 Prevalence of Type 2 Diabetes Mellitus in Coronary Artery Disease

Studies have shown a relatively high prevalence of undiagnosed dysglycemia in patients with CAD. In several studies the prevalence of prediabetes ranged from 35% to 66% and the prevalence of T2DM from 22% to 31%, with a higher prevalence in patients with ACS compared to healthy controls (Bartnik, Ryden, et al., 2004; Gyberg et al., 2015; Norhammar et al., 2002; Ritsinger et al., 2015). All of these studies were cohort studies screening for diabetes in patients with CAD without a previous history of diabetes where only one measurement was requried to detect diabetes. OGTT has been used as a “gold standard” to identify diabetes as studies have suggested that OGTT has a higher sensitivity, compared to FPG and HbA1c, to detect glucose derangements. This is due to the fact that the 2hPG level identifies patients with insulin resistance. Under those circumstances, the β cells in the pancreas need to increase the production of insulin to lower the blood glucose, causing hyperinsulinemia which is considered to be the first sign of abnormal glucose metabolism. However, in clinical practice both HbA1c and FPG may be more convenient than OGTT and are frequently the preferred diagnostic tools. Interestingly, studies on the diagnosis of diabetes, based on current ADA and WHO criteria, in patients with CAD but without previous history of diabetes have, to our knowledge, never been conducted. Moreover, there is no consensus on how to identify glucose metabolic derangements in high-risk groups, such as patients with CAD, either by ADA or WHO guidelines.

Diabetes is an established risk factor for CVD in the general population with a hazard ratio (HR) for CVD death of 2.6. The risk of death from CVD is similar among patients with established diabetes without history of CAD as it is in nondiabetic patients with prior MI (Barr et al., 2007; Go et al., 2014; Haffner, Lehto, Ronnemaa, Pyorala, & Laakso, 1998). However, as in the

general population, mortality from CVD has been decreasing over the last several years among patients with diabetes (Rawshani et al., 2017). Interestingly, patients with T2DM and optimal management of risk factors have minimally increased risk for death or CVD compared to the general population (Rawshani et al., 2018). This highlights the importance of treating and managing comorbidities in patients with T2DM.

It has been suggested that prediabetes (IFG and IGT) is associated with adverse future events in the general population (Barr et al., 2007). The same pattern has been seen in patients with a history of CAD. Patients with previously known type 2 diabetes mellitus (kT2DM) or new diagnosis of type 2 diabetes mellitus (nT2DM) and established, stable CAD are at significantly increased risk of 1-year mortality with HR 2.4 and 2.0, respectively. A 20-year follow-up in this patient population has indicated that the median survival is 3 years shorter among patients with T2DM compared to nondiabetic patients with CAD (Lenzen et al., 2006; P. A. Patel et al., 2016). Studies have suggested that patients with MI and hyperglycemia below the diabetic threshold have an increased risk of future adverse cardiovascular events and mortality compared to those with normal glucose metabolism (Coutinho et al., 1999; Sinnaeve et al., 2009). Increased risk of adverse events has been found in CAD patients with elevated FPG compared with NGM (HR 1.71; Sinnaeve et al., 2009). Several studies have specifically focused on patients without prior history of T2DM who present with ACS. These studies have reported a significantly increased rate of adverse events (HR 2.15 – 3.27) among patients with nT2DM, compared to patients with NGM who present with ACS. Significantly increased risk of adverse events (HR 1.54 – 2.65) has also been described among patients with abnormal glucose tolerance (IFG and/or IGT) compared to patients with NGM (Bartnik, Malmberg, et al., 2004; George et al., 2015; Ritsinger et al., 2015; Tamita et al., 2007). Like other studies that have evaluated dysglycemia in CAD, these were cohort studies where OGTT was performed once as a screening test before hospital discharge to classify patients as having NGM, abnormal glucose tolerance or T2DM, without verifying the classification or evaluating whether these patients had prediabetes or T2DM. HbA1c was not utilized to identify patients with dysglycemia. Consequently, some patients with dysglycemia may not have been identified, especially patients with prediabetes. Finally, some of these studies were performed before or during the time when double anti-platelet and high-dose statin therapy were introduced as powerful secondary preventive measures in patients with ACS. This could result in higher event rates than are currently present.

1.5 The Effect of Diabetes on Atherosclerosis

Several pathways may mediate the diabetic effect on atherogenesis and increase the risk of CVD. Insulin resistance and subsequent hyperinsulinemia, the two hallmarks of T2DM, have been suggested to increase the formation of reactive oxygen species and vascular dysfunction, causing vascular and atherosclerotic plaque inflammation and proliferation of smooth muscle cells, accelerating atherosclerotic plaque formation (Paneni, Beckman, Creager, & Cosentino, 2013). Fluctuating and abnormally high blood glucose levels, caused by postprandial hyperglycemia, can contribute to abnormal endothelial function (DeFronzo & Abdul-Ghani, 2011). Studies have also suggested that patients with diabetes have a higher prevalence of metabolic syndrome, including hypertension, dyslipidemia and central obesity, all being established risk factors for CVD (DeFronzo & Abdul-Ghani, 2011). Finally, insulin resistance and hyperglycemia are effective inducers of prolonged stress in the ER (the endoplasmic-reticulum stress pathway). By downregulating the insulin receptor signaling pathway in macrophages in the setting of insulin resistance, there is an increase in the unfolded protein response which finally results in apoptosis. The combination of macrophage apoptosis and defective phagocytic clearance (defective efferocytosis) seen in patients with diabetes leads to enhanced plaque necrosis and, in turn, large necrotic cores independent of lesion size (Moore & Tabas, 2011; Tabas, Tall, & Accili, 2010). The defect in the macrophage apoptosis pathway and other pathways in the cell, such as dyslipidemia-mediated proinflammatory effects and complement activation, synergistically accelerate the atherosclerotic process. The necrotic core is especially worrisome as defective efferocytosis leads to secondary cell necrosis with associated smooth muscle cell death and protease mediated degradation of the extracellular matrix. This contributes to vulnerable plaque with weakened fibrous cap that has high risk of rupture (Galis, Sukhova, Lark, & Libby, 1994). The thrombogenic material exposed from the ruptured atherosclerotic plaque activates platelets that aggregate and form thrombus (Virmani et al., 2002). Insulin resistance with hyperinsulinemia and transient hyperglycemia are conditions that can be undetected for years, contributing to atherosclerotic disease and increased risk for CVD.

1.6 Treatment of Type 2 Diabetes in Coronary Artery Disease

The first steps in the management of prediabetes are lifestyle interventions. Studies have shown that lifestyle interventions to promote weight loss,

including low-calorie and low-fat diets, restricted saturated fat intake and increased monounsaturated fatty acid intake with moderate intensity physical activity, reduce the risk of developing T2DM both in the short and long term (Nathan D.M., 2015; Tuomilehto et al., 2001). In addition, metformin has been found to reduce T2DM development in patients with prediabetes (Nathan D.M., 2015; Salpeter, Buckley, Kahn, & Salpeter, 2008). The ADA guidelines recommend lifestyle changes as the first-line treatment for prediabetes. Furthermore, they also recommend that metformin should be considered in patients with prediabetes, especially in patients who are <60 years old, with body mass index (BMI) >35 kg/m^2, with a history of gestational diabetes mellitus or in patients who are not responding to initial lifestyle changes with rising HbA1c (ADA, 2017). These recommendations are largely based on the Diabetes Prevention Program that demonstrated decreased incidence of diabetes in patients with prediabetes by 58% with lifestyle changes and by 31% with metformin, compared to placebo (Knowler et al., 2002). In addition to lifestyle interventions to promote weight loss, the European Society of Cardiology (ESC) recommends smoking cessation, physical exercise, antiplatelet therapy with low-dose aspirin and tight blood pressure and dyslipidemia management in patients with prediabetes and CVD, but there is no recommendation on specific antihyperglycemic therapy (Ryden et al., 2014).

Several studies have looked into whether intensive glycemic control is beneficial to lowering the risk of macrovascular complications. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) was a large study in which patients with T2DM and established CVD or additional risk factors for CVD were randomized to an intensive treatment group, with target HbA1c of 6.0%, and a standard treatment group. However, after 3.5 years of follow-up the study was terminated due to higher mortality in the intensive treatment group (Gerstein et al., 2008). Hypoglycemia was more common in the intensive treatment group and further analysis suggested that fluctuations in glucose and difficulty in controlling glucose to target HbA1c might have contributed to the higher mortality in the intensive treatment group (Bonds et al., 2010). The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) was another large randomized clinical trial in which the target HbA1c was 6.5% in the intensive treatment group. There was reduction in microvascular complications but not in macrovascular complications after 5 years of treatment (A. Patel et al., 2008). In addition, no difference was found in mortality between the intensive and standard treatment groups. The Veterans

Administration Diabetes Trial (VADT) and the Outcome Reduction with Initial Glargine Intervention (ORIGIN) focused on patients with T2DM with and without CVD. The intensive treatment group had a target HbA1c reduction of 1.5% and was treated with insulin in the former trial but with insulin glargine in the latter. No differences were found in cardiovascular complications between the intensive treatment and standard care groups in these two studies (Duckworth et al., 2009; Gerstein et al., 2008). Finally, the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 trial followed patients with T2DM who had been admitted with acute MI and discharged on sulphonylurea, metformin or insulin. After approximately 2 years of follow-up, no difference was found in cardiovascular mortality between the three groups. However, the risk for stroke and non-fatal MI was significantly increased in the insulin group (HR 1.73, 95% CI 1.26 - 2.27) while the risk in the sulphonylurea group was unchanged and lowered in the metformin group (HR 0.63, 95% CI 0.42 - 0.95; Mellbin et al., 2008). All of these studies had relatively short follow-up periods, ranging from 2.1 to 6 years. In the United Kingdom Prospective Diabetes Study (UKPDS), patients with T2DM were randomized to intensive treatment groups, either a sulfonylurea-insulin group or a metformin group, and a standard care group. Initially patients were followed annually for 5 years. At that time, no significant differences were found in macrovascular complications between the intensive care and standard care groups and the study concluded with no attempts to maintain assigned therapies. However, at 10-year follow-up there was a significant risk reduction for MI and all-cause death in the sulfonylurea-insulin group, 15% and 13% respectively, and the metformin group, 33% and 27% respectively, compared to standard care group. This was despite the fact that differences in HbA1c disappeared in the first year after the study concluded (Holman, Paul, Bethel, Matthews, & Neil, 2008). This phenomenon of risk reduction for future cardiovascular events and death years after early strict glycemic control has been called the “legacy effect” and has also been observed in patients with type 1 diabetes mellitus (Nathan et al., 2005). What these studies suggest is that metformin should be a part of standard care among patients with T2DM and CAD. Also, that early glycemic control is important in long-term reduction of macrovascular complications, especially in younger patients with a shorter cumulative duration of T2DM. However, there is concern that strict glycemic control in older patients may increase the risk of hypoglycemia and that strict glycemic control for long-term risk reduction might not be beneficial in older patients. As with prediabetes, the ESC guidelines recommend smoking cessation, physical exercise, antiplatelet therapy with low-dose aspirin and tight blood pressure and

dyslipidemia management in patients with T2DM and CVD as well as target HbA1c of <7.0% and around 6.5% in patients who are young, have short duration of T2DM and few comorbidities (Ryden et al., 2014).

Sodium-glucose transport protein 2 (SGLT-2) inhibitors have recently emerged as a treatment for T2DM (Cefalu & Riddle, 2015). The SGLT-2 is primary located in the epithelial cells of the proximal convoluted tubule in the kidneys. It is a major glucose transporter and is responsible for 90% of the kidney´s glucose reabsorption (Shubrook, Bokaie, & Adkins, 2015). SGLT-2 inhibitors act to prevent glucose reabsorption in the kidneys, thereby promoting glucose excretion in the urine (glucosuria) and lowering glucose levels (S. L. Anderson & Marrs, 2012; Li, Zhang, Greenberg, Lee, & Liu, 2011). In addition to be an effective antihyperglycemic agent, it has also been shown to promote weight loss and lower both systolic and diastolic blood pressure (Haas, Eckstein, Pfeifer, Mayer, & Hass, 2014). SGLT-2 inhibitors have also shown promise in lowering cardiovascular morbidity and mortality. The SGLT-2 inhibitor empagliflozin has been shown to lower the risk of cardiovascular death, non-fatal MI or non-fatal stroke (HR 0.86) compared to placebo (Zinman et al., 2015). The same risk reduction for cardiovascular death, non-fatal MI or non-fatal stroke was observed for the SGLT-2 inhibitor canagliflozin compared to placebo (Neal et al., 2017).

Glucagon-like peptide-1 (GLP-1) agonists have also emerged recently as a treatment option for T2DM. GLP-1 agonists have been shown to lower HbA1c by 1% by stimulating glucose-dependent insulin secretion and biosynthesis, suppressing glucagon secretion and delaying gastric emptying, which promotes satiety and weight loss (Koliaki & Doupis, 2011; Shyangdan et al., 2011). GLP-1 agonists have also shown some promise in lowering the risk for adverse cardiovascular events in patients with T2DM compared to placebo (Marso, Bain, et al., 2016; Marso, Daniels, et al., 2016). However, a GLP-1 agonist was not found to be superior in lowering the risk for cardiovascular events compared to placebo in patients with T2DM where the majority of patients (73%) had known CVD (Holman et al., 2017).

These data suggest that SGLT-2 inhibitors and GLP-1 agonists could be a reasonable choice as second- and third-line medical treatments for T2DM in patients with CVD after first-line treatment with metformin (Davies et al., 2018).

1.7 Measuring Atherosclerotic Plaque Burden

Coronary artery disease is common in the general population and is a leading cause of morbidity and mortality worldwide (Go et al., 2014). In addition, modern medicine has the means to identify certain risk factors for CAD such as dyslipidemia, hypertension, prediabetes and T2DM. Interventions to improve risk factors may be provided both at the population level as well as with individualized lifestyle recommendations and medical treatment. Therefore, CAD risk factors are suitable for screening in the general population. Several risk scoring systems have been developed where various risk factors for CAD, such as age, gender, cholesterol levels, blood pressure, smoking status and diabetes, are used to predict the risk of developing and acquiring future CAD (Goff et al., 2014; Wilson et al., 1998). The calculated risk can then be used to determine and individualize treatment, whether it is lifestyle changes or medication, to prevent disease progression. However, despite sophisticated risk scoring systems that are constantly undergoing refinement, most ACS occurs among the numerous low- or intermediate-risk subjects with few deaths among the much fewer high-risk individuals (Canto et al., 2011; G. Rose, 1981). The reason for this apparent paradox is that the risk scoring system identifies only a small proportion of patients with high risk, failing to identify people with high lifetime risk and that are wrongly classified to be in low- or intermediate-risk categories (Berry et al., 2009; Geoffrey Rose, 2001).

Coronary artery calcium (CAC) scanning with computed tomography (CT) has been suggested as an option to evaluate risk for future ACS, particularly in individuals who have been classified to be at intermediate risk (Agatston et al., 1990; Hecht, 2015). CAC has been shown to have robust predictive power for future ACS with relative risk exceeding other conventional risk factors (Arad, Goodman, Roth, Newstein, & Guerci, 2005; Detrano et al., 2008; Hecht, 2015; Hecht & Narula, 2012). Nevertheless, CAC scanning has not been widely established as a part of primary preventions for CAD in asymptomatic individuals, mainly due to the high cost of CT imaging and the radiation exposure of a large portion of asymptomatic, healthy people (Chen et al., 2010; Gerber et al., 2009).

Ultrasound imaging of the carotid arteries to evaluate carotid intima-media thickness (cIMT) and carotid plaque has been suggested as an affordable and less invasive measure for risk classification and determination of atherosclerotic burden. Intima-media thickness is the measurement of the two innermost layers of the arterial wall, the tunica intima and tunica media

(de Groot et al., 2008). However, while cIMT has been found to be predictive for future cardiovascular events in the setting of clinical trials, it does not improve cardiovascular risk classification of individuals in the general population (Lorenz, Schaefer, Steinmetz, & Sitzer, 2010). This might be because of high inter- and intra-operator variability of cIMT readings and limited general availability and applicability of the method in the clinical setting. On the other hand, the presence of atherosclerotic plaque in the carotid arteries has been found to be superior, compared to cIMT, in predicting future coronary artery disease and stroke (Inaba, Chen, & Bergmann, 2012; Mathiesen et al., 2011; Plichart et al., 2011). Carotid atherosclerotic plaque has also been found to improve risk stratification to predict future coronary artery disease when added to conventional risk factors (Polak et al., 2013). Finally, studies have shown an association between carotid atherosclerotic plaque and CAC with similar improvement in CVD risk classification when added to conventional risk factors (Baber et al., 2015; Cohen et al., 2013). Therefore, evaluation of carotid atherosclerotic plaques with ultrasound imaging is a non-invasive and affordable method to reliably estimate individual atherosclerotic burden.

2 Aims

Currently, the prevalence of prediabetes and undiagnosed T2DM among patients who present with ACS in Iceland is unknown. Previous studies on dysglycemia and ACS have utilized OGTT to identify dysglycemia. However, the best method to diagnose T2DM has not been defined in this patient population and it is unclear whether conventional diagnostic criteria of T2DM, based on current WHO and ADA criteria, apply to patients with ACS. In addition, carotid artery ultrasound has not been performed previously to evaluate differences in atherosclerotic burden of ACS patients with NGM, new prediabetes or nT2DM. Finally, the prognostic implications of glucometabolic perturbations according to current WHO and ADA criteria among ACS patients has not previously been evaluated.

Therefore, the aims of the present study were to evaluate prediabetes and T2DM in patients with acute coronary syndrome to:

- identify the most reliable method of diagnosing type 2 diabetes mellitus in patients with ACS
- evaluate the relationship between glucometabolic perturbations and atherosclerotic plaque burden in patients with ACS
- evaluate the prognostic implications of glucometabolic derangements in patients with ACS

3 Materials and methods

3.1 Study Population

Patients admitted to the coronary care unit of Landspitali, the University Hospital of Iceland, with a diagnosis of ACS were consecutively included in the study between June 2013 and October 2014. ACS was defined according to the joint American College of Cardiology and ESC recommendations (Alpert et al., 2000). Patients living outside the catchment area of the hospital, with cognitive dysfunction or patients who died during initial admission were excluded from the study. Informed written consent was obtained from all participants prior to any study-related procedure. The study protocol adhered to the principles of the Declaration of Helsinki (World Medical Association , 2013) and was approved by the Icelandic Bioethics Committee (VSN: 13-069-S1). Information on demographics, risk factors, medication, lifestyle and clinical endpoints were obtained from patients during admission, hospital records and from the Icelandic National Death Registry (Statistics Iceland, 2017). Hypertension was defined by documented history of hypertension or patient on antihypertensive medication at the time of admission. Smiliarly, patients taking HMG-CoA reductase inhibitors (statins) at the time of admission or those who had a documented history of hypercholesterolemia were classified as having dyslipidemia. Patients with a first-degree family member with a diagnosis of CAD were categorized as having a positive family history of CAD. All participants in the study were Caucasian and of European origin.

3.2 Diagnosis of Glucose Metabolism

In patients without a previous diagnosis of T2DM, an evaluation of their glucose metabolism was carried out with FPG, a standard two-hour OGTT and HbA1c. After an overnight fast of at least 10 hours, measurements of FPG and HbA1c were obtained, followed by ingestion of a solution containing 75g glucose. Two hours after ingesting the glucose solution, the 2hPG was obtained. Measurements of glucose metabolism were performed during hospitalization, preferably on admission days three to five, and then repeated at least three months after discharge. All samples collected for venous plasma glucose measurements were centrifuged and analyzed immediately after blood collection. Glucose levels were determined using reagents, calibrators and Vitros 250/950 analyzers from Ortho Clinical Diagnostics

(Rochester, NY, USA) and HbA1c levels were determined using reagents, calibrators and a Cobas c311 analyzer (Roche, Mannheim, Germany).

After obtaining glucose metabolism measurements during hospitalization and three months later, each patient was classified as having NGM, prediabetes or T2DM based on all six measurments. Classifications were determined according to WHO or ADA criteria. According to WHO criteria, prediabetes was defined as either FPG 6.1-6.9 mmol/l (110-125 mg/dL) or 2hPG 7.8-11.0 mmol/l (140-199 mg/dL). According to ADA criteria, prediabetes was defined as HbA1c 5.7-6.4% (39-47 mmol/mol) or FPG 5.6-6.9 mmol/l (100-125 mg/dL). Both WHO and ADA criteria define T2DM as HbA1c ≥6.5% (48 mmol/mol), FPG ≥7.0 mmol/l (126 mg/dL) or 2hPG ≥11.1 mmol/l (200 mg/dL) with at least two measurements above the diabetes cut-off value in asymptomatic patients (ADA, 2012b; WHO, 2011; WHO, 2006). Therefore, patients with at least two of the six measurements, obtained during admission and at follow-up three months later, above the diabetes cut-off value were diagnosed with T2DM.

3.3 Carotid Ultrasound Imaging (Paper II)

Patients without a previous diagnosis of T2DM underwent a standardized ultrasound imaging of the carotid arteries to evaluate for cIMT and atherosclerotic plaques three months after discharge from the hospital. A Toshiba Aplio 300 system with a two-dimensional 6.8 MHz linear array transducer was used to perform all ultrasound imaging procedures by a trained sonographer. Standardized longitudinal B-mode images of the common carotid artery, bifurcation and internal carotid artery from the near and far wall in both carotid arteries were examined. The lateral extent of the common carotid segment was defined relative to the tip of the flow divider, which is normally the most clearly defined anatomical reference in the proximity of the carotid bifurcation. The bifurcation and internal carotid segments were also defined by

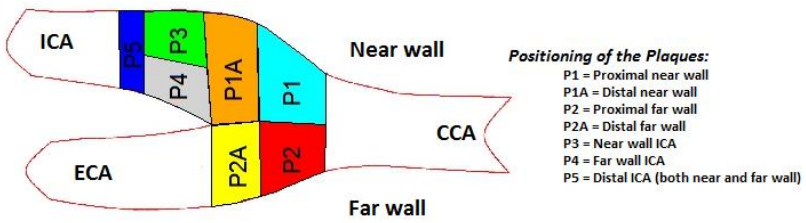

Figure 1. Simplified diagram of the common carotid artery bifurcation, external carotid artery and internal carotid artery.

using the tip of the flow divider. These segments were defined as: the near wall and far wall of the carotid bifurcation (BIF) beginning at the tip of the flow divider and extending 10 mm proximal to the flow divider tip; the near wall and far wall of the proximal 10 mm of the internal carotid artery (ICA); and the near wall and far wall of the arterial segment extending from 10 mm to 20 mm proximal to the tip of the flow divider into the common carotid artery (CCA) (Figure 1). A Meijers arc was applied to obtain standard imaging of the carotid arteries (Figure 2) (Bjornsdottir et al., 2014).

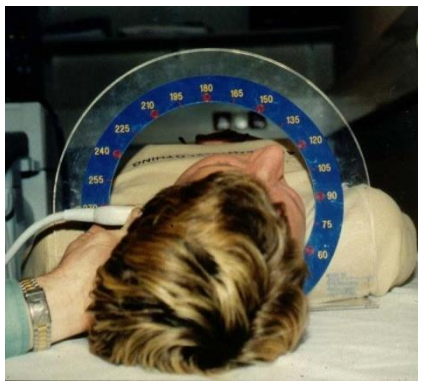

Figure 2. Meijers arc.

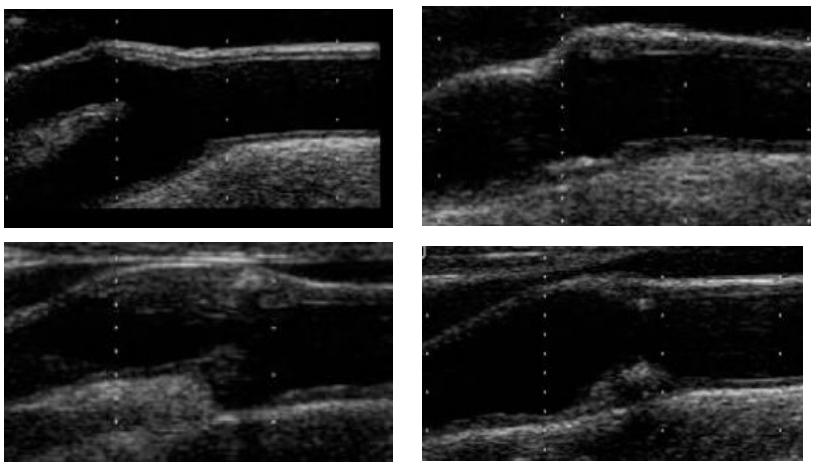

Figure 3. Carotid arteries without significant plaques (above) and with significant plaques (below).

A predefined 10 mm segment of the CCA, obtained from four angles at both carotid arteries, was used to assess for cIMT. The mean cIMT measurement of the near and far walls were determined from a single image at each interrogation for both CCA. The mean cIMT values from these sites comprised the cIMT outcome parameter.

Any atherosclerotic plaques in the carotid artery, evaluated from segments of the BIF and ICA extending 10 mm proximal and distal from the

tip of the flow divider, were categorized as significant lesions or not. The most severe lesion per segment was assessed (Sturlaugsdottir et al., 2016). Patients with at least one clear and easy to visualize atherosclerotic plaque, with intima media thickness of at least twice the thickness of adjacent sites, causing at least some diameter reduction of the vessel lumen, were classified as having significant plaque (Figure 3).

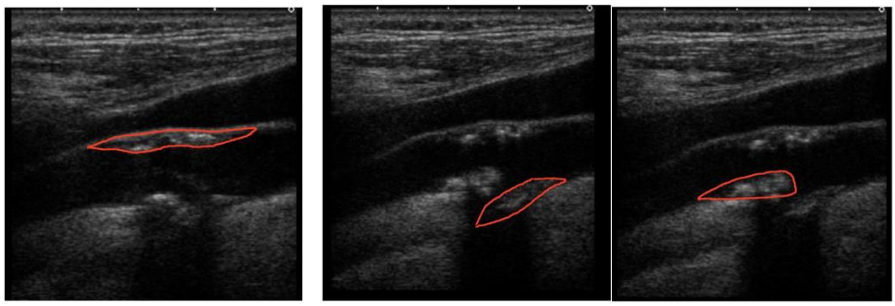

Figure 4. Significant plaque seen in the internal carotid artery with atherosclerotic plaque bounderies idendified with a red dotted line to calculate total plaque area.

To assess the atherosclerotic plaque quantitatively, Artery Measurements System software (v.2.02.) was applied to calculate the plaque area of all visible plaques in the BIF and ICA segments (Bjornsdottir et al., 2014). An isolated thickening at least double the adjacent normal cIMT by visual assessment was defined as an atherosclerotic plaque. The atherosclerotic plaque boundaries were traced with a cursor on the computer screen and the area, calculated in mm^2, for each plaque was automatically computed by the software (Figure 4). The total plaque area (TPA) was calculated by summing the area of all plaques identified. (Bjornsdottir et al., 2014).

3.4 Severity of Coronary Atherosclerosis (Paper II & III)

The majority of patients underwent coronary angiography during hospital admission. Coronary arteries with reduction of more than 70% of the coronary artery lumen were defined as having significant stenosis and patients were classified as having 0-, 1-, 2- or 3-vessel disease. Gensini score was also applied to evaluate the coronary artery disease burden and severity, by the degree of lumen reduction and the importance of the lesion's location (Gensini, 1983).

3.5 Paper I

In paper I, 250 patients admitted with ACS without previous diagnosis of T2DM underwent glucose metabolic measurement by HbA1c, FPG and 2hPG by standard OGTT, during admission and at 3-month follow-up. To follow WHO and ADA criteria for diagnosis of T2DM, at least two measurements above the cut-off value for diabetes were required to diagnose patients with T2DM. Patients with only one value above the diabetic cut-off value or at least one measurement above the cut-off value for prediabetes were diagnosed as prediabetic. Patients with all six measurements within normal limits were classified as having NGM.

3.6 Paper II

In paper II, 245 patients admitted with ACS without a previous history of T2DM underwent glucose metabolic measurements with HbA1c, FPG and 2hPG following standardized OGTT, during admission and at 3-month follow-up. Diagnosis of T2DM and prediabetes were based on ADA criteria. Evaluation of glucose metabolism was performed and classified as outlined for paper I. In addition, these patients underwent standardized ultrasound imaging of their bilateral carotid arteries for evaluation of atherosclerotic plaques and cIMT as well as measurement of the total plaque area in both carotid arteries.

3.7 Paper III

In paper III, a total of 372 patients who were admitted with ACS were consecutively included. Patients without prior history of T2DM were evaluated for possible dysglycemia with HbA1c, FPG and 2hPG following standard OGTT, during admission and at 3-month follow-up. As in paper II, diagnosis of dysglycemia was based on ADA criteria. Evaluation of glucose metabolism among patients without prior history of T2DM was performed and classified as outlined for paper I. Patients with known T2DM (kT2DM) were classified as such. Patients without a previous diagnosis of T2DM also underwent standardized ultrasound imaging of their carotid arteries to evaluate atherosclerotic plaque burden. Patients were followed for clinical end-points for a mean of 2.9 years. The clinical outcome parameters were combined, including all-cause death and MI as well as major adverse cardiac events (MACE), including all-cause mortality, MI, stroke, congestive heart failure requiring hospitalization and unstable angina requiring percutaneous coronary intervention. Differences in clinical event rates were then evaluated among patients with kT2DM, nT2DM, prediabetes and NGM and among patients with increased TPA in their carotid arteries.

3.8 Statistical Analysis

Normally distributed continuous variables were presented as means and standard deviation (SD) while non-normal distributed continuous variables were presented as median and interquartile range (IQR). Categorical variables were presented as percentage.

In paper I, the two-sample t-test was applied to estimate differences in continuous variables, Pearson's correlation coefficient was calculated, and significance of correlations was assessed with t-test. Receiver-operating-characteristic (ROC) curves and the area under the curve (AUC) were calculated to estimate the diagnostic capacity of HbA1c, FPG and 2hPG to detect T2DM. The optimal cut-off values were identified at the longest perpendicular distance from the diagonal line.

In papers II and III, the comparison between NGM, prediabetes, nT2DM and kT2DM (paper III) for continuous and categorical variables were made with analysis of variance or Kruskal Wallis test and chi-square test, respectively.

In paper II, the odds ratio (OR) of having significant plaque in the carotid arteries, with HbA1c, FPG and 2hPG as predictors, was found with multivariable logistic regression models. General linear regression models were used to estimate the association between TPA and risk factors for atherosclerosis, both unadjusted and adjusted for glucometabolic factors and conventional atherosclerotic risk factors, including age, gender, hypertension, hypercholesterolemia, smoking status and BMI. Other baseline variables did not affect the outcome in the multivariable logistic regression or linear regression models.

In paper III, to detect the association between glucometabolic status and clinical events, a multiple Cox proportional hazard regression analysis was applied. Adjustments were made for the following risk factors: age, gender, hypertension, hypercholesterolemia, smoking status, and BMI. Other baseline variables did not affect the outcome in multivariate analysis. Results from the multivariate analysis were reported as HR with 95% confidence intervals (CI). Kaplan-Meier curves were created for all-cause mortality or MI and MACE, including all-cause mortality, MI, stroke, congestive heart failure requiring hospitalization and unstable angina requiring percutaneous coronary intervention. Finally, Poisson regression was used to compare event-rates between glucometabolic groups. The level of statistical significance was set at $p<0.05$. Statistical analysis was executed by using R software, version 3.2.2 and 3.4.2 (R Core Team, 2016).

4 Results

Initially, 533 patients who were admitted to the coronary care unit for ACS during the study period were consecutively considered for inclusion in the study. Among these, 90 patients were discharged from the hospital before the OGTT could be performed and 60 refused participation. After inclusion, 10 patients withdrew their consent for participation in the study. Thus, 373 patients were included in the study (Figure 5).

In paper I, 100 patients were excluded due to prior diagnosis of T2DM, 18 patients did not return for the 3-month repeat glucose metabolism measurements and therefore did not complete the study protocol, while three died and one had a stroke. Additionally, one patient was prescribed metformin before discharge and therefore excluded. Hence, a total of 250 patients comprised the study population in paper I.

In paper II, 100 patients were excluded with prior diagnosis of T2DM, 24 patients did not undergo ultrasound examination of the carotid arteries, three patients died, and one had a stroke. The remaining 245 patients comprised the study population in paper II.

In paper III, one patient was lost to follow-up with the study population consisting of the remaining 372 patients. Of note, one patient was initially wrongly classified as kT2TM and later re-classified as nT2DM in paper III.

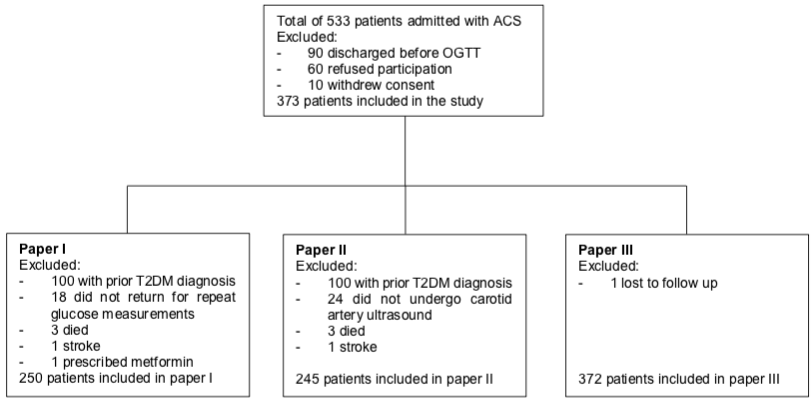

Figure 5. Flowchart demonstrating the study population of each paper.

4.1 Diagnosis of Dysglycemia in Acute Coronary Syndromes

In paper I, the mean age was 64.0 (SD 10.9) years and 78.0% were male (Table 2). FPG was found to be significantly lower at admission, 5.3 mmol/l (95 mg/dL) compared to 5.5 mmol/l (99 mg/dL) at follow-up ($p<0.005$) while 2hPG was significantly higher at admission, 7.8 mmol/l (140 mg/dL) compared to 6.7 mmol/l (121 mg/dL) at follow-up ($p<0.005$). No significant difference was detected for HbA1c at admission and at follow-up (5.4% [36 mmol/mol] compared to 5.5% [37 mmol/mol], respectively; $p=0.34$). Glucose measurements made on days 2, 3, 4, 5 and 6 or later after admission were completed among 4.4%, 24.8%, 30.8%, 26.0% and 14.0% of patients, respectively. No significant difference was found between measurement days and in the results of FPG and 2hPG. The correlation between glucose metabolic measurements during admission and at follow-up were 0.63, 0.60 and 0.50 for FPG, 2hPG and HbA1c, respectively ($p<0.005$).

Table 2. Baseline characteristics of patients included in paper I.

	Patients (n=250)
Age, years (SD)	64.0 (10.9)
Male sex, % (n)	78.0% (195)
Hypertension[a], % (n)	56.4% (141)
- Mean SBP, mmHg (SD)	139 (23)
- Mean DBP, mmHg (SD)	77 (13)
Hypercholesterolemia[b], % (n)	46% (115)
History of smoking[c], % (n)	73.6% (184)
- Mean pack per year (SD)	26.7 (20.7)
Family history of CHD[d], % (n)	66.0% (165)
Previous history of ACS, % (n)	33.2% (83)
BMI, kg/m^2 (SD)	28.6 (4.2)
Waist-to-hip ratio, cm (SD)	0.98 (0.07)
UAP, % (n)	30.0% (75)
NSTEMI, % (n)	40.8% (102)
STEMI, % (n)	29.2% (73)

SD: standard deviation, SBP: systolic blood pressure, DPB: diastolic blood pressure, CHD: coronary heart disease, BMI: body mass index, UAP: unstable angina pectoris, NSTEMI: non-ST elevation myocardial infarct, STEMI: ST elevation myocardial

[a]History of hypertension or is on antihypertensive medication.
[b]History of hypercholesterolemia or is on lipid lowering medication.
[c]History of being a current or previous smoker.
[d]First degree relative with history of coronary heart disease

During admission, 3%, 5% and 13% of patients were found to be above the diagnostic cut-off value for T2DM, based on HbA1c, FPG and 2hPG respectively. Similarly, 3%, 5% and 8% were measured above the diagnostic cut-off value of T2DM by HbA1c, FPG and 2hPG, respectively, at follow-up

three months later. Based on the ADA and WHO diagnostic criteria for T2DM, a total of 18 patients, 7.2% of the study population, were diagnosed with T2DM.

The reference to diagnose T2DM was at least two measurements out of the six above the diagnostic cut-off point for T2DM. This was the prerequisite for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) calculation.

During admission the sensitivity of HbA1c, FPG and 2hPG to diagnose T2DM was 33.3%, 61.1% and 77.8%, respectively. The specificity was found to be 100%, 99.6% and 94.3% for HbA1c, FPG and 2hPG, respectively. At follow-up the corresponding values for sensitivity were 27.8%, 61.1% and 72.2% and the specificity was 99.0%, 99.6% and 97.0% for HbA1c, FPB and 2hPG, respectively (Table 3).

During admission the PPV of HbA1c, FPG and 2hPG to diagnose T2DM was 100%, 91.7% and 51.9%, respectively, and the NPV 94.9%, 97.0% and 98.2% for HbA1c, FPG and 2hPG, respectively. At follow-up the corresponding PPV was found to be 71.4%, 91.7% and 65.0% and the NPV was 94.7%, 97.0% and 97.8% for HbA1c, FPB and 2hPG, respectively (Table 3).

When the results from all six measurements were combined, the sensitivity and NPV were both 100% while specificity and PPV were 89.7% and 44.2%, respectively. The ESC guidelines currently recommend initially obtaining HbA1c and FPG and if that is inconclusive, OGTT (including FPG and 2hPG) should be done at follow-up (Ryden et al., 2014). When those recommendations were applied to the participants in our study, the sensitivity to diagnose T2DM and NPV was 100% while the specificity and the PPV were 96.1% and 66.7%, respectively. If the HbA1c was discarded and only the results from OGTT at admission and at follow-up were used, the sensitivity and NPV remained 100% but the specificity and the PPV found to be 90.5% and 45.0%, respectively. Finally, when the OGTT was discarded and only the results from FPG and HbA1c obtained at admission and during follow-up, the sensitivity and the NPV fell to 88.9% and 99.1%, respectively, while the specificity and the PPV rose to 98.3% and 80.0%, respectively (Table 3).

Table 3. Sensitivity, specificity, PPV and NPV of different measurements for diagnosis of T2DM

	During admission			At follow up after 3 months			Combined results			
	HbA1c	FPG	2hPG	HbA1c	FPG	2hPG	Complete protocol*	ESC guidelines†	OGTT‡	HbA1c & FPG§
Sensitivity	33.3%	61.1%	77.8%	27.8%	61.1%	72.2%	100%	100%	100%	88.9%
Specificity	100%	99.6%	94.3%	99.0%	99.6%	97.0%	89.7%	96.1%	90.5%	98.3%
PPV	100%	91.7%	51.9%	71.4%	91.7%	65.0%	44.2%	66.7%	45.0%	80.0%
NPV	94.9%	97.0%	98.2%	94.7%	97.0%	97.8%	100%	100%	100%	99.1%

FPG: fasting plasma glucose, 2hPG: 2-hour plasma glucose, ESC: European Society of Cardiology, OGTT: oral glucose tolerance test, PPV: positive predictive value, NPV: negative predictive value.
*HbA1c, FPG and 2hPG during admission and at follow up three months later
†HbA1c and FPG during admission and FPG and 2hPG at follow up three months later if negative results at admission
‡FPG and 2hPG during admission and at follow up three months later
§HbA1c and FPG during admission and at follow up three months later

4.2 Diagnostic Capacity of Different Glucose Metabolic Measurements

ROC curves were constructed to analyze the diagnostic capacity of HbA1c, FPG and 2hPG to detect T2DM. At admission, the AUC for HbA1c, FPG and 2hPG was 0.93, 0.92 and 0.95, respectively (Figure 6, top). At follow-up, the corresponding AUC values were 0.88, 0.90 and 0.93 for HbA1c, FPG and 2hPG, respectively (Figure 6, bottom). According to the ROC analysis the optimal cut off value to diagnose T2DM with HbA1c is 6.0% (42 mmol/mol) during admission, with sensitivity of 77.8% and specificity of 94.6%, and 5.9% (41 mmol/mol) at follow-up, with sensitivity of 72.2% and specificity of 90.9%. Similarly, according to ROC calculations the optimal cut-off value to diagnose T2DM with FPG is 5.9 mmol/l (106 mg/dL) during admission, with sensitivity of 83.3% and specificity of 93.1%, and 6.3 mmol/l (113 mg/dL) at follow-up, with sensitivity of 77.8% and specificity of 93.5%. Corresponding values for 2hPG are 11.6 mmol/l (209 mg/dL) during admission, with sensitivity of 87.5% and specificity of 96.0%, and 8.1 mmol/l (146 mg/dL) at follow-up, with sensitivity of 94.4% and specificity of 84.0%.

4.3 Prediabetes

A total of 53.6% of the study cohort was found to have prediabetes, when the ADA criteria with HbA1c and FPG during admission and at follow-up were applied, while 39.2% had NGM. Of those found to have prediabetes, 53.0% were detected with elevated HbA1c and 77.6% with IFG, while 30.6% had both HbA1c and IFG elevated. Fewer were found to have prediabetes according to WHO criteria, using the OGTT (IFG and IGT) during admission and at follow-up, with 44.4% of the study cohort having prediabetes and 48.4% having NGM. Of those found to have prediabetes, 31.5% were identified with IFG and 86.5% with IGT, while 18.0% were identified with both IFG and IGT.

4.4 Atherosclerotic Plaque Burden

In paper II, the mean age was 64.0 (SD 10.9) years with males comprising 78.0% of the study cohort (Table 4). NGM, prediabetes or nT2DM was identified in 28.6%, 64.1% and 7.3% of patients, respectively. Significant atherosclerotic plaque was found in 62% of patients in the study cohort. The mean cIMT and TPA in the study cohort was 0.90 mm (SD 0.15) and 103.3 mm^2 (SD 64.7), respectively. In comparison, prevalence of significant plaques in an age- and gender-matched control group from the Icelandic general population was 20% with mean TPA of 39.1 mm^2 (Sturlaugsdottir et al., 2016).

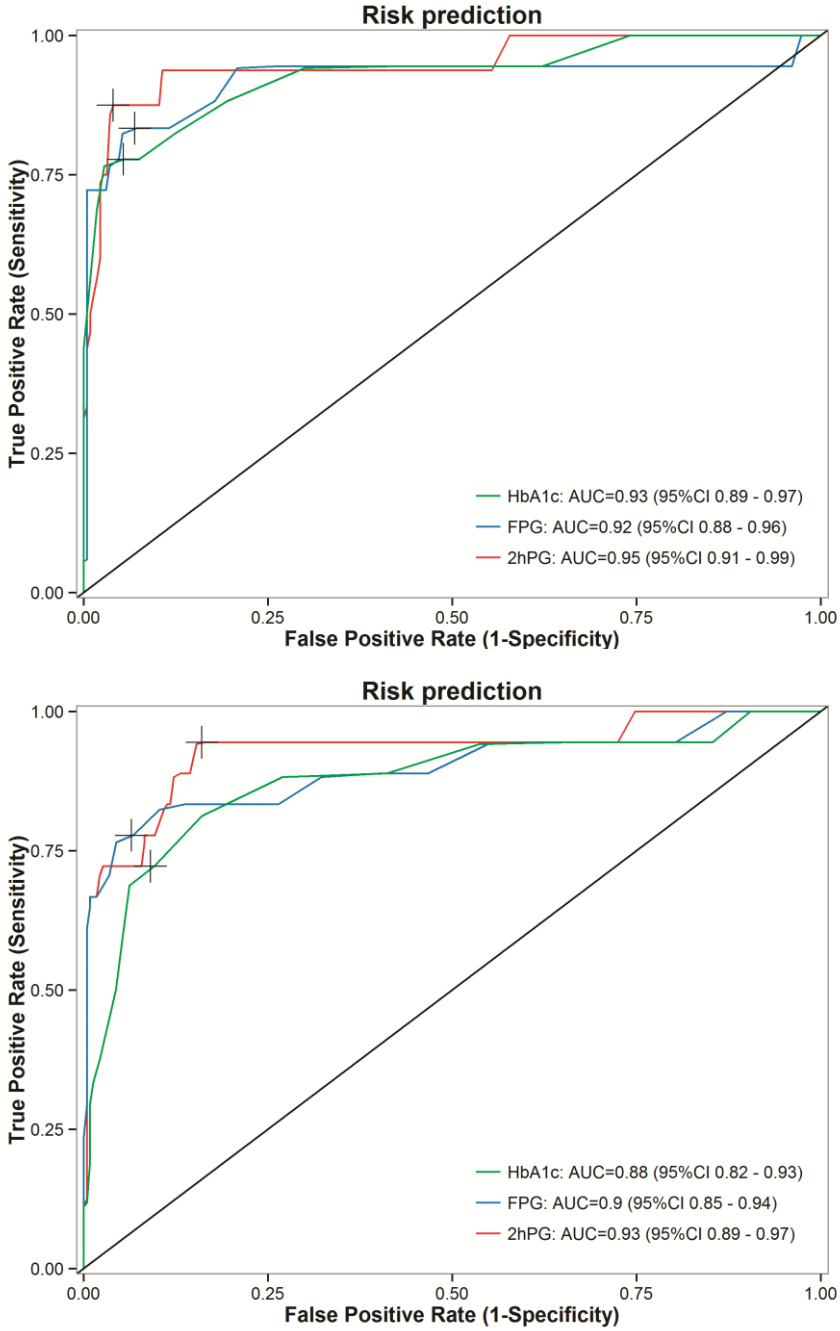

Figure 6. Receiver-operating-characteristic curves. The ability of HbA1c, fasting plasma glucose and 2-hour plasma glucose to diagnose T2DM during admission (above) and at follow-up three months later (below).

Atherosclerotic plaques were found in 48.5%, 66.9% and 72.2% of patients with NGM, prediabetes and nT2DM, respectively. In patients with NGM, prediabetes and nT2DM, TPAs were calculated to be 86.8 mm^2 (SD 57.2), 108.9 mm^2 (SD 66.1) and 118.0 mm^2 (SD 70.7), respectively, with significant differences between glucometabolic groups (p<0.04). Compared to patients with NGM, the incremental increase in TPA was 25.5% and 35.9% among patients diagnosed with prediabetes and T2DM, respectively.

In addition, a significant difference was found between different glucometabolic groups and the following factors: BMI (p<0.01), waist-to-hip ratio (p=0.02), smoking status (p=0.03), high-sensitivity C-reactive protein (hS-CRP; p<0.01), homeostatic model assessment of insulin resistance (HOMA-IR; p<0.01), number of diseased coronary arteries (p=0.03) and Gensini score (p=0.04; Table 4). Finally, patients with IGT, either alone or with IFG as well, were found to have increased TPA compared to patients with IFG alone (p<0.01; Table 5).

A significant association was seen with cIMT and increased age (for every 5 years) and male gender, 0.030 mm (SE; 0.004, p<0.01) and 0.057 mm (SE; 0.022, p=0.01), respectively, but no significant association was detected between cIMT and different glucometabolic groups (p=0.28).

4.5 Glucose Metabolic Measurements and Carotid Plaque

Patients with elevated 2hPG (IGT) were found to be at increased risk of having significant plaque in their carotid arteries, both during admission and at follow-up with unadjusted OR of 2.37 (95% CI 1.36 – 4.18) and 2.25 (1.21 – 4.35), respectively. When adjusted for conventional risk factors for atherosclerosis (age, gender, hypertension, hypercholesterolemia, smoking and BMI), the OR for patients with elevated 2hPG of having significant plaque in the carotid arteries was 1.92 (95% CI 1.05 – 3.55) and 1.51 (0.74 – 3.18) during admission and at follow-up, respectively. Neither patients with elevated FPG (IFG) nor HbA1c, during admission or at follow-up, were found to have significantly increased risk, unadjusted or adjusted, of having atherosclerotic plaque in the carotid arteries (Table 6a).

Table 4. Pertinent characteristics of patients in paper II divided according to their glucose metabolism.

	NGM (n=70)	Prediabetes (n=157)	DM (n=18)	p-value
Age, years (SD)	64.0 (12.0)	63.9 (10.2)	65.0 (12.5)	0.92
Gender				0.54
- Male	57 (81.4%)	119 (75.8%)	15 (83.3%)	
- Female	13 (18.6%)	38 (24.2%)	3 (16.7%)	
Glucose metabolism				
- At admission:				
HbA1c, % (SD)	5.1 (0.4)	5.4 (0.3)	6.5 (1.0)	<0.01
FPG, mmol/l (SD)	4.8 (0.4)	5.3 (0.6)	7.0 (1.5)	<0.01
2hPG, mmol/l (SD)	6.3 (0.9)	7.9 (2.1)	13.3 (3.3)	<0.01
- At follow up:				
HbA1c, % (SD)	5.2 (0.3)	5.5 (0.4)	6.1 (0.5)	<0.01
FPG, mmol/l (SD)	5.0 (0.4)	5.6 (0.5)	7.1 (1.4)	<0.01
2hPG, mmol/l (SD)	5.1 (1.0)	6.8 (2.3)	11.9 (3.2)	<0.01
hs-CRP, mg/L median (IQR)	0.7 (0.5, 1.3)	1.4 (0.7, 2.7)	1.4 (0.9, 1.4)	<0.01
Insulin, mU/L (SD)	10.47 (6.58)	13.51 (8.90)	16.42 (11.11)	0.07
HOMA-IR, units (SD)	2.33 (1.56)	3.40 (2.41)	4.96 (3.86)	<0.01
TPA, mm^2 (SD)	86.8 (57.2)	108.9 (66.1)	118.0 (70.7)	0.04
Grey-scale median (SD)	38 (11)	36 (10)	36 (11)	0.69
Mean cIMT, mm (SD)	0.87 (0.15)	0.91 (0.14)	0.90 (0.15)	0.28
Carotid plaque				0.13
- No plaque	36 (51.5%)	52 (33.1%)	5 (27.8%)	
- Significant plaque	34 (48.5%)	105 (66.9%)	13 (72.2%)	
BMI, kg/m^2 (SD)	27.8 (4.0)	28.8 (4.1)	31.4 (4.8)	<0.01
WHR (SD)	0.96 (0.07)	0.98 (0.08)	1.01 (0.06)	0.02
Smoking status:				0.03
- Never	44.3%	28.0%	22.2%	
- Previous	44.3%	44.0%	44.5%	
- Current	11.4%	28.0%	33.3%	
FH of CAD[a]	67.1%	64.3%	72.2%	0.78
Hypercholesterolemia	48.6%	43.9%	55.6%	0.54
Hypertension	52.9%	57.3%	66.7%	0.60
Previous CAD	35.7%	30.6%	50.0%	0.22
SBP, mmHg (SD)	139 (22)	139 (23)	137 (18)	0.93
DBP, mmHg (SD)	77 (12)	78 (13)	75 (12)	0.71
ACS				0.57
- UAP	31.4%	28.7%	38.9%	
- NSTEMI	45.7%	38.9%	33.3%	
- STEMI	22.9%	32.4%	27.8%	
CAD[b]				0.03
- 0-vessel	10.8%	7.1%	0%	
- 1-vessel	50.0%	35.4%	33.3%	
- 2-vessel	19.6%	37.0%	27.8%	
- 3-vessel	19.6%	20.5%	38.9%	
Gensini score (SD)	38.2 (37.5)	39.1 (32.4)	60.0 (36.3)	0.04

NGM: normal glucose metabolism, T2DM: type 2 diabetes mellitus, SD: standard deviation, FPG: fasting plasma glucose, 2hPG: 2-hour plasma glucose, hs-CRP: high-sensitivity C-reactive protein, IQR: interquartile range, HOMA-IR: homeostatic model assessment insulin resistance, TPA: total plaque area, cIMT: carotid intima-media thickness, BMI: body mass index, WHR: waist to hip ratio, FH: family history, CAD: coronary artery disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, ACS: acute coronary syndrome, UAP: unstable angina pectoris, NSTEMI: non-ST elevation myocardial infarct, STEMI: ST elevation myocardial infarct
[a]CAD with 1st degree family member, [b]≥70% of lumen reduction

Table 5. Carotid plaque burden among patients with IFG, IGT and combination of IFG and IGT.

	IFG (n=50)	IGT (n=42)	IFG & IGT (n=52)	p-value
TPA, mm^2 (SD)	87.8 (53.1)	127.4 (70.4)	123.1 (70.9)	<0.01
Mean cIMT, mm (SD)	0.88 (0.16)	0.91 (0.13)	0.92 (0.13)	0.30
Carotid plaque				0.67
- No plaque	36.0%	28.6%	28.8%	
- Significant plaque	64.0%	71.4%	71.2%	

IFG: impaired fasting glucose, IGT: impaired glucose tolerance, SD: standard deviation, TPA: total plaque area, cIMT: carotid intima-media thickness.

Similarly, elevated 2hPG (IGT) was also found to be significantly associated with increased TPA during admission and at follow-up, with, on average, 35.0 mm^2 (SE 8.3, p<0.01) and 37.0 mm^2 (9.2 SE, p<0.01) increase in TPA, respectively, compared with patients with NGM. Elevated HbA1c during admission was also associated with significantly increased TPA, 27.3 mm^2 (SE 10.3, p<0.01), but not at follow-up, 14.5 mm^2 (SE 9.4, p<0.12). No association was found between elevated FPG (IFG) and TPA. After adjusting for conventional risk factors for atherosclerosis, the multiple regression model showed that patients with elevated 2hPG (IGT) were at significantly increased risk of having increased TPA, with, on average, 25.5 mm^2 (SE 7.6, p<0.01) and 24.0 mm^2 (SE 8.8, p<0.01) greater TPA during admission and at follow-up, respectively, compared to those classified with NGM (Table 6b).

a) The OR of having significant plaque in the carotid arteries of patients diagnosed with dysglycemia based on different glucometabolic assessments compared to normal glucose level.				
	Unadjusted OR, (95% CI)	p-value	[a]Adjusted OR, (95% CI)	p-value
HbA1c				
- Dysglycemia during admission	1.31 (0.69 – 2.57)	0.41	0.89 (0.44 – 1.93)	0.74
- Dysglycemia at follow up	1.74 (0.96 – 3.27)	0.07	1.58 (0.82 – 3.13)	0.18
FPG				
- Dysglycemia during admission	1.46 (0.80 – 2.76)	0.23	1.52 (0.77 – 3.08)	0.24
- Dysglycemia at follow up	1.44 (0.85 – 2.46)	0.18	1.61 (0.89 – 2.96)	0.12
2hPG				
- Dysglycemia during admission	**2.37 (1.36 – 4.18)**	**<0.01**	**1.92 (1.05 – 3.55)**	**0.04**
- Dysglycemia at follow up	**2.25 (1.21 – 4.35)**	**0.01**	1.51 (0.74 – 3.18)	0.26
b) Difference in TPA among patients diagnosed with dysglycemia based on different glucometabolic assessment compared to normal glucose level.				
	Unadjusted Estimate (SE)	p-value	[a]Adjusted Estimate (SE)	p-value
HbA1c				
- Dysglycemia during admission	**27.3 (10.3)**	**<0.01**	15.1 (9.4)	0.11
- Dysglycemia at follow up FPG	14.5 (9.4)	0.12	13.2 (8.5)	0.12
FPG				
- Dysglycemia during admission	6.3 (9.8)	0.52	7.3 (8.9)	0.41
- Dysglycemia at follow up	1.67 (8.5)	0.84	6.9 (7.8)	0.38
2hPG				
- Dysglycemia during admission	**35.0 (8.3)**	**<0.01**	**25.5 (7.6)**	**<0.01**
- Dysglycemia at follow up	**37.0 (9.2)**	**<0.01**	**24.0 (8.8)**	**<0.01**

OR: odds-ratio, CI: confidence interval, SE: standard error, 2hPG: 2-hour plasma glucose, FPG: fasting plasma glucose.
[a]Adjusted for age, gender, hypertension, hypercholesterolemia, smoking status, and BMI

Table 6. Carotid plaque burden by different glucose methods.

4.6 Glucose Metabolic Derangements and Carotid Plaque Burden

Patients diagnosed with prediabetes or nT2DM were found to have unadjusted OR of 2.14 (95% CI; 1.21 - 3.81) and 2.75 (95% CI; 0.93 – 9.34), respectively, of having significant atherosclerotic plaque in the carotid arteries compared to patients with NGM. Having dysglycemia (prediabetes or nT2DM) was significantly associated with having a significant carotid atherosclerotic plaque, compared to patients with NGM (unadjusted OR 2.19 [95% CI; 1.25 – 3.87]; Table 7a). Two models were constructed with multiple logistic regression analysis. First, when adjustments were made for conventional risk factors for atherosclerosis where the adjusted ORs of having significant atherosclerotic plaque for patients diagnosed with prediabetes, nT2DM or dysglycemia, compared to NGM, were 2.14 (95% CI 1.13 – 4.12), 2.50 (0.75 – 9.51) and 2.17 (95% CI 1.15 – 4.15), respectively

(Table 7a). Secondly, adjustments were made for conventional atherosclerotic risk factors and different glucometabolic measurements (FPG, 2hPG and HbA1c) to evaluate whether these variables could explain this association. The risk of significant plaque for both prediabetes and dysglycemia remained statistically significant when adjusted for atherosclerotic risk factors and HbA1c. However, when adjusted for atherosclerotic risk factors and FPG, the statistical significance for prediabetes and dysclycemia of having significant atherosclerotic plaque compared to NGM was lost (OR 1.94 [95% CI 0.89 – 4.29] and 1.93 [95% CI 0.89 – 4.27], respectively). Similarly, when adjusted for atherosclerotic risk factors and 2hPG, the ORs for prediabetes and dysglycemia were attenuated to 1.78 (95% CI 0.83 – 3.88) and 1.77 (95% CI 0.83 – 3.84), respectively.

By regression analysis (Table 7b) patients with prediabetes, nT2DM or dysglycemia (prediabetes or nT2DM) were associated with increased TPA of 22.1 mm^2 (SE: 9.3, p=0.02), 31.2 mm^2 (SE: 17.0, p=0.07) and 23.0 mm^2 (SE 9.2, p=0.01), respectively, compared to patients with NGM. After adjusting for conventional risk factors for atherosclerosis, in a multiple variable regression model, both prediabetes and dysglycemia were associated with increased mean TPA of 22.5 mm^2 (SE: 8.5, p<0.01) and 23.1 mm^2 (SE 8.4, p<0.01), respectively, compared to patients with NGM. When adjustments were made for atherosclerotic risk factors and HbA1c, the TPA remained significantly increased in both prediabetic and dysglycemic patients compared to NGM patients. Similarly, when adjusted for atherosclerotic risk factors and FPG, the TPA remained significantly increased in both prediabetic and dysglycemic patients compared to NGM patients. However, when additionally adjusted for 2hPG, the differences in patients with prediabetes or dysglycemia compared to NGM patients were attenuated to 9.6 mm^2 (SE: 9.9, p=0.34) and 10.0 mm^2 (SE 10.0, p=0.32), respectively (Table 7b). This was a reduction in effect sizes by 57.3% and 56.7% for prediabetes and dysglycemia, respectively.

Table 7. Glucose metabolic derangements and carotid plaque burden.

a) The OR of having significant plaque in the carotid arteries among patients diagnosed with prediabetes, T2DM or dysglycemia defined as any of abnormal 2hPG, HbA1C and fasting glucose.						
	Model 1		Model 2		Model 3	
	Unadjusted OR (95% CI)	p-value	[a]Adjusted OR (95% CI)	p-value	[b]Adjusted OR (95% CI)	p-value
Prediabetes	**2.14 (1.21 – 3.81)**	**0.01**	**2.14 (1.13 – 4.12)**	**0.02**	1.78 (0.83 – 3.88)	0.14
T2DM	2.75 (0.93 – 9.34)	0.08	2.50 (0.75 – 9.51)	0.15	2.18 (0.44 – 12.03)	0.35
Dysglycemia	**2.19 (1.25 – 3.87)**	**<0.01**	**2.17 (1.15 – 4.15)**	**0.02**	1.77 (0.83 – 3.84)	0.14
b) Difference in TPA among patients diagnosed with prediabetes, T2DM and dysglycemia defined as any of abnormal 2hPG, HbA1C and fasting glucose.						
	Model 1		Model 2		Model 3	
	Unadjusted Estimate mm^2 (SE)	p-value	[a]Adjusted Estimate mm^2 (SE)	p-value	[b]Adjusted Estimate mm^2 (SE)	p-value
Prediabetes	**22.1 (9.3)**	**0.02**	**22.5 (8.5)**	**<0.01**	9.6 (9.9)	0.34
T2DM	31.2 (17.0)	0.07	29.4 (15.5)	0.06	1.1 (19.5)	0.95
Dysglycemia	**23.0 (9.2)**	**0.01**	**23.1 (8.4)**	**<0.01**	10.0 (10.0)	0.32

OR: odds ratio, CI: confidence interval, SE: standard deviation, T2DM: type 2 diabetes mellitus,
[a]Adjusted for age, gender, hypertension, hypercholesterolemia, smoking status, and BMI
[b]Adjusted for age, gender, hypertension, hypercholesterolemia, smoking status, BMI and 2hPG during admission and at follow up

4.7 Glucometabolic Status and Prognosis

In paper III, the mean age was 65.1 (SD 11.8) years and 75.8% of the study population were male. Patients diagnosed with NGM, prediabetes or nT2DM were 20.7%, 46.5% and 6.2% of the study cohort, respectively. The remaining 26.6% had previously been diagnosed with T2DM. As shown in Table 8 differences were found between glucometabolic groups with respect to age (p=0.01), smoking status (p=0.03), BMI (p<0.01), hypercholesterolemia (p<0.01), hypertension (p<0.01), previous CAD (p<0.01) and being on angiotensin converting enzyme inhibitor/angiotensin II receptor blocker (p<0.01) and calcium channel blockers (p<0.01) at discharge.

Table 8. Pertinent characteristics of patients in paper III divided according to their glucose metabolism.

	NGM (n=77)	Prediabetes (n=173)	nT2DM (n=23)	kT2DM (n=99)	p-value
Age, years (SD)	63.0 (12.4)	64.3 (10.7)	64.2 (11.9)	68.4 (12.4)	0.011
Gender					
- Male	83.1%	75.1%	78.3%	70.7%	0.288
- Female	16.9%	24.9%	21.7%	29.3%	
BMI, kg/m^2 (SD)	28.0 (4.0)	28.9 (4.2)	30.4 (4.8)	30.6 (5.3)	0.001
Smoking status					
- Never	42.9%	27.2%	26.1%	24.2%	
- Previous	44.2%	43.9%	39.1%	53.5%	0.025
- Current	13%	28.9%	34.8%	22.2%	
FH of CAD	67.5%	64.2%	65.2%	55.7%	0.386
Hypercholesterolemia	47.4%	42.8%	47.8%	74.7%	<0.001
Total cholesterol during follow up, mmol/l, mean (SD)	3.8 (0.9)	4.0 (0.9)	4.0(0.8)	4.0 (1.1)	0.326
Hypertension	51.3%	59.0%	56.5%	84.8%	<0.001
- SPB, mmHg (SD)	138 (20)	140 (23)	135 (18)	145 (21)	0.073
- DPB, mmHg (SD)	77 (12)	78 (13)	75 (11)	77 (12)	0.756
Previous CAD	35.5%	30.6%	39.1%	55.6%	0.001
ACS					
- UAP	29.8%	26.6%	34.8%	28.3%	
- NSTEMI	42.9%	38.7%	30.4%	54.5%	0.055
- STEMI	27.3%	34.7%	34.8%	17.2%	
Killip class					
- I	59.0%	60.0%	68.2%	47.9%	
- II	36.1%	33.6%	27.3%	49.3%	0.473
- III	4.9%	5.0%	4.5%	1.4%	
- IV	0.0%	1.4%	0.0%	1.4%	
Medications at discharge					
- ASA	92.9%	93.6%	95.7%	91.9%	0.894
- Other antiplatelet therapy*	75.3%	75.1%	78.3%	47.7%	0.988
- ACEi/ARB	45.5%	56.6%	69.6%	70.7%	0.005
- Beta-blocker	80.5%	90.2%	95.7%	87.9%	0.108
- CCB	9.1%	9.2%	13.0%	35.4%	<0.001
- Statin	97.4%	97.1%	100.0%	94.9%	0.576
- Oral diabetes medication	1.3%	0.6%	21.7%	69.7%	<0.001
- Insulin	0%	0%	0%	33.3%	<0.001
Extend of CAD (70% luminal narrowing					
- 0 vessel disease	11.7%	5.8%	0%	5.1%	
- 1 vessel disease	53.2%	37.2%	31.8%	27.3%	<0.001
- 2 vessel disease	16.9%	33.7%	36.4%	26.3%	
- 3 vessel disease	16.9%	19.2%	31.8%	31.3%	
- Not assessed	1.3%	4.1%	0%	10.1%	
Revascularization treatment					
- PCI	64.9%	68.8%	73.9%	58.6%	0.530
- CABG	11.7%	14.5%	8.7%	18.2%	
- Neither	23.4%	16.8%	17.4%	23.2%	

ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor blockers, ASA: acetylsalicylic acid, CCB: calcium channel blocker, ACS: acute coronary syndrome, BMI: body mass index, CABG: coronary artery bypass grafting, CAD: coronary artery disease, DPB: diastolic blood pressure, FH: family history, kT2DM: known type 2 diabetes mellitus, mm/l: mmoles per litre, NGM: normal glucose metabolism, NSTEMI: non-ST elevation myocardial infarct, nT2DM: new type 2 diabetes mellitus, PCI: percutaneous coronary intervention, SD: standard deviation, SPB: systolic blood pressure, STEMI: ST elevation myocardial infarct, UAP: unstable angina pectoris.
*clopidogrel, ticagrelor or prasugrel

Patients were followed on average for 2.9 years (range 2.3 – 4.1). During the follow-up period, 48 patients died or suffered MI and 76 patients had a MACE. For combined all-cause mortality or MI, the unadjusted HR was 7.1 (95% CI 0.9 – 54.0), 14.6 (95% CI 1.6 – 130.3) and 27.1 (95% CI 3.7 – 199.6) for prediabetes, nT2DM and kT2DM, respectively, compared to patients with NGM. For MACE, the unadjusted HR for prediabetes, nT2DM and kT2DM was 1.5 (95% CI 0.7 – 3.3), 3.1 (95% CI 1.1 – 8.4) and 4.2 (95% CI 2.0 – 9.1), respectively, compared to patients with NGM. By applying multiple Cox proportional hazard regression analysis, adjusting for conventional atherosclerotic risk factors (age, gender, hypertension, hypercholesterolemia, smoking status, and BMI) the HR for combined all-cause mortality or MI was 5.8 (95% CI 0.8 – 44.6), 10.9 (95% CI 1.2 – 98.3) and 14.9 (95% CI 2.0 – 113.7) for prediabetes, nT2DM and kT2DM, respectively, compared to patients with NGM. Similarly, the adjusted HR for MACE was 1.4 (95% CI 0.6 – 3.1), 2.9 (95% CI 1.0 – 8.0) and 3.3 (95% CI 1.5 – 7.6) for prediabetes, nT2DM and kT2DM, respectively, compared to patients with NGM (Table 9, Figure 7).

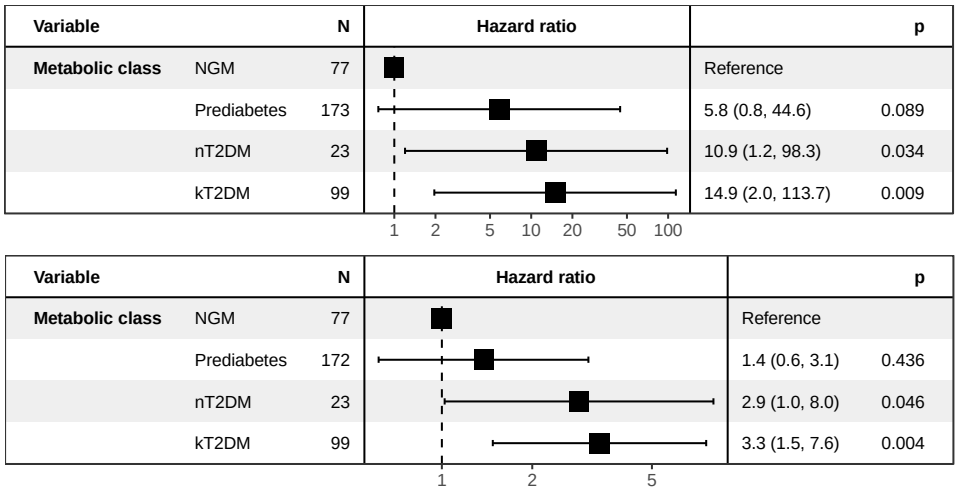

Figure 7. Forest plot for adjusted HR for death or MI (above) and MACE (below) by glucometabolic status.

Combined all-cause mortality or MI event rates per 1000 patient-years among patients with NGM, prediabetes, nT2DM and kT2DM were 4.2, 29.5, 60.3 and 114.2, respectively, with a statistically significant difference between glucometabolic groups ($p<0.01$). Likewise, a total of 36.0, 54.7, 113.9 and 163.6 MACE events per 1000 patient-years were ascertained among patients with NGM, prediabetes, nT2DM and kT2DM, respectively ($p<0.01$; Table 10).

Table 9. Risk of adverse outcomes between glucometabolic status groups.

	Unadjusted HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Death/MI						
- NGM	1.0	-	-	1.0	-	-
- Prediabetes	7.1	0.9 – 54.0	0.057	5.8	0.8 – 44.6	0.089
- nT2DM	**14.6**	**1.6 – 130.3**	**0.017**	**10.9**	**1.2 – 98.3**	**0.034**
- kT2DM	**27.1**	**3.7 – 199.6**	**0.001**	**14.9**	**2.0 – 113.7**	**0.009**
MACE						
- NGM	1.0	-	-	1.0	-	-
- Prediabetes	1.5	0.7 – 3.3	0.316	1.4	0.6 – 3.1	0.436
- nT2DM	**3.1**	**1.1 – 8.4**	**0.031**	**2.9**	**1.1 – 8.0**	**0.046**
- kT2DM	**4.2**	**2.0 – 9.1**	**<0.001**	**3.3**	**1.5 – 7.6**	**0.004**

CI: confidence interval, HR: hazard ratio, kT2DM: known type 2 diabetes, MACE: major adverse cardiac events, MI: myocardial infarction, NGM; normal glucose metabolism, nT2DM: new type 2 diabetes.

Patients diagnosed with IFG alone had the fewest events of all-cause mortality or MI, with a total of 5.9 events per 1000 patient-years, compared to 26.2, 63.2 and 34.2 among patients with both IFG and IGT, IGT alone and elevated HbA1c, respectively ($p<0.04$). No difference in MACE events was detected among different subgroups of patient categories with prediabetes ($p=0.15$; Table 11). Kaplan-Meier curves for glucometabolic status and combined all-cause mortality or MI and MACE, respectively, are shown in Figure 8.

The majority of STEMI patients (92%) were treated with urgent revascularization, primary percutaneous coronary intervention (PCI) (87%) or urgent coronary artery bypass graft (CABG) surgery (4.7%), and an invasive approach was used in 76% of NSTEMI patients (PCI 60% and CABG 16%). Upon admission, no patient was managed with intensive insulin treatment and no patient with prediabetes or nT2DM were treated with insulin during the follow-up period. At hospital discharge, oral diabetes medications were prescribed to 1.3%, 0.6%, 21.7% and 69.7% of patients with NGM, prediabetes, nT2DM and kT2DM, respectively. Oral diabetes medications were prescribed to 1.3%, 2.9%, 56.5% and 88.9% of patients with NGM, prediabetes, nT2DM and kT2DM, respectively, during the follow-up period. Metformin was prescribed to 43 patients, sulfonylureas to 27, dipeptidyl peptidase-4 (DDP-4) inhibitors to 11, SGLT2 inhibitors to 9, thiazolidinediones (TZD) to 3, GLP-1 inhibitors to 2 and insulin to 22 patients during the follow-up period.

Table 10. Events per 1000 patient years in different glucometabolic groups.

	NGM (n=77)	Prediabetes (n=173)	nT2DM (n=23)	kT2DM (n=99)	p-value
Death/MI	4.2	29.5	60.3	114.2	**<0.001**
Mean follow up years (range)	3.2 (2.3-3.7)	3.1 (0.4-4.1)	3.1 (0.7-3.7)	2.7 (0.1-3.7)	
MACE	36.0	54.7	113.9	164.6	**<0.001**
Mean follow up years (range)	3.0 (0.1-3.7)	3.0 (0-4.1)	2.9 (0.7-3.6)	2.5 (0-3.7)	

kT2DM: known type 2 diabetes, MACE: major adverse cardiac events, MI: myocardial infarction, NGM; normal glucose metabolism, nT2DM: new type 2 diabetes.

4.8 Carotid Atherosclerotic Plaque and Prognosis

Patients were divided into quartiles according to carotid TPA. In the lowest quartile, the TPA ranged from 0 – 56 mm^2, in the 2nd quartile the TPA ranged from 57 – 93 mm^2, from 94 – 137 mm^2 in the 3rd quartile and 138 - 333 mm^2 in the highest quartile. Among patients with TPA in the highest quartile the unadjusted HR for MACE was 2.8 (95% CI 1.09 – 7.11) compared to patients in the lowest quartile. However, after adjusting for conventional CVD risk factors a significant increase in HR by quartiles of TPA was no longer detected. No significant differences in risk for death or MI were detected between patients in different quartiles.

Table 11. Events per 1000 patient years between different prediabetes subgroups.

	HbA1c (n=20)	IFG (n=56)	IGT (n=46)	IFG & IGT (n=51)	p-value
Death/MI	34.2	5.9	63.2	26.2	**0.036**
MACE	76.5	24.6	56.2	80.7	0.153

HbA1c: Glycated hemoglobin, IFG: impaired fasting glucose, IGT: impaired glucose tolerance, MACE: major adverse cardiac events, MI: myocardial infarction

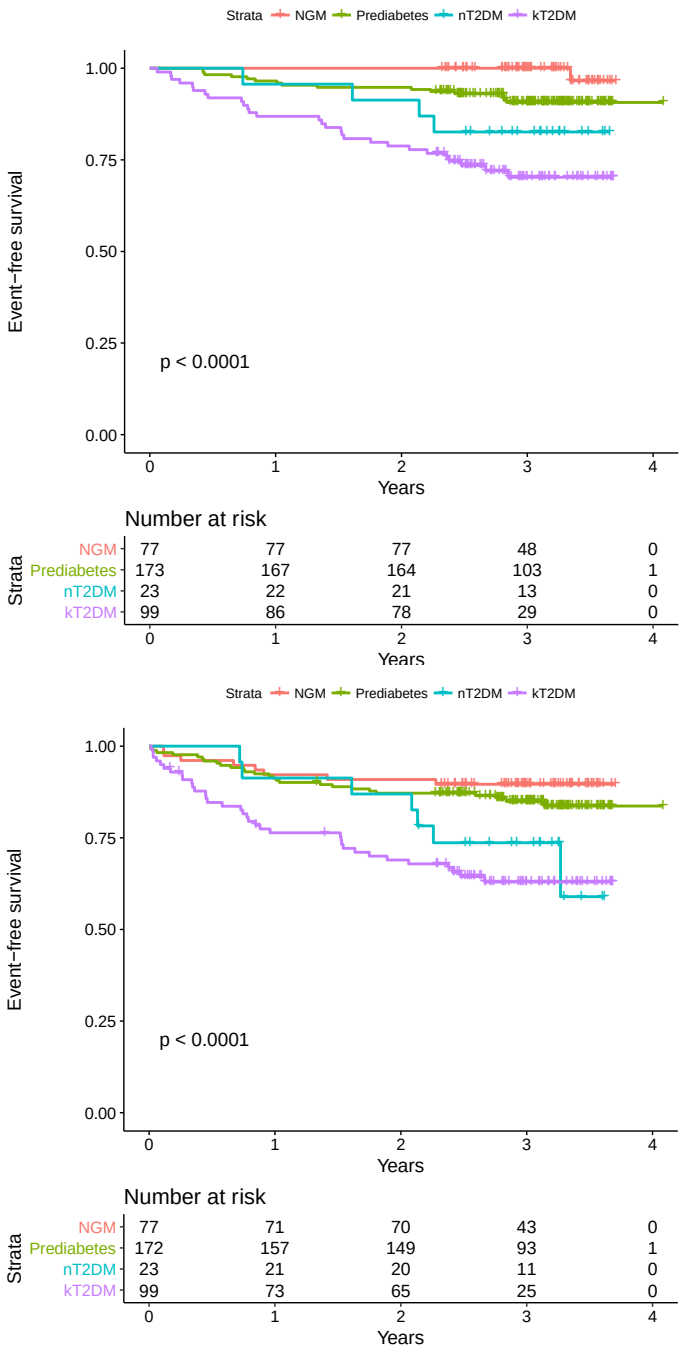

Figure 8. Kaplan-Meier curves for death or MI (above) and MACE (below) by glucometabolic status (p<0.001).

5 Discussion

5.1 Diagnosis of Type 2 Diabetes in Patients with Acute Coronary syndromes

In previous studies on diabetes and ACS, a single glucose metabolic measurements (FPG, 2hPG or HbA1c) above the diabetes cuf-off value has been sufficient to identify T2DM (Bartnik, Ryden, et al., 2004; Hage, Lundman, Ryden, & Mellbin, 2013; Norhammar et al., 2002). By using the current ADA and WHO criteria to diagnose T2DM, based on at least 2 measurements above the diagnostic cut-off point for T2DM, we apply a more robust clinical endpoint for our study, compared to using one measurement as a diagnostic reference.

As shown in previous studies, we found that measurements of 2hPG had the highest sensitivity in identifying patients with T2DM while HbA1c had the lowest sensitivity in identifying T2DM of the three diagnostic tests. On the other hand, the PPVs for diagnosing T2DM with HbA1c and FPG were relatively high, ranging from 71.4-100%, while the PPV for 2hPG was lower, 51.9% and 65.0% during admission and at follow-up, respectively. In practice, PPV is more useful for clinicians to diagnose disease. This is due to the fact that at the time of the diagnostic work-up the final diagnosis is not at hand. PPV and NPV provide the likelihood that any given patient will or will not have a specific diagnosis based on the results of the diagnostic test. Sensitivity and specificity, however, provide the post-hoc ability of the test to classify patients into correct diagnostic categories. In the clinical setting of diagnosing glucometabolic derangements among patients with ACS, the PPV and NPV are more clinically relevant than sensitivity and specificity. Moreover, of the 27 patients who were classified as having T2DM according to 2hPG during admission, only 14 patients were later confirmed to have T2DM based on ADA and WHO criteria. A lower cut-off point for T2DM was suggested, by the ROC curves, that would provide optimal sensitivity and specificity for HbA1c and FPG during admission and at follow-up and for 2hPG at follow-up. However, a higher cut-off point was suggested for 2hPG during admission for optimal sensitivity and specificity. This suggests that 2hPG may not be helpful shortly after ACS, most likely due to adrenergic activation with increased insulin resistance causing higher postprandial hyperglycemia following the insult. Lower cut-off points for T2DM may,

however, be appropriate for HbA1c and FPG in patients with ACS than those used in the general population.

No single method is perfect to screen for T2DM in patients with ACS nor sufficient to diagnose T2DM. When all six measurements from admission and follow-up are used, the sensitivity would obviously be 100% but the PPV only 44.2%. Similarly, by using the OGTT during admission and follow-up, and disregarding HbA1c, the sensitivity was 100% but PPV only 45.0%. The ESC recommends a staged approach to detect T2DM in patients with CVD as previously described (Ryden et al., 2014). When the ESC guidelines were applied, the sensitivity was 100% while the PPV was 66.7% and NPV 100%. However, the PPV improved when we relied solely on HbA1c and FPG measurements, during admission and at follow-up, with 88.9% sensitivity in diagnosing T2DM, PPV of 80.0% and NPV of 99.1%. By abandoning the OGTT, only 2 patients (0.8%) from a total of 250 would have been misclassified as having prediabetes instead of being diagnosed with T2DM, while the OGTT misclassified 20 (8%) of the 250 patients with T2DM according to WHO and ADA guidelines. Therefore, OGTT seems to have limitations as a diagnostic tool for T2DM among patients with ACS.

5.2 Identifying Prediabetes in Acute Coronary Syndromes

More patients were classified as having prediabetes according to ADA criteria using FPG or HbA1c, compared to WHO criteria using the OGTT (FPG or 2hPG), 53.6% and 44.4%, respectively. The proportion of patients found to have prediabetes on both FPG and HbA1c (ADA criteria) or on the OGTT (WHO criteria) was relatively low, 30.6% and 18.0%, respectively. Of all patients found to have prediabetes, 52.2% were found to have prediabetes by both ADA and WHO criteria. This highlights different aspects of glucometabolic derangement exposed by the different tests. FPG reflects hepatic insulin resistance, a failure to hamper gluconeogenesis in the liver, causing chronic glucose elevation. OGTT reflects insulin resistance in the muscle with subsequent failure of the islet β cells, resulting in postprandial hyperglycemia. Finally, HbA1c represents both chronic glucose elevation and episodes of postprandial hyperglycemia over the last 3 months.

5.3 Glucometabolic Status and Carotid Plaque

To our knowledge, paper II was the first study to evaluate TPA in patients with ACS in relation to glucose metabolism classification. A high prevalence of significant atherosclerotic plaques was observed in the carotid arteries with an incremental increase in TPA among patients with ACS and diagnosis of

prediabetes and nT2DM, compared to patients with NGM. By design, all patients in the study presented with ACS and a great majority of patients had established coronary artery atherosclerotic disease. For this reason, we expected to find a high prevalence of significant atherosclerotic disease in the carotid arteries in this study cohort. We found that the prevalence of significant atherosclerotic plaque was six-fold compared to the general population in Iceland, 62% in our study compared to 10% in the Icelandic general population (Sturlaugsdottir et al., 2016). When an age- and gender-matched control group from the Icelandic general population was explored, the prevalence of significant plaques was 20% with mean TPA of 39.1 mm^2 compared to 103.3 mm^2 in patients with ACS. This clear contrast highlights the difference in atherosclerotic burden found in patients with ACS compared to the general population.

Both prediabetes and dysglycemia were found to be independent predictors of significant atherosclerotic plaques being present in the carotid arteries and having increased TPA. Patients with nT2DM had increased risk of significant plaque and increased TPA in the carotid arteries, compared to patients with NGM, but the difference did not reach statistical significance. After adjusting for conventional atherosclerotic risk factors with multiple logistic regression and linear regression analysis, the statistically significant association between prediabetes or dysglycemia and having significant plaques or increased TPA in the carotid arteries remained significant and nearly unchanged. This suggested addition risk factors, other than the conventional atherosclerotic risk factors, are attributing to the increased TPA. Therefore, we evaluated whether different glucometabolic measurements (HbA1c, FPG and 2hPG) explained increased TPA beyond the atherosclerotic risk factors that had been previously accounted for. When further adjustment was made for 2hPG, both the risk of having significant atherosclerotic plaque and the difference in TPA size became non-significant. Adjusting for FPG affected the multiple logistic regression analysis and attenuated the OR of having significant plaque but did not have an effect on linear regression analysis. Adjusting for HbA1c did not affect either analysis. This suggests that among the three glucometabolic measurements, 2hPG has the strongest relation to atherosclerosis in patients with ACS and could potentially be the driving force for atherosclerosis development. This is supported by the fact that the 2hPG measurements, during a standard OGTT, were associated with an increased risk of having significant plaque and increased TPA, compared to NGM patients, while the association was insignificant for FPG and HbA1c. This is consistent with results from paper III,

showing that elevated 2hPG is associated with an increased clinical event rate of death or MI and MACE on follow-up.

As previously described, the 2hPG identifies patients with insulin resistance and postprandial hyperglycemia (DeFronzo et al., 1985; Ferrannini et al., 1988). In order to augment glucose uptake by muscles and to suppress hepatic gluconeogenesis, the islet β cells respond by producing and secreting more insulin, resulting in hyperinsulinemia (Nolan et al., 2011). This results in postprandial hyperglycemia. Both insulin resistance and hyperinsulinemia are considered to accelerate the development of atherosclerosis through vascular dysfunction and an increase in reactive oxygen species with subsequent vascular inflammation and proliferation of smooth muscle cells in the atherosclerotic plaque (Paneni et al., 2013). That can lead to plaque instability and rupture, a key process in the development of ACS. In addition, significant fluctuations in blood glucose, as in postprandial hyperglycemia, can increase risk of endothelial dysfunction (DeFronzo & Abdul-Ghani, 2011). Dysglycemia, with associated insulin resistance and hyperglycemia, can have subtle symptoms and signs that can go undetected for years, contributing to increased atherosclerotic burden until patients present with potentially fatal disease.

Patients with prediabetes below the diagnostic cut-off point for T2DM were found to have increased atherosclerotic burden compared to patients with NGM. This kind of detectable macrovascular complication in individuals below the diabetic threshold has also been observed in other studies (Coutinho et al., 1999; Sinnaeve et al., 2009). Guidelines from the ADA and WHO are currently based on glucose levels that have been related to the development of retinopathy (microvascular complication) in the general population. However, in view of the increased atherosclerotic burden (macrovascular complication) seen in ACS patients below the diabetic threshold, it might be appropriate to lower the cut-off values for T2DM. This view is also supported by the ROC analysis in paper I. Metabolic derangement and ACS are two clinical disease entities that could be considered to be two sides of the same coin, sharing atherogenic driving factors, including obesity, hypertension and a hypercoagulability state that may be responsible for disease development.

5.4 Glucometabolic Derangement and Prognosis in Acute Coronary Syndromes

In paper III, we observed a significantly increased risk of death and MI or

MACE among patients with nT2DM and kT2DM compared to patients with NGM, after three years of follow-up. Several studies have shown similar results in the past but there are differences that need to be highlighted (Bartnik, Malmberg, et al., 2004; George et al., 2015; Kuhl et al., 2015; Lenzen et al., 2006; Ritsinger et al., 2015). First, HR for increased risk of death and MI among patients with nT2DM and kT2DM is markedly higher in our study (paper III) than has previously been reported. In previous studies, a single OGTT was used to identify nT2DM while OGTT (FPG and 2hPG) and HbA1c on two separate occasions and a requirement to have at least two measurements elevated to diagnose nT2DM was used in our study. The more diagnostically robust method of appling the ADA and WHO criteria to diagnose nT2DM instead of a single OGTT will reduce the number of false positives results, and more accurately identify patients with severe dysglycemia. Therefore, it does not come as a surprise to see higher HRs for death and MI when more strict diagnostic criteria are applied. We also observed a much higher risk of death and MI in ACS patients with kT2DM than previous studies on patients with stable CAD have shown (Lenzen et al., 2006). The difference in observed risk is most likely due to poorer prognosis among patients with ACS compared to patients with stable CAD. Secondly, in contrast to previous studies, the study presented in paper III was carried out in the modern era of dual antiplatelet and high-dose statin therapy with a high proportion of the patients receiving early invasive treatment. The majority of STEMI patients (92%) were treated with urgent revascularization, primary PCI (87%) or urgent CABG surgery (4.7%), and an invasive approach was used in 76% of NSTEMI patients (PCI 60% and CABG 16%). This represents modern care of patients with ACS compared to previous studies most of which were retrospective analyses of datasets sampled 20-30 years ago. Furthermore, this was a prospective study where patients diagnosed with new dysclycemia were treated according to current recommendations with lifestyle interventions and pharmacologic therapy as clinically indicated. Dual antiplatelet and high-dose statin therapy, early invasive approach and lifestyle interventions with pharmacologic treatments, such as metformin, are all known to have a favourable effect on long-term prognosis. The risk of MACE among patients with nT2DM and kT2DM were similar in paper III as reported by previous studies.

Patients with kT2DM, unsurprisingly, were found to have a higher risk for future death or MI and MACE compared to nT2DM. However, the duration of kT2DM was not taken into consideration but it would be expected that long

exposure to this highly detrimental risk factor would contribute to higher morbidity and mortality compared to patients with nT2DM.

These results underscore the importance of detecting underlying dysglycemia in the management of patients with ACS. Current guidelines recommend antiplatelet therapy with strict control of hypertension and hypercholesterolemia in patients with T2DM and established CAD (Ryden et al., 2014). Good glycemic control in addition to adequate management of comorbities is paramount to lowering risk of future cardiovascular events (Rawshani et al., 2018). Lifestyle modification with dietary counselling and regular physical activity to promote weight loss is also recommended in patients with T2DM. In addition, studies have shown benefits of metformin in patients with T2DM and CAD, and more recently, SGLT-2 inhibitors, like empagliflozin and canagliflozin, have also been shown to reduce risk of future adverse events in this patient population (Mellbin et al., 2008; Neal et al., 2017; Zinman et al., 2015).

Patients with newly detected prediabetes were found to have increased near-future risk for cardiovascular events but this risk did not reach statistical significance, possibly due to a small sample size. Also, the progression from prediabetes to T2DM can take several years and three years is a relatively short follow-up period. It is also unknown which patients regress to NGM, which remain prediabetic for years and which progress to overt T2DM. Furthermore, clustering of IFG and IGT, two different glucometabolic abnormalities with different prognostic consequences, may be misleading. This is highlighted among patients with IGT who were found to have increased risk of death and MI compared to patients with IFG. A recent study by Chattopadhyay et al. showed that elevated 2hPG among patients with acute coronary events is an independent risk factor for future MACE, highlighting the prognostic value of elevated 2hPG (IGT) (Chattopadhyay, George, John, & Sathyapalan, 2018). Current guidelines from the ADA recommend lifestyle modifications to promote weight loss as well as offering metformin in patients with prediabetes, especially in patients younger than 60 years old, with BMI $\geq$35 kg/m^2 and in women with a history of gestational diabetes (ADA, 2017; Knowler et al., 2002). This could be even more important in patients with CAD as a secondary prevention.

5.5 Atherosclerotic Carotid Plaque and Prognosis in Acute Coronary Syndromes

The presence of carotid plaques has been suggested as a marker for risk

stratification of CAD in the general population (Polak et al., 2013). However, in paper III, after adjusting for conventional risk factors, no difference in outcome was detected among ACS patients with increased TPA in the carotid arteries. Even though TPA has been shown to be an independent risk factor for CAD in the general population, it does not seem to predict adverse outcome following ACS after nearly 3 years of follow-up. This might be due to secondary preventive interventions with rigorous anti-atherosclerotic treatment with platelet inhibitors, statins and tight blood pressure control according to current guidelines. Additionally, carotid plaque is a surrogate marker for atherosclerosis in the coronary arteries that is the underlying problem in the majority of patients with ACS. The culprit lesion is then addressed, with PCI or CABG surgery, rendering carotid plaque inconsequential in the prediction of future events following coronary intervention.

5.6 Limitations and Strengths

There are several limitations to these studies. First, the number of patients is relatively small, especially for evaluation of mortality and morbidity, and the follow-up period is short, considering the chronicity of T2DM causing organ damage over a long period of time. Secondly, in comparison to previous studies, the prevalence of T2DM was relatively low. This is most likely due to more strict diagnostic criteria applied to identify T2DM in our studies. Also, compared to other western countries, the prevalence of T2DM has been low in the Icelandic population (Bergsveinsson, Aspelund, Gudnason, & Benediktsson, 2007). Due to this low prevalence, the power to detect a significant association between T2DM and TPA was limited. Some glucose measurements were made earlier than the study protocol stated; however, no significant difference was found in measurements of FPG and 2hPG that were made on day five compared with measurements made on days 2, 3, 4, 5, 6 or later. It was not possible to determine the duration of T2DM among patients who had been diagnosed with T2DM before they presented with ACS. There are no baseline LDL measurements available for the study cohort. We did not have a control group with patients without ACS; instead patients with NGM and ACS were used as a control group in papers II and III. Additionally, we referred to an age- and gender-matched group from the Icelandic general population as a comparison in paper II. Finally, participants in all of the studies were Caucasian and of European origin.

The main strenghts of our study are that this is a prospective observational study where every patient in Iceland with ACS requiring

intervention, either with PCI or CABG surgery, are treated at Landspitali, the University Hospital of Iceland. The great majority of the study participants finished the study protocol with few dropouts. Due to the setup of the Icelandic health system, it is convenient to follow patients, making it highly unlikely that any clinical end-point was missed during the follow-up period. Finally, these are the first studies on new dysglycemia in ACS patient where WHO and ADA criteria are used to diagnose T2DM, a more robust method to diagnose T2DM than has been utilized in previous studies.

5.7 Future Prospects

These studies highlight the importance of evaluating ACS patients for underlying dysglycemia. Undiagnosed dysglycemia is common in ACS patients. Studies have shown the benefits of treating T2DM in CAD patients with lifestyle intervention and pharmacologic treatments for T2DM. In addition, appropriate management of comorbidities including high cholesterol, high blood pressure and smoking has shown to have significant impact to improve cardiovascular outcomes. Further research is needed to optimize T2DM management in patients with CAD, especially in younger individuals in this patient population.

It is unclear whether treatment with glucose-lowering medications improve outcome in ACS patients with prediabetes. Lifestyle interventions and metformin have shown to lower the risk of developing T2DM, but further research is needed to evaluate for hard clinical endpoints like mortality or MACE. A long follow-up period, even more than 10 years, would be required to evaluate the benefits of treating prediabetes in ACS patients, due to the slow progression of atherosclerosis over many years. However, current knowledge suggests that lifestyle interventions should be recommended and metformin offered to ACS patients with prediabetes to lower the risk of developing diabetes and potentially lower the lifetime risk for CVD.

In paper I, we suggested lower cut-off values for HbA1c and FPG to diagnose T2DM in ACS patients. It would be interesting to evaluate whether lower cut-off values for HbA1c and FPG would be useful in predicting future mortality and cardiovascular events in ACS patients.

Finally, we plan to continue follow-up on the patients in our study. A follow-up study on the patients diagnosed with prediabetes could be performed to see how many patients develop T2DM and whether IFG, IGT or elevated HbA1c has prognostic value in that aspect. It would be interesting to see whether further differences in cardiovascular events is observed in

patients with nT2DM, compared to NGM patients, and whether differences in cardiovascular events would be observed in patients with prediabetes, compared to NGM patients, after a longer follow-up period. Patients 65 years and younger with prediabetes are an especially interesting subgroup as they have the potential to live for years exposed to dysglycemia that could lead to poor outcome compared to patients with NGM.

6 Conclusions

The results of this thesis suggest that repeating FPG and HbA1c during admission for ACS and three months later can accurately identify previously unknown T2DM and prediabetes in patients who present with ACS. This method provides high sensitivity and PPV to diagnose T2DM, significantly reducing the need for OGTT in patients with ACS, something that is not clinically practical and generally not done in this patient population.

Patients with ACS have a high prevalence of atherosclerotic plaques in the carotid arteries with an incremental increase in TPA observed in patients diagnosed with prediabetes and T2DM compared to patients with NGM. Patients with elevated 2hPG had a significant increase in TPA and were at increased risk of having significant atherosclerotic plaques in the carotid arteries. Even after adjustment for conventional risk factors, the 2hPG remained a significant predictor of increased atherosclerotic burden in the carotid arteries. Furthermore, prediabetes was found to have a significant association with increased atherosclerotic burden in the carotid arteries. This highlights the risk for macrovascular disease with elevated 2hPG, even below the diabetic threshold, compared to microvascular disease that seems to develop at higher glucometabolic cut-off points.

Finally, patients admitted with ACS and kT2DM or nT2DM were found to be at increased risk of death or MI and MACE compared to ACS patients with NGM after three year follow-up. While the combination of FPG and HbA1c is effective in diagnosing T2DM in patients with ACS, elevated 2hPG is associated with increased atherosclerotic burden and is a predictor for future cardiovascular events.

This thesis highlights the importance of improving diagnosis of prediabetes and T2DM in ACS patients to identify a highly vulnerable patient group that warrants optimal secondary prevention measures, both glucometabolic and comorbidity management, to improve outcome.

References

Abi-Younes, S., Sauty, A., Mach, F., Sukhova, G. K., Libby, P., & Luster, A. D. (2000). The stromal cell-derived factor-1 chemokine is a potent platelet agonist highly expressed in atherosclerotic plaques. *Circ Res, 86*(2), 131-138.

Agatston, A. S., Janowitz, W. R., Hildner, F. J., Zusmer, N. R., Viamonte, M., Jr., & Detrano, R. (1990). Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol, 15*(4), 827-832.

Alberti, K. G., & Zimmet, P. Z. (1998). Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med, 15*(7), 539-553. doi:10.1002/(sici)1096-9136(199807)15:7<539::Aid-dia668>3.0.Co;2-s

American Diabetes Association. (2012a). Diagnosis and classification of diabetes mellitus. *Diabetes Care, 35 Suppl 1*, S64-71. doi:10.2337/dc12-s064

American Diabetes Association. (2012b). *Diagnosis and classification of diabetes mellitus*. (0149-5992). Retrieved from http://care.diabetesjournals.org/content/35/Supplement_1/S64.full.pdf.

American Diabetes Association. (2017). 5. Prevention or Delay of Type 2 Diabetes. *Diabetes Care, 40*(Suppl 1), S44-s47. doi:10.2337/dc17-S008

Andersen, K., Aspelund, T., Gudmundsson, E. F., Siggeirsdottir, K., Thorolfsdottir, R. B., Sigurdsson, G., & Gudnason, V. (2017). [Five decades of coronary artery disease in Iceland. Data from the Icelandic Heart Association]. *Laeknabladid, 103*(10), 411-420. doi:/10.17992/lbl.2017.10.153

Anderson, K. M., Castelli, W. P., & Levy, D. (1987). Cholesterol and mortality. 30 years of follow-up from the Framingham study. *JAMA, 257*(16), 2176-2180.

Anderson, S. L., & Marrs, J. C. (2012). Dapagliflozin for the treatment of type 2 diabetes. *Ann Pharmacother, 46*(4), 590-598. doi:10.1345/aph.1Q538

Andresdottir, M. B., Sigurdsson, G., Sigvaldason, H., & Gudnason, V. (2002). Fifteen percent of myocardial infarctions and coronary revascularizations explained by family history unrelated to conventional risk factors. The Reykjavik Cohort Study. *Eur Heart J, 23*(21), 1655-1663.

Arad, Y., Goodman, K. J., Roth, M., Newstein, D., & Guerci, A. D. (2005). Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. *J Am Coll Cardiol, 46*(1), 158-165. doi:10.1016/j.jacc.2005.02.088

Aspelund, T., Gudnason, V., Magnusdottir, B. T., Andersen, K., Sigurdsson, G., Thorsson, B., . . .Capewell, S. (2010). Analysing the large decline in coronary heart disease mortality in the Icelandic population aged 25-74 between the years 1981 and 2006. *PLoS One, 5*(11), e13957. doi:10.1371/journal.pone.0013957

Baber, U., Mehran, R., Sartori, S., Schoos, M. M., Sillesen, H., Muntendam, P., . . . Fuster, V. (2015). Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. *J Am Coll Cardiol, 65*(11), 1065-1074. doi:10.1016/j.jacc.2015.01.017

Barr, E. L., Zimmet, P. Z., Welborn, T. A., Jolley, D., Magliano, D. J., Dunstan, D. W., . . . Shaw, J. E. (2007). Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). *Circulation, 116*(2), 151-157. doi:10.1161/CIRCULATIONAHA.106.685628

Bartnik, M., Malmberg, K., Norhammar, A., Tenerz, A., Ohrvik, J., & Ryden, L. (2004). Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction. *Eur Heart J, 25*(22), 1990-1997. doi:10.1016/j.ehj.2004.09.021

Bartnik, M., Ryden, L., Ferrari, R., Malmberg, K., Pyorala, K., Simoons, M., . . . Ohrvik, J. (2004). The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart. *Eur Heart J, 25*(21), 1880-1890. doi:10.1016/j.ehj.2004.07.027

Bergsveinsson, J., Aspelund, T., Gudnason, V., & Benediktsson, R. (2007). [Prevalence of type 2 diabetes mellitus in Iceland 1967-2002]. *Laeknabladid, 93*(5), 397-402.

Berlin, J. A., & Colditz, G. A. (1990). A meta-analysis of physical activity in the prevention of coronary heart disease. *Am J Epidemiol, 132*(4), 612-628.

Berry, J. D., Liu, K., Folsom, A. R., Lewis, C. E., Carr, J. J., Polak, J. F., . . . Lloyd-Jones, D. M. (2009). Prevalence and progression of subclinical atherosclerosis in younger adults with low short-term but high lifetime estimated risk for cardiovascular disease: the coronary artery risk development in young adults study and multi-ethnic study of atherosclerosis. *Circulation, 119*(3), 382-389. doi:10.1161/circulationaha.108.800235

Bjornsdottir, G., Sigurdsson, S., Sturlaugsdottir, R., Gudmundsdottir, A., Eiriksdottir, G., Thorsson, B., . . . Gudnason, V. (2014). Longitudinal Changes in Size and Composition of Carotid Artery Plaques Using Ultrasound: Adaptation and Validation of Methods (Inter- and Intraobserver Variability). *Journal for Vascular Ultrasound, 38*(4), 198-208.

Bonds, D. E., Miller, M. E., Bergenstal, R. M., Buse, J. B., Byington, R. P., Cutler, J. A., . . . Sweeney, M. E. (2010). The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *Bmj, 340*, b4909. doi:10.1136/bmj.b4909

Boyle, J. P., Thompson, T. J., Gregg, E. W., Barker, L. E., & Williamson, D. F. (2010). Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. *Popul Health Metr, 8*, 29. doi:10.1186/1478-7954-8-29

Brown, M. S., Ho, Y. K., & Goldstein, J. L. (1980). The cholesteryl ester cycle in macrophage foam cells. Continual hydrolysis and re-esterification of cytoplasmic cholesteryl esters. *J Biol Chem, 255*(19), 9344-9352.

Canto, J. G., Kiefe, C. I., Rogers, W. J., Peterson, E. D., Frederick, P. D., French, W. J., . . . Greenland, P. (2011). Number of coronary heart disease risk factors and mortality in patients with first myocardial infarction. *Jama, 306*(19), 2120-2127. doi:10.1001/jama.2011.1654

Cefalu, W. T., & Riddle, M. C. (2015). SGLT2 inhibitors: the latest "new kids on the block"! *Diabetes Care, 38*(3), 352-354. doi:10.2337/dc14-3048

Chattopadhyay, S., George, A., John, J., & Sathyapalan, T. (2018). Adjustment of the GRACE score by 2-hour post-load glucose improves prediction of long-term major adverse cardiac events in acute coronary syndrome in patients without known diabetes. *Eur Heart J*. doi:10.1093/eurheartj/ehy233

Chen, J., Einstein, A. J., Fazel, R., Krumholz, H. M., Wang, Y., Ross, J. S., . . . Nallamothu, B. K. (2010). Cumulative exposure to ionizing radiation from diagnostic and therapeutic cardiac imaging procedures: a population-based analysis. *J Am Coll Cardiol, 56*(9), 702-711. doi:10.1016/j.jacc.2010.05.014

Cohen, G. I., Aboufakher, R., Bess, R., Frank, J., Othman, M., Doan, D., . . . Szpunar, S. (2013). Relationship between carotid disease on ultrasound and coronary disease on CT angiography. *JACC Cardiovasc Imaging, 6*(11), 1160-1167. doi:10.1016/j.jcmg.2013.06.007

Coutinho, M., Gerstein, H. C., Wang, Y., & Yusuf, S. (1999). The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care, 22*(2), 233-240.

Davies, M. J., D'Alessio, D. A., Fradkin, J., Kernan, W. N., Mathieu, C., Mingrone, G., . . . Buse, J. B. (2018). Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care, 41*(12), 2669-2701. doi:10.2337/dci18-0033

de Groot, E., van Leuven, S. I., Duivenvoorden, R., Meuwese, M. C., Akdim, F., Bots, M. L., & Kastelein, J. J. (2008). Measurement of carotid intima-media thickness to assess progression and regression of atherosclerosis. *Nat Clin Pract Cardiovasc Med, 5*(5), 280-288. doi:10.1038/ncpcardio1163

DeFronzo, R. A., & Abdul-Ghani, M. (2011). Assessment and treatment of cardiovascular risk in prediabetes: impaired glucose tolerance and impaired fasting glucose. *Am J Cardiol, 108*(3 Suppl), 3B-24B. doi:10.1016/j.amjcard.2011.03.013

DeFronzo, R. A., Gunnarsson, R., Bjorkman, O., Olsson, M., & Wahren, J. (1985). Effects of insulin on peripheral and splanchnic glucose metabolism in noninsulin-dependent (type II) diabetes mellitus. *J Clin Invest, 76*(1), 149-155. doi:10.1172/jci111938

Detrano, R., Guerci, A. D., Carr, J. J., Bild, D. E., Burke, G., Folsom, A. R., . . . Kronmal, R. A. (2008). Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med, 358*(13), 1336-1345. doi:10.1056/NEJMoa072100

Doyle, J. T., Dawber, T. R., Kannel, W. B., Heslin, A. S., & Kahn, H. A. (1962). Cigarette smoking and coronary heart disease. Combined experience of the Albany and Framingham studies. *N Engl J Med, 266*, 796-801.

Duckworth, W., Abraira, C., Moritz, T., Reda, D., Emanuele, N., Reaven, P. D., . . . Huang, G. D. (2009). Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med, 360*(2), 129-139. doi:10.1056/NEJMoa0808431

Edelman, D., Olsen, M. K., Dudley, T. K., Harris, A. C., & Oddone, E. Z. (2004). Utility of hemoglobin A1c in predicting diabetes risk. *J Gen Intern Med, 19*(12), 1175-1180. doi:10.1111/j.1525-1497.2004.40178.x

Ferrannini, E., Simonson, D. C., Katz, L. D., Reichard, G., Jr., Bevilacqua, S., Barrett, E. J., . . . DeFronzo, R. A. (1988). The disposal of an oral glucose load in patients with non-insulin-dependent diabetes. *Metabolism, 37*(1), 79-85.

Ford, E. S., Ajani, U. A., Croft, J. B., Critchley, J. A., Labarthe, D. R., Kottke, T. E., . . . Capewell, S. (2007). Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med, 356*(23), 2388-2398. doi:10.1056/NEJMsa053935

Forouhi, N. G., Luan, J., Hennings, S., & Wareham, N. J. (2007). Incidence of Type 2 diabetes in England and its association with baseline impaired fasting glucose: the Ely study 1990-2000. *Diabet Med, 24*(2), 200-207. doi:10.1111/j.1464-5491.2007.02068.x

Galis, Z. S., Sukhova, G. K., Lark, M. W., & Libby, P. (1994). Increased expression of matrix metalloproteinases and matrix degrading activity in vulnerable regions of human atherosclerotic plaques. *J Clin Invest, 94*(6), 2493-2503. doi:10.1172/jci117619

Gensini, G. G. (1983). A more meaningful scoring system for determining the severity of coronary heart disease. *Am J Cardiol, 51*(3), 606.

George, A., Bhatia, R. T., Buchanan, G. L., Whiteside, A., Moisey, R. S., Beer, S. F., . . . John, J. (2015). Impaired Glucose Tolerance or Newly Diagnosed Diabetes Mellitus Diagnosed during Admission Adversely Affects Prognosis after Myocardial Infarction: An Observational Study. *PLoS One, 10*(11), e0142045. doi:10.1371/journal.pone.0142045

Gerber, T. C., Carr, J. J., Arai, A. E., Dixon, R. L., Ferrari, V. A., Gomes, A. S., . . . Yester, M. V. (2009). Ionizing radiation in cardiac imaging: a science advisory from the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention. *Circulation, 119*(7), 1056-1065. doi:10.1161/circulationaha.108.191650

Gerstein, H. C., Miller, M. E., Byington, R. P., Goff, D. C., Jr., Bigger, J. T., Buse, J. B., . . . Friedewald, W. T. (2008). Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med, 358*(24), 2545-2559. doi:10.1056/NEJMoa0802743

Go, A. S., Mozaffarian, D., Roger, V. L., Benjamin, E. J., Berry, J. D., Blaha, M. J., . . . Stroke Statistics, S. (2014). Executive summary: heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation, 129*(3), 399-410. doi:10.1161/01.cir.0000442015.53336.12

Goff, D. C., Jr., Lloyd-Jones, D. M., Bennett, G., Coady, S., D'Agostino, R. B., Sr., Gibbons, R., . . . Wilson, P. W. (2014). 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol, 63*(25 Pt B), 2935-2959. doi:10.1016/j.jacc.2013.11.005

Gyberg, V., De Bacquer, D., Kotseva, K., De Backer, G., Schnell, O., Sundvall, J., . . . Investigators, E. I. (2015). Screening for dysglycaemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test, and HbA1c: a report from EUROASPIRE IV--a survey from the European Society of Cardiology. *Eur Heart J, 36*(19), 1171-1177. doi:10.1093/eurheartj/ehv008

Haas, B., Eckstein, N., Pfeifer, V., Mayer, P., & Hass, M. D. (2014). Efficacy, safety and regulatory status of SGLT2 inhibitors: focus on canagliflozin. *Nutr Diabetes, 4*, e143. doi:10.1038/nutd.2014.40

Haffner, S. M., Lehto, S., Ronnemaa, T., Pyorala, K., & Laakso, M. (1998). Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med, 339*(4), 229-234. doi:10.1056/nejm199807233390404

Hage, C., Lundman, P., Ryden, L., & Mellbin, L. (2013). Fasting glucose, HbA1c, or oral glucose tolerance testing for the detection of glucose abnormalities in patients with acute coronary syndromes. *Eur J Prev Cardiol, 20*(4), 549-554. doi:10.1177/2047487312444371

Hecht, H. S. (2015). Coronary artery calcium scanning: past, present, and future. *JACC Cardiovasc Imaging, 8*(5), 579-596. doi:10.1016/j.jcmg.2015.02.006

Hecht, H. S., & Narula, J. (2012). Coronary artery calcium scanning in asymptomatic patients with diabetes mellitus: a paradigm shift. *J Diabetes, 4*(4), 342-350. doi:10.1111/j.1753-0407.2012.00212.x

Holman, R. R., Bethel, M. A., Mentz, R. J., Thompson, V. P., Lokhnygina, Y., Buse, J. B., . . . Hernandez, A. F. (2017). Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med, 377*(13), 1228-1239. doi:10.1056/NEJMoa1612917

Holman, R. R., Paul, S. K., Bethel, M. A., Matthews, D. R., & Neil, H. A. (2008). 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med, 359*(15), 1577-1589. doi:10.1056/NEJMoa0806470

Hubert, H. B., Feinleib, M., McNamara, P. M., & Castelli, W. P. (1983). Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation, 67*(5), 968-977.

Inaba, Y., Chen, J. A., & Bergmann, S. R. (2012). Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. *Atherosclerosis, 220*(1), 128-133. doi:10.1016/j.atherosclerosis.2011.06.044

Inouye, M., Abraham, G., Nelson, C. P., Wood, A. M., Sweeting, M. J., Dudbridge, F., . . . Samani, N. J. (2018). Genomic Risk Prediction of Coronary Artery Disease in 480,000 Adults: Implications for Primary Prevention. *J Am Coll Cardiol, 72*(16), 1883-1893. doi:10.1016/j.jacc.2018.07.079

Knowler, W. C., Barrett-Connor, E., Fowler, S. E., Hamman, R. F., Lachin, J. M., Walker, E. A., & Nathan, D. M. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med, 346*(6), 393-403. doi:10.1056/NEJMoa012512

Koliaki, C., & Doupis, J. (2011). Incretin-based therapy: a powerful and promising weapon in the treatment of type 2 diabetes mellitus. *Diabetes Ther, 2*(2), 101-121. doi:10.1007/s13300-011-0002-3

Kuhl, J., Jorneskog, G., Wemminger, M., Bengtsson, M., Lundman, P., & Kalani, M. (2015). Long-term clinical outcome in patients with acute coronary syndrome and dysglycaemia. *Cardiovasc Diabetol, 14*, 120. doi:10.1186/s12933-015-0283-3

Lafont, A. (2003). Basic aspects of plaque vulnerability. *Heart, 89*(10), 1262-1267.

Lenzen, M., Ryden, L., Ohrvik, J., Bartnik, M., Malmberg, K., Scholte Op Reimer, W., . . . Euro Heart Survey, I. (2006). Diabetes known or newly detected, but not impaired glucose regulation, has a negative influence on 1-year outcome in patients with coronary artery disease: a report from the Euro Heart Survey on diabetes and the heart. *Eur Heart J, 27*(24), 2969-2974. doi:10.1093/eurheartj/ehl363

Li, A. R., Zhang, J., Greenberg, J., Lee, T., & Liu, J. (2011). Discovery of non-glucoside SGLT2 inhibitors. *Bioorg Med Chem Lett, 21*(8), 2472-2475. doi:10.1016/j.bmcl.2011.02.056

Lloyd-Jones, D. M., Nam, B. H., D'Agostino, R. B., Sr., Levy, D., Murabito, J. M., Wang, T. J., . . . O'Donnell, C. J. (2004). Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *Jama, 291*(18), 2204-2211. doi:10.1001/jama.291.18.2204

Lorenz, M. W., Schaefer, C., Steinmetz, H., & Sitzer, M. (2010). Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS). *Eur Heart J, 31*(16), 2041-2048. doi:10.1093/eurheartj/ehq189

Lotta, L. A. (2010). Genome-wide association studies in atherothrombosis. *Eur J Intern Med, 21*(2), 74-78. doi:10.1016/j.ejim.2009.11.003

Marso, S. P., Bain, S. C., Consoli, A., Eliaschewitz, F. G., Jodar, E., Leiter, L. A., . . . Vilsboll, T. (2016). Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med, 375*(19), 1834-1844. doi:10.1056/NEJMoa1607141

Marso, S. P., Daniels, G. H., Brown-Frandsen, K., Kristensen, P., Mann, J. F., Nauck, M. A., . . . Buse, J. B. (2016). Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med, 375*(4), 311-322. doi:10.1056/NEJMoa1603827

Mathiesen, E. B., Johnsen, S. H., Wilsgaard, T., Bonaa, K. H., Lochen, M. L., & Njolstad, I. (2011). Carotid plaque area and intima-media thickness in prediction of first-ever ischemic stroke: a 10-year follow-up of 6584 men and women: the Tromso Study. *Stroke, 42*(4), 972-978. doi:10.1161/STROKEAHA.110.589754

Mehta, N. N., Li, M., William, D., Khera, A. V., DerOhannessian, S., Qu, L., . . . Reilly, M. P. (2011). The novel atherosclerosis locus at 10q11 regulates plasma CXCL12 levels. *Eur Heart J, 32*(8), 963-971. doi:10.1093/eurheartj/ehr091

Mellbin, L. G., Anselmino, M., & Ryden, L. (2010). Diabetes, prediabetes and cardiovascular risk. *Eur J Cardiovasc Prev Rehabil, 17 Suppl 1*, S9-14. doi:10.1097/01.hjr.0000368192.24732.2f

Mellbin, L. G., Malmberg, K., Norhammar, A., Wedel, H., Ryden, L., & Investigators, D. (2008). The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. *Eur Heart J, 29*(2), 166-176. doi:10.1093/eurheartj/ehm518

Moore, K. J., & Tabas, I. (2011). Macrophages in the pathogenesis of atherosclerosis. *Cell, 145*(3), 341-355. doi:10.1016/j.cell.2011.04.005

Moreno, P. R. (2010). Vulnerable plaque: definition, diagnosis, and treatment. *Cardiol Clin, 28*(1), 1-30. doi:10.1016/j.ccl.2009.09.008

Alpert, J. S., Thygesen, K., Antman, E., & Bassand, J. P. (2000). Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J, 21*(18), 1502-1513. doi:10.1053/euhj.2000.2305

Nathan D.M., B.-C. E., Crandall J.P., Edelstein S.L., Goldberg R.B., Horton E.S., Knowler W.C., Mather K.J., Orchard T.J., Pi-Sunyer X., Schade D., Temprosa M. . (2015). Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol, 3*(11), 866-875. doi:10.1016/s2213-8587(15)00291-0

Nathan, D. M., Cleary, P. A., Backlund, J. Y., Genuth, S. M., Lachin, J. M., Orchard, T. J., . . . Zinman, B. (2005). Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med, 353*(25), 2643-2653. doi:10.1056/NEJMoa052187

Nathan, D. M., Davidson, M. B., DeFronzo, R. A., Heine, R. J., Henry, R. R., Pratley, R., . . . American Diabetes, A. (2007). Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care, 30*(3), 753-759. doi:10.2337/dc07-9920

Neal, B., Perkovic, V., Mahaffey, K. W., de Zeeuw, D., Fulcher, G., Erondu, N., . . . Matthews, D. R. (2017). Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. doi:10.1056/NEJMoa1611925

Nolan, C. J., Damm, P., & Prentki, M. (2011). Type 2 diabetes across generations: from pathophysiology to prevention and management. *Lancet, 378*(9786), 169-181. doi:10.1016/s0140-6736(11)60614-4

Norhammar, A., Tenerz, Å., Nilsson, G., Hamsten, A., Efendíc, S., Rydén, L., & Malmberg, K. (2002). Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *The Lancet, 359*(9324), 2140-2144. doi:10.1016/s0140-6736(02)09089-x

World Health Organization. (2011). Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus http://apps.who.int/iris/bitstream/10665/70523/1/WHO_NMH_CHP_CPM_11.1_eng.pdf

World Health Organization. (2006). Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia. http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf

Paneni, F., Beckman, J. A., Creager, M. A., & Cosentino, F. (2013). Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. *Eur Heart J, 34*(31), 2436-2443. doi:10.1093/eurheartj/eht149

Patel, A., MacMahon, S., Chalmers, J., Neal, B., Billot, L., Woodward, M., . . . Travert, F. (2008). Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med, 358*(24), 2560-2572. doi:10.1056/NEJMoa0802987

Patel, P. A., Cubbon, R. M., Sapsford, R. J., Gillott, R. G., Grant, P. J., Witte, K. K., . . . Hall, A. S. (2016). An evaluation of 20 year survival in patients with diabetes mellitus and acute myocardial infarction. *Int J Cardiol, 203*, 141-144. doi:10.1016/j.ijcard.2015.10.094

Plichart, M., Celermajer, D. S., Zureik, M., Helmer, C., Jouven, X., Ritchie, K., . . . Empana, J. P. (2011). Carotid intima-media thickness in plaque-free site, carotid plaques and coronary heart disease risk prediction in older adults. The Three-City Study. *Atherosclerosis, 219*(2), 917-924. doi:10.1016/j.atherosclerosis.2011.09.024

Polak, J. F., Szklo, M., Kronmal, R. A., Burke, G. L., Shea, S., Zavodni, A. E., & O'Leary, D. H. (2013). The value of carotid artery plaque and intima-media thickness for incident cardiovascular disease: the multi-ethnic study of atherosclerosis. *J Am Heart Assoc, 2*(2), e000087. doi:10.1161/JAHA.113.000087

Pradhan, A. D., Rifai, N., Buring, J. E., & Ridker, P. M. (2007). Hemoglobin A1c predicts diabetes but not cardiovascular disease in nondiabetic women. *Am J Med, 120*(8), 720-727. doi:10.1016/j.amjmed.2007.03.022

Rawshani, A., Rawshani, A., Franzen, S., Eliasson, B., Svensson, A. M., Miftaraj, M., . . . Gudbjornsdottir, S. (2017). Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. *N Engl J Med, 376*(15), 1407-1418. doi:10.1056/NEJMoa1608664

Rawshani, A., Rawshani, A., Franzen, S., Sattar, N., Eliasson, B., Svensson, A. M., . . . Gudbjornsdottir, S. (2018). Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med, 379*(7), 633-644. doi:10.1056/NEJMoa1800256

Icelandic National Death Registry. (2017). Retrieved from https://www.statice.is/statistics/population/births-and-deaths/

Ritsinger, V., Tanoglidi, E., Malmberg, K., Nasman, P., Ryden, L., Tenerz, A., & Norhammar, A. (2015). Sustained prognostic implications of newly detected glucose abnormalities in patients with acute myocardial infarction: long-term follow-up of the Glucose Tolerance in Patients with Acute Myocardial Infarction cohort. *Diab Vasc Dis Res, 12*(1), 23-32. doi:10.1177/1479164114551746

Rose, G. (1981). Strategy of prevention: lessons from cardiovascular disease. *Br Med J (Clin Res Ed), 282*(6279), 1847-1851.

Rose, G. (2001). Sick individuals and sick populations. *International Journal of Epidemiology, 30*(3), 427-432. doi:https://doi.org/10.1093/ije/30.3.427

Roth, G. A., Huffman, M. D., Moran, A. E., Feigin, V., Mensah, G. A., Naghavi, M., & Murray, C. J. (2015). Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation, 132*(17), 1667-1678. doi:10.1161/circulationaha.114.008720

Ryden, L., Grant, P. J., Anker, S. D., Berne, C., Cosentino, F., Danchin, N., . . . Zamorano, J. L. (2014). ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD - summary. *Diab Vasc Dis Res, 11*(3), 133-173. doi:10.1177/1479164114525548

Salpeter, S. R., Buckley, N. S., Kahn, J. A., & Salpeter, E. E. (2008). Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. *Am J Med, 121*(2), 149-157.e142. doi:10.1016/j.amjmed.2007.09.016

Sato, K. K., Hayashi, T., Harita, N., Yoneda, T., Nakamura, Y., Endo, G., & Kambe, H. (2009). Combined measurement of fasting plasma glucose and A1C is effective for the prediction of type 2 diabetes: the Kansai Healthcare Study. *Diabetes Care, 32*(4), 644-646. doi:10.2337/dc08-1631

Shimazaki, T., Kadowaki, T., Ohyama, Y., Ohe, K., & Kubota, K. (2007). Hemoglobin A1c (HbA1c) predicts future drug treatment for diabetes mellitus: a follow-up study using routine clinical data in a Japanese university hospital. *Transl Res, 149*(4), 196-204. doi:10.1016/j.trsl.2006.09.008

Shubrook, J. H., Bokaie, B. B., & Adkins, S. E. (2015). Empagliflozin in the treatment of type 2 diabetes: evidence to date. *Drug Des Devel Ther, 9*, 5793-5803. doi:10.2147/dddt.S69926

Shyangdan, D. S., Royle, P., Clar, C., Sharma, P., Waugh, N., & Snaith, A. (2011). Glucagon-like peptide analogues for type 2 diabetes mellitus. *Cochrane Database Syst Rev*(10), Cd006423. doi:10.1002/14651858.CD006423.pub2

Sinnaeve, P. R., Steg, P. G., Fox, K. A., Van de Werf, F., Montalescot, G., Granger, C. B., . . . Avezum, A. (2009). Association of elevated fasting glucose with increased short-term and 6-month mortality in ST-segment elevation and non-ST-segment elevation acute coronary syndromes: the Global Registry of Acute Coronary Events. *Arch Intern Med, 169*(4), 402-409. doi:10.1001/archinternmed.2008.572

Stamler, J., Stamler, R., & Neaton, J. D. (1993). Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. *Arch Intern Med, 153*(5), 598-615.

Stamler, J., Wentworth, D., & Neaton, J. D. (1986). Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *Jama, 256*(20), 2823-2828.

Sturlaugsdottir, R., Aspelund, T., Bjornsdottir, G., Sigurdsson, S., Thorsson, B., Eiriksdottir, G., & Gudnason, V. (2016). Prevalence and determinants of carotid plaque in the cross-sectional REFINE-Reykjavik study. *BMJ Open, 6*(11), e012457. doi:10.1136/bmjopen-2016-012457

Tabas, I., Tall, A., & Accili, D. (2010). The impact of macrophage insulin resistance on advanced atherosclerotic plaque progression. *Circ Res, 106*(1), 58-67. doi:10.1161/circresaha.109.208488

Tamita, K., Katayama, M., Takagi, T., Akasaka, T., Yamamuro, A., Kaji, S., . . . Kihara, Y. (2007). Impact of newly diagnosed abnormal glucose tolerance on long-term prognosis in patients with acute myocardial infarction. *Circ J, 71*(6), 834-841.

The R Foundation. (2016). R: A language and environment for statistical computing: R Foundation for Statistical Computing, Vienna, Austria. Retrieved from http://www.R-project.org/

Tregouet, D. A., Konig, I. R., Erdmann, J., Munteanu, A., Braund, P. S., Hall, A. S., . . . Samani, N. J. (2009). Genome-wide haplotype association study identifies the SLC22A3-LPAL2-LPA gene cluster as a risk locus for coronary artery disease. *Nat Genet, 41*(3), 283-285. doi:10.1038/ng.314

Tuomilehto, J., Lindstrom, J., Eriksson, J. G., Valle, T. T., Hamalainen, H., Ilanne-Parikka, P., . . . Uusitupa, M. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med, 344*(18), 1343-1350. doi:10.1056/nejm200105033441801

Virmani, R., Burke, A. P., & Farb, A. (1999). Plaque rupture and plaque erosion. *Thromb Haemost, 82 Suppl 1*, 1-3.

Virmani, R., Burke, A. P., Kolodgie, F. D., & Farb, A. (2002). Vulnerable plaque: the pathology of unstable coronary lesions. *J Interv Cardiol, 15*(6), 439-446.

Whiting, D. R., Guariguata, L., Weil, C., & Shaw, J. (2011). IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract, 94*(3), 311-321. doi:10.1016/j.diabres.2011.10.029

Wilson, P. W., D'Agostino, R. B., Levy, D., Belanger, A. M., Silbershatz, H., & Kannel, W. B. (1998). Prediction of coronary heart disease using risk factor categories. *Circulation, 97*(18), 1837-1847.

World Health Organization. (2006). Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: Report of WHO/IDF consultation. Retrieved from

https://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/

World Health Organization. (2011). Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus*. Abbreviated report of WHO consultation.* Retrieved from

https://www.who.int/diabetes/publications/report-hba1c_2011.pdf

World Health Organization. (2017). Fact sheets: Diabetes. Retrieved from http://www.who.int/news-room/fact-sheets/detail/diabetes

World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. (2013). *JAMA, 310*(20), 2191-2194. doi:10.1001/jama.2013.281053

Zinman, B., Wanner, C., Lachin, J. M., Fitchett, D., Bluhmki, E., Hantel, S., . . . Inzucchi, S. E. (2015). Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med, 373*(22), 2117-2128. doi:10.1056/NEJMoa1504720

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Editor's Choice- Diagnosis of type 2 diabetes and prediabetes among patients with acute coronary syndromes

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Abstract

Background: Previously undetected dysglycaemia is common among patients with acute coronary syndromes (ACSs). The aim of this study was to identify the most reliable method of diagnosing type 2 diabetes mellitus (T2DM) and prediabetes in ACS patients.

Methods: Patients admitted to the coronary care unit with ACSs and no previous history of T2DM were consecutively included in the study. Glucose metabolism was measured by glycated haemoglobin (HbA1c), fasting plasma glucose (FPG) and 2-hour plasma glucose (2hPG) with a standard oral glucose tolerance test during hospital admission, and this process was repeated 3 months later. In this study, the diagnosis of T2DM required at least two measurements above the diabetes cut-off point according to current American Diabetes Association and World Health Organization criteria.

Results: A total of 250 patients were included in the study. T2DM was diagnosed in 7.2%. The sensitivities for detecting T2DM were 33.3%, 61.1% and 77.8% during admission and 27.8%, 61.1% and 72.2% at follow-up for HbA1c, FPG and 2hPG, respectively. The positive predictive values (PPVs) for diagnosing T2DM were 100%, 91.7% and 51.9% during admission and 71.4%, 91.7% and 65.0% at follow-up for HbA1c, FPG and 2hPG, respectively. The specificities and negative predictive values were high for all methods. By combining all measurements, the sensitivity was 100% and the PPV was 44.2%, while the combination of all HbA1c and FPG measurements provided 88.9% sensitivity and 80.0% PPV.

Conclusion: Diagnosis of T2DM can be reliably carried out by repeated measurements of FPG and HbA1c in ACS patients, with limited added value of an oral glucose tolerance test.

Keywords

Type 2 diabetes, prediabetes, diagnosis, acute coronary syndrome, cardiovascular disease(s)

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Background

Type 2 diabetes mellitus (T2DM) is a serious metabolic derangement characterised by hyperglycaemia, insulin resistance and hyperinsulinaemia leading to micro- and macro-vascular complications, and it is a major risk factor for cardiovascular disease (CVD).[1] The prevalence of T2DM has been increasing in recent years.[2]

Several studies have shown a high prevalence of undiagnosed dysglycaemia in patients with acute coronary syndromes

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(ACSs).[3–5] Recently detected dysglycaemia in patients with myocardial infarction is known to convey a significantly increased risk of cardiovascular morbidity and mortality.[6,7]

Currently, there are two main diagnostic criteria for dysglycaemia: the World Health Organization (WHO) criteria[8,9] and the American Diabetes Association (ADA) criteria.[10] Both of these criteria concur on the diagnosis of T2DM using fasting plasma glucose (FPG), a standardised 2-hour oral glucose tolerance test (OGTT) and glycated haemoglobin (HbA1c) with at least two measurements required to be above a specific diagnostic cut-off point.[8–11] However, there is a difference in the diagnostic criteria for prediabetes (presenting a high risk for diabetes). While the ADA criteria for prediabetes include using FPG, 2-hour plasma glucose (2hPG) and HbA1c, the WHO criteria include only FPG and 2hPG, with a higher cut-off value for FPG compared to the ADA criteria.[8–11]

These criteria are applied as diagnostic tests in the general population. However, the ADA and WHO guidelines provide no consensus on how to identify metabolic derangement in high-risk groups such as patients with ACSs.

In clinical practice, FPG and HbA1c are frequently applied diagnostic tools, as they are considered to be more convenient compared to the OGTT. However, studies suggest that the OGTT identifies a larger proportion of CVD patients with metabolic derangements than HbA1c or FPG alone and has been used as the 'gold standard' for the diagnosis of T2DM for many years. These previous studies have relied on single measurements of metabolic perturbations as a screening test for diabetes and prediabetes.[3,4,12] A study on the detection of T2DM in patients with established CVD with at least two measurements above the diagnostic cut-off points according to the current ADA and WHO guidelines has not been published previously.

The aim of this study was to evaluate the diagnostic capacity of different methods for identifying T2DM and prediabetes in patients with ACSs who have not previously been diagnosed with T2DM.

Methods

Patients admitted to the coronary care unit of Landspitali, the University Hospital of Iceland, with a diagnosis of ACS were consecutively included in the study. ACS was defined according to the joint European Society of Cardiology (ESC) and American College of Cardiology recommendations.[13] Patients with known T2DM, cognitive dysfunction or living outside the catchment area of the hospital were excluded from the study.

Informed written consent was obtained from each participant prior to any study-related procedure. The study protocol adhered to the principles laid out in the Declaration of Helsinki[14] and was approved by the Icelandic Bioethics Committee (VSN: 13-069-S1). Information on demographics, risk factors, medication and lifestyle was obtained from the patients during admission and from hospital records.

Glucose metabolism was evaluated by using FPG, HbA1c and a standard 2-hour OGTT. The OGTT was performed after an overnight fast of at least 10 hours and after study subjects ingested a solution containing 75 g of glucose. Blood samples for the measurement of plasma glucose were obtained 2 hours later. Measurements of glucose metabolism were performed during hospitalisation, ideally 3–5 days after admission, and repeated by at least 3 months after discharge from hospital. All samples collected for venous plasma glucose measurements were centrifuged and analysed immediately after blood collection. Glucose levels were determined using reagents, calibrators and Vitros 250/950 analysers from Ortho Clinical Diagnostics (Rochester, NY, USA) and HbA1c levels were determined using reagents, calibrators and Cobas c311 analysers from Roche (Mannheim, Germany).

After a complete set of measurements during hospitalisation and by 3 months later had been obtained, each patient was classified into one of the following three categories: normal glucose metabolism (NGM), prediabetes or T2DM. The classification was based on the WHO or the ADA criteria, where prediabetes was defined as either FPG 6.1–6.9 mmol/L (110–125 mg/dL) or 2hPG 7.8–11.0 mmol/L (140–199 mg/dL) according to the WHO criteria and HbA1c 5.7–6.4% (39–47 mmol/mol) or FPG 5.6–6.9 mmol/l (100–125 mg/dL) according to the ADA criteria. Both the WHO and the ADA criteria define T2DM as HbA1c $\geqslant$6.5% (48 mmol/mol), FPG $\geqslant$7.0 mmol/L (126 mg/dL) or 2hPG $\geqslant$11.1 mmol/L (200 mg/dL).[8–10]

The reference or 'gold standard' for the diagnosis of T2DM according to the ADA and WHO guidelines was when any two measurements were above the specific cut-off value for HbA1c, FPG or 2hPG during admission and follow-up, respectively. At least one measurement above the diagnostic cut-off point for T2DM or for prediabetes during admission or at follow-up was needed in order to be classified as having prediabetes.

Standard descriptive statistical methods were used and the results presented as mean (SD). Differences in continuous variables were estimated with two-sample *t*-tests. Pearson's correlation coefficient was calculated and the significance of correlations was estimated with *t*-tests. The diagnostic capacity of HbA1c, FPG and 2hPG to detect T2DM was analysed with receiver operating characteristic (ROC) curves and the area under the curve (AUC) was calculated. Optimal cut-off values were those that maximised the perpendicular distance from the diagonal line. R (version 3.2.2) was used for all statistical analyses.[15]

Results

A total of 435 patients admitted to the coronary care unit with a diagnosis of ACS were eligible for inclusion in the study. Among these, 90 were discharged before the OGTT could be performed, 60 refused participation and two died

shortly after admission. Therefore, 283 patients provided written informed consent for participation and were included in the study. Before the follow-up visit at 3 months, 18 patients were lost to follow-up, 10 patients withdrew consent, three died and one had a stroke. One was prescribed metformin before discharge and was therefore excluded. The remaining 250 patients comprised the study population.

The baseline characteristics of the study population are presented in Table 1. The mean age was 64.0 (10.9) years, 78.0% were male and all participants in the study were Caucasian of European origin. During admission, 4.4%, 24.8%, 30.8%, 26% and 14% of patients had their glucose measurements taken on day 2, 3, 4, 5 and 6 or later after admission, respectively. There were no significant differences in FPG and 2hPG measurements taken on different days after admission. The mean value of HbA1c was 5.4% (36 mmol/mol) during admission and was 5.5% (37 mmol/mol) at follow-up ($p=0.338$). FPG was significantly lower during admission, being 5.3 mmol/L (95 mg/dL) compared to 5.5 mmol/L (99 mg/dL) at follow-up ($p<0.005$). However, 2hPG was significantly higher during admission, being 7.8 mmol/L (140 mg/dL) compared to 6.7 mmol/L (121 mg/dL) at follow-up ($p<0.005$). The correlations between measurements during admission and at follow-up were 0.50, 0.63 and 0.60 for HbA1c, FPG and 2hPG, respectively ($p<0.005$).

Table 1. Baseline characteristics of the patients included in the study.

Variable	Patients ($n=250$)
Age, years (SD)	64.0 (10.9)
Male sex, % (*n*)	78.0% (195)
Hypertension[a], % (*n*)	56.4% (141)
Mean SBP, mmHg (SD)	139 (23)
Mean DBP, mmHg (SD)	77 (13)
Hypercholesterolaemia[b], % (*n*)	46% (115)
History of smoking[c], % (*n*)	73.6% (184)
Mean pack-years (SD)	26.7 (20.7)
Family history of CHD[d], % (*n*)	66.0% (165)
Previous history of ACS, % (*n*)	33.2% (83)
BMI, kg/m^2 (SD)	28.6 (4.2)
Waist-to-hip ratio, cm (SD)	0.98 (0.07)
UAP, % (*n*)	30.0% (75)
NSTEMI, % (*n*)	40.8% (102)
STEMI, % (*n*)	29.2% (73)

[a]History of hypertension or is on antihypertensive medication.
[b]History of hypercholesterolaemia or is on lipid-lowering medication.
[c]History of being a current or previous smoker.
[d]First-degree relative with a history of CHD.
SBP: systolic blood pressure; DPB: diastolic blood pressure; CHD: coronary heart disease; BMI: body mass index; UAP: unstable angina pectoris; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction.

During admission, 3%, 5% and 13% of the study population was measured above the cut-off value of T2DM for HbA1c, FPG and 2hPG, respectively. At follow-up 3 months later, 3%, 5% and 8% were measured above the cut-off value of T2DM for HbA1c, FPG and 2hPG, respectively. When applying the ADA and WHO criteria, 7.2% of patients with ACSs were diagnosed with T2DM.

The sensitivities of HbA1c, FPG and 2hPG for diagnosing T2DM during admission were 33.3%, 61.1% and 77.8%, respectively. The specificities were 100%, 99.6% and 94.3% for HbA1c, FPG and 2hPG, respectively. The corresponding values at follow-up for sensitivity were 27.8%, 61.1% and 72.2% and for specificity were 99.0%, 99.6% and 97.0% for HbA1c, FPB and 2hPG, respectively (Table 2).

The positive predictive values (PPVs) of HbA1c, FPG and 2hPG for diagnosing T2DM during admission were 100%, 91.7% and 51.9%, respectively. The negative predictive values (NPVs) during admission were 94.9%, 97.0% and 98.2% for HbA1c, FPG and 2hPG, respectively. The corresponding PPVs at follow-up were 71.4%, 91.7% and 65.0% and the NPVs were 94.7%, 97.0% and 97.8% for HbA1c, FPB and 2hPG, respectively.

Table 2. Sensitivities, specificities, positive predictive values and negative predictive values of different measurements for the diagnosis of type 2 diabetes mellitus.

	During admission			At follow-up after 3 months			Combined results			
	HbA1c	*FPG*	*2hPG*	*HbA1c*	*FPG*	*2hPG*	*Complete protocol*[a]	*ESC guidelines*[b]	*OGTT*[c]	*HbA1c and FPG*[d]
Sensitivity	33.3%	61.1%	77.8%	27.8%	61.1%	72.2%	100%	100%	100%	88.9%
Specificity	100%	99.6%	94.3%	99.0%	99.6%	97.0%	89.7%	96.1%	90.5%	98.3%
PPV	100%	91.7%	51.9%	71.4%	91.7%	65.0%	44.2%	66.7%	45.0%	80.0%
NPV	94.9%	97.0%	98.2%	94.7%	97.0%	97.8%	100%	100%	100%	99.1%

[a]HbA1c, FPG and 2hPG during admission and at follow-up 3 months later.
[b]HbA1c and FPG during admission and FPG and 2hPG at follow-up 3 months later.
[c]FPG and 2hPG during admission and at follow-up 3 months later.
[d]HbA1c and FPG during admission and at follow-up 3 months later.
HbA1c: glycated haemoglobin; FPG: fasting plasma glucose; 2hPG: 2-hour plasma glucose; ESC: European Society of Cardiology; OGTT: oral glucose tolerance test; PPV: positive predictive value; NPV: negative predictive value.

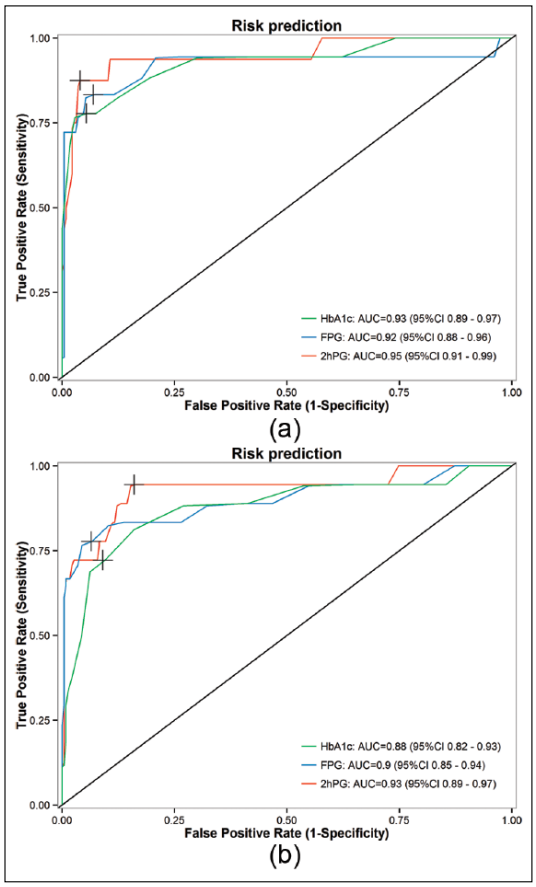

Figure 1. Receiver operating characteristic curves. The ability of HbA1c, FPG and 2hPG to diagnose types 2 diabetes mellitus during admission (a) and at follow-up 3 months later (b). HbA1c: glycated haemoglobin; FPG: fasting plasma glucose; 2hPG: 2-hour plasma glucose; AUC: area under the curve; CI: confidence interval.

When combining results from HbA1c and FPG during admission and FPG and 2hPG (OGTT) at follow-up 3 months later according to current ESC guidelines,[16] the sensitivity was 100% and the PPV was 66.7%, while for the combined results from HbA1c and FPG during admission and at follow-up, the sensitivity was 88.9% and the PPV was 80.0%.

The diagnostic capacity of HbA1c, FPG and 2hPG for detecting T2DM was analysed with ROC curves. For HbA1c, FPG and 2hPG during admission, the AUCs were 0.93, 0.92 and 0.95, respectively (Figure 1(a)). The corresponding values of AUCs at follow-up for HbA1c, FPG and 2hPG were 0.88, 0.90 and 0.93, respectively (Figure 1(b)).

By ROC analysis, the optimal cut-off values for T2DM were as follows: HbA1c of more than 6.0% (42 mmol/mol) during admission was able to predict newly diagnosed T2DM with a sensitivity of 77.8% and a specificity of 94.6%. The corresponding values for FPG of more than 5.9 mmol/L (106 mg/dL) were 83.3% and 93.1%, and for 2hPG of more than 11.6 mmol/L (209 mg/dL) the corresponding values were 87.5% and 96.0% (Figure 1(a)). At follow-up 3 months later, a HbA1c value of more than 5.9% (41 mmol/mol) was able to predict newly diagnosed T2DM with a sensitivity of 72.2% and a specificity of 90.9%. The corresponding values for FPG of more than 6.3 mmol/L (113 mg/dL) were 77.8% and 93.5%, and for 2hPG of more than 8.1 mmol/L (146 mg/dL) the corresponding values were 94.4% and 84.0% (Figure 1(b)).

The ADA criteria using HbA1c and FPG during admission and follow-up identified 53.6% of the study cohort as having prediabetes, while 39.2% had NGM. Impaired fasting glucose (IFG) on the FPG identified 77.6% and HbA1c identified 53.0% as having prediabetes. The proportion of patients classified as having prediabetes by both tests was 30.6%. When applying the WHO criteria, using the OGTT (FPG and 2hPG) during admission and at follow-up, 44.4% of the study population was found to have prediabetes, while 48.4% had NGM. IFG on the FPG identified 31.5% and impaired glucose tolerance on the 2hPG identified 86.5% as having prediabetes. The proportion of patients classified as having prediabetes by both tests was 18.0%.

Discussion

In the present study, we used current ADA and WHO guidelines in order to evaluate the diagnostic capacity of different measurements of glucose metabolism in patients who had been hospitalised with ACSs. Previous studies in this patient population have used single measurements of FPG and HbA1c as screening tests in order to detect T2DM as defined by an abnormal OGTT, and are therefore not directly comparable to the present study.[3,4,12] By basing the diagnosis of T2DM on at least two values above the cut-off point for T2DM as outlined in current ADA and WHO guidelines, we have a more robust clinical endpoint compared to using OGTT alone.

In concordance with previous studies on dysglycaemia in patients with ACSs, we found 2hPG to have the highest sensitivity for identifying patients with T2DM, while the HbA1c has the lowest sensitivity among the three diagnostic tests. However, in this study, the PPVs for diagnosing T2DM by 2hPG were low, being 51.9% and 65.0% during admission and at follow-up, respectively. Among the 27 patients classified as having T2DM based on 2hPG during admission, only 14 patients were later confirmed as having T2DM according to ADA and WHO guidelines. On the other hand, the PPVs for HbA1c and FPG were considerably higher, ranging from 71.4% to 100%. The ROC curve analyses suggest that a lower cut-off point for T2DM would provide optimal sensitivity and specificity for HbA1c and

FPG during admission and for all three measurements during follow-up, while a higher cut-off point is suggested for 2hPG during admission for optimal sensitivity and specificity. This indicates that lower cut-off points might be appropriate for HbA1c and FPG in this patient population, while 2hPG is not helpful shortly after ACS due to adrenergic activation and insulin resistance.

The results shown in Table 2 demonstrate that any single method is not sufficient to identify T2DM among ACS patients. When applying the OGTT during admission and at follow-up, the sensitivity was 100%, but the PPV was only 45.0%. The ESC guidelines for the diagnosis of dysglycaemia in patients with CVD recommend a staged approach of HbA1c and FPG measurements as the first screening test for all patients with CVD, adding OGTT only for those with inconclusive results.[16] When applying the protocol from the ESC guidelines, the sensitivity was 100%, while the PPV was 66.7% and the NPV was 100%. By abandoning the OGTT and relying solely on HbA1c and FPG during admission and at follow-up 3 months later, the sensitivity for diagnosing T2DM was 88.9%, the PPV was 80% and the NPV was 99.1% (Table 2). Without the OGTT, only two patients (0.8%) from a total of 250 would have been misclassified with prediabetes instead of T2DM. A total of 20 (8%) out of 250 patients were wrongly classified as having T2DM by the OGTT according to ADA and WHO guidelines.

The prevalence of dysglycaemia is considerably lower in our study compared to previous studies.[5] The proportions of patients classified as having prediabetes by both tests according to the ADA and WHO criteria were relatively low, being 30.6% and 18.0%, respectively. The concordance in classifying patients as having prediabetes with both the ADA and WHO criteria was 52.2%. This reflects the different aspects of metabolic derangement identified by HbA1c, FPG and 2hPG.

Several studies have shown an increased risk of future cardiovascular events and mortality among patients with acute myocardial infarction and hyperglycaemia, even below the diabetic threshold.[17,18] Lifestyle interventions should be offered to patients with prediabetes in order to prevent them from developing T2DM.[19] In addition, patients who have been identified with prediabetes could be offered pharmacotherapy with metformin in order to reduce the risk of T2DM development.[20] The benefits of metformin has also been illustrated in the UK Prospective Diabetes Study, where a long-term follow-up of patients with T2DM showed a reduced risk of myocardial infarction and all-cause mortality in patients who had been treated with metformin.[21] Guidelines recommend lifestyle changes for patients with T2DM of improving diet and increasing physical activity in order to promote weight loss and lower cardiovascular risk.[16] This underscores the importance of identifying ACS patients with dysglycaemia.

The risk of CVD is a continuum across glucose values in the setting of primary prevention. Current guidelines use cut-off values for diabetes identified by the level that has been shown to cause microvascular complications in the general population. While macrovascular complications of metabolic derangements may occur at lower levels of plasma glucose,[17,18] it might be appropriate to identify lower cut-off values in patients suffering from ACSs. This view is supported by the ROC analysis in the current results. The two clinical disease entities of metabolic derangement and ACS may indeed be considered to be two faces of the same coin, with a few common driving risk factors such as obesity, hypertension and a hypercoagulability state that may be responsible for disease development.[22] Both conditions call for aggressive secondary preventive interventions, but more importantly, a broad and comprehensive upstream approach in order to reduce the burden of disease in the future.

A limitation of our study is the relatively low prevalence of T2DM compared to earlier studies. This is due to the strict diagnostic criteria applied for T2DM in our study and the relatively low prevalence of T2DM in the Icelandic population compared to other western countries.[23] During admission, some measurements were taken early, even though previous studies have suggested that glucose measurements should be taken on day 4 or 5 after admission due to insulin resistance during the first days after admission.[3,16] However, when FPG and 2hPG measurements made on day 5 were compared with measurements made on day 2, 3 or 4 or on day 6 or later, no significant differences were found. Finally, the participants in the study were all Caucasian of European origin.

In conclusion, by applying strict diagnostic criteria according to current ADA and WHO guidelines, our findings indicate that repeated measurements of FPG and HbA1c during hospitalisation and 3 months after discharge reliably identifies previously unknown T2DM in patients with ACSs. This approach can be used with high sensitivities and PPVs of detecting T2DM, significantly reducing the need for OGTT in these patients. Lower cut-off values for HbA1c and FPG might be appropriate in order to optimise the diagnostic sensitivity with high specificity in this group of patients with macrovascular disease.

Conflict of interest

The authors declare that there is no conflict of interest.

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References

1. Go AS, Mozaffarian D, Roger VL, et al. Executive summary: Heart disease and stroke statistics – 2014 update: A report from the American Heart Association. *Circulation* 2014; 129: 399–410.

2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: A pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016; 387: 1513–1530.
3. Norhammar A, Tenerz A, Nilsson G, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: A prospective study. *Lancet* 2002; 359: 2140–2144.
4. Bartnik M, Ryden L, Ferrari R, et al. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart. *Eur Heart J* 2004; 25: 1880–1890.
5. Gyberg V, De Bacquer D, Kotseva K, et al. Screening for dysglycaemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test, and HbA1c: A report from EUROASPIRE IV – A survey from the European Society of Cardiology. *Eur Heart J* 2015; 36: 1171–1177.
6. Bartnik M, Malmberg K, Norhammar A, et al. Newly detected abnormal glucose tolerance: An important predictor of long-term outcome after myocardial infarction. *Eur Heart J* 2004; 25: 1990–1997.
7. Lenzen M, Ryden L, Ohrvik J, et al. Diabetes known or newly detected, but not impaired glucose regulation, has a negative influence on 1-year outcome in patients with coronary artery disease: A report from the Euro Heart Survey on diabetes and the heart. *Eur Heart J* 2006; 27: 2969–2974.
8. World Health Organization. *Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: Report of a WHO/IDF consultation*. Geneva: WHO, 2006.
9. World Health Organization. *Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Abbreviated report of WHO consultation*. Geneva: WHO, 2011.
10. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2012; 35(Suppl. 1): S64–S71.
11. Alberti KG and Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; 15: 539–553.
12. Hage C, Lundman P, Ryden L, et al. Fasting glucose, HbA1c, or oral glucose tolerance testing for the detection of glucose abnormalities in patients with acute coronary syndromes. *Eur J Prev Cardiol* 2013; 20: 549–554.
13. Myocardial infarction redefined – A consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 2000; 21: 1502–1513.
14. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; 310: 2191–2194.
15. R Core Team (2015). *R: A language and environment for statistical computing. R foundation for statistical computing*. Vienna: Austria, 2015.
16. Ryden L, Grant PJ, Anker SD, et al. ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD – Summary. *Diab Vasc Dis Res* 2014; 11: 133–173.
17. Coutinho M, Gerstein HC, Wang Y, et al. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* 1999; 22: 233–240.
18. Sinnaeve PR, Steg PG, Fox KA, et al. Association of elevated fasting glucose with increased short-term and 6-month mortality in ST-segment elevation and non-ST-segment elevation acute coronary syndromes: The Global Registry of Acute Coronary Events. *Arch Intern Med* 2009; 169: 402–409.
19. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; 344: 1343–1350.
20. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: The Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol* 2015; 3: 866–875.
21. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; 359: 1577–1589.
22. Leon BM and Maddox TM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. *World J Diabetes* 2015; 6: 1246–1258.
23. Bergsveinsson J, Aspelund T, Gudnason V, et al. [Prevalence of type 2 diabetes mellitus in Iceland 1967–2002]. *Laeknabladid* 2007; 93: 397–402.

Paper II

PLOS ONE

RESEARCH ARTICLE

Oral glucose tolerance test predicts increased carotid plaque burden in patients with acute coronary syndrome

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Abstract

Background

Type 2 diabetes and prediabetes are established risk factors for atherosclerosis. The aim of this study was to evaluate the atherosclerotic plaque burden in the carotid arteries of patients with acute coronary syndrome according to their glycemic status.

Methods

Patients with acute coronary syndrome and no previous history of type 2 diabetes were consecutively included in the study. Glucose metabolism was evaluated with fasting glucose in plasma, HbA1c and a standard two-hour oral glucose tolerance test. Atherosclerotic plaque in the carotid arteries was evaluated with a standardized ultrasound examination where total plaque area was measured and patients classified as having no plaque or a significant plaque formation.

Results

A total of 245 acute coronary syndrome patients (male 78%, 64 years (SD: 10.9)) were included. The proportion diagnosed with normal glucose metabolism, prediabetes and type 2 diabetes was 28.6%, 64.1% and 7.3%, respectively. A significant atherosclerotic plaque was found in 48.5%, 66.9% and 72.2% of patients with normal glucose metabolism, prediabetes and type 2 diabetes, respectively. An incremental increase in total plaque area was found from normal glucose metabolism to prediabetes (25.5%) and from normal glucose metabolism to type 2 diabetes (35.9%) ($p = 0.04$). When adjusted for conventional cardiovascular risk factors the OR of having significant atherosclerotic plaque in the carotid arteries was 2.17 (95% CI 1.15–4.15) for patients with newly diagnosed dysglycemia compared to patients with normal glucose metabolism. When additionally adjusted for the 2-hour plasma glucose after glucose loading (2hPG) the OR attenuated to 1.77 (95% CI 0.83–3.84).

and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Conclusion

Newly detected dysglycemia is an independent predictor of significant atherosclerotic plaque in the carotid arteries with oral glucose tolerance test as a major determinant of carotid plaque burden in this group of individuals with acute coronary syndrome.

Introduction

Type 2 diabetes mellitus (T2DM) and prediabetes are established risk factors for atherosclerosis and cardiovascular disease (CVD) and associated with increased mortality compared to those with normal glucose metabolism (NGM) [1]. Patients with acute coronary syndromes (ACS) have a high prevalence of undiagnosed T2DM and prediabetes [2, 3] at hospital admission. There is evidence that myocardial damage may already be present at the time of clinical diagnosis of T2DM indicating that the dysglycemia (T2DM or prediabetes) has remained undiagnosed for months or years [4]. Moreover, studies have indicated that newly diagnosed dysglycemia in patients with myocardial infarction is a major risk factor for future cardiovascular events [5, 6]. It therefore has been recommended to screen for metabolic derangements in patients admitted to hospital for ACS [7].

Atherosclerotic disease in the carotid arteries has been associated with coronary artery disease and is an indicator of an increased atherosclerotic burden [8]. Measuring total plaque area (TPA) in the carotid arteries is a noninvasive method to quantify atherosclerotic burden. Carotid plaque is also an independent predictor of CVD and improves risk stratification in addition to traditional risk factors for CVD [9, 10].

We hypothesized that patients with ACS have a high prevalence of atherosclerotic plaque in the carotid arteries and that ACS patients with newly diagnosed T2DM and prediabetes have increased atherosclerotic burden compared to ACS patients with NGM. Therefore, we set out to evaluate the atherosclerotic plaque burden in the carotid arteries of patients with ACS and related the plaque burden to newly detected metabolic derangements.

Methods

Study population

Patients admitted to the coronary care unit of Landspitali, the University Hospital of Iceland with the diagnosis of ACS were consecutively included in the study between June 2013 to October 2014. ACS was defined according to the joint European Society of Cardiology (ESC) and American College of Cardiology recommendations [11]. Patients with previously known T2DM, cognitive dysfunction, living in a nursing home or outside the catchment area of the hospital were excluded from the study.

Prior to any study related procedure informed written consent was obtained for each participant. The study protocol adhered to the principles laid out in the Declaration of Helsinki [12] and was approved by the Icelandic Bioethics Committee (VSN: 13-069-S1). Information on prespecified demographic, personal, medication and lifestyle data were obtained from patients during admission and from hospital records. Patients with previous history of hypertension or on blood pressure lowering medication were classified as having hypertension. Likewise, patients with previous history of hypercholesterolemia or on statins were classified as hypercholesterolemia. Patients with 1st degree family members with coronary artery disease (CAD) were defined as having family history of CAD.

Diagnosis of glucose metabolism

Glucose metabolism was evaluated after an overnight fast of at least ten hours with fasting plasma glucose (FPG), glycated hemoglobin (HbA1c) and a standard oral glucose tolerance test (OGTT). Two hours after ingesting a solution containing 75 g of glucose measurements of plasma glucose (2hPG) were made. Measurements of glucose metabolism were made during hospitalization, generally on third to fifth day after admission, and repeated at least three months later. All samples collected for venous plasma glucose measurements were centrifuged and analyzed immediately after blood collection. Glucose levels were determined using reagents, calibrators and Vitros 250/950 analyzers from Ortho Clinical Diagnostics, Rochester, USA and HbA1c levels were determined using reagents, calibrators and Cobas c311 analyzer from Roche, Mannheim, Germany.

The classification of glucose metabolism was based on the American Diabetes Association (ADA) criteria, where prediabetes was defined as HbA1c 5.7–6.4% (39–47 mmol/mol), FPG 5.6–6.9 mmol/l (100–125 mg/dL) or 2hPG 7.8–11.0 mmol/l (140–199 mg/dL) and T2DM as HbA1c $\geq$6.5% (48 mmol/mol), FPG $\geq$7.0 mmol/l (126 mg/dL) or 2hPG $\geq$11.1 mmol/l (200 mg/dL) [13]. Patients were classified as having T2DM if at least two measurements were above the cut-point for T2DM according to the ADA criteria while patients with one measurement above the cut-point of T2DM or at least one measurement above the cut-point for prediabetes were classified as having prediabetes.

Carotid imaging

Three months after discharge an ultrasound imaging of the carotids was performed according to a standardized protocol [14]. A Toshiba Aplio 300 system with a two-dimensional 6.8 MHz linear array transducer was used for all ultrasound imaging by a trained sonographer. Standardized longitudinal B-mode images of the common carotid artery, bifurcation and internal carotid artery from the near and far wall in the left and right carotid arteries were examined. The lateral extent of the common carotid segment was defined relative to the tip of the flow divider, which is normally the most clearly defined anatomical reference in the proximity of the carotid bifurcation. The bifurcation and internal carotid segments were also defined by using the tip of the flow divider. The segments were defined as: the near wall and far wall of the arterial segment extending from 10 mm to 20 mm proximal to the tip of the flow divider into the common carotid artery (CCA); the near wall and far wall of the carotid bifurcation beginning at the tip of the flow divider and extending 10 mm proximal to the flow divider tip (BIF); and the near wall and far wall of the proximal 10 mm of the internal carotid artery (ICA). Images for the assessment of the carotid intima-media thickness (cIMT) were acquired from the predefined 10 mm segment of each CCA at defined interrogation angles using the Meijers arc [15] and standard images obtained from four angels at each site. The mean cIMT of the near and far walls were determined from a single image at each interrogation for both CCA and the mean cIMT values from these sites comprised the cIMT outcome parameter.

Atherosclerotic plaques in the carotid artery segments (BIF and ICA) extending 10 mm proximal and distal from the tip of the flow divider, were categorized as a significant or not. The most severe lesion per segment was assessed [16]. Patients with a least one, clear, reasonable easy to be visualized plaque with intima media thickness of at least twice the thickness of adjacent sites causing at least some diameter reduction of the vessel lumen were classified as having significant plaque. In addition, the Artery Measurements System software (v.2.02.) was used to assess quantitatively the plaque area of all visible plaques in the BIF and ICA segments. An atherosclerotic plaque was defined by an isolated thickening at least double the adjacent normal cIMT by visual assessment. The plaque boundaries were traced with a cursor on the

computer screen and the area (mm^2) for each plaque automatically computed by the program. The TPA was calculated by summing the area of all individual plaques. Acquisition and interpretations were made by trained sonographers [14].

Severity of coronary atherosclerosis

All patients underwent coronary angiography during admission. Coronary arteries with lumen reduction of more than 70% were considered to have a significant stenosis and patients classified of having 0-, 1-, 2- or 3-vessel disease. Gensini score was applied to evaluate the coronary artery disease by the degree of lumen reduction and the importance of the lesion´s location [17].

Statistical analysis

Categorical variables were presented as percentage. Normally distributed continuous variables were presented as means (standard deviation, SD), otherwise as median with interquartile range (IQR). Between group comparison of NGM, prediabetes and T2DM was made using the chi-square test and analysis of variance or Kruskal Wallis test for categorical and continuous variables, respectively. The odds ratio (OR) of having significant plaque in the carotid arteries was estimated with a multivariable logistic regression model. The predictors used were HbA1c, FPG and 2hPG. The association between TPA and risk factors for atherosclerosis was evaluated with general linear regression models, both unadjusted and adjusted for glucometabolic factors and conventional atherosclerotic risk factors: age, gender, hypertension, hypercholesterolemia, smoking status and BMI. The level of statistical significance was set at $p<0.05$. All statistical analyses were performed using the R software version 3.2.2. [18]

Results

A total of 435 patients admitted to the coronary care unit with the diagnosis of ACS were considered for inclusion in the study. Among these, 90 were discharged before the OGTT could be performed, 60 refused participation and two died shortly after admission. Therefore, 283 patients were included in the study shortly after admission. Before the follow-up visit at 3 months, 21 patients were lost to follow-up, 13 patients withdrew consent, three died and one had a stroke. The remaining 245 patients comprised the study population.

The baseline characteristics of the study population are presented in Table 1. The mean age was 64.0 (SD 10.9) years, 78.0% were male and all participants in the study were Caucasian of European origin. A total of 28.6%, 64.1% and 7.3% were diagnosed with NGM, prediabetes and T2DM, respectively. The mean TPA and cIMT in the study population was 103.3 mm^2 (SD 64.7) and 0.90 mm (SD 0.15), respectively.

At least one atherosclerotic plaque was detected in 48.5%, 66.9% and 72.2% of patients with NGM, prediabetes and T2DM, respectively (Table 2). A significant difference in TPA was found between patients diagnosed with NGM (86.8 mm^2 (SD 57.2)) prediabetes (108.9 mm^2 (SD 66.1)) and T2DM (118.0 mm^2 (SD 70.7)) ($p<0.04$). The incremental increase in TPA was 25.5% and 35.9% among patients diagnosed with prediabetes and T2DM, respectively, compared to patients with NGM. A significant difference in BMI, waist-to-hip ratio, smoking status, high-sensitivity C-reactive protein (hS-CRP), insulin resistance (HOMA-IR), number of diseased coronary arteries and Gensini score was found between different glucose metabolism categories (Table 2). Increased TPA was detected among patients with impaired glucose tolerance (IGT), either alone or in combination with impaired fasting glucose (IFG), compared with patients with isolated IFG (Table 3). No difference was detected in cIMT between patients with different glucose metabolism categories while an association with cIMT was found

Table 1. Baseline characteristics.

	(n = 245)
Age, years (SD)	64.0 (10.9)
Gender	
- Male	191 (78%)
- Female	54 (22%)
Glucose metabolism	
- At admission:	
HbA1c, % (SD)	5.4 (0.5)
FPG, mmol/l (SD)	5.3 (0.9)
2hPG, mmol/l (SD)	7.8 (2.6)
- At follow-up:	
HbA1c, % (SD)	5.5 (0.4)
FPG, mmol/l (SD)	5.5 (0.8)
2hPG, mmol/l (SD)	6.7 (2.6)
hs-CRP, mg/L (IQR)	1.1 (0.6, 2.3)
Insulin, mU/L (SD)	12.8 (8.6)
HOMA-IR (SD)	3.2 (2.4)
TPA, mm^2 (SD)	103.3 (64.7)
Grey-scale median (SD)	37 (10)
Mean cIMT, mm (SD)	0.90 (0.15)
Carotid plaque	
- No plaque	93 (38.0%)
- Significant plaque	152 (62.0%)
BMI, kg/m^2 (SD)	28.7 (4.2)
WHR (SD)	0.98 (0.07)
Smoking status:	
- Never	32.2%
- Previous	44.1%
- Current	23.7%
FH of CAD[a]	65.7%
Hypercholesterolemia	46.1%
Hypertension	56.7%
Previous CAD	33.5%
SBP, mmHg (SD)	139 (22)
DBP, mmHg (SD)	77 (13)
ACS	
- UAP	30.2%
- NSTEMI	40.4%
- STEMI	29.4%
CAD [b]	
- 0-vessel	7.8%
- 1-vessel	39.8%
- 2-vessel	28.7%
- 3-vessel	23.7%
Gensini score (SD)	40.4 (34.6)

SD: standard deviation, FPG: fasting plasma glucose, 2hPG: 2-hour plasma glucose, hs-CRP: high-sensitivity C-reactive protein, IQR: interquartile range, HOMA-IR: homeostatic model assessment insulin resistance, TPA: total plaque area, cIMT: carotid intima-media thickness, BMI: body mass index, WHR: waist to hip ratio, FH: family history, CAD: coronary artery disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, ACS: acute coronary syndrome, UAP: unstable angina pectoris, NSTEMI: non-ST elevation myocardial infarct, STEMI: ST elevation myocardial infarct

[a]CAD with 1st degree family member

[b]$\geq$70% of lumen reduction

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Table 2. Pertinent characteristics of patients divided according to their glucose metabolism.

	NGM (n = 70)	Prediabetes (n = 157)	DM (n = 18)	p-value
Age, years (SD)	64.0 (12.0)	63.9 (10.2)	65.0 (12.5)	0.92
Gender				0.54
- Male	57 (81.4%)	119 (75.8%)	15 (83.3%)	
- Female	13 (18.6%)	38 (24.2%)	3 (16.7%)	
Glucose metabolism				
- At admission:				
HbA1c, % (SD)	5.1 (0.4)	5.4 (0.3)	6.5 (1.0)	**<0.01**
FPG, mmol/l (SD)	4.8 (0.4)	5.3 (0.6)	7.0 (1.5)	**<0.01**
2hPG, mmol/l (SD)	6.3 (0.9)	7.9 (2.1)	13.3 (3.3)	**<0.01**
- At follow-up:				
HbA1c, % (SD)	5.2 (0.3)	5.5 (0.4)	6.1 (0.5)	**<0.01**
FPG, mmol/l (SD)	5.0 (0.4)	5.6 (0.5)	7.1 (1.4)	**<0.01**
2hPG, mmol/l (SD)	5.1 (1.0)	6.8 (2.3)	11.9 (3.2)	**<0.01**
hs-CRP, mg/L median (IQR)	0.7 (0.5, 1.3)	1.4 (0.7, 2.7)	1.4 (0.9, 1.4)	**<0.01**
Insulin, mU/L (SD)	10.47 (6.58)	13.51 (8.90)	16.42 (11.11)	0.07
HOMA-IR, units (SD)	2.33 (1.56)	3.40 (2.41)	4.96 (3.86)	**<0.01**
TPA, mm^2 (SD)	86.8 (57.2)	108.9 (66.1)	118.0 (70.7)	**0.04**
Grey-scale median (SD)	38 (11)	36 (10)	36 (11)	**0.69**
Mean cIMT, mm (SD)	0.87 (0.15)	0.91 (0.14)	0.90 (0.15)	0.28
Carotid plaque				0.13
- No plaque	36 (51.5%)	52 (33.1%)	5 (27.8%)	
- Significant plaque	34 (48.5%)	105 (66.9%)	13 (72.2%)	
BMI, kg/m^2 (SD)	27.8 (4.0)	28.8 (4.1)	31.4 (4.8)	**<0.01**
WHR (SD)	0.96 (0.07)	0.98 (0.08)	1.01 (0.06)	**0.02**
Smoking status:				**0.03**
- Never	44.3%	28.0%	22.2%	
- Previous	44.3%	44.0%	44.5%	
- Current	11.4%	28.0%	33.3%	
FH of CAD[a]	67.1%	64.3%	72.2%	0.78
Hypercholesterolemia	48.6%	43.9%	55.6%	0.54
Hypertension	52.9%	57.3%	66.7%	0.60
Previous CAD	35.7%	30.6%	50.0%	0.22
SBP, mmHg (SD)	139 (22)	139 (23)	137 (18)	0.93
DBP, mmHg (SD)	77 (12)	78 (13)	75 (12)	0.71
ACS				0.57
- UAP	31.4%	28.7%	38.9%	
- NSTEMI	45.7%	38.9%	33.3%	
- STEMI	22.9%	32.4%	27.8%	
CAD[b]				**0.03**
- 0-vessel	10.8%	7.1%	0%	
- 1-vessel	50.0%	35.4%	33.3%	
- 2-vessel	19.6%	37.0%	27.8%	
- 3-vessel	19.6%	20.5%	38.9%	
Gensini score (SD)	38.2 (37.5)	39.1 (32.4)	60.0 (36.3)	**0.04**

NGM: normal glucose metabolism, T2DM: type 2 diabetes mellitus, SD: standard deviation, FPG: fasting plasma glucose, 2hPG: 2-hour plasma glucose, hs-CRP: high-sensitivity C-reactive protein, IQR: interquartile range, HOMA-IR: homeostatic model assessment insulin resistance, TPA: total plaque area, cIMT: carotid intima-media thickness, BMI: body mass index, WHR: waist to hip ratio, FH: family history, CAD: coronary artery disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, ACS: acute coronary syndrome, UAP: unstable angina pectoris, NSTEMI: non-ST elevation myocardial infarct, STEMI: ST elevation myocardial infarct

[a]CAD with 1st degree family member

[b]$\geq$70% of lumen reduction

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Table 3. Carotid plaque burden among patients with IFG, IGT and combination of IFG and IGT.

	IFG (n = 50)	IGT (n = 42)	IFG & IGT (n = 52)	p-value
TPA, mm^2 (SD)	87.8 (53.1)	127.4 (70.4)	123.1 (70.9)	<0.01
Mean cIMT, mm (SD)	0.88 (0.16)	0.91 (0.13)	0.92 (0.13)	0.30
Carotid plaque				0.67
- No plaque	36.0%	28.6%	28.8%	
- Significant plaque	64.0%	71.4%	71.2%	

IFG: impaired fasting glucose, IGT: impaired glucose tolerance, SD: standard deviation, TPA: total plaque area, cIMT: carotid intima-media thickness.

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between different age categories (per 5 years) and gender, 0.030 mm (SE; 0.004, p<0.01) and 0.057 mm (SE; 0.022, p = 0.01), respectively.

When the relationship between the different glucometabolic assessments and carotid plaque were examined, only the 2hPG during admission and at follow-up showed statistically significant unadjusted OR of having significant plaque in the carotid arteries, being 2.37 (95% CI 1.36–4.18) and 2.25 (1.21–4.35), respectively. For HbA1c and FPG classification of dysglycemia the unadjusted OR for the detection of atherosclerotic plaque in the carotids did not reach statistical significance (Table 4A).

When adjusted for conventional atherosclerotic risk factors, the OR for patients diagnosed with dysglycemia according to the 2hPG during admission of having significant plaque in the carotid arteries was 1.92 (95% CI 1.05–3.55) and 1.51 (0.74–3.18) at follow-up. However, the ORs for HbA1c and FPG remained statistically non significant.

Table 4. Carotid plaque burden by different glucose methods.

a) The OR of having significant plaque in the carotid arteries of patients diagnosed with dysglycemia based on different glucometabolic assessments compared to normal glucose level.

	Unadjusted OR, (95% CI)	p-value	[a]Adjusted OR, (95% CI)	p-value
HbA1c				
- Dysglycemia during admission	1.31 (0.69–2.57)	0.41	0.89 (0.44–1.93)	0.74
- Dysglycemia at follow-up	1.74 (0.96–3.27)	0.07	1.58 (0.82–3.13)	0.18
FPG				
- Dysglycemia during admission	1.46 (0.80–2.76)	0.23	1.52 (0.77–3.08)	0.24
- Dysglycemia at follow-up	1.44 (0.85–2.46)	0.18	1.61 (0.89–2.96)	0.12
2hPG				
- Dysglycemia during admission	**2.37 (1.36–4.18)**	**<0.01**	**1.92 (1.05–3.55)**	**0.04**
- Dysglycemia at follow-up	**2.25 (1.21–4.35)**	**0.01**	1.51 (0.74–3.18)	0.26

b) Difference in TPA among patients diagnosed with dysglycemia based on different glucometabolic assessment compared to normal glucose level.

	Unadjusted Estimate (SE)	p-value	[a]Adjusted Estimate (SE)	p-value
HbA1c				
- Dysglycemia during admission	**27.3 (10.3)**	**<0.01**	15.1 (9.4)	0.11
- Dysglycemia at follow-up	14.5 (9.4)	0.12	13.2 (8.5)	0.12
FPG				
- Dysglycemia during admission	6.3 (9.8)	0.52	7.3 (8.9)	0.41
- Dysglycemia at follow-up	1.67 (8.5)	0.84	6.9 (7.8)	0.38
2hPG				
- Dysglycemia during admission	**35.0 (8.3)**	**<0.01**	**25.5 (7.6)**	**<0.01**
- Dysglycemia at follow-up	**37.0 (9.2)**	**<0.01**	**24.0 (8.8)**	**<0.01**

OR: odds-ratio, CI: confidence interval, SE: standard error, 2hPG: 2-hour plasma glucose, FPG: fasting plasma glucose.

[a]Adjusted for age, gender, hypertension, hypercholesterolemia, smoking status, and BMI

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The relationship between the diagnosis of dysglycemia by the three different methods and TPA is shown in Table 4B. Only 2hPG showed a statistically significant association with TPA both during admission and follow up. HbA1c during admission was associated with an increase in mean TPA but was not statistically significant at the follow up. Based on the multiple regression model, after adjusting for conventional atherosclerotic risk factors, TPA was significantly associated with 2hPG during admission and at follow-up with 25.5 mm^2 (SE 7.6, $p<0.01$) and 24.0 mm^2 (SE 8.8, $p<0.01$) greater TPA, respectively, compared to those with normal glucose level.

The unadjusted OR of patients diagnosed with prediabetes, T2DM and dysglycemia of having significant atherosclerotic plaque in their carotid arteries compared to patients with NGM was 2.14 (95% CI; 1.21–3.81), 2.75 (95% CI; 0.93–9.34) and 2.19 (95% CI; 1.25–3.87), respectively (Table 5A, model 1).

From the multiple logistic regression analysis after adjusting for conventional atherosclerotic risk factors the ORs of having significant atherosclerotic plaque for patients diagnosed with prediabetes, T2DM and dysglycemia (determined by abnormal results in either 2hPG, HbA1C or FPG) compared to NGM was 2.14 (95% CI 1.13–4.12), 2.50 (0.75–9.51) and 2.17 (95% CI 1.15–4.15), respectively (Table 5A, model 2). To examine if any of the dysglycemic metabolic determinants might explain this association we additionally adjusted for 2hPG, HbA1C and fasting glucose both during admission and at follow-up. When adjusted for 2hPG the statistical significance of the ORs for patients diagnosed with prediabetes and dysglycemia of having significant atherosclerotic plaque compared to NGM was lost and became 1.78 (95% CI 0.83–3.88) and 1.77 (95% CI 0.83–3.84), respectively (Table 5A, model 3). When adjusted for FPG during admission and at follow-up the ORs were also attenuated 1.94 (95% CI 0.89–4.29) and 1.93 (95% CI 0.89–4.27) for prediabetes and dysglycemia respectively, but remained significant when adjusted for HbA1c during admission and at follow-up.

Based on regression analysis, the diagnosis of prediabetes, T2DM and dysglycemia was associated with an increase in TPA of 22.1 mm^2 (SE: 9.3, $p = 0.02$), 31.2 mm^2 (SE: 17.0, $p = 0.07$) and 23.0 mm^2 (SE 9.2, $p = 0.01$), respectively, compared to patients with NGM (Table 5B, model 1). From the multiple variable regression model after adjusting for conventional atherosclerotic risk factors a significant increase in TPA was associated with the diagnosis of prediabetes and

Table 5. Glucose metabolic derangements and carotid plaque burden.

a) The OR of having significant plaque in the carotid arteries among patients diagnosed with prediabetes, T2DM or dysglycemia defined as any of abnormal 2hPG, HbA1C and fasting glucose.

	Model 1		Model 2		Model 3	
	Unadjusted OR (95% CI)	p-value	[a]Adjusted OR (95% CI)	p-value	[b]Adjusted OR (95% CI)	p-value
Prediabetes	**2.14 (1.21–3.81)**	**0.01**	**2.14 (1.13–4.12)**	**0.02**	1.78 (0.83–3.88)	0.14
T2DM	2.75 (0.93–9.34)	0.08	2.50 (0.75–9.51)	0.15	2.18 (0.44–12.03)	0.35
Dysglycemia	**2.19 (1.25–3.87)**	**<0.01**	**2.17 (1.15–4.15)**	**0.02**	1.77 (0.83–3.84)	0.14

b) Difference in TPA among patients diagnosed with prediabetes, T2DM and dysglycemia defined as any of abnormal 2hPG, HbA1C and fasting glucose.

	Model 1		Model 2		Model 3	
	Unadjusted Estimate mm^2 (SE)	p-value	[a]Adjusted Estimate mm^2 (SE)	p-value	[b]Adjusted Estimate mm^2 (SE)	p-value
Prediabetes	**22.1 (9.3)**	**0.02**	**22.5 (8.5)**	**<0.01**	9.6 (9.9)	0.34
T2DM	31.2 (17.0)	0.07	29.4 (15.5)	0.06	1.1 (19.5)	0.95
Dysglycemia	**23.0 (9.2)**	**0.01**	**23.1 (8.4)**	**<0.01**	10.0 (10.0)	0.32

OR: odds ratio, CI: confidence interval, SE: standard deviation, T2DM: type 2 diabetes mellitus

[a]Adjusted for age, gender, hypertension, hypercholesterolemia, smoking status, and BMI

[b] Adjusted for age, gender, hypertension, hypercholesterolemia, smoking status, BMI and 2hPG during admission and at follow-up

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dysglycemia (Table 5B, model 2). When additionally adjusted for 2hPG during admission the difference in TPA among patients with prediabetes and dysglycemia was attenuated to 9.6 mm^2 (SE: 10.0, p = 0.34) and 10.0 mm^2 (SE 10.0, p = 0.32), respectively, compared to patients with NGM (Table 5B, model 3) which is a reduction of the effect sizes by 57.3% and 56.7% for prediabetes and dysglycemia, respectively. When adjusted independently for FPG and HbA1c during admission and at follow-up the difference in TPA among patients diagnosed with prediabetes and dysglycemia still remained statistically significant.

Discussion

In the current study, a high prevalence of atherosclerotic plaque in the carotid arteries was detected with incremental increase in TPA in ACS patients diagnosed with prediabetes and T2DM compared to patients with NGM. Detection of dysglycemia by measurement of 2hPG rather than FPG or HbA1c identified increased risk of significant atherosclerotic plaque and increased TPA. Therefore, newly detected glucose derangements are associated with increased atherosclerotic burden in ACS patients.

All patients in the present study had established atherosclerotic disease in their coronary arteries. Therefore it was expected to detect a high prevalence of atherosclerotic plaque in the carotids in the study population. In this study the prevalence for significant atherosclerotic plaque was 62% compared to 10% reported from a general population study in Iceland that used the same ultrasound protocol as in the current study [16]. When compared to an age- and gender-matched control group from that population study the prevalence of significant plaque was 20% and mean TPA 39.1 mm^2 compared to 103.3 mm^2 in the present study. This highlights the high atherosclerotic burden found in patients with CVD compared to the general population.

When the individual glucose measurement methods were evaluated separately the 2hPG for dysglycemia during admission and at follow-up were found to be independent predictors of having significant atherosclerotic plaque in the carotid arteries. Likewise, patients diagnosed with dysglycemia on the 2hPG had significantly increased TPA compared to patients with NGM. The 2hPG identifies patients who are nearly or completely insulin resistant, a condition where the liver and muscles require more insulin to suppress the hepatic glucose production and glucose uptake, respectively, that results in postprandial hyperglycemia [19, 20]. While the pancreatic β-cells are able to increase their insulin production and secretion, causing hyperinsulinemia, the glucose tolerance remains normal. In time, however, the postprandial glucose levels and subsequently the FPG levels rises due to increased insulin resistance and failure of the β-cells to produce insulin, leading to overt T2DM [21].

Prediabetes and dysglycemia were found to be independent predictors of having significant atherosclerotic plaque in the carotid arteries. A significant association was also detected between TPA and metabolic derangements whether defined as prediabetes or dysglycemia. No significant association was found between T2DM and TPA but there was a clear trend in that direction. After being adjusted for conventional CVD risk factors the association between dysglycemia and TPA remained significant. However, when additionally adjusting for different glucose metabolic measurements the 2hPG had a greater effect on the relationship between dysglycemia and TPA as well as the OR of having significant plaque compared to FPG and HbA1c. This indicates that among the three methods of glucometabolic measurement 2hPG has the strongest relation to atherosclerosis development in this group of patients with ACS.

The 2hPG, based on the OGTT, had stronger association with increased TPA and significant plaque in the carotid arteries than either FPG or HbA1c.

Elevated 2hPG is an indicator of insulin resistance and hyperinsulinemia. Insulin resistance and hyperinsulinemia have been suggested to cause vascular dysfunction and an increase in

reactive oxygen species, which leads to vascular inflammation and proliferation of smooth muscle cells that, in turn, accelerate the atherosclerotic process [22]. Also, postprandial hyperglycemia represents the highest blood glucose levels during the day and the greatest fluctuations in glycaemia that could contribute to abnormal endothelial function [21]. Finally, patients with postprandial hyperglycemia have higher prevalence of metabolic syndrome, with central obesity, dyslipidemia and hypertension, which in itself increases risk for CVD [21]. Insulin resistance and hyperinsulinemia are conditions that are undetected for many years that contribute to greater atherosclerotic disease and increased risk for CVD. Our results concur with these findings in that 2hPG was found to have a stronger association with atherosclerosis compared to FPG and HbA1c.

To our knowledge, this is the first study to evaluate TPA in patients with ACS in relation to glucose metabolism classification. Increased TPA in patients newly diagnosed with prediabetes and dysglycemia suggests that these patients have had undiagnosed dysglycemia for some time before being admitted with ACS, causing accelerated atherosclerotic plaque formation and perhaps leading to plaque instability and rupture which is a key process in the development of ACS. Our results also support this assumption in that prediabetes and dysglycemia are shown to be independents risk factors of having significant plaque on carotid ultrasound examination. These findings are in line with previous studies indicating a high proportion of undiagnosed dysglycemia in the general population and they underscore the importance of timely preventive measures to enhance public health [23]. Patients who are diagnosed with dysglycemia should receive lifestyle counselling, mainly improving diet and increased physical activity to promote weight loss and lower cardiovascular risk [24]. Patients diagnosed with prediabetes and T2DM could also be offered pharmacotherapy with metformin to reduce risk of developing T2DM and reduce risk of myocardial infarction, respectively [25, 26]. In addition, it has been reported that reducing post-prandial hyperglycemia with acarbose, an alpha-glycosidase inhibitor, can attenuate the progression of IMT in patients with IGT [27].

A limitation in the present study is a low prevalence of T2DM that is due to the strict diagnostic criteria applied for T2DM and a relatively low prevalence of T2DM in the general population in Iceland compared to other western countries [28]. Due to this low prevalence the power to detect significant association between T2DM and TPA is limited.

Conclusion

A high prevalence of atherosclerotic plaque in the carotid arteries was detected with incremental increase in TPA in ACS patients diagnosed with prediabetes and T2DM compared to patients with NGM. Patients diagnosed with dysglycemia according to the 2hPG were at increased risk of significant atherosclerotic plaque in their carotid arteries and had significantly increased TPA. The importance of the 2hPG in the risk stratification of these patients is reflected by the fact that after adjustment for conventional risk factors and the 2hPG no increased burden of atherosclerotic plaque remains, indicating the role of OGTT as a predictor of increased carotid plaque burden. Thus newly detected metabolic derangements by screening are an important indicator of accelerated atherosclerotic plaque formation in the ACS population. Timely detection and treatment of dysglycemia might prove advantageous for the future care in this high-risk population.

Supporting information

S1 File. Available dataset.
(CSV)

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References

1. Mellbin LG, Anselmino M, Ryden L. Diabetes, prediabetes and cardiovascular risk. European journal of cardiovascular prevention and rehabilitation: official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology. 2010; 17 Suppl 1:S9–14. https://doi.org/10.1097/01.hjr.0000368192.24732.2f PMID: 20489420.
2. Gyberg V, De Bacquer D, Kotseva K, De Backer G, Schnell O, Sundvall J, et al. Screening for dysglycaemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test, and HbA1c: a report from EUROASPIRE IV—a survey from the European Society of Cardiology. European heart journal. 2015; 36(19):1171–7. Epub 2015/02/12. https://doi.org/10.1093/eurheartj/ehv008 PMID: 25670820.
3. Bjarnason TA, Kristinsdottir LB, Oskarsdottir ES, Hafthorsson SO, Olafsson I, Lund SH, et al. Diagnosis of type 2 diabetes and prediabetes among patients with acute coronary syndromes. European heart journal Acute cardiovascular care. 2016. Epub 2016/09/15. https://doi.org/10.1177/2048872616669060 PMID: 27625341.
4. Davis TM, Coleman RL, Holman RR. Prognostic significance of silent myocardial infarction in newly diagnosed type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 79. Circulation. 2013; 127(9):980–7. Epub 2013/01/31. https://doi.org/10.1161/CIRCULATIONAHA.112.000908 PMID: 23362315.
5. Bartnik M, Malmberg K, Norhammar A, Tenerz A, Ohrvik J, Ryden L. Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction. European heart journal. 2004; 25(22):1990–7. https://doi.org/10.1016/j.ehj.2004.09.021 PMID: 15541834.
6. Tamita K, Katayama M, Takagi T, Akasaka T, Yamamuro A, Kaji S, et al. Impact of newly diagnosed abnormal glucose tolerance on long-term prognosis in patients with acute myocardial infarction. Circulation journal: official journal of the Japanese Circulation Society. 2007; 71(6):834–41. Epub 2007/05/29. PMID: 17526977.
7. Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). European heart journal. 2007; 28(1):88–136. https://doi.org/10.1093/eurheartj/ehl260 PMID: 17220161.

8. Cohen GI, Aboufakher R, Bess R, Frank J, Othman M, Doan D, et al. Relationship between carotid disease on ultrasound and coronary disease on CT angiography. JACC Cardiovascular imaging. 2013; 6 (11):1160–7. Epub 2013/11/16. https://doi.org/10.1016/j.jcmg.2013.06.007 PMID: 24229768.
9. Baber U, Mehran R, Sartori S, Schoos MM, Sillesen H, Muntendam P, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. Journal of the American College of Cardiology. 2015; 65(11):1065–74. Epub 2015/03/21. https://doi.org/10.1016/j.jacc.2015.01.017 PMID: 25790876.
10. Plichart M, Celermajer DS, Zureik M, Helmer C, Jouven X, Ritchie K, et al. Carotid intima-media thickness in plaque-free site, carotid plaques and coronary heart disease risk prediction in older adults. The Three-City Study. Atherosclerosis. 2011; 219(2):917–24. Epub 2011/10/19. https://doi.org/10.1016/j.atherosclerosis.2011.09.024 PMID: 22005196.
11. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. European heart journal. 2000; 21(18):1502–13. Epub 2000/09/07. https://doi.org/10.1053/euhj.2000.2305 PMID: 10973764.
12. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama. 2013; 310(20):2191–4. Epub 2013/10/22. https://doi.org/10.1001/jama.2013.281053 PMID: 24141714.
13. American Diabetes A. Diagnosis and classification of diabetes mellitus. Diabetes care. 2012/01/04 ed2012. p. S64–71. https://doi.org/10.2337/dc12-s064 PMID: 22187472
14. Bjornsdottir G, Sigurdsson S, Sturlaugsdottir R, Gudmundsdottir A, Eiriksdottir G, Thorsson B, et al. Longitudinal Changes in Size and Composition of Carotid Artery Plaques Using Ultrasound: Adaptation and Validation of Methods (Inter- and Intraobserver Variability). Journal for Vascular Ultrasound. 2014; 38(4):198–208.
15. Oren A, Vos LE, Uiterwaal CS, Grobbee DE, Bots ML. Cardiovascular risk factors and increased carotid intima-media thickness in healthy young adults: the Atherosclerosis Risk in Young Adults (ARYA) Study. Archives of internal medicine. 2003; 163(15):1787–92. Epub 2003/08/13. https://doi.org/10.1001/archinte.163.15.1787 PMID: 12912713.
16. Sturlaugsdottir R, Aspelund T, Bjornsdottir G, Sigurdsson S, Thorsson B, Eiriksdottir G, et al. Prevalence and determinants of carotid plaque in the cross-sectional REFINE-Reykjavik study. BMJ open. 2016; 6(11):e012457. Epub 2016/11/26. https://doi.org/10.1136/bmjopen-2016-012457 PMID: 27884845.
17. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. The American journal of cardiology. 1983; 51(3):606. Epub 1983/02/01. PMID: 6823874.
18. R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria2015.
19. DeFronzo RA, Gunnarsson R, Bjorkman O, Olsson M, Wahren J. Effects of insulin on peripheral and splanchnic glucose metabolism in noninsulin-dependent (type II) diabetes mellitus. The Journal of clinical investigation. 1985; 76(1):149–55. Epub 1985/07/01. https://doi.org/10.1172/JCI111938 PMID: 3894418; PubMed Central PMCID: PMCPMC423730.
20. Ferrannini E, Simonson DC, Katz LD, Reichard G Jr., Bevilacqua S, Barrett EJ, et al. The disposal of an oral glucose load in patients with non-insulin-dependent diabetes. Metabolism: clinical and experimental. 1988; 37(1):79–85. Epub 1988/01/01. PMID: 3275860.
21. DeFronzo RA, Abdul-Ghani M. Assessment and treatment of cardiovascular risk in prediabetes: impaired glucose tolerance and impaired fasting glucose. The American journal of cardiology. 2011; 108(3 Suppl):3b–24b. Epub 2011/08/10. https://doi.org/10.1016/j.amjcard.2011.03.013 PMID: 21802577.
22. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. European heart journal. 2013; 34(31):2436–43. Epub 2013/05/04. https://doi.org/10.1093/eurheartj/eht149 PMID: 23641007; PubMed Central PMCID: PMCPMC3743069.
23. Demmer RT, Zuk AM, Rosenbaum M, Desvarieux M. Prevalence of diagnosed and undiagnosed type 2 diabetes mellitus among US adolescents: results from the continuous NHANES, 1999–2010. American journal of epidemiology. 2013; 178(7):1106–13. Epub 2013/07/28. https://doi.org/10.1093/aje/kwt088 PMID: 23887044; PubMed Central PMCID: PMCPMC3783093.
24. Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al. ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD—summary. Diabetes & vascular disease research. 2014; 11(3):133–73. Epub 2014/05/08. https://doi.org/10.1177/1479164114525548 PMID: 24800783.

25. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. The lancet Diabetes & endocrinology. 2015. Epub 2015/09/18. https://doi.org/10.1016/s2213-8587(15)00291-0 PMID: 26377054.

26. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. The New England journal of medicine. 2008; 359(15):1577–89. Epub 2008/09/12. https://doi.org/10.1056/NEJMoa0806470 PMID: 18784090.

27. Hanefeld M, Chiasson JL, Koehler C, Henkel E, Schaper F, Temelkova-Kurktschiev T. Acarbose slows progression of intima-media thickness of the carotid arteries in subjects with impaired glucose tolerance. Stroke; a journal of cerebral circulation. 2004; 35(5):1073–8. Epub 2004/04/10. https://doi.org/10.1161/01.STR.0000125864.01546.f2 PMID: 15073402.

28. Bergsveinsson J, Aspelund T, Gudnason V, Benediktsson R. [Prevalence of type 2 diabetes mellitus in Iceland 1967–2002]. Laeknabladid. 2007; 93(5):397–402. Epub 2007/05/16. PMID: 17502682.

Paper III

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The prognostic effect of known and newly detected type 2 diabetes in patients with acute coronary syndrome

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Abstract

Background: Dysglycemia is a well-established risk factor of coronary artery disease. Less is known of the prognostic effect of dysglycemia in acute coronary syndromes (ACSs). The aim of this study was to evaluate the long-term outcome of patients with ACSs according to glucometabolic categories.

Methods: Patients with ACSs were consecutively included in the study. Among those with no previous history of type 2 diabetes (T2DM) glucose metabolism was evaluated with fasting glucose in plasma, glycated hemoglobin and a standard 2-h oral glucose tolerance test. Patients were classified having normal glucose metabolism, prediabetes, newly detected T2DM (nT2DM) and previously known T2DM (kT2DM). The clinical outcome parameters were death or myocardial infarction and other major adverse cardiac events (MACEs).

Results: A total of 372 ACS patients (male 75.8%, 65.1 years (SD: 11.8)) constituted the study population. The proportion diagnosed with normal glucose metabolism, prediabetes, nT2DM and kT2DM was 20.7%, 46.5%, 6.2% and 26.6%, respectively. The mean follow-up period was 2.9 years. Patients with prediabetes, nT2DM and kT2DM had a hazard ratio of 5.8 (95% confidence interval (CI) 0.8–44.6), 10.9 (95% CI 1.2–98.3) and 14.9 (95% CI 2.0–113.7), respectively, for death/myocardial infarction and 1.4 (95% CI 0.6–3.1), 2.9 (95% CI 1.1–8.0) and 3.3 (95% CI 1.5–7.6), respectively, for a composite of MACEs.

Conclusion: Patients with ACS and nT2DM or kT2DM were at increased risk of death/myocardial infarction and MACE compared with patients with normal glucose metabolism after approximately three years of follow-up.

Keywords

Acute coronary syndrome, type 2 diabetes, survival, prognosis

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Background

The global prevalence of type 2 diabetes mellitus (T2DM) has been increasing over the past decades and it is estimated to continue to rise in the future.[1,2] T2DM is a well-established risk factor for atherosclerosis and is associated with accelerated atherosclerotic plaque formation through insulin resistance and hyperinsulinemia that cause vascular dysfunction, increased reactive oxygen species with vascular inflammation and proliferation of smooth muscle cells.[3] Patients with acute coronary syndrome (ACS) and a new

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diagnosis of dysglycemia have been found to have increased atherosclerotic burden at the time of diagnosis compared with patients with normal glucose metabolism (NGM). This may suggest that the dysglycemia could have remained undiagnosed for months or years before the acute event in these patients.[4]

Whether previously known or newly detected, T2DM is associated with cardiovascular disease (CVD) and increased mortality in the general population.[5,6] Similarly, in patients with both stable coronary artery disease (CAD) and ACS, subgroups with an increased risk of future cardiovascular events have been identified based on a hyperglycemic response on a standard oral glucose tolerance test (OGTT).[7–10] However, these studies have relied on the OGTT for identification of dysglycemia rather than a comprehensive assessment of glucometabolic derangements according to current American Diabetes Association (ADA) and World Health Organization (WHO) guidelines.

Glucometabolic perturbations are very common among patients with stable CAD and ACS, with prevalence of newly detected dysglycemia being more than 60% among ACS patients in previous studies.[11–14] Therefore, we set out to evaluate whether the clinical event rate among patients with ACS and previously diagnosed T2DM, newly diagnosed T2DM or prediabetes differed from that of ACS patients with NGM during long-term follow-up.

Methods

Patients admitted to the coronary care unit of Landspitali, the University Hospital of Iceland with the diagnosis of ACS were consecutively included in the study between June 2013 and October 2014. The definition of ACS was according to the joint European Society of Cardiology and American College of Cardiology recommendations considering chest pain, elevated troponins and electrocardiogram changes consistent with ischemia, at least two of which needed to be present for the diagnosis of ACS.[15] Patients with cognitive dysfunction, those living in a nursing home or outside the catchment area of the hospital and patients who died during the initial admission were excluded from the study. Informed written consent was obtained from each participant prior to any study related procedures. The study protocol adhered to the principles laid out in the Declaration of Helsinki[16] and was approved by the Icelandic Bioethics Committee (VSN: 13-069-S1). Information on prespecified demographic, personal, medication and lifestyle data and events after discharge were obtained from patients during admission, from hospital records and the Icelandic National death registry, Statistics Iceland.[17] Patients with a previous history of hypertension and those taking blood pressure lowering medication were classified as having hypertension. Patients with a previous documented history of hypercholesterolemia and those taking HMG-CoA reductase inhibitors (statins) were classified as having hypercholesterolemia. A family history of CAD was determined if any first degree family member had been diagnosed with CAD.

Patients without prior diagnosis of T2DM underwent an evaluation of their glucose metabolism status. After an overnight fast of at least 10 h, measurements of fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) were made in addition to a standard OGTT where 2-h plasma glucose (2hPG) was measured after ingesting a solution containing 75 g of glucose. Measurements of glucose metabolism were made during hospitalization, generally three to five days after admission, and repeated three months later. All samples collected for venous plasma glucose measurements were centrifuged and analyzed immediately after blood collection. Glucose levels were determined using reagents, calibrators and Vitros 250/950 analyzers from Ortho Clinical Diagnostics, Rochester, USA and HbA1c levels were determined using reagents, calibrators and Cobas c311 analyzer from Roche, Mannheim, Germany.

The classification of glucose metabolism was based on the ADA criteria, where prediabetes was defined as HbA1c 5.7–6.4% (39–47 mmol/mol), FPG 5.6–6.9 mmol/l or 2hPG 7.8–11.0 mmol/l and T2DM as HbA1c $\geq$6.5% ($\geq$48 mmol/mol), FPG $\geq$7.0 mmol/l or 2hPG $\geq$11.1 mmol/l.[18] Patients were classified as having newly detected T2DM (nT2DM) if at least two measurements were above the cut-point for T2DM according to the ADA criteria, while patients with one measurement above the cut-point of T2DM or at least one measurement above the cut-point for prediabetes were classified as having new prediabetes. Patients with all glucose values within normal range were classified as having NGM. Patients with previously known T2DM (kT2DM) were classified as such. Patients diagnosed with prediabetes were treated by lifestyle and dietary counseling during hospitalization. In addition, those with nT2DM were referred for further evaluation and treatment in a specialized outpatient diabetes clinic.

Normally distributed continuous variables are presented as mean (standard deviation (SD)) and categorical variables are presented as percentage. Comparison between groups of patients with NGM, prediabetes, nT2DM and kT2DM was made using the chi-square test and analysis of variance for categorical and continuous variables, respectively. Multiple Cox proportional hazard regression analysis was applied to detect the association between glucometabolic status and clinical events during follow-up. Adjustments were made for the following risk factors: age, gender, hypertension, hypercholesterolemia, smoking status and body mass index (BMI). Other baseline variables did not affect the outcome in multivariate analysis. Results are reported as hazard ratios with 95% confidence intervals (CIs). Kaplan–Meier curves were made for combined all-cause mortality or myocardial infarction (MI) and major adverse cardiovascular events (MACEs), including all-cause mortality, MI, stroke, congestive heart failure requiring hospitalization and unstable angina requiring

percutaneous coronary intervention, with log rank test to determine significance. The definition of MI as an end point was according to the joint European Society of Cardiology and American College of Cardiology guidelines.[15] Poisson regression was used to compare event-rates between glucometabolic groups. The level of statistical significance was set at $p<0.05$. All statistical analyses were performed using the R software version 3.2.2.[19]

Results

During the study period a total of 639 patients consecutively admitted to the coronary care unit for ACS were considered for inclusion in the study. Before inclusion, 46 patients were excluded due to cognitive impairment, 60 patients because of frailty, 90 were discharged before the OGTT was performed and 60 refused participation. Hence, 383 patients were included in the study. After inclusion 10 patients withdrew consent and one patient was lost to follow-up. The remaining 372 patients constituted the study population.

The baseline characteristics of the study population are presented in Table 1. The mean age was 65.1 (SD 11.7) years and 75.8% were male. A total of 77 (20.7%), 173 (46.5%) and 23 (6.2%) were diagnosed with NGM, prediabetes and nT2DM, respectively. The remaining 99 patients (26.6%) had previously diagnosed diabetes at admission and were classified as kT2DM (Table 2). A significant difference in age, smoking status, BMI, hypercholesterolemia, hypertension and previous CAD were detected between different glucometabolic groups (Table 2). During admission 4.4%, 24.8%, 30.8%, 26% and 14% of patients had their glucose measurements made on day 2, 3, 4, 5 and 6 or later after admission, respectively. There was no significant difference in FPG or 2hPG measurements made on different days after admission.

The mean duration of follow-up was 2.9 (range 2.3 4.1) years. A total of 48 patients had either died or presented with MI during the follow-up period and 76 patients presented with MACE. Unadjusted hazard ratio for combined all-cause mortality or MI was 7.1 (95% CI 0.9–54.0), 14.6 (95% CI 1.6–130.3) and 27.1 (95% CI 3.7–199.6) for prediabetes, nT2DM and kT2DM, respectively, compared with patients with NGM and 1.5 (95% CI 0.7–3.3), 3.1 (95% CI 1.1–8.4) and 4.2 (95% CI 2.0–9.1) for prediabetes, nT2DM and kT2DM, respectively, for MACE. After adjusting for conventional CVD risk factors the hazard ratio for combined all-cause mortality or MI was 5.8 (95% CI 0.8–44.6), 10.9 (95% CI 1.2–98.3) and 14.9 (95% CI 2.0–113.7) for prediabetes, nT2DM and kT2DM, respectively, compared with patients with NGM. The adjusted hazard ratio for MACE was 1.4 (95% CI 0.6–3.1), 2.9 (95% CI 1.0–8.0) and 3.3 (95% CI 1.5–7.6) for prediabetes, nT2DM and kT2DM, respectively, compared with patients with NGM (Table 3, Figure 1(a) and (b)). Figure 1(a) and (b) show forest plots for adjusted hazard ratio for death or MI and MACE according to glucometabolic status. Combined all-cause mortality or MI differed between glucometabolic groups with 4.2, 29.5, 60.3 and 114.2 events per 1000 patient-years among NGM, prediabetes, nT2DM and kT2DM, respectively ($p<0.001$) (Table 4). Similarly, difference was detected in MACE with 36.0, 54.7, 113.9 and 163.6 events per 1000 patient-years among NGM, prediabetes, nT2DM and kT2DM, respectively ($p<0.001$).

Figure 2(a) and (b) show Kaplan–Meier curves for glucometabolic status and combined all-cause mortality or MI and MACE, respectively ($p<0.0001$). During hospitalization, no

Table 1. Baseline characteristics.

	N=372
Age, years (SD)	65.1 (11.7)
Gender	
- Male	75.8%
- Female	24.2%
BMI, kg/m^2 (SD)	29.2 (4.6)
Smoking status	
- Never	29.6%
- Previous	46.2%
- Current	24.2%
FH of CAD	62.7%
Hypercholesterolemia	52.6%
Hypertension	64.2%
- SBP, mmHg (SD)	141 (22)
- DBP, mmHg (SD)	77 (13)
Previous CAD	38.8%
ACS	
- UAP	28.2%
- NSTEMI	43.3%
- STEMI	28.5%
Killip class	
- I	57.4%
- II	37.5%
- III	4.1%
- IV	1.0%
Medications at discharge	
- ASA	93.0%
- Other antiplatelet therapy[a]	75.3%
- ACEi/ARB	58.9%
- Beta-blocker	87.9%
- CCB	16.4%
- Statin	96.8%
- Oral diabetes medication	20.4%
- Insulin	8.9%

[a]Clopidogrel, ticagrelor or prasugrel.
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ASA: acetylsalicylic acid; ACS: acute coronary syndrome; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blocker; DBP: diastolic blood pressure; FH: family history; NSTEMI: non-ST elevation myocardial infarct; SD: standard deviation; SBP: systolic blood pressure; STEMI: ST elevation myocardial infarct; UAP: unstable angina pectoris.

Table 2. Pertinent characteristics of patients divided according to their glucose metabolism.

	NGM *n*=77	Prediabetes *n*=173	nT2DM *n*=23	kT2DM *n*=99	*p*-value
Age, years (SD)	63.0 (12.4)	64.3 (10.7)	64.2 (11.9)	68.4 (12.4)	**0.011**
Gender					0.288
- Male	83.1%	75.1%	78.3%	70.7%	
- Female	16.9%	24.9%	21.7%	29.3%	
BMI, kg/m^2 (SD)	28.0 (4.0)	28.9 (4.2)	30.4 (4.8)	30.6 (5.3)	**0.001**
Smoking status					**0.025**
- Never	42.9%	27.2%	26.1%	24.2%	
- Previous	44.2%	43.9%	39.1%	53.5%	
- Current	13%	28.9%	34.8%	22.2%	
FH of CAD	67.5%	64.2%	65.2%	55.7%	0.386
Hypercholesterolemia	47.4%	42.8%	47.8%	74.7%	<**0.001**
Total cholesterol during follow-up, mmol/l, mean (SD)	3.8 (0.9)	4.0 (0.9)	4.0 (0.8)	4.0 (1.1)	0.326
Hypertension	51.3%	59.0%	56.5%	84.8%	<**0.001**
- SBP, mmHg (SD)	138 (20)	140 (23)	135 (18)	145 (21)	0.073
- DBP, mmHg (SD)	77 (12)	78 (13)	75 (11)	77 (12)	0.756
Previous CAD	35.5%	30.6%	39.1%	55.6%	**0.001**
ACS					0.055
- UAP	29.8%	26.6%	34.8%	28.3%	
- NSTEMI	42.9%	38.7%	30.4%	54.5%	
- STEMI	27.3%	34.7%	34.8%	17.2%	
Killip class					0.473
- I	59.0%	60.0%	68.2%	47.9%	
- II	36.1%	33.6%	27.3%	49.3%	
- III	4.9%	5.0%	4.5%	1.4%	
- IV	0.0%	1.4%	0.0%	1.4%	
Medications at discharge					
- ASA	92.9%	93.6%	95.7%	91.9%	0.894
- Other antiplatelet therapy[a]	75.3%	75.1%	78.3%	47.7%	0.988
- ACEi/ARB	45.5%	56.6%	69.6%	70.7%	**0.005**
- Beta-blocker	80.5%	90.2%	95.7%	87.9%	0.108
- CCB	9.1%	9.2%	13.0%	35.4%	<**0.001**
- Statin	97.4%	97.1%	100.0%	94.9%	0.576
- Oral diabetes medication	1.3%	0.6%	21.7%	69.7%	<**0.001**
- Insulin	0%	0%	0%	33.3%	<**0.001**
Extent of CAD, 70% luminal narrowing					
- 0 vessel disease	11.7%	5.8%	0%	5.1%	<**0.001**
- 1 vessel disease	53.2%	37.2%	31.8%	27.3%	
- 2 vessel disease	16.9%	33.7%	36.4%	26.3%	
- 3 vessel disease	16.9%	19.2%	31.8%	31.3%	
- Not assessed	1.3%	4.1%	0%	10.1%	
Revascularization treatment					
- PCI	64.9%	68.8%	73.9%	58.6%	
- CABG	11.7%	14.5%	8.7%	18.2%	0.53
- Neither	23.4%	16.8%	17.4%	23.2%	

[a]Clopidogrel, ticagrelor or prasugrel.

ACEi: angiotensin-converting enzyme inhibitor; ACS: acute coronary syndrome; ARB: angiotensin II receptor blocker; ASA: acetylsalicylic acid; BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CCB: calcium channel blocker; DBP: diastolic blood pressure; FH: family history; kT2DM: previously known type 2 diabetes mellitus; mmol/l: millimoles per liter, NGM: normal glucose metabolism; NSTEMI: non-ST-elevation myocardial infarction; nT2DM: newly detected type 2 diabetes mellitus; PCI: percutaneous coronary intervention; SD: standard deviation; SBP: systolic blood pressure; STEMI: ST-elevation myocardial infarction; UAP: unstable angina pectoris

Table 3. Risk of adverse outcomes between glucometabolic status.

	Unadjusted HR	95% CI	*p*-value	Adjusted HR	95% CI	*p*-value
Death/MI						
NGM	1.0	–	–	1.0	–	–
Prediabetes	7.1	0.9–54.0	0.057	5.8	0.8–44.6	0.089
nT2DM	**14.6**	**1.6–130.3**	**0.017**	**10.9**	**1.2–98.3**	**0.034**
kT2DM	**27.1**	**3.7–199.6**	**0.001**	**14.9**	**2.0–113.7**	**0.009**
MACE						
NGM	1.0	–	–	1.0	–	–
Prediabetes	1.5	0.7–3.3	0.316	1.4	0.6–3.1	0.436
nT2DM	**3.1**	**1.1–8.4**	**0.031**	**2.9**	**1.1–8.0**	**0.046**
kT2DM	**4.2**	**2.0–9.1**	**<0.001**	**3.3**	**1.5–7.6**	**0.004**

CI: confidence interval; HR: hazard ratio; kT2DM: known type 2 diabetes mellitus; MACE: major adverse cardiac event; MI: myocardial infarction; NGM; normal glucose metabolism; nT2DM: new type 2 diabetes mellitus

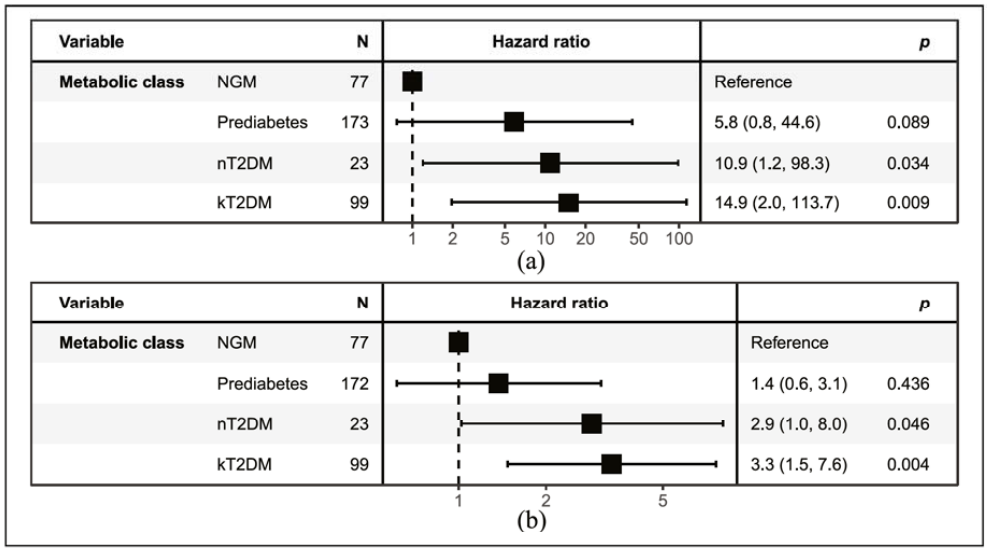

Figure 1. Forest plots for adjusted hazard ratio for death or myocardial infarction (a) and major adverse cardiovascular event (b) by glucometabolic status.
NGM: normal glucose metabolism; nT2DM: newly detected type 2 diabetes mellitus; kT2DM: previously known type 2 diabetes mellitus

patient was treated with intensive insulin treatment and no patient with prediabetes or nT2DM received insulin in the follow-up period. At discharge, oral diabetes medications were prescribed to 1.3%, 0.6%, 21.7% and 69.7% of patients with NGM, prediabetes, nT2DM and kT2DM, respectively. During the follow-up period, 1.3%, 2.9%, 56.5% and 88.9% of patients with NGM, prediabetes, nT2DM and kT2DM, respectively, were prescribed oral diabetes medications. Metformin was used in 43 patients, sulfonylureas in 27, DDP4 inhibitors in 11, SLGT2 inhibitors in nine, TZDs in three, GLP-1 inhibitors in two and insulin in 22 patients during the follow-up period.

Discussion

Cardiovascular disease is the single most common cause of death among patients with T2DM. An increased risk of future cardiovascular events and mortality is observed among patients with MI and hyperglycemia, even below the diabetic threshold.[20,21] In our study patients with ACS and kT2DM or nT2DM had a significantly increased risk of death or MI and MACE compared with patients with NGM after approximately three years of follow-up while increased risk was not found in patients with newly detected prediabetes.

Table 4. Events per 1000 patient-years in different glucometabolic groups.

	NGM *n*=77	Prediabetes *n*=173	nT2DM *n*=23	kT2DM *n*=99	*p*-value
Death/MI	4.2	29.5	60.3	114.2	**<0.001**
Mean follow-up years (range)	3.2 (2.3–3.7)	3.1 (0.4–4.1)	3.1 (0.7–3.7)	2.7 (0.1–3.7)	
MACE	36.0	54.7	113.9	164.6	**<0.001**
Mean follow-up years (range)	3.0 (0.1–3.7)	3.0 (0–4.1)	2.9 (0.7–3.6)	2.5 (0–3.7)	

kT2DM: previously known type 2 diabetes mellitus; MACE: major adverse cardiac event; MI: myocardial infarction; NGM; normal glucose metabolism; nT2DM: newly detected type 2 diabetes mellitus

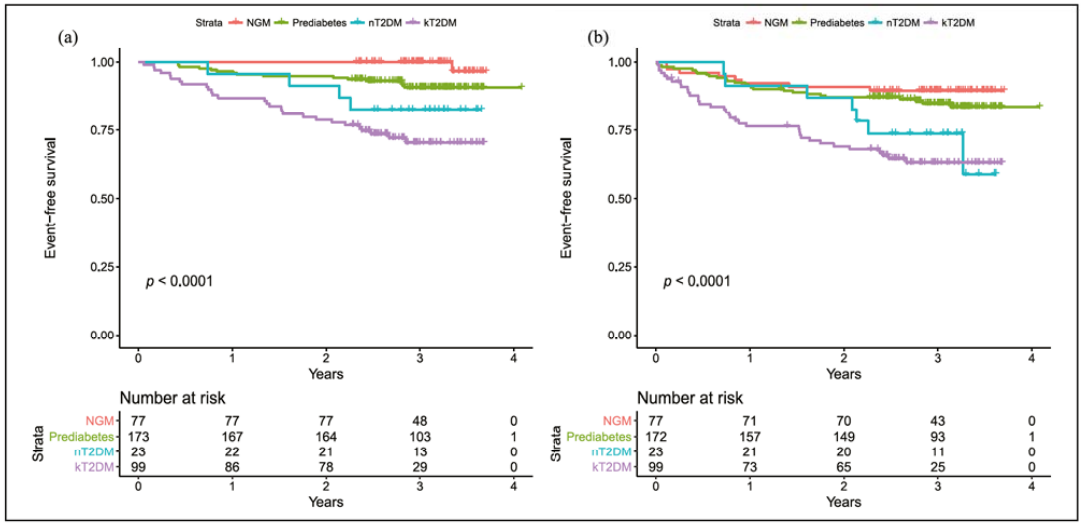

Figure 2. Kaplan–Meier curves for death or myocardial infarction (a) and major adverse cardiac events (b) by glucometabolic status ($p<0.0001$).
NGM: normal glucose metabolism; nT2DM: newly detected type 2 diabetes mellitus; kT2DM: previously known type 2 diabetes mellitus

Previous studies on dysglycemia in patients with CAD have consistently shown an increased risk of future adverse events, among patients with prediabetes, nT2DM and kT2DM, during 3–10 years of follow-up.[8,22–25] However, all of these studies have relied on one single OGTT to classify patients into different glucometabolic groups. As previously shown by our group and others, the diagnostic accuracy of a single OGTT is less than optimal and not according to current ADA and WHO guidelines.[14] The main findings of these previous studies have been to identify an increased risk of composite MACE rather than a more robust end point of death/MI used in our study. Also, most of these studies were retrospective analyses performed on registry patients who accordingly were not treated in a uniform manner according to current ACS guidelines and many of them did not receive lifestyle treatment for glucometabolic derangements. The current study was a prospective follow-up study where patients diagnosed with metabolic derangements were treated according to current guideline recommendations with lifestyle intervention and pharmacologic therapy when clinically indicated, all of which are known to affect long-term prognosis favorably. Also, in contrast to some of the previous ones, the current study was done in the modern era of dual antiplatelet therapy in ACS with a high proportion of patients treated invasively. The majority of ST-elevation MI patients (92%) were treated with urgent revascularization (primary percutaneous coronary intervention (PCI) (87%) or urgent coronary artery bypass grafting (CABG) (4.7%)) and an invasive approach was used in 76% of non-ST-elevation MI patients (PCI 60% and CABG 16%). Moreover, a more robust method was used to diagnose prediabetes and nT2DM, where at least two measurements above the diabetic cut off value was required to diagnose nT2DM. This method identified a true high-risk subgroup, which is reflected in higher hazard ratios for all cause death or MI and MACE in the current study than have been found in previous ones on this patient group. The information that

our study adds to the current knowledge is that after almost three years of follow-up, patients with ACS and T2DM, whether known or newly detected, are at significantly increased risk of death or MI and MACE in spite of optimal medical treatment. Unsurprisingly, patients with kT2DM had a higher hazard ratio for death or MI and MACE compared with nT2DM in our study. Even though the duration of T2DM was not evaluated it would be expected to involve a longer exposure of the risk factor among patients with kT2DM, attributing to higher morbidity compared with patients with nT2DM. This is reflected in a long-term follow-up of patients with acute MI that demonstrated increased mortality among patients with T2DM compared with patients with NGM 20 years following the MI.[25]

These results show that metabolic derangements, prediabetes and diabetes are present in the majority of ACS patients and they cause an increased risk of significant clinical events in the nearest future. However, active lifestyle and/or pharmacological intervention will improve the prognosis of these patients. For patients with prediabetes, lifestyle intervention, to promote weight loss with low caloric diet and physical exercise, has shown to reduce the risk of developing T2DM and it has been suggested that pharmacotherapy with metformin can also halt the development of T2DM in prediabetic patients.[26,27] Although strict glycemic strategies have not been shown to lower mortality in patients with acute MI and T2DM[28] current guidelines recommend that patients with established T2DM and prediabetes should be managed with lifestyle modification and/or medication in order to delay organ damage. Therefore, the identification of metabolic derangements among ACS patients may have important therapeutic implications that could be used to improve long-term outcome. The American Heart Association and ADA recommend dietary counseling and regular physical activity for patients with CAD and T2DM to lose weight and lower cardiovascular risk in addition to strict hypertension and cholesterol management.[29] The UK Prospective Diabetes Study was a large study on patients with newly diagnosed T2DM who were assigned to be treated with sulfonylurea or insulin, metformin or dietary restrictions.[30] Even though the difference in HbA1c was lost after the first year, a reduction in all-cause mortality and MI was maintained during 10 years of follow-up in the groups treated with medications as compared with the patients who received only dietary recommendations. This phenomenon of long-term risk reduction of future cardiovascular events and death after early strict glycemic control indicates benefit of strict glucose managements, especially in patients of age 60 and younger. The DIGAMI 2 trial showed benefit of metformin in patients with MI and T2DM to reduce risk of non-fatal reinfarction or stroke while, surprisingly, patients treated with strict insulin regimens had an increased risk of death, reinfarction or stroke.[28] This suggests that metformin should be part of standard care among patients with T2DM and CAD. The SGLT-2 inhibitors empagliflozin and canagliflozin are glycemic-lowering agents that have been shown to lower risk of death when added to standard care among patients with T2DM.[31,32] However, is should be noted the studies on SGLT-2 inhibitors were published after the recruitment period of our study was completed and therefore only a few of our patients received SGLT-2 inhibitors during the follow-up period.

No increased risk for cardiovascular events was found among ACS patients with newly detected prediabetes even though there was a clear trend in that direction. This could be because of the relatively small sample size and short follow-up period in this study as the progression from prediabetes to T2DM can take several years. Some of the prediabetic patients will regress to NGM, others remain prediabetic for years while yet other patients progress to overt T2DM. In our study only 2.9% of prediabetic patients were prescribed oral diabetes medication during the follow-up period, which indicates that they were generally well controlled by lifestyle management.

A limitation of our study is the relatively small sample size especially regarding patients with newly diagnosed prediabetes and T2DM and a relatively short follow-up period as T2DM is a chronic disease that causes chronic organ damage over a long period of time. We were unable to determine the duration of T2DM in each case of kT2DM as this assessment is subject to recall error and inaccuracy. Finally, information regarding low-density lipoprotein cholesterol and high-sensitivity C-reactive protein measurements were not available at baseline.

In conclusion, ACS patients with kT2DM and nT2DM were at increased risk of death or MI and MACEs compared with ACS patients with NGM after approximately three years of follow-up. These results underscore the importance for clinicians to be aware of potential glucometabolic derangements among patients with ACS and apply appropriate lifestyle recommendations and treatment. ACS patients with T2DM constitute a high-risk group which should be actively evaluated and treated accordingly.

Conflict of interest

The authors declare that there is no conflict of interest.

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References

1. Selvin E, Parrinello CM, Sacks DB, et al. Trends in prevalence and control of diabetes in the United States, 1988–1994 and 1999–2010. *Ann Intern Med* 2014; 160: 517–525.
2. Shaw JE, Sicree RA and Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010; 87: 4–14.

3. Paneni F, Beckman JA, Creager MA, et al. Diabetes and vascular disease: Pathophysiology, clinical consequences, and medical therapy: Part I. *Eur Heart J* 2013; 34: 2436–2443.
4. Bjarnason TA, Hafthorsson SO, Kristinsdottir LB, et al. Oral glucose tolerance test predicts increased carotid plaque burden in patients with acute coronary syndrome. *PLoS One* 2017; 12: e0183839.
5. Barr EL, Zimmet PZ, Welborn TA, et al. Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: The Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). *Circulation* 2007; 116: 151–157.
6. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; 339: 229–234.
7. Sinnaeve PR, Steg PG, Fox KA, et al. Association of elevated fasting glucose with increased short-term and 6-month mortality in ST-segment elevation and non-ST-segment elevation acute coronary syndromes: The Global Registry of Acute Coronary Events. *Arch Intern Med* 2009; 169: 402–409.
8. Bartnik M, Malmberg K, Norhammar A, et al. Newly detected abnormal glucose tolerance: An important predictor of long-term outcome after myocardial infarction. *Eur Heart J* 2004; 25: 1990–1997.
9. Tamita K, Katayama M, Takagi T, et al. Impact of newly diagnosed abnormal glucose tolerance on long-term prognosis in patients with acute myocardial infarction. *Circ J* 2007; 71: 834–841.
10. Lenzen M, Ryden L, Ohrvik J, et al. Diabetes known or newly detected, but not impaired glucose regulation, has a negative influence on 1-year outcome in patients with coronary artery disease: A report from the Euro Heart Survey on diabetes and the heart. *Eur Heart J* 2006; 27: 2969–2974.
11. Norhammar A, Tenerz Å, Nilsson G, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: A prospective study. *Lancet* 2002; 359: 2140–2144.
12. Bartnik M, Ryden L, Ferrari R, et al. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart. *Eur Heart J* 2004; 25: 1880–1890.
13. Hage C, Lundman P, Ryden L, et al. Fasting glucose, HbA1c, or oral glucose tolerance testing for the detection of glucose abnormalities in patients with acute coronary syndromes. *Eur J Prev Cardiol* 2013; 20: 549–554.
14. Bjarnason TA, Kristinsdottir LB, Oskarsdottir ES, et al. Editor's Choice-Diagnosis of type 2 diabetes and prediabetes among patients with acute coronary syndromes. *Eur Heart J Acute Cardiovasc Care* 2017; 6(8): 744–749.
15. Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000; 36: 959–969.
16. World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA* 2013; 310: 2191–2194.
17. Statistics Iceland. Icelandic National death registry, http://www.statice.is (2017, accessed 25 May 2017).
18. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2012; 35(Suppl. 1): S64–S71.
19. RC Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2016.
20. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011; 364: 829–841.
21. Coutinho M, Gerstein HC, Wang Y, et al. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* 1999; 22: 233–240.
22. Ritsinger V, Tanoglidi E, Malmberg K, et al. Sustained prognostic implications of newly detected glucose abnormalities in patients with acute myocardial infarction: Long-term follow-up of the Glucose Tolerance in Patients with Acute Myocardial Infarction cohort. *Diab Vasc Dis Res* 2015; 12: 23–32.
23. George A, Bhatia RT, Buchanan GL, et al. Impaired glucose tolerance or newly diagnosed diabetes mellitus diagnosed during admission adversely affects prognosis after myocardial infarction: An observational study. *PLoS One* 2015; 10: e0142045.
24. Kuhl J, Jorneskog G, Wemminger M, et al. Long-term clinical outcome in patients with acute coronary syndrome and dysglycaemia. *Cardiovasc Diabetol* 2015; 14: 120.
25. Patel PA, Cubbon RM, Sapsford RJ, et al. An evaluation of 20 year survival in patients with diabetes mellitus and acute myocardial infarction. *Int J Cardiol* 2016; 203: 141–144.
26. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; 344: 1343–1350.
27. The Diabetes Prevention Program. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: The Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol* 2015; 3: 866–875.
28. Mellbin LG, Malmberg K, Norhammar A, et al. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: A report from the DIGAMI 2 trial. *Eur Heart J* 2008; 29: 166–176.
29. Fox CS, Golden SH, Anderson C, et al. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: A Scientific Statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* 2015; 38: 1777–1803.
30. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; 359: 1577–1589.
31. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128.
32. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377: 644–657.