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DIABETES AND GLUCOSE ABNORMALITIES IN CARDIOVASCULAR DISEASE – STUDIES ON PREVALENCE AND PROGNOSIS IN MYOCARDIAL INFARCTION AND ATRIAL FIBRILLATION

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To my family

Diabetes and glucose abnormalities in cardiovascular disease

THESIS FOR A DOCTORAL DEGREE (PhD)

By

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POPULAR SCIENCE SUMMARY OF THE THESIS

Background:
Diabetes is a strong risk factor for cardiovascular disease and increases the risk for dismal prognosis after cardiovascular events. The aim of this thesis was to describe the prevalence of established diabetes and newly diagnosed glucose abnormalities and how these affect the prognosis of patients with different cardiovascular diseases, such as myocardial infarction and atrial fibrillation. The term glucose abnormalities refer in this thesis to newly diagnosed diabetes or prediabetes.

Aims:
The specific aims were:

1. To study the prognosis in patients with a specific type of myocardial infarction (ST-elevation myocardial infarction) och compare those with and without diabetes. The studied patients had been previously enrolled in a large register-based, randomised clinical trial **(Study I)**.

2. To study the long-term prognosis in patients with newly diagnosed glucose abnormalities after an acute myocardial infarction, to compare the performance of the two screening methods for the diagnosis of diabetes, i.e. the Oral Glucose Tolerance Test (OGTT) and HbA1c and elucidate if these methods can predict the prognosis **(Study II).**

3. To report if diabetes is common in a nationwide population with atrial fibrillation and study the importance of diabetes in prognosis regarding the risk of premature death and the risk of being afflicted with heart failure, myocardial infarction and stroke **(Study III)**.

4. To study if among individuals with atrial fibrillation, there are differences in prognosis between those without diabetes, those with type 1 diabetes and those with type 2 diabetes regarding the risk of death and the risk of getting heart failure, myocardial infarction, stroke and dementia. In addition, we studied if episodes of low blood sugar (hypoglycaemia) affect the prognosis **(Study IV)**.

5. To report on the percent of people with glucose abnormalities in a population with atrial fibrillation and compare the differences in percentages if the criteria for diagnosis of diabetes and prediabetes from the American Diabetes Association compared to the criteria from the World Health Organisation (WHO) were used **(Study V)**.

Results:
Study I included patients with ST-elevation myocardial infarction from 2010-2013. Diabetes increased the risk for death at 1-year by 60%. The risk was higher in insulin-treated patients. This increased risk was observed when coronary artery disease severity and thrombus burden were taken into account. The explanation for this increased risk of death needs further investigation.

Study II screened 841 patients with myocardial infarction at Danderyd University Hospital for glucose abnormalities between 2006-2013. These patients were followed for death and cardiovascular events for a mean follow-up time of around five years. Previously undetected glucose abnormalities were common and 80% of patients with myocardial infarction had undiagnosed glucose abnormalities when screened with both OGTT and HbA1c, when the criteria for diagnosis of diabetes and prediabetes from the American Diabetes Association (ADA) were used. These two screening methods identified different persons as high-risk individuals. In our study population, only HbA1c prediabetes values (39-47 mmol/mol) could predict an increased risk (30%) of premature death and cardiovascular events. These results could however have been influenced by the fact that patients were informed of the OGTT-results and those with glucose abnormalities according to OGTT were offered lifestyle modification counselling and follow-up by their general practitioner.

Study III identified and collected information on all patients with atrial fibrillation in Sweden by using and linking data from different national registries. Around 18% of patients with atrial fibrillation had established diabetes. The presence of diabetes led to a 30% increased risk of premature death, 20% increased risk of heart failure, 25% increased risk of myocardial infarction and 10% increased risk of ischaemic stroke compared to those without diabetes.

Study IV showed that in individuals with atrial fibrillation, both diabetes mellitus type 1 and diabetes mellitus type 2 led to an increased risk of premature death, heart failure, myocardial infarction, stroke and dementia compared to those without diabetes. This increase in risk was more pronounced in those with type 1-diabetes than type 2-diabetes for premature death (87% vs. 51%) and myocardial infarction (149% vs. 70%) when both groups were compared to the patients without diabetes. Among individuals with atrial fibrillation and type 2-diabetes, a history of previous episodes of severe hypoglycaemia was associated with a 25% increased risk of premature death and 35% increased risk of dementia compared to those with type 2-diabetes and no previous episodes of severe hypoglycaemia.

Study V is an interim analysis of the ongoing Early Detection of Glucose Abnormalities in Atrial Fibrillation (EDGA-AF) study, where patients with atrial fibrillation undergoing electrical cardioversion were screened for glucose abnormalities with both OGTT and HbA1c. A high proportion of patients had previously unknown glucose abnormalities and the criteria for the diagnosis of diabetes from the American Diabetes Association identified a larger proportion of patients with glucose abnormalities than the criteria from the World Health Organisation (75% vs. 45%). If this is important for the future prognosis of these patients is not yet studied. HbA1c and OGTT identified different phenotypes of at-high-risk individuals, where the 2-hour postload plasma glucose of the OGTT identified more persons with features of the metabolic syndrome.

Conclusion:

This thesis confirms that diabetes and previously unknown glucose abnormalities are common in patients with myocardial infarction, but also in patients with atrial fibrillation and are associated with an increased risk of premature death and cardiovascular events, especially in those individuals with diabetes treated with insulin. Among patients with AF, type 1 diabetes confers similar risks of adverse events as type 2 diabetes and even higher risk than type 2 diabetes for the events of premature death and myocardial infarction. The available screening methods for glucose abnormalities, fasting plasma glucose, 2-hour postload plasma glucose and HbA1c, identify different at-high-risk individuals. In our studies, the combination of fasting plasma glucose and HbA1c identified more than 80% of patients with undiagnosed glucose abnormalities. The best screening method to predict cardiovascular prognosis needs to be further explored.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund:
Diabetes är en stark riskfaktor för hjärtkärlsjukdom och ökar risken för en sämre prognos efter hjärtkärlhändelser. Målsättningen med denna avhandling var att beskriva förekomst av diabetes och tidigare okända blodsockerstörningar och hur dessa påverkar patienters prognos vid olika hjärt-kärlsjukdomar, såsom hjärtinfarkt och förmaksflimmer. Uttrycket blodsockerstörningar i denna avhandling innebär tidigare okänd diabetes eller förstadium till diabetes, så kallad prediabetes.

Mål:
De specifika målen med denna avhandling var:

1. Att studera prognos hos patienter med så kallad ST-höjnings-hjärtinfarkt och jämföra de med och utan diabetes. Patienterna som ingick i studien deltog i en stor register-baserad, randomiserad klinisk studie **(Studie I)**.

2. Att studera det långsiktiga utfallet hos patienter med nyupptäckta blodsocker-störningar efter en akut hjärtinfarkt och jämföra betydelsen av två olika screeningmetoder för diagnos av blodsockerstörningar, oralt glukostoleranstest (OGTT) och HbA1c (långtidsblodsocker) och om dessa kan förutsäga prognos. **(Studie II)**.

3. Att studera hur vanligt förekommande diabetes är hos personer med förmaksflimmer i en rikstäckande population och att studera betydelsen av diabetes för prognos avseende död och insjuknande i hjärtsvikt, hjärtinfarkt och stroke **(Studie III)**.

4. Att studera om det bland personer med förmaksflimmer finns skillnader i prognos mellan de utan diabetes och de med typ 1- och typ 2-diabetes för död och insjuknande i hjärtsvikt, hjärtinfarkt, stroke och demens. Vi studerade dessutom om förekomst av lågt blodsocker (hypoglykemi) påverkar denna prognos **(Studie IV)**.

5. Att studera förekomst av okända blodsockerstörningar i en population med förmaks-flimmer samt jämföra skillnader i andelen personer med blodsockerstörningar om vi använder kriterier för diabetesdiagnos från Amerikanska diabetesförbundet (ADA) jämfört med kriterier från Världshälsoorganisationen (WHO) **(Studie V)**.

Metoder och resultat:
Studie I inkluderade patienter med ST-höjningsinfarkt mellan 2010–2013. Diabetes ökade risken för 1-års dödlighet med 60%. Risken var högre hos insulinbehandlade patienter. Den ökade risken observerades även när graden av kranskärlssjukdom och propputbredning i kranskärlet beaktades. Förklaringen till denna ökade risk bör utredas vidare.

Studie II screenade 841 patienter med hjärtinfarkt vid Danderyds sjukhus för glukosstörningar mellan 2006–2013. Dessa patienter följdes upp avseende död och hjärtkärlhändelser med en medeluppföljningstid på ca fem år. Tidigare okända blodsockerstörningar var vanliga och 80% av patienterna med hjärtinfarkt hade odiagnostiserade blodsockerstörningar

när de kontrollerades med både OGTT och HbA1c och kriterierna för diabetes- och prediabetesdiagnos från ADA användes. De två olika screeningmetoderna identifierade olika personer som högriskindivider. I studien var det endast HbA1c i prediabetesintervallet (39–47 mmol/mol) som kunde förutspå en ökad risk (30%) för förtida död och hjärtkärlhändelser. Resultatet kan ha påverkats av att patienterna med blodsockerstörning enligt sockerbelastningstest (OGTT) informerades om resultatet och fick bl. a livsstilsråd och uppföljning via primärvården för optimering av riskfaktorer för hjärtkärlhändelser.

Studie III identifierade och samlade information om alla patienter med förmaksflimmer i Sverige genom att använda data från nationella register. Cirka 18% av patienterna med förmaksflimmer hade känd diabetes. Diabetes ledde till 30% ökad risk för förtida död, 20% ökad risk för hjärtsvikt, 25% ökad risk för hjärtinfarkt och 10% ökad risk för stroke jämfört med personer utan diabetes.

Studie IV visade att hos personer med förmaksflimmer leder både typ 1- och typ 2-diabetes till ökad risk för förtida död, hjärtsvikt, hjärtinfarkt, stroke och demens jämfört med personer utan diabetes. Denna riskökning var mer uttalad hos de med typ 1-diabetes än de med typ 2-diabetes för död (87% vs. 51%) och hjärtinfarkt (149% vs. 70%) när båda grupperna jämfördes med personer utan diabetes. Hos individer med förmaksflimmer och typ 2-diabetes var förekomst av tidigare allvarlig hypoglykemi associerad med 25% ökad risk för förtidadöd och 35% ökad risk för demens jämfört med personer med typ 2-diabetes utan tidigare allvarlig hypoglykemi.

Studie V är en interims analys av den pågående Early Detection of Glucose Abnormalities in Atrial Fibrillation (EDGA-AF) -studien, där personer med förmaksflimmer som genomgår s k elkonvertering screenas för blodsockerstörningar med både OGTT och HbA1c. En hög andel av patienterna hade tidigare odiagnostiserade blodsockerstörningar. När kriterier från ADA användes hittades flera personer med blodsockerstörningar jämfört med när WHO användes (75% vs. 45%). Om detta är av betydelse för framtida prognos är ännu inte studerat. HbA1c och OGTT identifierade olika typer av högrisk personer, där blodsockervärdet vid 2 timmar vid OGTT hittade fler individer med tecken till s k metabolt syndrom än HbA1c.

Konklusion:

Denna avhandling bekräftar att diabetes och tidigare okända blodsockerstörningar är vanliga hos patienter med hjärtinfarkt, men visar också att det är vanligt hos patienter med förmaksflimmer, och att blodsockerstörningar är associerade med ökad risk för död och hjärtkärlhändelser, speciellt hos insulinbehandlade individer. Hos patienter med förmaksflimmer medför typ 1-diabetes generellt liknande risk för negativa händelser som typ 2-diabetes och även högre risk än typ 2-diabetes för förtida död och hjärtinfarkt. De tillgängliga screeningmetoderna för blodsockerstörningar, fasteglukos, 2-timmars-sockervärde vid OGTT och HbA1c identifierar olika högriskindivider. I våra studier, hittar en kombination av fasteglukos och HbA1c mer än 80% av patienterna med glukosstörningar. Den bästa screeningmetoden för att förutse framtida risk för hjärt-kärlhändelser bör undersökas vidare.

ΠΕΡΙΛΗΨΗ ΤΗΣ ΔΙΔΑΚΤΟΡΙΚΗΣ ΔΙΑΤΡΙΒΗΣ

Πλαίσιο:

Ο διαβήτης είναι ένας σημαντικός παράγοντας κινδύνου για καρδιαγγειακές παθήσεις και η παρουσία του επηρεάζει δυσμενώς την πρόγνωση μετά από καρδιαγγειακά επεισόδια. Ο στόχος αυτής της διδακτορικής διατριβής ήταν να περιγράψει τον επιπολασμό του διαβήτη και προσφάτως διαγνωσμένων διαταραχών μεταβολισμού της γλυκόζης σε ασθενείς με καρδιαγγειακές νόσους, όπως το έμφραγμα του μυοκαρδίου και η κολπική μαρμαρυγή, καθώς και να μελετήσει την σημασία αυτών των διαταραχών μεταβολισμού της γλυκόζης στην πρόγνωση των ασθενών αυτών. Ο όρος διαταραχές μεταβολισμού της γλυκόζης αναφέρεται στα πλαίσια αυτής της διδακτορικής διατριβής σε προσφάτως διαγνωσμένο διαβήτη ή προδιαβήτη.

Στόχοι:

Οι συγκεκριμένοι στόχοι αυτής της διδακτορικής διατριβής ήταν:

1. Να μελετήσει την πρόγνωση σε ασθενείς με ένα συγκεκριμένο τύπο εμφράγματος του μυοκαρδίου (έμφραγμα του μυοκαρδίου με ανάσπαση του ST διαστήματος) και να συγκρίνει τους ασθενείς με και χωρίς διαβήτη. Τα άτομα που εξετάστηκαν είχαν συμμετάσχει σε μια μεγάλη, βασισμένη σε μητρώα, τυχαιοποιημένη ελεγχόμενη δοκιμή **(Μελέτη Ι)**.

2. Να μελετήσει την μακροχρόνια πρόγνωση σε ασθενείς με προσφάτως διαγνωσμένες διαταραχές του μεταβολισμού της γλυκόζης μετά από οξύ έμφραγμα του μυοκαρδίου, να συγκρίνει την απόδοση δύο διαφορετικών μεθόδων ελέγχου για την διάγνωση διαταραχών μεταβολισμού της γλυκόζης, δηλαδή της δοκιμασίας ανοχής στην γλυκόζη (OGTT) και της γλυκοζυλιωμένης αιμοσφαιρίνης (HbA1c) καθώς και να διευκρινίσει αν αυτές οι μέθοδοι μπορούν να προβλέψουν την πρόγνωση σε αυτούς τους ασθενείς **(Μελέτη ΙΙ)**.

3. Να μελετήσει πόσο συχνός είναι ο διαβήτης σε ένα πανεθνικό, Σουηδικό πληθυσμό με κολπική μαρμαρυγή και να μελετήσει τη σημασία του διαβήτη στην πρόγνωση όσον αφορά στον κίνδυνο θανάτου και τον κίνδυνο νόσησης με καρδιακή ανεπάρκεια, έμφραγμα του μυοκαρδίου και εγκεφαλικό επεισόδιο (Μελέτη ΙΙΙ).

4. Να μελετήσει αν η πρόγνωση σε ασθενείς με κολπική μαρμαρυγή διαφέρει μεταξύ των ασθενών χωρίς διαβήτη, διαβήτη τύπου 1 και διαβήτη τύπου 2 όσον αφορά στον κίνδυνο θανάτου και τον κίνδυνο νόσησης με καρδιακή ανεπάρκεια, έμφραγμα του μυοκαρδίου, εγκεφαλικό επεισόδιο και άνοια. Επίσης να εξετάσει αν τυχόν επεισόδια υπογλυκαιμίας επηρεάζουν την πρόγνωση **(Μελέτη ΙV)**.

5. Να μελετήσει το ποσοστό των ανθρώπων με προηγουμένως αδιάγνωστες διαταραχές μεταβολισμού της γλυκόζης σε ένα πληθυσμό με κολπική μαρμαρυγή καθώς και να εντοπίσει τις διαφορές στα ποσοστά αν εφαρμοστούν τα κριτήρια για την διάγνωση του διαβήτη και προδιαβήτη της Αμερικάνικης Διαβητολογικής Εταιρείας συγκριτικά με τα κριτήρια του Παγκόσμιου Οργανισμού Υγείας **(Μελέτη V)**.

Αποτελέσματα:

Στην **μελέτη Ι** συμμετείχαν ασθενείς με οξύ έμφραγμα του μυοκαρδίου με ανάσπαση του ST διαστήματος μεταξύ των ετών 2010-2013. Η παρουσία διαβήτη αύξησε τον κίνδυνο θανάτου εντός ενός έτους με 60%. Η αύξηση του κινδύνου ήταν ακόμη μεγαλύτερη σε

ασθενείς που είχαν θεραπεία ινσουλίνης. Αυτός ο αυξημένος κίνδυνος υπήρχε ακόμα και όταν συνυπολογίστηκαν η βαρύτητα της στεφανιαίας νόσου και η έκταση του θρόμβου. Τα αίτια για αυτό τον αυξημένο κίνδυνο χρήζουν περαιτέρω διερεύνησης.

Στην **μελέτη ΙΙ** έγινε έλεγχος για διαταραχές μεταβολισμού της γλυκόζης σε 841 ασθενείς μετά από οξύ έμφραγμα του μυοκαρδίου στο Πανεπιστημιακό νοσοκομείο του Danderyd στην Στοκχόλμη μεταξύ των ετών 2006-2013. Αυτοί οι ασθενείς παρακολουθήθηκαν για τυχόν έλευση θάνατου και μελλοντικών καρδιαγγειακών επεισοδίων για μια μέση περίοδο περίπου 5 ετών. Προηγουμένως αδιάγνωστες διαταραχές μεταβολισμού της γλυκόζης ήταν συχνές και βρέθηκαν σε ποσοστό περίπου 80% αυτών των ασθενών σε έλεγχο με δοκιμασία ανοχής γλυκόζης και γλυκοζυλιωμένης αιμοσφαιρίνης. Αυτές οι δύο μέθοδοι ελέγχου εντοπίζουν διαφορετικούς ασθενείς σαν άτομα υψηλού κινδύνου. Στον πληθυσμό της μελέτης μας, μόνο οι προδιαβητικές τιμές της γλυκοζυλιωμένης αιμοσφαιρίνης (39-47 mmol/mol) μπορούσαν να προβλέψουν αυξημένο κίνδυνο (30%) θανάτου και καρδιαγγειακών επεισοδίων. Τα αποτελέσματα της μελέτης μας θα μπορούσαν ωστόσο να είχαν επηρεαστεί από το γεγονός ότι οι ασθενείς ενημερώνονταν για τυχόν παθολογικό αποτέλεσμα της δοκιμασίας ανοχής γλυκόζης και δέχονταν συμβουλές για πιο υγιεινό τρόπο ζωής και παραπεμπτικό για παρακολούθηση από τον προσωπικό τους γιατρό.

Στην **μελέτη ΙΙΙ** ταυτοποιήθηκαν και συλλέχθηκαν πληροφορίες για όλους τους ασθενείς με κολπική μαρμαρυγή στην Σουηδία χρησιμοποιώντας πληροφορίες από πολλαπλές, εθνικές, Σουηδικές βάσεις δεδομένων. Περίπου 18% των ασθενών με κολπική μαρμαρυγή είχαν και διαγνωσμένο διαβήτη. Στους ασθενείς με κολπική μαρμαρυγή, η παρουσία του διαβήτη αύξησε κατά 30% τον κίνδυνο πρόωρου θανάτου, κατά 20% τον κίνδυνο καρδιακής ανεπάρκειας, κατά 25% τον κίνδυνο εμφράγματος του μυοκαρδίου και κατά 10% τον κίνδυνο ισχαιμικού εγκεφαλικού επεισοδίου συγκριτικά με τα άτομα χωρίς διαβήτη.

Η **μελέτη ΙV** έδειξε ότι σε άτομα με κολπική μαρμαρυγή, τόσο ο διαβήτης τύπου 1 όσο και ο διαβήτης τύπου 2 αύξησαν τον κίνδυνο πρόωρου θανάτου, καρδιακής ανεπάρκειας, εμφράγματος του μυοκαρδίου, ισχαιμικού εγκεφαλικού επεισοδίου και άνοιας συγκριτικά με τα άτομα χωρίς διαβήτη. Ο κινδύνος ήταν περισσότερο αυξημένος σε ασθενείς με διαβήτη τύπου 1 συγκριτικά με ασθενείς με διαβήτη τύπου 2 όσον αφορά στον κίνδυνο πρόωρου θανάτου (87% vs. 51%) και εμφράγματος του μυοκαρδίου (149% vs. 70%) χρησιμοποιώντας την ομάδα ασθενών χωρίς διαβήτη σαν μέτρο σύγκρισης. Στα άτομα με κολπική μαρμαρυγή και διαβήτη τύπου 2, προηγούμενα επεισόδια σοβαρής υπογλυκαιμίας συσχετίζονταν με 25% αυξημένο κίνδυνο πρόωρου θανάτου και 35% αυξημένο κίνδυνο άνοιας συγκριτικά με άτομα με διαβήτη τύπου 2 χωρίς προηγούμενα επεισόδια σοβαρής υπογλυκαιμίας.

Η **μελέτη V**, μια ενδιάμεση ανάλυση της μελέτης Early Detection of Glucose Abnormalities in Atrial Fibrillation (EDGA-AF), στην οποία ασθενείς με κολπική μαρμαρυγή που υπόκεινται σε ηλεκτρική ανάταξη, ελέγχονται για διαταραχές μεταβολισμού της γλυκόζης με δοκιμασία ανοχής γλυκόζης και έλεγχο γλυκοζυλιωμένης αιμοσφαιρίνης. Ένα ψηλό ποσοστό ασθενών βρέθηκε να έχει προηγουμένως αδιάγνωστες διαταραχές μεταβολισμού της γλυκόζης αλλά τα κριτήρια για διάγνωση του διαβήτη της Αμερικάνικης Διαβητολογικής Εταιρείας ταυτοποίησαν μεγαλύτερο ποσοστό ασθενών με διαταραχές μεταβολισμού της γλυκόζης συγκριτικά με τα κριτήρια του Παγκόσμιου Οργανισμού Υγείας (75% vs. 45%). Το αποτέλεσμα της γλυκοζυλιωμένης αιμοσφαιρίνης και της δοκιμασίας ανοχής γλυκόζης ταυτοποίησαν άτομα με διαφορετικούς φαινότυπους σαν άτομα ψηλού κινδύνου, όπου η παθολογική τιμή γλυκόζης στις 2 ώρες κατά την δοκιμασία ανοχής γλυκόζης ταυτοποίησε περισσότερα άτομα με χαρακτηριστικά του μεταβολικού συνδρόμου σε σχέση με τις παθολογικές τιμές της γλυκοζυλιωμένης αιμοσφαιρίνης.

Συμπεράσματα:
Τα αποτελέσματα αυτής της διδακτορικής διατριβής επιβεβαιώνουν ότι ο διαβήτης και οι προηγουμένως αδιάγνωστες διαταραχές μεταβολισμού της γλυκόζης είναι συχνές τόσο σε ασθενείς με έμφραγμα του μυοκαρδίου όσο και σε ασθενείς με κολπική μαρμαρυγή και συσχετίζονται με αυξημένο κίνδυνο πρόωρου θανάτου και καρδιαγγειακών επεισοδίων, ειδικά στα άτομα με διαβήτη που έχουν θεραπεία ινσουλίνης. Στους ασθενείς με κολπική μαρμαρυγή, ο διαβήτης τύπου 1 και ο διαβήτης τύπου 2 συνδέονται με παρόμοιες αυξήσεις στον κίνδυνο ανεπιθύμητων συμβάντων και όσον αφορά στον κίνδυνο πρόωρου θανάτου και εμφράγματος του μυοκαρδίου η αύξηση του κινδύνου στον διαβήτη τύπου 1 είναι ακόμα μεγαλύτερη συγκριτικά με την αύξηση στον διαβήτη τύπου 2. Οι υπάρχουσες μέθοδοι ελέγχου για διαταραχές μεταβολισμού της γλυκόζης, δηλαδή η γλυκόζης νηστείας, η γλυκόζη στις 2 ώρες κατά την δοκιμασία ανοχής γλυκόζης και η γλυκοζυλιωμένη αιμοσφαιρίνη ταυτοποιούν διαφορετικά άτομα σαν άτομα ψηλού κινδύνου. Στις μελέτες μας ο συνδυασμός της γλυκόζης νηστείας και της γλυκοζυλιωμένης αιμοσφαιρίνης ταυτοποίησε περισσότερο από 80% των ασθενών με διαταραχές του μεταβολισμού της γλυκόζης. Ο καλύτερος μέθοδος ελέγχου για την όσον αφορά στην ταυτοποίηση των ατόμων με τον ψηλότερο κίνδυνο μελλοντικών καρδιαγγειακών επεισοδίων χρειάζεται να διερευνηθεί περαιτέρω.

ABSTRACT

Background:
Cardiovascular disease and diabetes are both common chronic conditions associated with a high disease and economic burden globally. Diabetes increases the risk of cardiovascular disease and leads to a worse prognosis after a cardiovascular event. In order to prevent complications, the early detection and treatment of risk factors is important. Many patients with established cardiovascular disease have undiagnosed glucose abnormalities, both diabetes and prediabetes, which can negatively influence the prognosis. The proposed criteria for diagnosing prediabetes from the American Diabetes Association (ADA) and the World Health Organisation (WHO) differ, with the ADA adopting lower cut-offs for fasting plasma glucose and HbA1c for the diagnosis of prediabetes. There is a need for improved knowledge of the impact of the early detection of glucose abnormalities in high-risk populations with cardiovascular disease and of the prognosis and complication burden in patients with established diabetes and atrial fibrillation. In this thesis the term glucose abnormalities includes both newly diagnosed diabetes and prediabetes.

Aims:
The overall aim of this thesis was to study the prognostic significance of glucose abnormalities and diabetes in patients with cardiovascular disease. The specific aims were:

1. To investigate the baseline characteristics and prognostic differences between patients with and without diabetes in a contemporary cohort with an ST-elevation myocardial infarction **(Study I)**

2. To investigate the association of glucose abnormalitites and long-term prognosis after acute myocardial infarction and to compare the predictive importance of the Oral Glucose Tolerance Test (OGTT, i.e. fasting plasma glucose and two-hour postload plasma glucose) and HbA1c **(Study II)**

3. To investigate the prevalence of diabetes and its prognostic importance for cardiovascular events and mortality in a nationwide cohort with atrial fibrillation **(Study III)**

4. To investigate, in a nationwide cohort with atrial fibrillation, the prognostic differences between type 1 and type 2 diabetes, using patients without diabetes as a reference group, and the impact of severe hypoglycaemia on mortality, cardiovascular events and dementia. **(Study IV)**

5. To investigate the prevalence of undetected glucose abnormalities in a selected cohort with atrial fibrillation and compare the differences in prevalence when using the criteria for diagnosis of diabetes and prediabetes from the American Diabetes Association compared to the criteria from the World Health Organisation (WHO) **(Study V)**.

Methods and results:
In Study I, participants in the register-based, randomised Thrombus Aspiration in ST-segment Elevation Myocardial Infarction in Scandinavia (TASTE) trial (n=7,244) were included between 2010-2013, of whom 13.9% had diabetes. The main finding was that diabetes mellitus was associated with an increase in one-year mortality after STEMI (HR 1.57; 95% CI 1.23-2.00). This risk was higher in insulin-treated patients, who also displayed a higher risk of recurrent myocardial infarction. This risk was not explained by an increased thrombus burden in the coronary vessels or by a more extensive coronary artery disease.

In Study II, 841 patients with an acute myocardial infarction at Danderyd University Hospital, Stockholm, Sweden, without known diabetes, were screened for glucose abnormalities before discharge in 2006 to 2013 and were followed for mortality and future cardiovascular events (mean

follow-up 4.8 years). Values for both the OGTT and HbA1c were available. When using the ADA cut-offs for diagnosis of diabetes and prediabetes, 754 of 841 patients (89.7%) had previously unknown glucose abnormalities. The OGTT and HbA1c identified different at-risk populations. The combination of fasting plasma glucose and HbA1c identified 626 of the 754 (83%) patients with previously unknown glucose abnormalities. In our population, only prediabetes identified by HbA1c according to ADA criteria (39-47 mmol/mol) was associated with an increased risk of the combined event of first of mortality, myocardial infarction, ischaemic stroke or hospitalisation for heart failure (HR 1.31; 95% CI 1.05–1.63) compared with patients with normoglycaemia. However, individuals with glucose abnormalities according to OGTT results were referred for follow-up and risk factor optimisation, which could have affected our results.

In Study III, all patients hospitalised with atrial fibrillation in Sweden (n=326,832) were included between 2006-2012, of whom 17.7% had diabetes. Information regarding comorbidities, pharmacological therapies and outcomes was collected from national health data registers. The combination of atrial fibrillation and diabetes was associated, after adjustments, with a higher risk of heart failure (HR 1.19; 95% CI 1.15-1.24), myocardial infarction (HR 1.25; 95% CI 1.18-1.33), ischaemic stroke (HR 1.11; 95% CI 1.05-1.17) and all-cause mortality (HR 1.28; 95% CI 1.25-1.31) compared with those without diabetes. The combination of diabetes and atrial fibrillation doubled the standardised mortality ratio (2.06; 95% CI 2.00-2.12) compared with the general population, while the standardised mortality ratio in those with atrial fibrillation but without diabetes was only slightly increased (1.33; 95% CI 1.31-1.35).

In Study IV, using data from Swedish national registers, we included 309,611 patients with atrial fibrillation between 2013-2014, of whom 19.5% had diabetes (n=60,294). Of patients with diabetes, 96.3% were classified as diabetes mellitus type 2 and 3.7% had type 1 diabetes. Diabetes, regardless of type, was associated with increased risks of premature death, heart failure, myocardial infarction, stroke and dementia, compared with patients without diabetes. Patients with type 1 diabetes compared with those with type 2 diabetes had a somewhat higher risk of all-cause mortality (Type 1 vs. Type 2 respectively; HR 1.87; 95% CI 1.73-2.02 vs. HR 1.51; 95% CI 1.47-1.55) and myocardial infarction (HR 2.49; 95% CI 2.17-2.85 vs. HR 1.70; 95% CI 1.59-1.81), when both groups were compared with the group without diabetes (HR=1). A history of severe hypoglycaemia was associated with an increased risk of mortality and dementia, although this did not reach statistical significance in type 1 diabetes.

In an interim analysis (Study V) of the ongoing EDGA-AF study, which started inclusion in 2019, 119 patients with AF were screened for glucose abnormalities four weeks after cardioversion. Using the ADA criteria for a diagnosis of diabetes and prediabetes, 92 (77.3%) patients were identified with newly detected glucose abnormalities by either the OGTT or the HbA1c, most of them with prediabetes. The WHO criteria identified 54 patients (45.3%) with glucose abnormalities. Individuals with undiagnosed glucose abnormalities identified by the OGTT had features of the metabolic syndrome, such as a larger waist circumference.

Conclusion:

This thesis confirms that established diabetes and newly detected glucose abnormalities are common in patients with a myocardial infarction but also in patients with atrial fibrillation and are associated with an increased risk of mortality and cardiovascular events, especially in insulin-treated individuals with diabetes. Among patients with atrial fibrillation, type 1 diabetes confers risks of adverse events similar to those in type 2 diabetes and an even higher risk than type 2 diabetes for the events of premature death and myocardial infarction. The available screening methods for glucose abnormalities, fasting plasma glucose, two-hour postload plasma glucose and HbA1c, identify different at-risk populations. In our studies, the combination of fasting plasma glucose and HbA1c identified more than 80% of patients with undiagnosed glucose abnormalities. The best screening method to predict cardiovascular prognosis needs to be further explored.

LIST OF SCIENTIFIC PAPERS

I. Karayiannides S, Norhammar A, Frøbert O, James SK, Lagerqvist B, Lundman P.
Prognosis in Patients With Diabetes Mellitus and STEMI Undergoing Primary PCI.
J Am Coll Cardiol. 2018;72(12):1427-8.

II. Karayiannides S, Djupsjö C, Kuhl J, Hofman-Bang C, Norhammar A, Holzmann MJ, Lundman P.
Long-term prognosis in patients with acute myocardial infarction and newly detected glucose abnormalities: predictive value of oral glucose tolerance test and HbA1c.
Cardiovasc Diabetol. 2021;20(1):122

III. Karayiannides S, Lundman P, Friberg L, Norhammar A.
High overall cardiovascular risk and mortality in patients with atrial fibrillation and diabetes: A nationwide report.
Diabetes Vasc Dis Res. 2017;15(1):31-38

IV. Karayiannides S, Norhammar A, Landstedt-Hallin L, Friberg L, Lundman P.
Prognosis in patients with atrial fibrillation and type 1 and 2 diabetes mellitus and the effects of severe hypoglycaemia: a nationwide cohort study.
Eur J Prev Cardiol. 2022;zwac093.

V. Karayiannides S, Lind V, Lundwall K, Landstedt-Hallin L, Friberg L, Norhammar A, Lundman P.
Prevalence of glucose abnormalities in patients with atrial fibrillation undergoing electrical cardioversion: an interim analysis of the Early Detection of Glucose Abnormalities in Atrial Fibrillation (EDGA-AF) trial.
Manuscript

CONTENTS

LIST OF ABBREVIATIONS

2h-PG	2-hour postload plasma glucose
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADA	American Diabetes Association
AF	Atrial fibrillation
AGT	Abnormal glucose tolerance
AMI	Acute myocardial infarction
BMS	Bare-metal stent
CABG	Coronary Artery Bypass Grafting
CAD	Coronary artery disease
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DES	Drug-eluting stent
DM	Diabetes mellitus
EASD	European Association for the Study of Diabetes
eGFR	Estimated glomerular filtration rate
EHRA	European Heart Rhythm Association
fPG	Fasting plasma glucose
GAMI	Glucose Abnormalities in patients with Myocardial Infarction
GLT	Glucose-lowering treatment
HbA1c	Haemoglobin A1c
ICD-10	International classification of diseases, 10th revision
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction
NGT	Normoglycaemia
NHANES	National health and nutrition examination survey
NOAC	Non-vitamin K oral anticoagulants
NPR	National Patient Register
NSTEMI	Non-ST-elevation myocardial infarction
OAD	Oral antiglycaemic drug
OGTT	Oral glucose tolerance test
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
PLATO	Platelet Inhibition and Patient Outcomes
RCT	Randomised clinical trial
SCAAR	Swedish Angiography and Angioplasty Registry
SGLT-2	Sodium-glucose cotransporter-2
STEMI	ST-elevation myocardial infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies
TASTE	Thrombus Aspiration in ST-segment Elevation Myocardial Infarction in Scandinavia
TIA	Transient ischaemic attack
TIMI	Thrombolysis In Myocardial Infarction
UKPDS	UK Prospective Diabetes Study
WHO	World Health Organisation

1 INTRODUCTION

Diabetes mellitus is a group of metabolic disorders, defined by hyperglycaemia, which is caused by defects in insulin secretion, insulin action or a combination of both (1). The two main types of diabetes are type 1 diabetes, resulting from β-cell destruction which usually leads to absolute insulin deficiency, and type 2 diabetes, which is primarily caused by a combination of insulin resistance and a relative (as opposed to absolute) insulin deficiency. Around 90 to 95% of persons with diabetes have type 2 diabetes, while around 5 to 10% have type 1 diabetes (1). There are also several other rare forms of diabetes, which account for fewer than 1% of all people with diabetes. The traditional categorisation of diabetes has been questioned and a categorisation based on patient characteristics and future complication risks has been suggested (2). This new suggested classification has not been widely accepted and further studies are needed before a new diabetes classification can eventually be adopted.

The global prevalence of diabetes mellitus is continuously increasing, and this increase predominantly affects the Middle Eastern and African countries (3). At present, more than 540 million persons worldwide have diabetes and around seven million deaths in 2021 were attributed to diabetes and its complications, where cardiovascular disease (CVD) is a significant contributor to reduced longevity (3). Typical microvascular complications in diabetes are nephropathy, neuropathy and retinopathy. The common macrovascular complications are coronary artery disease (CAD), peripheral artery disease (PAD) and stroke. Beyond the above-mentioned well-known diabetes complications, there is increasing awareness that diabetes affects essentially all the organs in the body, with many other complications that are not often discussed, such as cardiac autonomic neuropathy, non-alcoholic fatty liver disease, diabetic cardiomyopathy, cerebral small-vessel disease, dementia and cognitive decline (4) (**Figure 1**). Moreover, heart failure should also be regarded as one of the significant complications of diabetes. In a commentary published in *Diabetes Care* by David Bell in 2003, heart failure is referred to as "the frequent, forgotten and often fatal complication of diabetes" (5). A recent consensus report from the American Diabetes Association and American College of Cardiology highlights heart failure as an underappreciated complication of diabetes and gives guidance to treating physicians for patients with concomitant diabetes and heart failure in order to reduce the risks of serious complications (6).

1.1 DIAGNOSIS OF DIABETES

Diabetes and prediabetes can be diagnosed using different tests, i.e. fasting plasma glucose (fPG), two-hour postload plasma glucose (2h-PG) during an oral glucose tolerance test (OGTT) and HbA1c. A two-hour plasma glucose value during an oral glucose tolerance test (OGTT) using a 50g or 100g glucose load was used for the first time to diagnose diabetes in 1965 (7). The standardisation of the OGTT to the current method using a 75g glucose load was implemented in 1979 (8). In 1997, the American Diabetes Association (ADA) lowered the cut-off value for fasting plasma glucose (fPG) for a diagnosis of diabetes from 7.8 mmol/L to 7.0 mmol/L, a change which was also implemented by the World Health Organisation (WHO) in 1998 (9). In 2009, an international expert committee recommended the addition of HbA1c as a diagnostic criterion for the diagnosis of diabetes, with a cut-off value of 48 mmol/mol (10), a recommendation which was adopted by the ADA in 2010 (11) and the WHO in 2011 (12). In Sweden, HbA1c was adopted as a criterion for the diagnosis of diabetes in 2014. A timeline showing the evolution of the criteria for the diagnosis of diabetes and prediabetes is presented in **Figure 2**.

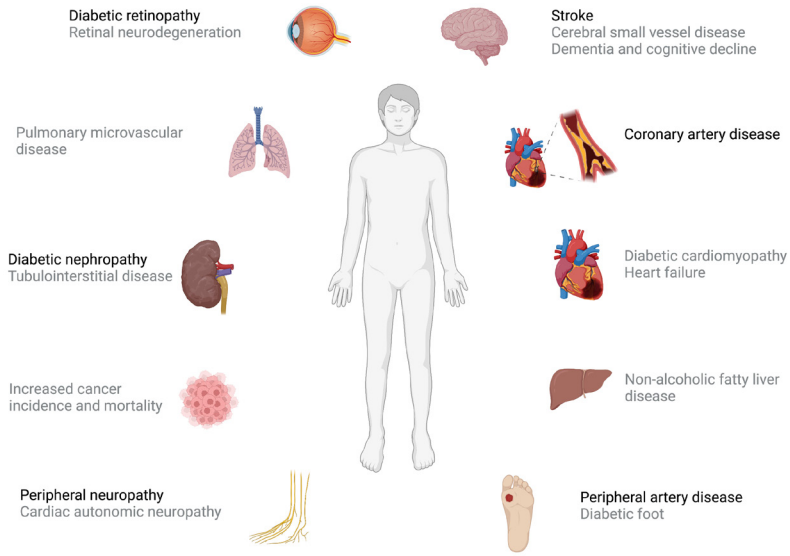

Figure 1: Schematic figure of the traditional chronic diabetes-related complications (black font) and some additional, often overlooked complications (grey font).
Adapted from *Trends in Endocrinology & Metabolism*, Vol. 31, No. 4, Mauricio, D., Alonso, N. & Gratacòs, M. Chronic Diabetes Complications: The Need to Move beyond Classical Concepts, 287-295, Copyright (2020), with permission from Elsevier. Created with BioRender.com.

WHO 1965	NDDG 1979	WHO 1980 WHO 1985	ADA 1997 WHO 1999	ADA 2003	IEC 2009 ADA 2010 WHO 2011
First established criteria for diagnosis of diabetes. Diagnosis of diabetes in persons under the age of 45 years if 2h venous plasma glucose after OGTT was ≥ 7.22 mmol/L after loading with oral glucose of 50 or 100 g. "Borderline state" if 2h venous plasma glucose after OGTT 6.11-7.17 mmol/L.	The term "impaired glucose tolerance" (IGT) is introduced. First definition was having a venous fPG < 7.8 mmol/L and 2h-PG after OGTT between 7.8-11.1 mmol/L. Standardization of OGTT protocol using 75g of anhydrous glucose load. Diabetes diagnosis if fPG ≥ 7.78 mmol/L and/or 2h-PG after OGTT ≥ 11.11 mmol/L.	**WHO 1980:** Diabetes diagnosis if fPG ≥ 8 mmol/L and/or 2h-PG after OGTT ≥ 11 mmol/L. The term IGT is endorsed and defined as having a venous fPG < 8 mmol/L and 2h-PG after OGTT between 8-11 mmol/L. **WHO 1985:** The fPG and 2-h PG OGTT thresholds were slightly changed to 7.8 mmol/L and 11.1 mmol/L respectively	The cut-off for fPG for the diagnosis of diabetes is lowered to 7.0 mmol/L. The cut-offs for the 2h-PG after OGTT were retained. Impaired fasting glucose (IFG) was introduced and defined as fPG ≥ 6.1 mmol/L and < 7.0 mmol/L.	Reduction of the cut-off value for fPG defining IFG from 6.1 mmol/L to 5.6 mmol/L.	Introduction of HbA1c as a diagnostic criterium for the diagnosis of diabetes with a cut-off value of ≥48 mmol/mol. ADA recommended also diagnosing prediabetes with HbA1c values 39-47 mmol/mol. IEC recommended defining prediabetes using HbA1c values 42-47 mmol/mol. WHO concluded that there was not enough evidence to interpret HbA1c values <48 mmol/mol.

Figure 2: Evolution of the criteria for the diagnosis of diabetes and prediabetes. HbA1c was introduced as a criterion for the diagnosis of diabetes in Sweden in 2014.
This figure was created by the author using information from references 7-12.
WHO=World Health Organisation, NDDG=National Diabetes Data Group, ADA=American Diabetes Association, IEC=International Expert Committee.

The specific cut-off values which are currently in use for the diagnosis of diabetes and prediabetes are listed in **Table 1**. The ADA and WHO have slightly different cut-off values for prediabetes (13). Two pathological values or one pathological value and typical hyperglycaemic symptoms including a random p-glucose of ≥ 11,1 mmol/L are required for diagnosis (14). However, as noted by Bergman, these values should not be regarded as absolute thresholds of disease and the risk of developing complications, as well as that of progression to diabetes constitutes a risk continuum (15). The addition of HbA1c to the diagnostic criteria has practical advantages because this test does not require fasting conditions, is less time consuming than the OGTT, has better reproducibility and is not impaired by the acute inflammatory response after a myocardial infarction as the fPG tests are (16). On the other hand, HbA1c identifies one-third fewer cases than fPG in the event of universal screening in the NHANES data (1).

Table 1: Diagnostic criteria for the diagnosis of diabetes and prediabetes.

	Normal	Prediabetes			Diabetes
		IFG	IGT		
Venous fasting plasma glucose (fPG) (mmol/L)	<5.6 (ADA) <6.1 (WHO)	5.6-6.9 (ADA) 6.1-6.9 (WHO)			≥7.0
Venous two-hour postload plasma glucose (2h-PG)* (mmol/L)	<7.8	<7.8	7.8-11.0		≥11.1
HbA1c (mmol/mol)	<39 (ADA) <42 (IEC)			39-47 (ADA) 42-47 (IEC)	≥48

* after 75g oral glucose load [oral glucose tolerance test (OGTT)]

ADA=American Diabetes Association; WHO=World Health Organisation; IFG=Impaired fasting glucose; IGT= Impaired glucose tolerance; IEC=International Expert Committee.

Insulin, which was discovered in 1921 by a research team at the University of Toronto, was the first available medication for the treatment of diabetes and is still the only available treatment for type 1 diabetes. Since then, many more groups of medication have become available for the treatment of type 2 diabetes. An historical overview of the introduction of different diabetes medications is presented in **Figure 3**.

1.2 CARDIOVASCULAR DISEASE (CORONARY ARTERY DISEASE, HEART FAILURE AND ATRIAL FIBRILLATION)

Cardiovascular diseases (CVDs) are a group of diseases affecting the heart and blood vessels. They are categorised as CVDs resulting from atherosclerosis, such as ischaemic heart disease (e.g. myocardial infarction), cerebrovascular disease (e.g. stroke) and diseases of the aorta and arteries [e.g. hypertension and peripheral artery disease (PAD)] and other CVDs, such as congenital heart disease, rheumatic heart disease, cardiomyopathies (e.g. heart failure) and cardiac arrhythmias (e.g. atrial fibrillation) (17). The highest proportion of cardiovascular deaths globally in 2019 were attributed to ischaemic heart disease and stroke, followed

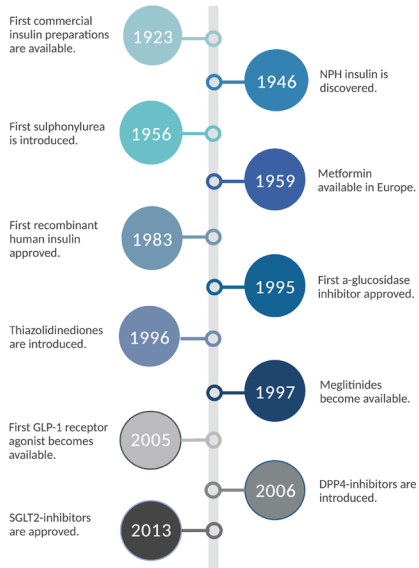

Figure 3: A timeline of the introduction of different diabetes medications.
NPH indicates neutral protamine Hagedorn; GLP-1, glucagon-like peptide 1; DPP4, dipeptidyl peptidase 4; SGLT2, sodium-glucose co-transporter 2. Created with BioRender.com.

by hypertensive heart disease (18). Among cardiac arrhythmias, atrial fibrillation is the most common (19), with an estimated prevalence of around 3% in adults (20). Globally, cardiovascular disease is the leading cause of death, accounting for around 17.9 million deaths in 2015, a 12.5% rise compared with 2005, although the age-standardised mortality rates after CVD decreased by 15.6% during the same period in the western world (21–23).

1.3 THE RELATIONSHIP BETWEEN DIABETES MELLITUS AND CARDIOVASCULAR DISEASE

Among the first studies that really brought attention to diabetes mellitus as a risk factor for cardiovascular disease in the 1970s, and possibly the most well-known regarding this aspect from that time period, was the Framingham Study. Two publications from that study, the first in 1974, associated diabetes with an increased risk of congestive heart failure (24) and the second in 1979, showed that diabetes increased the risk of cardiovascular disease two times in men and three times in women (25).

For many years, diabetes was regarded as a coronary disease equivalent in calculating the future CVD risk. In a study published in 1998, Haffner et al. demonstrated that patients with diabetes without a prior myocardial infarction had a cardiovascular risk similar to that of patients with a prior myocardial infarction but without diabetes (26). The same conclusion was reached in a nationwide Danish study that was published ten years later by Schramm et al. (27). However, other studies were unable to replicate these findings. Rana et al. demonstrated in 2016, that only a subset of high-risk diabetes patients, such as those with longer diabetes duration, had a cardiovascular risk similar to that of those with a prior myocardial infarction (28). Nevertheless, diabetes still entails a significant excess morbidity and mortality risk.

Recently published nationwide data by Rawshani et al. showed that, despite a substantial decrease in the mortality and incidence of cardiovascular disease in persons with diabetes in Sweden in the last 20 years, there is a significant remaining excess mortality and morbidity risk in persons with diabetes compared with the general population (29).

Diabetes is associated with a higher risk of many types of cardiovascular complication and the excess risk differs, depending on the type of investigated population and the studied time periods. For instance, while results from the Framingham Study in the 1970s suggested a two- to threefold increase in the risk of myocardial infarction (25) and a two- to fivefold increase in the risk of heart failure (24), more recent data in Swedish patients with diabetes mellitus type 2 from 2006-2013 showed that patients with diabetes had a 70% higher age-standardised risk of myocardial infarction, a 50% higher risk of stroke, a 30% higher risk of all-cause death, a 20% higher risk of atrial fibrillation and an 80% higher risk of heart failure compared with the general population (30). This excess risk for cardiovascular events is not stable across the whole spectrum of the type 2 diabetes population but varies and depends on factors such as the age at diabetes diagnosis (31) and whether other cardiovascular risk factors are well-treated or not (32).

The optimisation of glucose values has been shown to reduce the risk of cardiovascular events in both type 1 (33) and type 2 diabetes (34,35). These results were mainly based on the long-term follow-up of the Diabetes Control and Complications (DCCT) trial for type 1 diabetes (33) and the UK Prospective Diabetes Study (UKPDS) for type 2 diabetes (35), though the results for type 2 diabetes have been somewhat conflicting, depending on the characteristics of the studied population, with the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study showing that intensive glucose lowering treatment increased mortality (36). One possible complication of diabetes treatment with insulin and certain oral antiglycaemic drugs, such as sulphonylureas, is hypoglycaemia, i.e. a below normal concentration of glucose in the blood. Hypoglycaemia can have multiple negative effects, including arrhythmias, impaired endothelial dysfunction and impaired cognitive function (37) (**Figure 4**).

1.4 PATHOPHYSIOLOGICAL MECHANISMS BETWEEN DIABETES AND CARDIOVASCULAR DISEASE

Diabetes is linked to the development of atherosclerotic cardiovascular disease, heart failure and atrial fibrillation through several pathophysiological mechanisms summarised below.

The pathophysiological mechanism that leads to cardiovascular disease in patients with diabetes is complicated and depends on both macro- and microvascular dysfunction. Patients with diabetes have accelerated atherosclerosis depending on hyperglycaemia, dyslipidaemia and endothelial dysfunction (38,39) and the increased inflammation of the coronary vascular wall (40). Moreover, diabetic autonomic neuropathy causes the impairment of the regulation of vascular tone and patients with diabetes have reduced bioavailability of nitric oxide, which is a vasodilator, and the increased secretion of vasoconstrictor endothelin-1 (38). Persons with diabetes have a chronic state of low-grade inflammation, higher oxidative stress and hypercoagulability (38), which manifests itself among other mechanisms as increased platelet activation and aggregation (41), all of which have a detrimental effect on the cardiovascular system. A detailed description of the development of atherosclerosis in diabetes mellitus is presented in **Figure 5**.

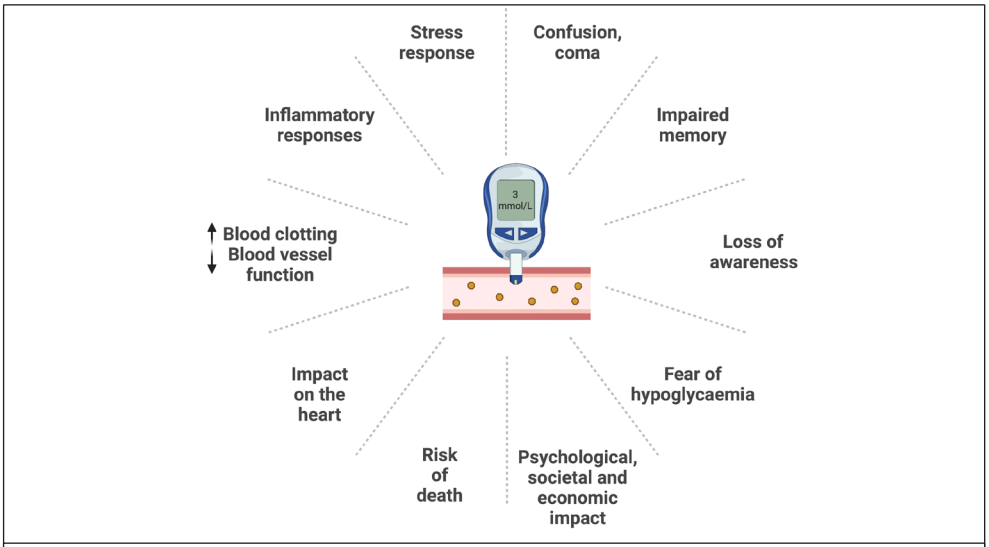

Figure 4: The consequences of hypoglycaemia.
Adapted under the terms of the CC BY 4.0 attribution licence from Amiel SA. The consequences of hypoglycaemia. Diabetologia. 2021;64(5):963–70, Copyright Springer Nature. Created with BioRender.com.

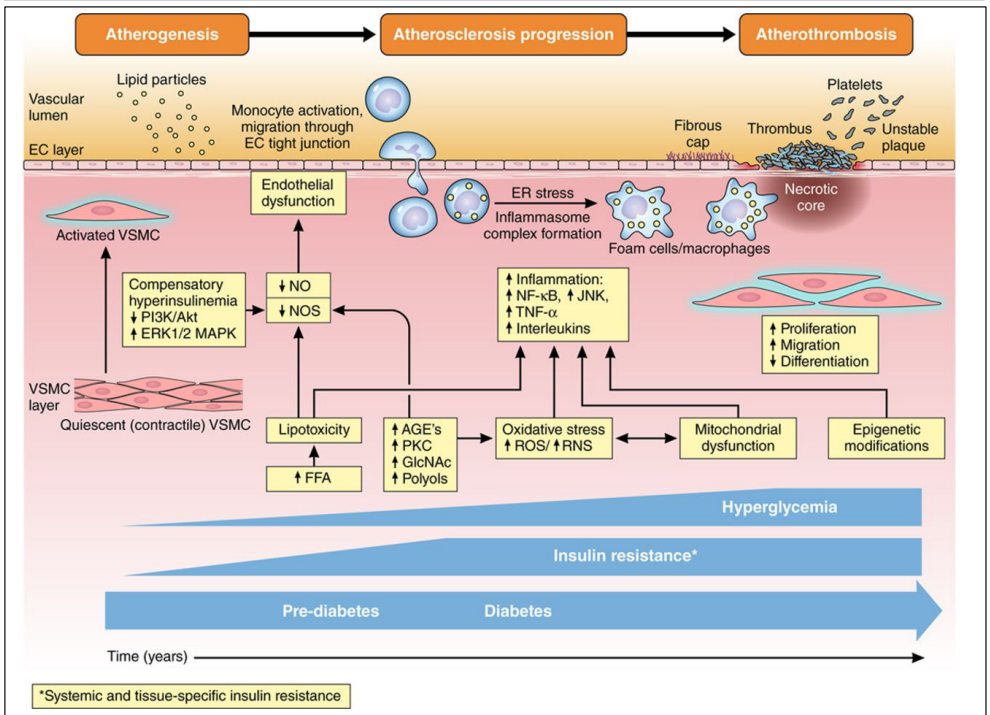

Figure 5: The development and progression of atherosclerosis in diabetes mellitus.
FFA indicates free fatty acids; AGE, advanced glycation end-product; PKC, protein kinase C; VSMC, vascular smooth muscle cells; EC, endothelial cells; TNF-a, tumour necrosis factor-α; ER, endoplasmic reticulum; Akt, protein kinase B; ERK, extracellular signal-regulated kinase; GlcNAc, N-Acetylglucosamine; IL, interleukin; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NF-κβ, nuclear factor-kappa beta; NOS, nitric oxide synthase; PI3K, phosphoinositide 3-kinase; RNS, reactive nitrogen species; and ROS, reactive oxygen species. Reproduced with permission from Cecilia C. Low Wang. Circulation. Clinical Update: Cardiovascular Disease in Diabetes Mellitus, Volume: 133, Issue: 24, Pages: 2459-2502, Copyright Wolters Kluwer Health, Inc.

Regarding the link between diabetes and heart failure, it has been suggested that diabetes leads to a particular form of diabetic cardiomyopathy, which successively leads to systolic and diastolic dysfunction (42). This diabetic cardiomyopathy occurs independently and not through the mediation of other risk factors, such as atherosclerosis, hypertension or dyslipidaemia, and, as suggested by Jia et al., begins as an early diastolic relaxation defect and progresses to clinical congestive heart failure (43). The presence of ischaemic heart disease and hypertension, which are common co-existing diseases in individuals with diabetes and can lead to ischaemic and hypertensive cardiomyopathy respectively, is another factor that increases the risk of developing heart failure in diabetes (**Figure 6**).

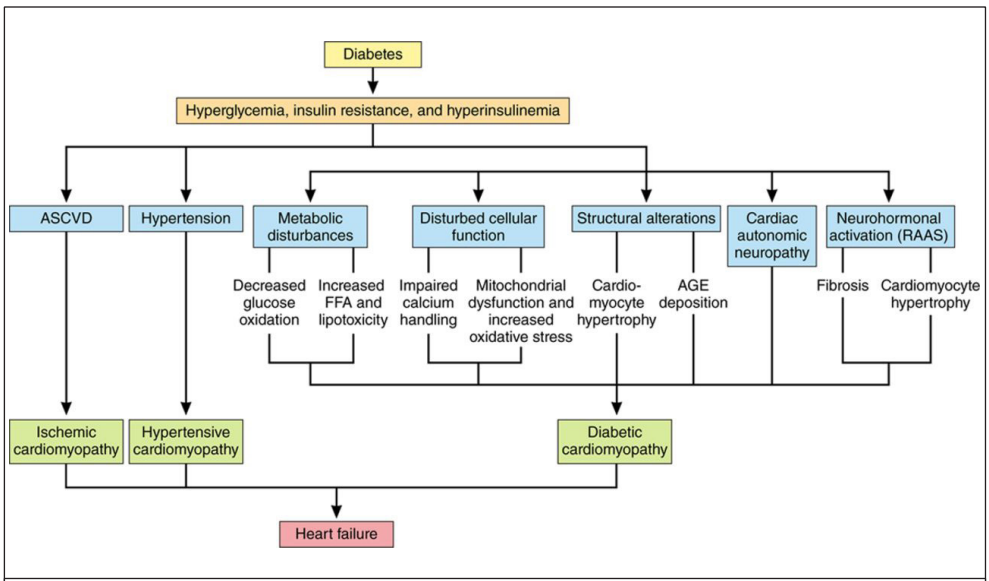

Figure 6: Pathophysiological mechanisms of heart failure in diabetes mellitus.
ASCVD indicates atherosclerotic cardiovascular disease; RAAS, renin-angiotensin-aldosterone system; AGE, advanced glycation end-product; FFA, free fatty acids. Reproduced with permission from Cecilia C. Low Wang. Circulation. Clinical Update: Cardiovascular Disease in Diabetes Mellitus, Volume: 133, Issue: 24, Pages: 2459-2502, Copyright Wolters Kluwer Health, Inc.

Several pathophysiological mechanisms have been suggested to explain the increased risk of atrial fibrillation incidence in patients with diabetes and the poorer cardiovascular prognosis in patients with both atrial fibrillation and diabetes. Risk factors independently associated with increased atrial fibrillation risk and cardiovascular disease, such as obesity, hypertension, coronary artery disease and arterial stiffness, exist more frequently in patients with diabetes mellitus (20). At the myocardial level, diabetes is suggested to lead to structural, metabolic, electrical and electromechanical atrial remodelling changes which predispose the patient to the occurrence of atrial fibrillation (44) (**Figure 7**). In addition, diabetic cardiomyopathy leads to the development of heart failure either with a preserved or reduced ejection fraction, increasing the risk of atrial fibrillation and worsening the cardiovascular prognosis (42).

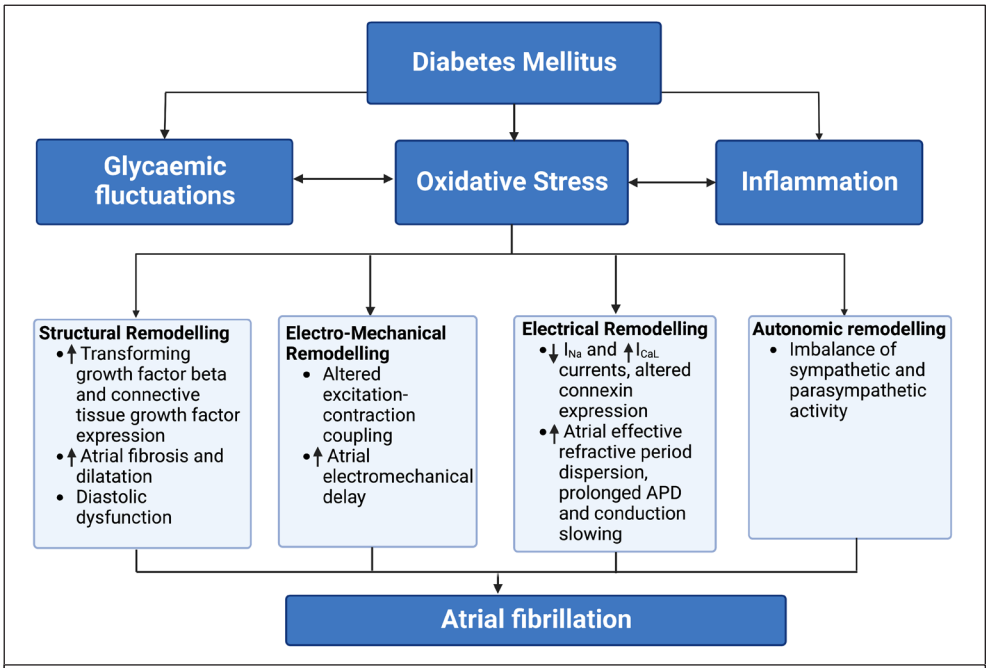

Figure 7: Pathophysiology of diabetes and atrial fibrillation.
APD indicates action potential duration. Adapted from Allen Wang et al. *J Am Coll Cardiol* 2019; 74:1107-1115, with permission from Elsevier. Created with BioRender.com.

1.5 ABNORMAL GLUCOSE TOLERANCE AND PROGNOSIS IN ACUTE CORONARY SYNDROME (ACS)

The prevalence of undiagnosed glucose abnormalities in patients with acute coronary syndromes (ACS) is high, occurring in around two-thirds of all patients with ACS (45). The latest European Society of Cardiology guidelines on diabetes, prediabetes and cardiovascular disease recommend screening with HbA1c or fPG and, if in doubt, with OGTT for diabetes in all patients with established cardiovascular disease (46). The question of which glucose test is best to use is still the subject of debate. HbA1c is less time consuming and more convenient, while OGTT is more sensitive in detecting glucose abnormalities and is the only test that can detect IGT (16,47). In a report from the EUROASPIRE IV cohort, it was shown that, in patients with coronary artery disease, only 17% of patients were identified as having diabetes by using the HbA1c criterion alone (47).

The OGTT and HbA1c seem to identify two different cohorts of patients with glucose abnormalities (48) and which of these methods is most predictive of future cardiovascular morbidity and mortality in these patients is still unclear.

There are not many published studies comparing the long-term prognosis in patients with abnormal glucose tolerance diagnosed by OGTT as opposed to HbA1c. Determining whether these markers have prognostic importance beyond other well-known risk factors for cardiovascular morbidity and mortality, such as smoking, hypertension and hyperlipidaemia, is important. Regarding studies examining the predictive value of the different screening

methods in the general population, an analysis of the data from the DECODE database, which includes more than 180,000 person-years of follow-up in 16 different European populations, showed that the 2h-PG but not the fPG is linked with an increased all-cause mortality risk (49). The predictive value of HbA1c was not examined in that study. On the other hand, Selvin et al. showed that, in a population without established cardiovascular disease, HbA1c, but not fPG, was associated with an increased risk of cardiovascular disease (50). The predictive value of 2h-PG was not examined in that study. In a meta-analysis by Santos-Oliveira et al., that included over 44,000 patients, it was also shown that HbA1c had a significant association with higher cardiovascular morbidity and all-cause mortality in persons without known diabetes, though some the studied populations had established coronary artery disease (51).

In patients with coronary artery disease, there are conflicting results as to whether HbA1c is associated with a poorer prognosis, with some studies showing an association between HbA1c and a poorer prognosis (52,53) and others showing no association (54). In a report from EUROASPIRE IV, where fPG, 2h-PG and HbA1c were used to screen for diabetes in around 4,000 patients with coronary artery disease, it was shown that only the 2h-PG and thus only information from the OGTT was of prognostic significance (55). It has also been shown that abnormal glucose tolerance (AGT), defined as either newly detected diabetes mellitus or impaired glucose tolerance (IGT) by the OGTT, affects the future prognosis in patients with ACS. A follow-up of the Glucose Abnormalities in Myocardial Infarction (GAMI) study (median follow-up time 11.6 years) showed that cardiovascular events and cardiovascular mortality were significantly more frequent in patients with AGT (56). The predictive value of 2h-PG in patients with no previously known glucose abnormalities was also shown in other studies in patients with stable coronary artery disease (57) and in patients undergoing coronary angiography (58).

To summarise, the screening test for diabetes which confers the best cardiovascular prognostic information in individuals with and without established cardiovascular disease is still the subject of debate and further studies are needed to elucidate this.

Patients with established diabetes mellitus have a relatively poor prognosis following ACS [non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI)], in both the subsequent short- and long-term perspectives (59–61). The underlying reason for the poorer prognosis is not entirely understood, but it has been suggested that more advanced coronary artery disease, incomplete revascularisation, higher rates of restenosis, stent occlusions and the increased risk of heart failure are plausible explanations (61,62). Furthermore, patients with diabetes are more prone to thromboembolic complications, increased platelet reactivity, higher platelet turnover and resistance to platelet-stabilising drugs (63–66). A recent meta-analysis of 139 studies (118 cohort studies and 21 randomised clinical trials), which included patients with both NSTEMI and STEMI from 1970 to 2011 and where the proportion of patients with diabetes varied from 7.7% to 49.2%, suggested that diabetes continues to be associated with increased mortality following a myocardial infarction, albeit in a population without contemporary treatment (67). Acute coronary care has improved in recent decades, with the development of more potent platelet aggregation-inhibiting therapies alongside with favourable acute reperfusion strategies using primary percutaneous coronary intervention (PCI) and the increased use of drug-eluting stents (DES).

The use of potent platelet aggregation inhibitors in diabetes appears to be of particular importance in patients with poor glycaemic control and those on insulin treatment. In the PLATO trial, ticagrelor versus clopidogrel was compared in patients with ACS; subgroup analyses showed that patients with an HbA1c over 42 mmol/mol had a reduced event rate when randomised to ticagrelor compared with clopidogrel (68). The benefits of using drug-eluting stents (DES) as compared to bare-metal stents (BMS) in patients with diabetes undergoing PCI have been demonstrated, with studies showing that the risk of re-stenosis is halved in these patients, with no significant difference in mortality or the risk of myocardial infarction after four years (69).

It is unclear whether diabetes is still associated with a similar excess morbidity and mortality risk after a myocardial infarction in a population with modern treatment and optimal secondary prevention and, for this reason, studies performed in a contemporary setting are of interest.

1.6 DIABETES AND ATRIAL FIBRILLATION

Atrial fibrillation (AF) is a pathological condition that affects the heart's electrical conduction system and leads to an irregular and often fast heart rhythm (70). AF is present in around 3% of all adults and its prevalence is rising, mainly because of the ageing population (20). AF is associated with a five times higher risk of stroke and a two times higher risk of mortality (71). Diabetes mellitus is a well-known risk factor for AF and increases the risk of AF by 40% (70). There is a similar increase in AF risk even in patients with impaired fasting glucose (72) or the metabolic syndrome (73). Previously published retrospective studies have shown a 70-90% increase in stroke risk in patients with concomitant AF and diabetes compared this with those with AF alone (74). In the well-established CHA_2DS_2-VASc risk score system that is used in clinical practice to calculate the risk of stroke in patients with AF, the presence of diabetes adds one point (75). In large population studies, it has also been shown that the risk of thromboembolism is not equal in all the AF patients with diabetes but increases with longer diabetes duration (76).

In a sub-analysis of the ROCKET-AF trial (5,695 patients with diabetes and AF) published in 2015, which studied the treatment with rivaroxaban in patients with AF and diabetes, it was shown that patients with concomitant AF and diabetes have a 30%, 50% and 90% higher two-year risk of stroke, vascular mortality and myocardial infarction respectively, compared with those with AF alone (77). In a cohort study from the ORBIT-AF register with 9,749 patients published in 2017, which, at the time of publication, offered the most complete appraisal of outcomes in patients with AF and diabetes (78), it was shown that diabetes is associated with a 63% increased risk of mortality in AF patients < 70 years and a 25% increased risk of mortality in AF patients ≥ 70 years (79). Patients with concomitant AF and diabetes did not, however, run a higher risk of thromboembolism, bleeding-related events and new-onset heart failure compared with those with AF alone (79).

There is limited information on the prognosis in patients with AF and diabetes from a real-world population, with most of the previous information derived from clinical trials, except for the increased stroke risk that comes with diabetes. Up-to-date information on the complications closely related with diabetes in AF is essential to optimise our future preventive strategies and the planning of healthcare resources.

The prevalence of undiagnosed diabetes and glucose abnormalities in patients with AF is unknown. A small case-control study that screened 75-year-old individuals using OGTT (46 with cases with AF and 108 controls without) reported a diabetes prevalence of 13.0% in those with AF compared with 3.7% in those without AF (80). There is also limited knowledge of the effects of glucose abnormalities on the recurrence of AF after electrical cardioversion and how they affect the prognosis in general. If the increased prevalence of diabetes can be replicated in a larger AF population, this could have significant clinical implications in the form of introducing screening for glucose abnormalities in patients with AF, in the same way that is recommended today in other cardiovascular high-risk groups, especially if associated with a poorer prognosis in patients with AF.

1.7 KNOWLEDGE GAPS

The knowledge gaps this thesis aimed to address are listed below.

- Is the presence of diabetes still an adverse risk factor, leading to increased morbidity and mortality in patients with STEMI receiving contemporary treatment, despite the improvement in acute coronary care in recent decades?
- Which of the screening methods for glucose abnormalities, i.e., the OGTT or HbA1c, has the best predictive value regarding the risk of premature death and cardiovascular events in patients after an acute myocardial infarction?
- Is the presence of diabetes an adverse prognostic risk factor in patients with atrial fibrillation in a nationwide setting, i.e., what is the external validity of the previous results of smaller studies that showed a poorer prognosis in patients with atrial fibrillation and concomitant diabetes?
- Are there prognostic differences between type 1 and type 2 diabetes in patients with atrial fibrillation and is a history of severe hypoglycaemia a further aggravating risk factor in these patients?
- What is the prevalence of undiagnosed glucose abnormalities in a population with atrial fibrillation and what is the best screening method to use in these patients?

2 RESEARCH AIMS

The overall aim of this thesis is to study the characteristics and prognosis in patients with diabetes mellitus and glucose abnormalities in background populations with a myocardial infarction and atrial fibrillation to acquire a deeper understanding of factors that worsen the prognosis in these patients and identify improved screening and treatment strategies.

The specific aims are:

- To investigate the prognosis in patients with diabetes in a contemporary population with an ST-elevation myocardial infarction (STEMI), the extent of coronary artery disease, the thrombus burden and the prognosis for patients with diabetes after an ST-elevation myocardial infarction (STEMI) (**Study I**).
- To investigate the importance of newly discovered glucose abnormalities in the long-term prognosis in a post-myocardial infarction cohort and to compare the predictive values of the Oral Glucose Tolerance Test and HbA1c (**Study II**).
- To investigate the prevalence of diabetes and its prognostic importance for cardiovascular events and mortality in a nationwide cohort with atrial fibrillation (**Study III**).
- To investigate the prognostic differences between different types of diabetes (type 1 and type 2) and the impact of severe hypoglycaemia on mortality, cardiovascular events and dementia in a nationwide cohort with atrial fibrillation (**Study IV**).
- To investigate the prevalence of undetected glucose abnormalities in a cohort with atrial fibrillation and compare the performance of OGTT and HbA1c as screening methods in these patients (**Study V**).

3 MATERIALS AND METHODS

3.1 SUMMARY

This thesis comprises five different studies summarised in **Table 2**.

Table 2: Summary of the characteristics of the studies included in this thesis.

	Study I	Study II	Study III	Study IV	Study V
Design study	Retrospective analysis of register-based randomised control trial	Retrospective cohort study			Prospective cohort study
Study population	STEMI with and without DM	MI without known diabetes	Non-valvular AF with and without DM	Non-valvular AF with and without T1DM and T2DM	Non-valvular AF after electrical cardioversion without DM
Number of patients (n)	7,244	841	326,832	317,558	119
Inclusion setting	Participants in TASTE trial	Admissions at Department of Cardiology, Danderyd Hospital	Nationwide through all-inclusive registers	Nationwide through all-inclusive registers	Outpatients at Department of Cardiology, Danderyd Hospital
Inclusion period	2010-2013	2006-2013	2006-2012	2013-2014	2019-2021
Outcomes	Mortality, MI, stent thrombosis	Mortality, MI, HF, ischaemic stroke	Mortality, MI, ischaemic stroke, HF, bleeding	Mortality, MI, ischaemic stroke, HF, dementia	Prevalence of glucose abnormalities
End of follow-up	December 2014	December 2017 for mortality and December 2014 for other outcomes	December 2013	March 2017 for mortality and December 2015 for other outcomes	Ongoing
Percentage with diabetes	13.9%	0%	17.7%	19.5%	0%
Statistical analyses	Descriptive statistics, hypothesis testing. Survival analysis using Kaplan-Meier curves and Cox regression hazard analysis. Competing risk analysis in Study IV. Multiple imputation was used to impute variables with missing data in Study I.				
Adjustments	Age, sex, co-morbidities	Age, sex	Age, sex, comorbidities and medication		n/a

Abbreviations: AMI: acute myocardial infarction; OGTT: oral glucose tolerance test; HbA1c: glycosylated haemoglobin; STEMI: ST-elevation myocardial infarction; TASTE: Thrombus Aspiration during ST-Segment Elevation myocardial infarction; MI: myocardial infarction; HF: heart failure; AF: atrial fibrillation; DM: diabetes mellitus; T1DM: type 1 diabetes; T2DM: type 2 diabetes.

3.2 DESCRIPTIONS OF REGISTERS USED AND DEFINITIONS

3.2.1 Descriptions of registers used in Studies I-IV

Sweden has a long tradition of register-based research, due mainly to the use of the unique personal identity number that has been assigned to every Swedish resident since 1947 and facilitates nationwide coverage, cross-linking between different registers and minimal loss to follow-up (81).

Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) register (Studies I, II)

Web-based, nationwide register containing information on patients admitted to Swedish hospitals with the acute coronary syndrome and those undergoing coronary angiography, percutaneous coronary intervention or heart surgery. SWEDEHEART was started in December 2009 after merging four smaller quality registers (RIKS-HIA, SCAAR, SEPHIA and the Swedish cardiac surgery register) and has 100% coverage of patients undergoing angiography, PCI or heart surgery and almost 100% for patients admitted with ACS to coronary care units (82).

The quality of data is checked yearly and there is > 95% agreement between register data and data from patient records (82).

Swedish National Patient Register (NPR) (Studies I, II, III, IV)

The register is maintained by the Swedish National Board of Health and Welfare. Data collection was initiated in 1964 by registering hospital discharge diagnoses according to the Swedish International Classification of Disease (ICD) system. The coverage was gradually increased and by 1987 the register contained all inpatient (i.e. hospital) diagnoses nationwide. Since 2001, the register has also covered diagnoses from hospital-affiliated outpatient specialist clinics coded using International Classification of Diseases 10 codes (ICD-10).

The validity of the data is generally high and the proportion of correct diagnoses in the NPR is generally around 85-95%, comparable with similar registers in countries with well-developed healthcare systems such as Denmark and the USA (83).

Swedish Causes of Death Register (Studies I, II, III, IV)

This register includes information on the date and underlying cause of death, based on the international version of ICD classification, of all Swedish residents, even those living abroad, since 1952 (84). There is virtually complete coverage of the number of deaths and around 96% of deaths have a specific recorded cause of death (84). Since 2012, the register has also contained information for non-residents who have died in Sweden.

Prescribed Drug Register (Studies II, III, IV)

Contains information on all dispensed pharmaceutical prescriptions since July 2005. The register has complete nationwide coverage and information on all prescription medication, classified according to the Anatomical Therapeutic Chemical (ATC) classification system, is included (85).

Longitudinal integrated database for health insurance and labour market studies (LISA) register (Study III)

Includes socioeconomic information on all Swedish residents aged ≥ 16 years since 1990, such as information on income, education, civil status, country of birth, foreign background, employment and family-related variables (86).

3.2.2 Definitions

A list of the most important definitions used in our studies follows below. A full list of ICD-10 codes used, and descriptions of definitions divided by study can be found in the method description and the appendix of each published study.

***Diabetes mellitus**: Study I:* Self-reported diabetes upon inclusion in the TASTE trial or treatment with glucose-lowering medication. *Study II:* Diabetes mellitus at baseline was defined as self-reported diabetes registered in SWEDEHEART. *Studies III and IV:* The presence of a registered ICD-10 code for diabetes (E10-14) or filled prescription for glucose-lowering medication (ATC codes beginning with A10) before inclusion. *Study V:* Self-reported diabetes upon inclusion.

***Diabetes mellitus type 1 (Study IV)**:* At least one filled prescription for rapid-acting insulin, the absence of oral glucose-lowering medication (including a GLP-1 receptor agonist) and at least one registered ICD-10 diagnosis of type 1 diabetes (E10) within two years before study inclusion.

***Diabetes mellitus type 2 (Study IV)**:* All patients with diabetes mellitus except those with diabetes mellitus type 1 according to the above definition.

Glucose abnormalities: Newly diagnosed diabetes or prediabetes.

***Newly diagnosed diabetes mellitus (Studies II and V)**:* Criteria for diagnosing diabetes according to the American Diabetes Association (ADA) or World Health Organisation (WHO) as listed in Introduction.

***Newly diagnosed prediabetes (Studies II and V)**:* Criteria for diagnosing prediabetes according to the ADA or WHO as listed in Introduction.

***Severe hypoglycaemia (Study IV)**:* Primary or secondary hospital ICD-10 diagnosis of E16.0, E16.1, E16.2, E10.0, E11.0, E12.0, E13.0 or E14.0.

Atrial fibrillation: Any ICD-10 diagnosis of I48 registered in the NPR.

3.3 MATERIALS AND METHODS

3.3.1 Study I

The TASTE trial was a multicentre (all 29 PCI centres in Sweden, one centre in Iceland and one centre in Denmark), prospective, register-based randomised study, including 7,244 unselected patients with STEMI from 2010 to 2013 with randomisation to manual thrombus aspiration followed by PCI or to PCI alone (87). The inclusion criteria were the following: PCI due to STEMI, the absence of a requirement for emergency coronary bypass grafting (CABG) and age > 18 years. Information regarding mortality, rehospitalisation for myocardial infarction (MI), heart failure, new PCI/CABG, stent thrombosis and restenosis was collected from the SCAAR register, which is part of the SWEDEHEART register, the Swedish National Patient Register and the Swedish Causes of Death Register.

The primary endpoint of 30-day all-cause mortality in the TASTE study did not differ between the two studied groups (HR:0.94; 0.72-1.22) (87), nor did one-year mortality (HR: 0.94; 0.78-1.15) (88). The one-year mortality rate was as low as 5.4% and the composite endpoint of mortality, rehospitalisation for MI and stent thrombosis also occurred at low rates of 8.0% in the PCI plus thrombus aspiration group and 8.5% in the PCI only group (p=0.48).

The TASTE database provides additional information on the findings of coronary vessel disease distribution, target vessel, thrombus grading, Thrombolysis In Myocardial Infarction (TIMI) flow grading, left ventricular function by echocardiography, platelet inhibition/ anticoagulant therapy, time to PCI from symptom onset and glucose-lowering medication, including insulin therapy.

Patients were defined as having diabetes mellitus if they self-reported the diagnosis at the point of study inclusion or the point of discharge from hospital or if medical treatment with oral glucose-lowering medication or insulin treatment was registered at discharge (per the information collected from SWEDEHEART).

Primary and secondary outcomes

The primary outcome of the TASTE trial was all-cause mortality at one year and the secondary outcomes were hospitalisation for recurrent MI or stent thrombosis and triple event at one year. *Triple event* was defined as the first of all-cause mortality, rehospitalisation for MI or stent thrombosis. MI was defined according to ICD-10 codes I21 and I22. Stent thrombosis was defined according to the Academic Research Consortium definition for “definitive and confirmed stent thrombosis” and the diagnosis in all cases was confirmed by angiography (89). Thrombus grade was evaluated after the passage of a coronary guidewire according to Sianos et al. (90). In this post hoc analysis of the TASTE trial, we studied the baseline characteristics of the individuals with diabetes among the participants in this trial and investigate whether there are differences in outcomes in those with diabetes.

3.3.2 Study II

Using the SWEDEHEART register, we identified, 3,417 patients with acute coronary syndrome under the age of 80 years that were admitted to the Department of Cardiology

at Danderyd University Hospital from January 2006-December 2013. Most patients without diabetes were screened for undiagnosed dysglycaemia with a standardised 75-g OGTT after an overnight fast, with plasma glucose values analysed at 0 and 120 min, no earlier than four days after admission. HbA1c was also controlled in many patients, albeit not consistently, especially at the beginning of our study period. We excluded 433 AMI patients with a known history of diabetes according to registration in SWEDEHEART and 1,300 patients who were not screened for diabetes, most of them for clinical reasons. In total, 1,684 patients with AMI were screened with an OGTT and 841 (50%) of them also had an HbA1c taken simultaneously, and this thus constituted our study population. A flowchart for our study population is shown in **Figure 8**.

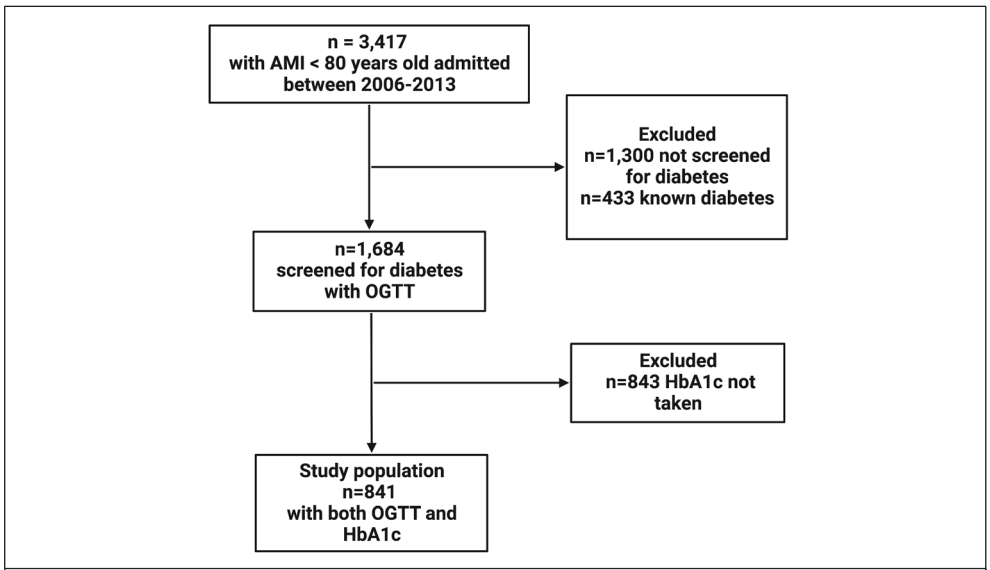

Figure 8: Flowchart for the inclusion of the study population.
Created with BioRender.com.

We collected data on comorbidities, medication and all-cause mortality from four different registers: (1) the SWEDEHEART register, (2) the National Patient Register (NPR), (3) the Prescribed Drug Register and (4) the Cause of Death Register.

Outcomes

All patients were followed up for all-cause mortality until 25 December 2017 and for hospitalisation for myocardial infarction, ischaemic stroke or heart failure until 31 December 2014. The primary outcome was the incidence of a combined event [CE (first of myocardial infarction, heart failure, ischaemic stroke or mortality)] and the mean follow-up period for our patients was 4.8 years. Information on medication at baseline was collected from filled prescriptions from five months before admission with AMI to one month after discharge. We also tested the prognostic significance of the combined event of different cut-offs for glucose abnormalities according to both ADA and WHO definitions.

Definitions

Based on the results of an OGTT, the patients were categorised into three groups according to ADA criteria (**Table 1**) for the diagnosis of diabetes and prediabetes:
1) normoglycaemia (NGT),
2) prediabetes [Impaired glucose tolerance (IGT), impaired fasting glucose (IFG) or both] and
3) type 2 diabetes.

Glucose abnormalities according to the OGTT could be diagnosed by using either the OGTT individual components, i.e., fasting glucose (fPG) or two-hour postload glucose (2h-PG). Patients were also classified into three groups based on the HbA1c according to ADA criteria:
1) normoglycaemia (NGT),
2) prediabetes and
3) type 2 diabetes.

Known diabetes was defined as the registration of diabetes in SWEDEHEART on admission.

3.3.3 Study III

In this nationwide study of patients with atrial fibrillation, we included 326,832 patients with non-valvular AF. We started by identifying 345,123 patients with a registered AF diagnosis according to ICD-10 in the National Patient Register from 1 January 2006 to 31 December 2012. We excluded those aged ≤ 20 years (n=409) and those with valvular atrial fibrillation (n=17,882). A flowchart of the study population is shown in **Figure 9**.

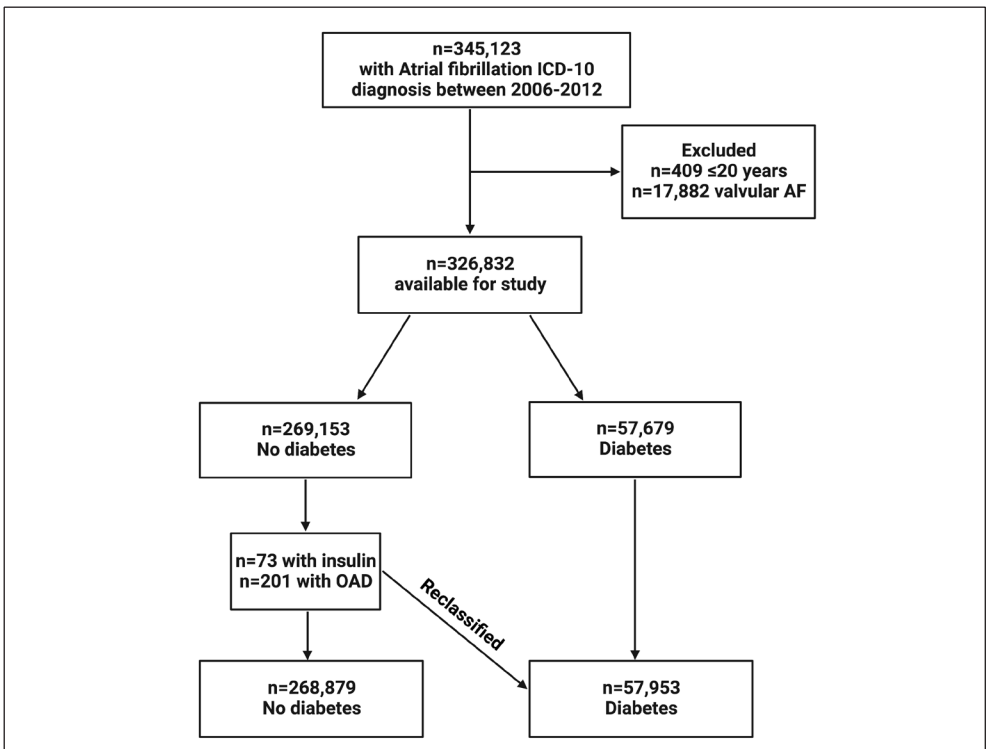

Figure 9: Flowchart of the study patient selection.
Created with BioRender.com.

We merged data from four different registers: 1. The Swedish National Patient Register (NPR), 2. The Prescribed Drug Register, 3. The Cause of Death Register and 4. The LISA register. All patients were followed for the incidence of death, heart failure, myocardial infarction, ischaemic stroke or any bleeding until 31 December 2013. The mean follow-up period was 3.7 years (range 0.9 to 8 years). We used freely available data from Statistics Sweden on mortality in different age groups for 2012 to calculate the standardised mortality ratios (SMR) for our study population.

3.3.4 Study IV

For this study, we included all the patients in Sweden that received an AF diagnosis in the NPR from January 2013-December 2014 (n=317,558). After excluding those with mechanical heart valves or mitral stenosis (n= 7,796) and those < 18 years old (n= 151), we ended up with our final study population of 309,611 patients. A flowchart for patient selection is presented in **Figure 10**.

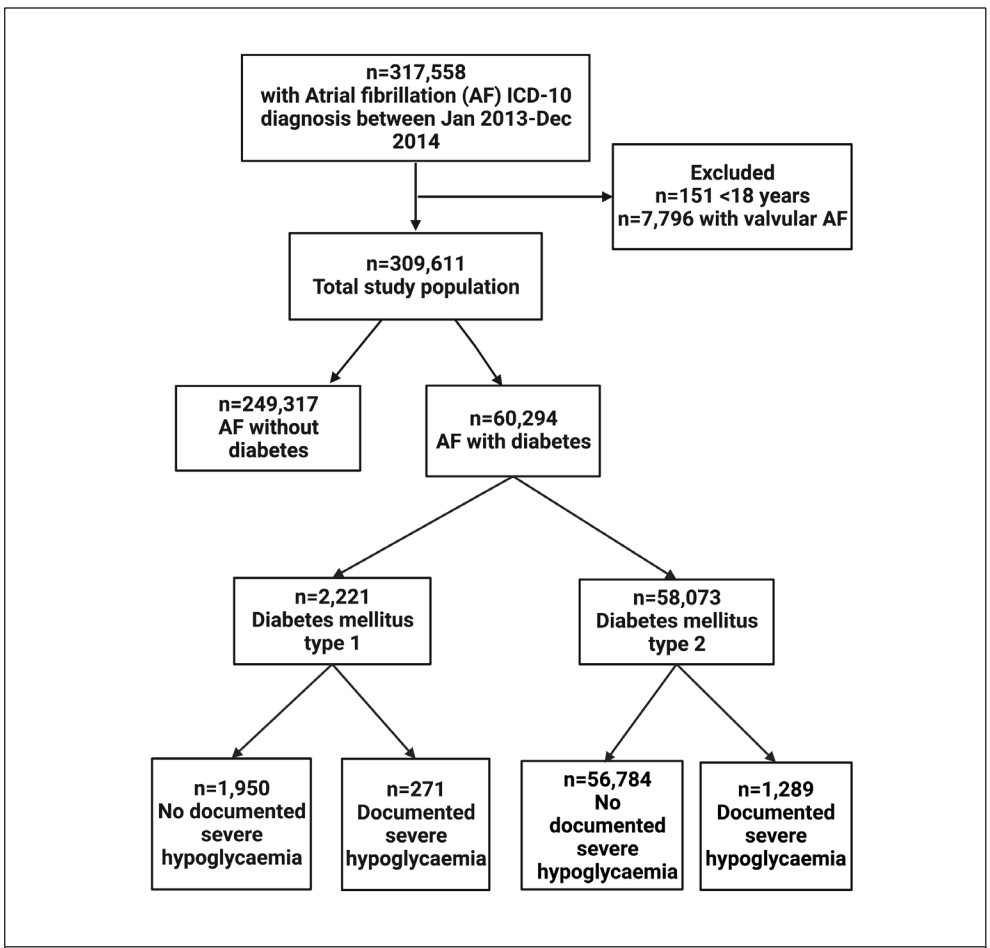

Figure 10: Flowchart depicting the selection of our study population.
Created with BioRender.com.

We defined all those with an ICD-10 diagnosis of E10-14 in the NPR or those filling a prescription for glucose-lowering medication as having diabetes. Among them, we categorised as having diabetes mellitus type 1 all those with a filled prescription for rapid-acting insulin and the absence of filled prescriptions for medications commonly used in type 2 diabetes and a registered E10 ICD-10 diagnosis of type 1 diabetes in the last 24 months before inclusion in our study. We identified those with a history of severe hypoglycaemia by looking for those that received a primary or first secondary ICD-10 diagnosis in the inpatient (hospital) register signifying hypoglycaemia.

All patients were followed for all-cause death until March 2017 and for myocardial infarction, ischaemic stroke, heart failure or dementia until December 2015. For the outcomes of heart failure and dementia, we analysed only those that did not have these diagnoses at inclusion, as both diseases are regarded as chronic and exist continuously from the time of the first diagnosis. In order to have a control group completely free from diabetes, we censored the patients that received the diagnosis of diabetes during the follow-up period at the date of the first ICD-10 diagnosis of diabetes.

3.3.5 Study V

The Early Detection of Glucose Abnormalities in Atrial Fibrillation (EDGA-AF) is a single-centre, prospective cohort study that aims to report the prevalence of undiagnosed glucose abnormalities in patients with atrial fibrillation undergoing electric cardioversion and to describe how these glucose abnormalities affect prognosis. All patients less than 80 years of age with atrial fibrillation undergoing electric cardioversion at the Cardiology Department, Danderyd University Hospital, Stockholm, Sweden, since October 2018 were invited to participate in this study. We included both patients with no previously known diabetes and patients with established type 2 diabetes, where the latter would be used as comparison group in future planned analyses. The study was halted during the Covid-19 pandemic, but inclusion is now continuing.

The study participants were called to a study visit approximately four weeks after the electric cardioversion in order to reduce the stress burden from the cardioversion (an interval of up to six weeks was allowed) and were screened for glucose abnormalities with both a standardised 75-g oral glucose tolerance test (OGTT) after an overnight fast with plasma glucose values analysed at 0, 60 and 120 minutes and a Haemoglobin A1c (HbA1c). The OGTT was not performed in those with known diabetes. During the study visit, additional blood samples were taken (lipid panel, electrolytes, creatinine, troponin-T, NT-proBNP, fS-insulin, hs-CRP), a 12-lead-electrocardiogram was registered, and an echocardiogram was performed. Additional blood samples were drawn and frozen for later analysis.

This is an interim analysis of 119 patients without established diabetes enrolled from October 2018 to December 2021 and it aims to describe both the prevalence of previously undiagnosed glucose abnormalities in these patients and the agreement between the two screening methods used (OGTT and HbA1c). Another aim with this interim analysis was to decide if inclusions, that had been hampered by the Covid-19 pandemic, should continue.

3.4 STATISTICAL METHODS FOR ALL STUDIES

Continuous variables were summarised as the mean ± standard deviation (SD) or the median with interquartile range (IQR) for non-normal distributed variables. An assessment for normal distribution was tested using the Shapiro-Wilk test or examined visually using

histograms. Categorical variables were presented as absolute numbers and percentages. Comparisons were made using the chi-square test for categorical variables and with the Wilcoxon rank-sum test or the Kruskal-Wallis test for continuous variables, as applicable.
Time-to-event analysis was used in **Studies I-IV** to compare the risk of premature death and adverse cardiovascular events between groups of patients. Kaplan-Meier curves were used to present the percentage of patients free from a specific event at each time interval during the follow-up period in different patient groups. The curves were compared using the log-rank test. To be able to compare the risks after adjustments for confounders, we used the Cox proportional hazards analysis. The proportional hazard assumption was either tested using the Schoenfeld residuals or assessed visually using log-log survival curves.

In **Study I,** we used multiple imputation using the fully conditional specification method with ten imputed data sets to account for missing data. The missing data were assumed to be missing at random (MAR). Imputed variables were creatinine, body mass index, information on complete revascularisation and left ventricular function at discharge.
In **Study III**, we determined the standardised mortality ratios in AF patients with and without diabetes using freely available mortality data from Statistics Sweden for the general Swedish population for 2012.
In **Study IV,** we used competing risk regression according to the Fine and Gray method (91), adjusting for the competing risk of all-cause mortality, for all other endpoints.
In **Study V,** we used Cohen's kappa coefficient to calculate the agreement of the OGTT and HbA1c in categories of glucose abnormalities.

A two-sided probability of $p < 0.05$ was considered statistically significant in all tests. Statistical analyses were conducted using SPSS (version 23 software from SPSS Inc., Chicago, IL) for **Study I** and STATA version 14 (STATA Corp, College Station, TX 77845, USA) for **Studies II-V**.

3.5 ETHICAL CONSIDERATIONS

All the studies complied with the ethical principles of the Declaration of Helsinki. Approval from the relevant regional ethics committees was obtained for all the studies. All the studies were approved by the Regional Ethical Review board of Uppsala University, Sweden (**Study I**), and the Regional Ethics Committee in Stockholm (**Studies II-V**) (**Table 3**).

Table 3: List of diary number (DNR) of the ethics committee approval for the studies included in this thesis.

Study number	DNR
I	2010/111, 2010/111/6
II	2014/338-31/2, 2015/1077-32, 2015/1104-32, 2018/1321-32
III	2014/894-31, 2016/1255-32
IV	2014/894-31, 2016/1255-32
V	2017/1878-31/2

In **Studies I and V**, all the included patients provided written informed consent. For **Studies II-IV,** individual consent was not obtained. For **Study II,** screening for glucose abnormalities was performed in all patients after a myocardial infarction as part of the usual clinical care at the study centre, as suggested by multiple guidelines, including those from the European Society of Cardiology. Moreover, data for **Studies II-IV** were collected from Swedish national registers which use an opt-out approach. The Swedish Patient Data Act (2008:355) states that it is permitted to enter patient data in a register if the purpose is the improvement of the quality of care. Before inclusion, the person is informed by the caregiver and may oppose registration, but there is no legal requirement for signed, individual consent.

4 RESULTS

4.1 STUDY I

Since this paper was published as a short communication, there will be additional reported data in this thesis section. A total of 7,244 patients were included in the original trial, of whom 901 (12.4%) were reported as having diabetes mellitus. A subgroup analysis did not indicate any different effects of the randomised procedure in patients with diabetes (HR: 0.97; 95% CI: 0.63-1.49). However, for this post-hoc analysis, an additional 104 patients receiving glucose-lowering medication but without having a registered diabetes diagnosis at inclusion were identified and reclassified as having diabetes (n=1,005, 13.9%). Even when including these additional patients, the effect of the randomised procedure did not reach statistical significance (1.04; 0.69-1.58). For this reason, all patients with diabetes, irrespective of randomisation in TASTE, were studied as one cohort. The baseline characteristics of all patients stratified by diabetes status are presented in **Table 4**.

Table 4: Baseline characteristics of all patients with STEMI (n=7,244) with and without diabetes.

Characteristic	n	No diabetes	Diabetes	p-value
All patients N=7,244		N= 6,239 (86.1%)	N=1,005 (13.9%)	
Age (years), mean ± SD	7,244	66.03±11.69	67.60±10.84	<0.001
Male sex – no. (%)	7,244	4,698 (75.3)	726 (72.2)	0.038
Body-mass index (kg/m^2), mean ± SD	7,042	26.79±4.33	28.68±4.9	<0.001
Weight (kg), mean ± SD	7,174	80.97±15.21	86.01±16.61	<0.001
Creatinine (mmol/L), mean ± SD	6,851	82.87±29.84	87.28±40.99	<0.001
Current smoking – no. (%)	7,244	1,987 (31.8)	269 (26.8)	<0.001
Previous MI – no. (%)	7,244	642 (10.3)	200 (19.9)	<0.001
Previous PCI – no. (%)	7,244	525 (8.4)	174 (17.3)	<0.001
Previous CABG– no. (%)	7,244	111 (1.8)	33 (3.3)	0.006
Previous ischaemic stroke – no. (%)	7,244	21 (0.3)	5 (0.5)	0.429
Previous HF – no. (%)	7,244	417 (6.7)	70 (7.0)	0.741
Killip class 2-4 – no. (%)	7,244	392 (6.3)	81 (8.1)	0.034
TIMI flow grade 0-1 – no. (%)	6,365	4,854 (88.4)	778 (88.7)	0.820
Thrombus aspiration (yes) – no. (%)	7,244	3,093 (49.6)	484 (48.2)	0.405
Stent (yes) – no. (%)	7,239	5,958 (95.6)	950 (94.5)	0.141
DES – no. (%)	6,913	2,884 (48.4)	561 (59.0)	<0.001
Complete revascularisation – no. (%)	7,189	3,802 (61.0)	537 (53.5)	<0.001
Success PCI (open vessel) –- no. (%)	7,244	6,063 (97.3)	969 (96.4)	0.136
Radial-artery approach – no. (%)	7,244	4,273 (68.5)	720 (71.6)	0.045
EF (non-imputed), during hospitalisation	6,247			<0.001
Normal > 50% – no. (%)		2,810 (52.2)	379 (44.0)	
40-49% – no. (%)		1,430 (26.6)	247 (28.7)	
30-39% – no. (%)		863 (16.0)	158 (18.4)	
< 30 – no. (%)		234 (4.3)	60 (7.0)	
Unknown – no. (%)		49 (0.9)	17 (2.0)	
Medication at procedure				
Aspirin - no. (%)	7,239	6,107 (98.0)	981 (97.6)	0.470
Clopidogrel - no. (%)	7,239	4,439 (71.2)	693 (69.0)	0.288
Ticagrelor - no. (%)	7,244	1,761 (28.2)	304 (30.2)	0.333
Prasugrel - no. (%)	7,239	969 (15.5)	131 (13.0)	0.102
Anticoagulants (warfarin) - no. (%)	7,137	83 (1.3)	29 (2.9)	0.001

MI=Myocardial infarction; PCI=Percutaneous coronary intervention; CABG=Coronary artery bypass grafting; HF=Heart failure; TIMI=Thrombolysis in myocardial infarction; DES=Drug-eluting stent; SD=Standard deviation.

Patients with diabetes were slightly older, were less frequently men or current smokers and more frequently had a history of previous CVD and revascularisation, a higher body mass index, creatinine and C-reactive protein levels. Furthermore, they more frequently had three-vessel disease (20.9 vs. 13.6%, p<0.001) (**Figure 11**), were more frequently treated with drug-eluting stents (DES) (59.0 vs. 48.4%, p<0.001) and less frequently achieved complete revascularisation (53.5 vs. 61.0%, p<0.001).

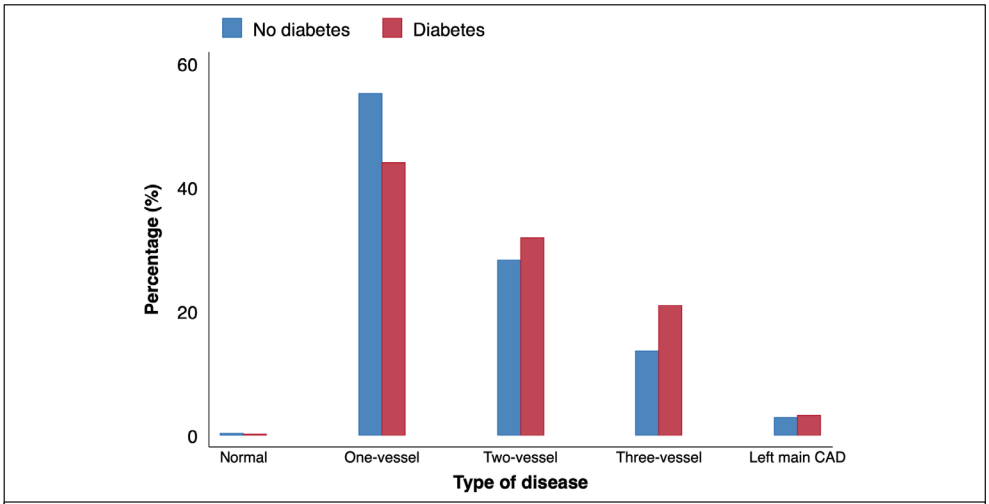

Figure 11: Type of coronary artery disease in STEMI patients (n=7,244) with and without diabetes.

There was no difference in thrombus grade (Grade 0 to Grade 5, p=0.909) and the type of affected coronary vessel did not differ between patients with or without diabetes (left anterior descending artery; 44.5 vs. 44.5%, p=0.992) (**Figure 12**).

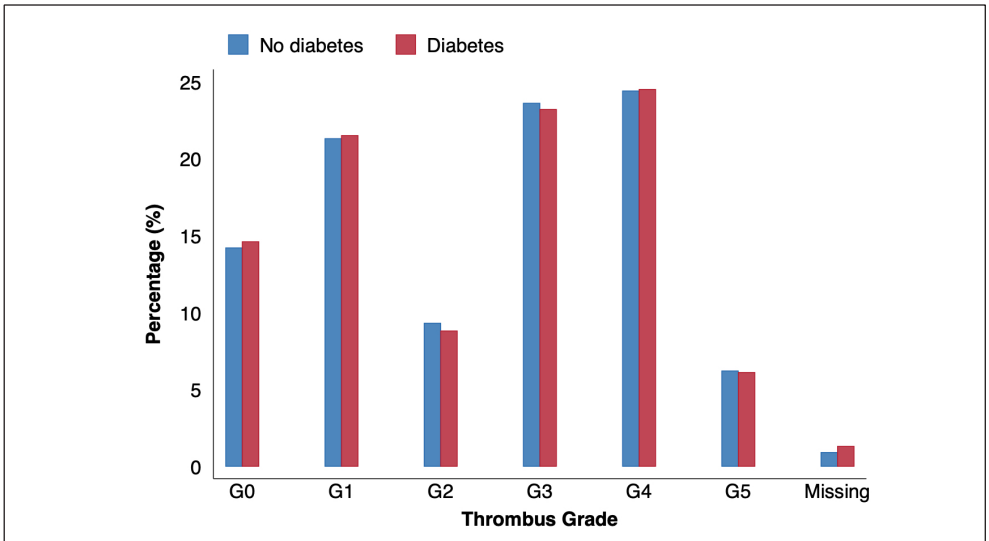

Figure 12: Thrombus grade (Grade 0-5) in STEMI patients (n=7,244) with and without diabetes.

A history of previous heart failure at the point of inclusion did not differ significantly in those individuals with or without diabetes (7.0% vs. 6.7%, p=0.741). However, patients with diabetes were less frequently found to have a normal ejection fraction (EF) in the echocardiography examination performed during hospitalisation (EF > 50%; 44.0 vs. 52.2%, p<0.001). The administered antiplatelet therapy did not differ between the patients with and without diabetes. Patients with diabetes were more frequently treated with warfarin (2.9% vs. 1.3%, p=0.001).

Among the patients with diabetes, 39.5% were treated with insulin and 60.5% with other glucose-lowering treatments. Insulin-treated patients with diabetes had more frequently had a previous MI and three-vessel disease (25.4 vs. 17.9%, p<0.001) (**Figure 13**), compared with non-insulin-treated patients with diabetes.

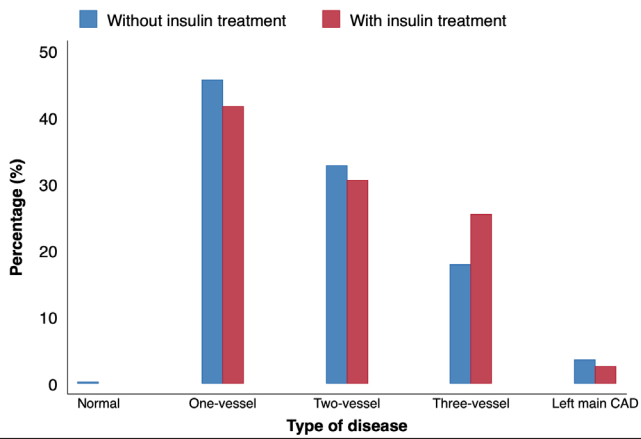

Figure 13: Type of coronary artery disease in patients with STEMI and diabetes (n=1,005) stratified by the type of diabetes treatment.

They were also more frequently treated with drug-eluting stents and less frequently achieved complete revascularisation. Within the diabetes group, thrombus grade (Grade 0 to Grade 5, p=0.774) (**Figure 14**) and the affected coronary vessel did not differ, irrespective of the type of diabetes treatment.

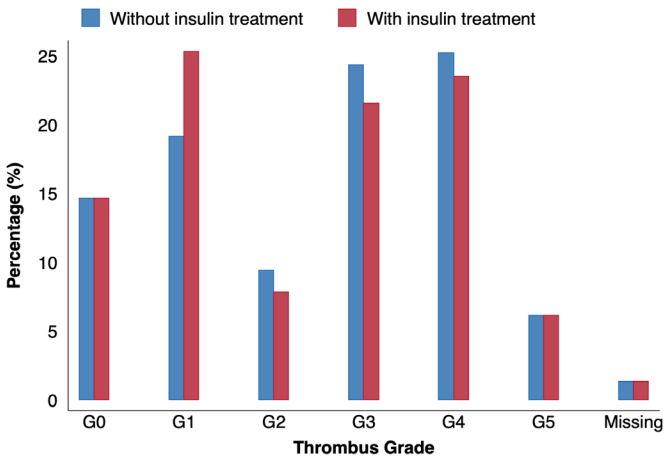

Figure 14: Thrombus grade (Grade 0 to 5) in patients with STEMI and diabetes (n=1,005) stratified by the type of diabetes treatment.

We did not observe significant differences in pharmacotherapy between those with and without insulin treatment. The baseline characteristics of the patients with diabetes stratified by diabetes treatment are listed in **Table 5**.

Table 5: Baseline characteristics in patients with STEMI and diabetes (n=1,005) stratified by the type of diabetes treatment.

Characteristic	Diabetes		p-value
All patients N=7,244	N=1,005 (13.9%)		
	Without insulin treatment	With insulin treatment	
	N=608 (60.5%)	N=397 (39.5%)	
Age (years), mean ± SD	67.21±10.77	68.2±10.94	<0.001
Male sex – no. (%)	458 (75.3)	268 (67.5)	0.002
Body-mass index (kg/m^2), mean ± SD	28.51 (4.81)	28.95±5.02	<0.001
Weight (kg), mean ± SD	85.86±16.93	86.25±16.11	<0.001
Creatinine (mmol/L), mean ± SD	84.05±32.94	92.31±50.73	<0.001
Current smoking – no. (%)	180 (29.6)	89 (22.4)	<0.001
Previous MI – no. (%)	118 (19.4)	82 (20.7)	< 0.001
Previous PCI – no. (%)	101 (16.6)	73 (18.4)	< 0.001
Previous CABG – no. (%)	18 (3.0)	15 (3.8)	0.024
Previous ischaemic stroke – no. (%)	0 (0.0)	5 (1.3)	0.004
Previous HF – no. (%)	47 (7.7)	23 (5.8)	0.462
Killip class 2-4 – no. (%)	46 (7.6)	35 (8.8)	0.078
TIMI flow grade 0-1 – no. (%)	472 (88.6)	306 (89.0)	0.959
Thrombus aspiration (yes) – no. (%)	304 (50.0)	180 (45.3)	0.249
Stent (yes) – no. (%)	576 (94.7)	374 (94.2)	0.313
DES – no. (%)	331 (57.5)	230 (61.3)	< 0.001
Complete revascularisation – no. (%)	334 (55.0)	203 (51.1)	<0.001
Success PCI (open vessel) – no. (%)	585 (96.2)	384 (96.7)	0.168
Radial-artery approach – no. (%)	434 (71.4)	286 (72.0)	0.131
EF (non-imputed), during hospitalisation			< 0.001
Normal > 50% – no. (%)	239 (45.0)	140 (42.4)	
40-49% – no. (%)	147 (27.7)	100 (30.3)	
30-39% – no. (%)	98 (18.5)	60 (18.2)	
< 30 – no. (%)	34 (6.3)	26 (7.9)	
Unknown – no. (%)	13 (2.4)	4 (1.2)	
Medication at procedure			
Aspirin - no. (%)	597 (98.2)	384 (96.7)	0.218
Clopidogrel - no. (%)	422 (69.4)	271 (68.3)	0.619
Ticagrelor - no. (%)	194 (31.9)	110 (27.7)	0.370
Prasugrel - no. (%)	70 (11.5)	61 (15.4)	0.119
Anticoagulants (warfarin) - no. (%)	12 (2.0)	17 (4.3)	<0.001

MI=Myocardial infarction; PCI=Percutaneous coronary intervention; CABG=Coronary artery bypass grafting; HF=Heart failure; TIMI=Thrombolysis in myocardial infarction; DES=Drug-eluting stent; SD=Standard deviation.

Outcomes

Patients with diabetes had a poorer one-year outcome with higher rates of all-cause mortality (9.0 vs. 4.9%, p<0.001) and triple event (incidence of all-cause mortality, rehospitalisation for MI or stent thrombosis; 12.5 vs. 7.5%, p<0.001). Within the diabetes group, insulin-treated patients had a significantly higher all-cause mortality (12.6 vs. 6.6%, p<0.001), triple event (17.6 vs. 9.2%, p<0.001) and MI (5.8 vs. 2.9%, p<0.001) at one year when compared with patients without diabetes. No significant difference in the occurrence of stent thrombosis between the groups was observed.

Following adjustments, diabetes was independently associated with an increased risk of all-cause mortality (HR:95% confidence interval (CI); 1.57;1.23-2.00, p<0.001) and triple event (HR:95% CI; 1.40;1.15-1.72, p=0.001). The mortality risk was more pronounced in those treated with insulin (2.04; 1.46-2.78, p<0.001), as was the triple event (1.83; 1.41-2.37, p<0.001). Insulin-treated patients had an increased risk of recurrent MI (1.72; 1.08-2.73, p=0.023). Kaplan-Meier curves for the cumulative rates of all-cause mortality, triple event, MI and stent thrombosis stratified by diabetes status and treatment are shown in **Figures 15** and **16**.

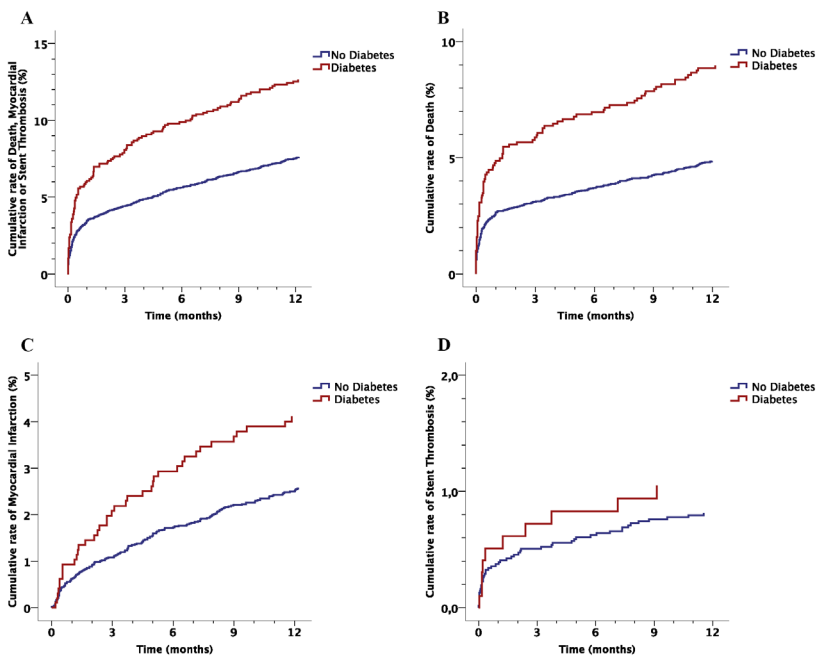

Figure 15: A. Cumulative rate of mortality, myocardial infarction or stent thrombosis (%) stratified by diabetes status, **B.** Cumulative rate of mortality (%) stratified by diabetes status, **C.** Cumulative rate of myocardial infarction (%) stratified by diabetes status, **D.** Cumulative rate of stent thrombosis (%) stratified by diabetes status. HRs adjusted for age, sex, smoking status, previous MI, previous PCI, creatinine level, body mass index, complete revascularisation, radial-artery approach, Killip class, type of disease (one- or multivessel coronary artery disease) and ejection fraction during hospitalisation.

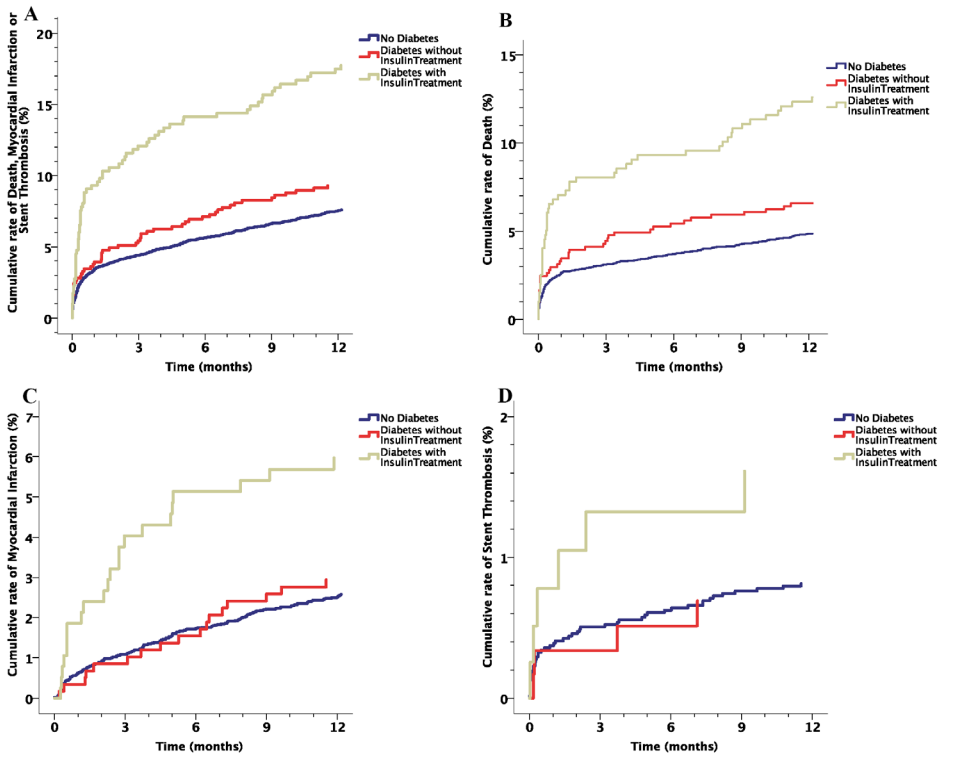

Figure 16: A. Cumulative rate of mortality, myocardial infarction or stent thrombosis (%) stratified by diabetes status and treatment, **B.** Cumulative rate of mortality (%) stratified by diabetes status and treatment, **C.** Cumulative rate of myocardial infarction (%) stratified by diabetes status and treatment, **D.** Cumulative rate of stent thrombosis (%) stratified by diabetes status and treatment. HRs adjusted for age, sex, smoking status, previous MI, previous PCI, creatinine level, body mass index, complete revascularisation, radial-artery approach, Killip class, type of disease (one- or multivessel coronary artery disease) and ejection fraction during hospitalisation.

4.2 STUDY II

When using the ADA criteria for classifying glucose abnormalities and the OGTT as the screening method, 139 (17%) individuals had normal glucose tolerance, 398 (47%) had prediabetes (IGT and/or IFG) and 304 (36%) had newly discovered diabetes. If the HbA1c was used as a screening method, 320 (38%) individuals had a normal HbA1c (< 39 mmol/mol), 461 (55%) had a HbA1c in the prediabetes range (39-47 mmol/mol) and 60 (7%) had diabetes (HbA1c ≥48 mmol/mol). The numbers (and percentages) of individuals in the different glucose status groups according to the OGTT and HbA1C results are illustrated in **Figure 17**.

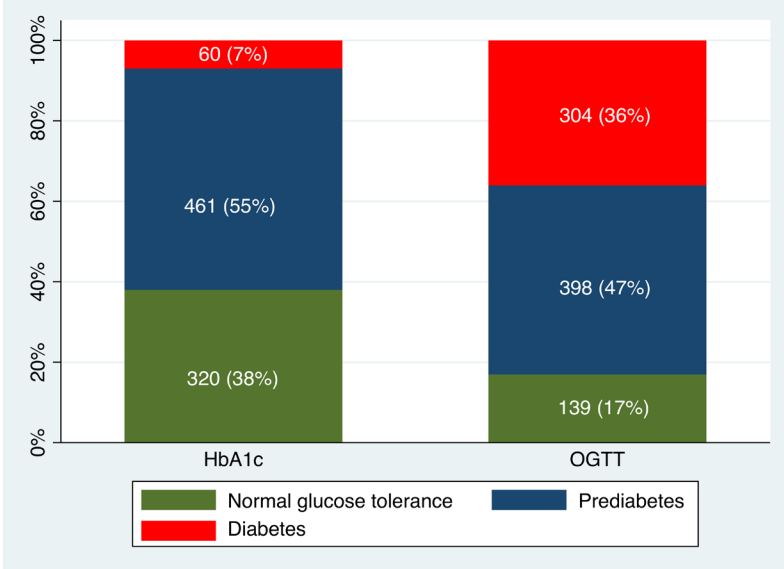

Figure 17: Number and percentage of patients with normoglycaemia and glucose abnormalities according to the OGTT and HbA1c results (ADA criteria).

Patients with diabetes were older and had a higher BMI than those in the other two groups, regardless of using the OGTT or HbA1c for classification into groups. No significant differences in comorbidities were observed between groups. Patients with diabetes according to the OGTT were less frequently treated with ticagrelor compared with patients with normoglycaemia and prediabetes (**Table 6**).

Those with diabetes according to HbA1c were less frequently treated with angiotensin II receptor-blockers and ticagrelor compared with patients with normoglycaemia and prediabetes (**Table 7**).

Agreement between the OGTT and HbA1c in classifying glucose abnormalities

There was only a modest agreement between the OGTT and HbA1c in classifying glucose abnormalities, with only 62% of patients having glucose abnormalities with both screening methods.

Only 87 (10%) patients had normoglycaemia according to both the OGTT and HbA1c.

Of the 754 patients classified as having glucose abnormalities by one or both screening methods, 425 (56%) were identified by a fPG, 636 (84%) by a 2h-PG and 521 (69%) by an HbA1c. The OGTT (fPG and 2h-PG) identified 702 patients (93%) as having glucose abnormalities and the combination of fPG and HbA1c identified 626 patients (83%). A Venn diagram showing proportions and their overlap for the 754 patients with glucose abnormalities (prediabetes or diabetes) according to the OGTT and HbA1c results is presented in **Figure 18**.

Table 6: Baseline characteristics of our study population stratified by presence of glucose abnormalities according to OGTT (ADA criteria).

Characteristic	Available data	NGT	Prediabetes (IFG/IGT)	Diabetes	p-value
Study population - no known diabetes, n= 841		139 (16.5%)	398 (47.3%)	304 (36.2%)	
Age - yr [median (IQR)]	841/841	63 (54-69)	64 (58-71)	66 (58-71)	0.019
Male sex	841/841	104 (74.8%)	304 (76.4%)	212 (69.7%)	0.133
Body-mass index [median (IQR)]	796/841	25 (23-28)	27 (24-30)	28 (25-30)	<0.001
Smokers	801/841	38 (29.5%)	142 (37.3%)	118 (40.5%)	0.054
Snuff users	560/841	2 (2.0%)	23 (8.4%)	12 (6.5%)	0.083
eGFR (mL/min/1.73 m2) - MDRD equation [median (IQR)]	769/841	81 (69-89)	83 (72-97)	83 (70-96)	0.177
Medical history					
Previous myocardial infarction	841/841	40 (28.8%)	101 (25.4%)	63 (20.7%)	0.143
Hypertension	841/841	36 (25.9%)	88 (22.1%)	71 (23.4%)	0.658
Heart failure	841/841	3 (2.2%)	5 (1.3%)	3 (1.0%)	0.598
Atrial fibrillation	841/841	8 (5.8%)	14 (3.5%)	13 (4.3%)	0.520
Previous PCI or CABG	841/841	32 (23.0%)	84 (21.1%)	58 (19.1%)	0.612
Stroke	841/841	5 (3.6%)	8 (2.0%)	12 (3.9%)	0.291
Peripheral artery disease	841/841	2 (1.4%)	6 (1.5%)	3 (1.0%)	0.825
Chronic kidney disease	841/841	2 (1.4%)	2 (0.5%)	2 (0.7%)	0.523
Chronic obstructive pulmonary disease	841/841	3 (2.2%)	3 (0.8%)	3 (1.0%)	0.377
Medications at discharge					
Aspirin	841/841	121 (87.1%)	342 (85.9%)	246 (80.9%)	0.121
Clopidogrel	841/841	79 (56.8%)	225 (56.5%)	188 (61.8%)	0.334
Ticagrelor	841/841	44 (31.7%)	95 (23.9%)	46 (15.1%)	<0.001
Prasugrel	841/841	0 (0%)	4 (1.0%)	3 (1.0%)	0.497
ACE-inhibitors	841/841	89 (64.0%)	257 (64.6%)	189 (62.2%)	0.802
ARB	841/841	25 (18.0%)	65 (16.3%)	54 (17.8%)	0.845
Beta-receptor blockers	841/841	126 (90.7%)	341 (85.7%)	251 (82.6%)	0.08
Statins	841/841	122 (87.8%)	342 (85.9%)	252 (82.9%)	0.338
Dihydropyridines	841/841	22 (15.8%)	70 (17.6%)	69 (22.7%)	0.129
Diuretics	841/841	15 (10.8%)	65 (16.3%)	59 (19.4%)	0.076
Warfarin	841/841	7 (5.0%)	21 (5.3%)	14 (4.6%)	0.921

eGFR=Estimated glomerular filtration rate; MDRD=Modification of Diet in Renal Disease; PCI=Percutaneous coronary intervention; CABG=Coronary artery bypass grafting; ACE=Angiotensin converting enzyme; ARB=Angiotensin II receptor blocker.

Table 7: Baseline characteristics of our study population stratified by presence of glucose abnormalities according to HbA1c (ADA criteria).

Characteristic	Available data	NGT	Prediabetes	Diabetes	p-value
Study population - no known diabetes, n= 841		320 (38.1%)	461 (54.8%)	60 (7.1%)	
Age - yr [median (IQR)]	841/841	63 (56-70)	66 (59-71)	66 (57-72)	0.026
Male sex	841/841	242 (75.6%)	334 (72.5%)	44 (73.3%)	0.610
Body-mass index [median (IQR)]	796/841	26 (24-29)	27 (25-30)	29 (25-32)	<0.001
Smokers	801/841	103 (33.1%)	169 (39.1%)	26 (44.8%)	0.035
Snuff users	560/841	11 (4.9%)	26 (8.9%)	0 (0%)	0.034
eGFR (mL/min/1.73 m2) - MDRD equation [median (IQR)]	769/841	85 (71-96)	81 (71-94)	85 (76-98)	0.104
Medical history					
Previous myocardial infarction	841/841	82 (25.6%)	108 (23.4%)	14 (23.3%)	0.769
Hypertension	841/841	72 (22.5%)	110 (23.9%)	13 (21.7%)	0.869
Heart failure	841/841	3 (0.9%)	7 (1.5%)	1 (1.7%)	0.756
Atrial fibrillation	841/841	10 (3.1%)	21 (4.6%)	4 (6.7%)	0.371
Previous PCI or CABG	841/841	64 (20.0%)	99 (21.5%)	11 (18.3%)	0.791
Stroke	841/841	7 (2.2%)	17 (3.7%)	1 (1.7%)	0.395
Peripheral artery disease	841/841	3 (0.9%)	6 (1.3%)	2 (3.3%)	0.325
Chronic kidney disease	841/841	2 (0.6%)	4 (0.9%)	0 (0%)	0.733
Chronic obstructive pulmonary disease	841/841	2 (0.6%)	6 (1.3%)	1 (1.7%)	0.596
Medications at discharge					
Aspirin	841/841	271 (84.7%)	391 (84.8%)	47 (78.3%)	0.418
Clopidogrel	841/841	175 (54.7%)	282 (61.2%)	35 (58.3%)	0.195
Ticagrelor	841/841	92 (28.8%)	82 (17.8%)	11 (18.3%)	0.001
Prasugrel	841/841	2 (0.6%)	5 (1.1%)	0 (0%)	0.599
ACE-inhibitors	841/841	218 (68.1%)	278 (60.3%)	39 (65.0%)	0.08
ARB	841/841	44 (13.8%)	96 (20.8%)	4 (6.7%)	0.003
Beta-receptor blockers	841/841	278 (86.9%)	394 (85.5%)	46 (76.7%)	0.121
Statins	841/841	276 (86.3%)	393 (85.3%)	47 (78.3%)	0.285
Dihydropyridines	841/841	60 (18.8%)	88 (19.1%)	13 (21.7%)	0.870
Diuretics	841/841	49 (15.3%)	80 (17.4%)	10 (16.7%)	0.752
Warfarin	841/841	11 (3.4%)	26 (5.6%)	5 (8.3%)	0.178

eGFR=Estimated glomerular filtration rate; MDRD=Modification of Diet in Renal Disease; PCI=Percutaneous coronary intervention; CABG=Coronary artery bypass grafting; ACE=Angiotensin converting enzyme; ARB=Angiotensin II receptor blocker.

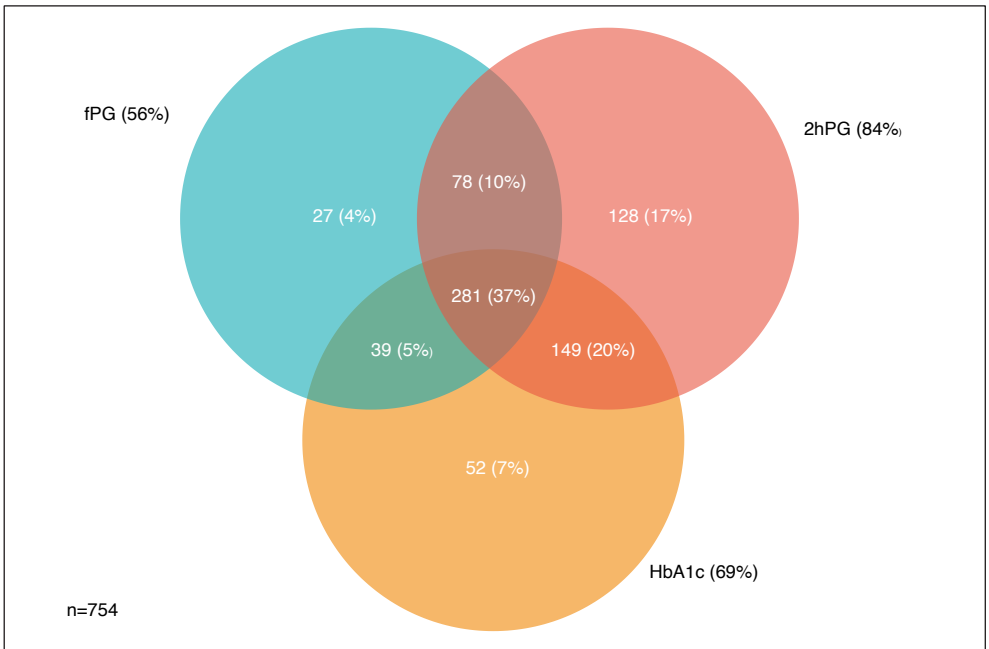

Figure 18: Venn diagram showing proportions and their overlap for the 754 patients with glucose abnormalities (prediabetes or diabetes) according to the OGTT and HbA1c results (ADA criteria).

Event rates and primary outcome

Of a total of 841 patients, 108 (12.8%) died. Regarding cardiovascular events, 175 (20.8%) patients had a myocardial infarction, 19 (2.3%) patients had an ischaemic stroke, and 120 (14.3%) patients were hospitalised for heart failure. The total number of combined events (first of mortality, myocardial infarction, stroke or heart failure) was 372 (44.2%).

When stratifying glycaemic status according to the OGTT, 58 (41.7%) patients with normoglycaemia had events, 174 (43.7%) events occurred in the prediabetes group and 140 (46.1%) events in the group of patients with newly discovered diabetes. When stratifying according to the HbA1c, the combined event occurred in 121 (37.8%) patients with normoglycaemia (HbA1c < 39 mmol/mol), in 223 (48.4%) patients with prediabetes (HbA1c 39-47 mmol/mol) and in 28 (46.7%) patients with newly discovered diabetes (HbA1c ≥48 mmol/mol).

We did not observe an increased risk for the combined event in those with newly diagnosed glucose abnormalities according to OGTT, both unadjusted and adjusted for age and sex. Patients with prediabetes according to the HbA1c had an adverse prognosis, with a significantly higher risk of cardiovascular events and mortality. When adjusted for age and sex, the HR for the combined event was 1.31 (95% CI:1.05-1.63) compared with the group with a normal HbA1c. **Figure 19** illustrates Kaplan-Meier curves with freedom from the CE between the three patient groups according to the OGTT (**Figure 19A**) and HbA1c (**Figure 19B**).

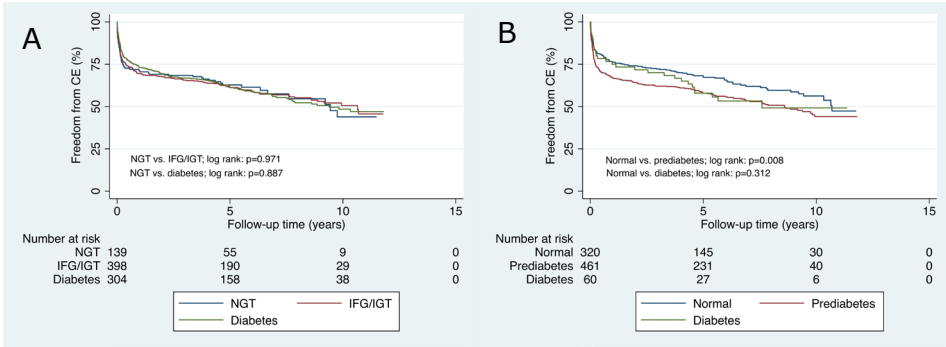

Figure 19: Kaplan-Meier curve showing time to freedom from combined event (CE; first of mortality, myocardial infarction, ischaemic stroke, hospitalisation for heart failure) for different categories of glucose abnormalities according to A. OGTT and B. HbA1c.

Regarding the prognostic significance of different proposed cut-offs for glucose abnormalities, a forest plot with sex- and age-adjusted HRs for the combined event using different cut-offs according to WHO and ADA criteria is presented in **Figure 20**.

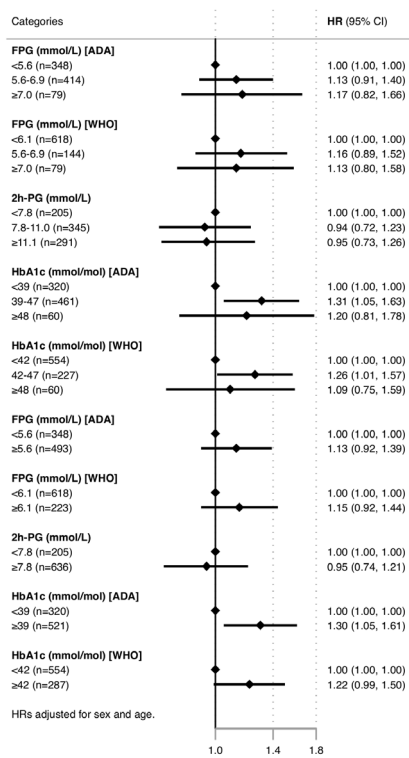

Figure 20: Forest plot with HR (95% CI) for the prognostic value of fPG, 2h-PG and HbA1c for the combined event (first of mortality, heart failure, ischaemic stroke and myocardial infarction) using different cut-offs for glucose abnormalities according to ADA and WHO definitions. HRs adjusted for age and sex.

4.3 STUDY III

In total, 326,832 patients with atrial fibrillation were included, of whom 57,953 (17.7%) had diabetes. Among those with diabetes, 28.9% had no glucose-lowering treatment, 35.4% were treated with oral glucose-lowering medication (or GLP-1 receptor agonist) and 35.7% had insulin, probably combined with other glucose-lowering medication in most of the patients with type 2 diabetes. Patients with diabetes were generally older, had comorbidities to a greater extent and were more frequently treated with cardiovascular medication and anticoagulants compared with those without diabetes. Of those with AF and diabetes (n=57,278), 99% had a CHA_2DS_2-VASc score of ≥ 2, but only 27,435 (47%) were treated with anticoagulants. Insulin-treated patients with diabetes generally had more cardiovascular co-morbidities. The baseline characteristics of our study population stratified by diabetes status and treatment are shown in **Table 8**.

Table 8: Baseline characteristics for our study population stratified by diabetes status and diabetes treatment.

Characteristic	No diabetes	Diabetes	Diabetes-no GLT	Diabetes-OAD	Diabetes-insulin
All patients n=326,832	n= 268,879 (82.3)	n = 57,953 (17.7)	n= 16,733 (28.9)	n= 20,507 (35.4)	n = 20,713 (35.7)
Age – yrs, mean ± SD	74.5±12.7	75.8±9.9	76.8±10.1	75.5±9.7	75.3±9.9
Male sex – no. (%)	147,213 (54.7)	33,648 (58.1)	9,275 (55.4)	12,214 (59.6)	12,159 (58.7)
CHA2DS2-VASc score, mean ± SD	3.3±1.8	4.9±1.7	5.0±1.7	4.7±1.6	5.0±1.7
HAS-BLED score, mean ± SD	1.7±1.1	2.2±1.1	2.3±1.1	2.1±1.0	2.3±1.1
Previous diseases					
Hypertension – no. (%)	119,422 (44.4)	39,212 (67.7)	11,741 (70.2)	13,379 (65.2)	14,092 (68.0)
Ischaemic heart disease – no. (%)	73,320 (27.3)	25,014 (43.2)	7,163 (42.8)	7,953 (38.8)	9,898 (47.8)
Previous stroke – no. (%)	42,808 (15.9)	12,677 (21.9)	3,811 (22.8)	4,013 (19.6)	4,853 (23.4)
Previous any bleeding – no. (%)	34,064 (12.7)	9,146 (15.8)	3,043 (18.2)	2,759 (13.5)	3,344 (16.1)
Previous heart failure – no. (%)	72,745 (27.1)	23,681 (40.9)	6,662 (39.8)	7,290 (35.6)	9,729 (47.0)
Peripheral artery disease – no. (%)	15,115 (5.6)	6,030 (10.4)	1,744 (10.4)	1,485 (7.2)	2,801 (13.5)
Chronic kidney disease – no. (%)	9,763 (3.6)	5,399 (9.3)	1,690 (10.1)	854 (4.2)	2,855 (13.8)
Socio-economic factors					
Living alone – no. (%)	146,270 (54.4)	33,109 (57.1)	6,819 (40.8)	9,309 (45.4)	11,997 (57.9)
Annual income and/or pension after taxes > 200,000 SEK – no. (%)	65,456 (26.1)	10,659 (20.2)	3,139 (20.8)	4,133 (21.6)	3,387 (18.3)
Medication					
Aspirin – no. (%)	127,592 (47.4)	32,449 (56.0)	9,317 (55.7)	11,268 (55.0)	11,864 (57.3)
ACEI or ARB – no. (%)	117,851 (43.8)	40,153 (69.3)	10,706 (64.0)	14,338 (69.9)	15,109 (72.9)
Beta-blockers – no. (%)	187,914 (69.9)	43,266 (74.7)	12,217 (73.0)	15,501 (75.6)	15,548 (75.1)
Dihydropyridines – no. (%)	50,552 (18.8)	17,843 (30.8)	4,984 (29.8)	6,441 (31.4)	6,418 (31.0)
Statins – no. (%)	71,784 (26.7)	29,326 (50.6)	7,534 (45.0)	10,573 (51.6)	11,219 (54.2)
Diuretics – no. (%)	123,240 (45.8)	37,547 (64.8)	10,393 (62.1)	12,391 (60.4)	14,763 (71.3)
P2Y12 receptor antagonists – no. (%)	13,224 (4.9)	4,733 (8.2)	1,300 (7.8)	1,497 (7.3)	1,936 (9.3)
Anticoagulants – no. (%)	116,176 (43.2)	27,345 (47.2)	7,256 (43.4)	10,660 (51.2)	9,429 (45.5)

ACEI=Angiotensin-converting enzyme inhibitors; ARB=Angiotensin II receptor blocker. All differences diabetes treatment subgroups were significant with p-values <0.001 for all comparisons except for dihydropyridines where p=0.003.

Outcomes – long term prognosis in patients with and without diabetes

We compared the absolute number of events and incidence rates between patients with AF and diabetes and those without diabetes. All events occurred significantly more frequently in those with AF and diabetes (**Figure 21**).

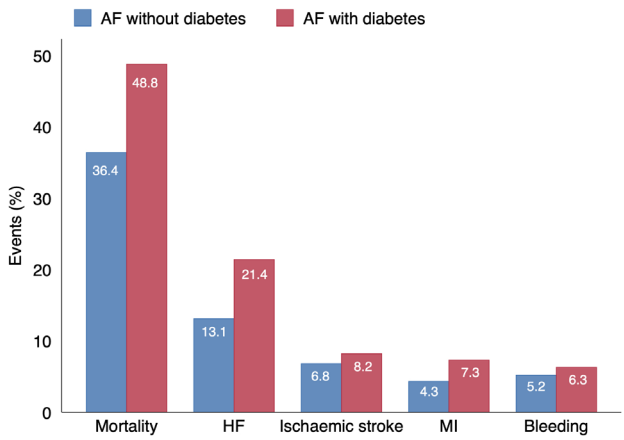

Figure 21: Proportion of events (%) in patients with (red) and without diabetes (blue) after a diagnosis of atrial fibrillation. All differences in event proportion between those with and without diabetes are significant (p<0.001).

Figure 22 presents the incidence rates per 100 patient-years (PY) for all events in AF patients with and without diabetes. In those with diabetes, the incidence rates for all events were generally higher than in those without diabetes. The highest incidence rates were observed for mortality, followed by HF, ischaemic stroke, MI and bleeding. The incidence rate for combined events was 22.3 per 100 patient-years for those with AF and diabetes compared with 13.6 per 100 patient-years for those without diabetes.

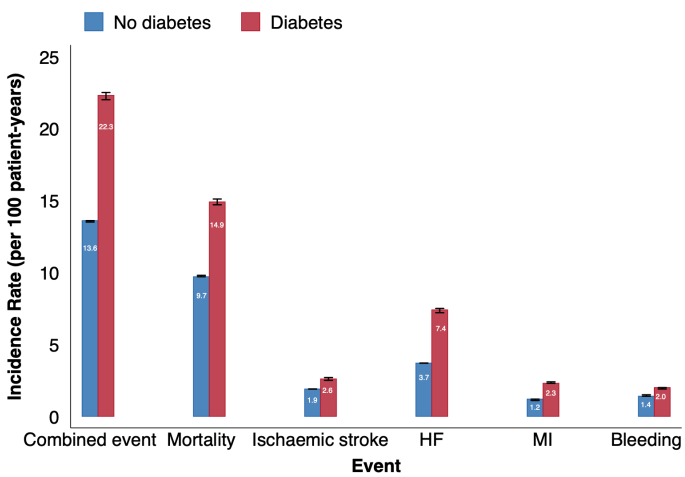

Figure 22: Incidence rates of events per 100 person-years in AF patients with and without diabetes.

Among those with diabetes, insulin-treated patients had the poorest prognosis. Kaplan-Meier curves showing the time to freedom for all events stratified by the presence of diabetes and type of diabetes treatment are shown in **Figure 23**.

The presence of diabetes was independently associated with a poorer prognosis for all the studied outcomes and for the combined event even after adjustments for age, sex, co-morbidities, medication and socioeconomic parameters. A forest plot with adjusted HRs for all events stratified by the presence of diabetes and the type of treatment compared with patients without diabetes is presented in **Figure 24**.

We calculated the standardised mortality ratio (SMR), using freely available mortality data from Statistics Sweden for 2012, in patients with AF with and without diabetes, both in the whole population and stratified by age groups. The SMR in patients with AF and diabetes was 2.06 (95% CI: 2.00-2.12) and, in those with AF but no diabetes, it was 1.33 (95% CI: 1.31-1.35). The SMR was consistently higher in all age groups in those with AF and diabetes as compared to those without diabetes and was especially high in younger age groups, as illustrated in **Figure 25**.

We also listed mortality causes for our study population stratified by the presence of diabetes and the type of diabetes treatment. The most common causes of death in patients with AF, regardless of the presence of diabetes, were cardiovascular disease and cancer. Patients with AF and diabetes had more frequently listed death from endocrine/metabolic disease as the cause of death compared with those without diabetes (10.2% vs. 0.7%). In those with AF and diabetes, death from cerebrovascular disease was a less common cause of death compared with those without diabetes (8.7% vs. 9.5%) (**Figure 26**).

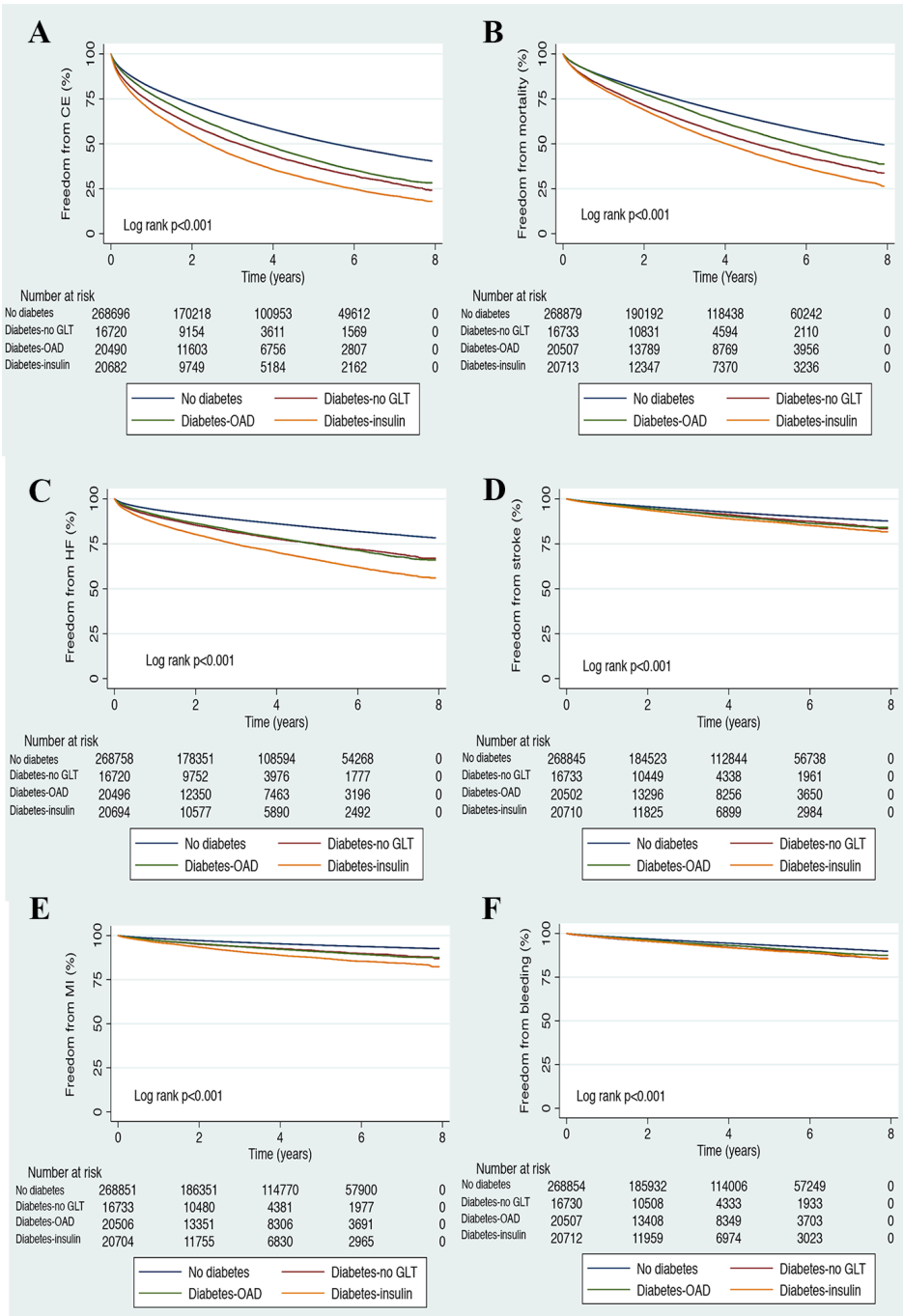

Figure 23: Kaplan-Meier curves showing the time to freedom from A. Combined event [CE] (first of mortality, heart failure, ischaemic stroke, myocardial infarction), B. Mortality, C. Heart failure, D. Ischaemic stroke, E. Myocardial infarction and F. Any bleeding stratified by the presence of diabetes and type of treatment.
GLT=glucose-lowering treatment, OAD=oral antiglycaemic drugs.

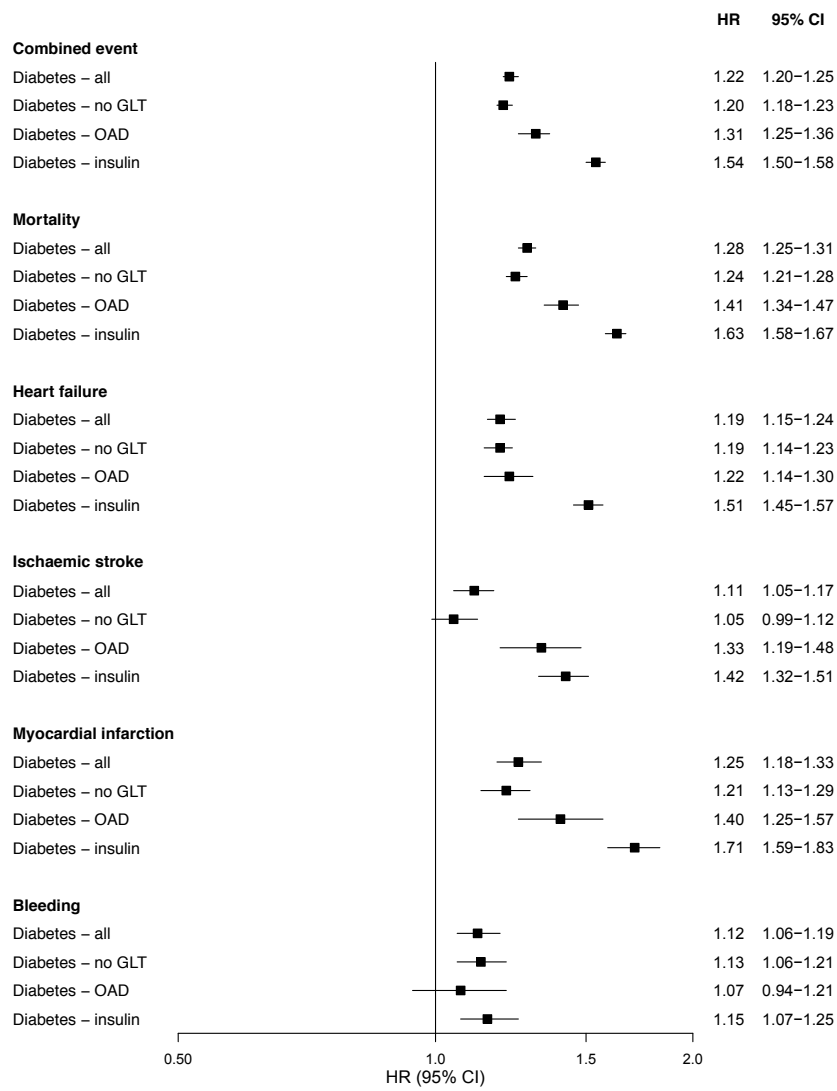

Figure 24: Forest plots with HRs (95% CI) for combined event (first of mortality, heart failure, ischaemic stroke, myocardial infarction), single events and any bleeding, adjusted for co-morbidities and medication, stratified by diabetes status and treatment as compared to patients without diabetes (HR=1.00). HRs are adjusted for age, sex, the presence of heart failure, stroke, venous thromboembolism, bleeding, platelet or coagulation defect, anaemia, myocardial infarction or ischaemic heart disease, peripheral artery disease, valvular disease, pacemaker/ICD, hypertension, chronic kidney disease, liver disease, hypothyroidism, thyrotoxicosis, previous revascularisation (CABG or PCI), chronic obstructive pulmonary disease, alcohol overconsumption, dementia, cancer within three years before inclusion, income, education, working or not, living alone or not, use of anticoagulants, antiplatelets, antiarrhythmics, beta-blockers, digoxin, calcium channel blockers, diuretics, ACE inhibitors or angiotensin II-receptor blockers, statins, NSAID, insulin or other diabetes medications, PPI and SSRI at baseline.

GLT=glucose-lowering treatment, OAD=oral antiglycaemic drugs.

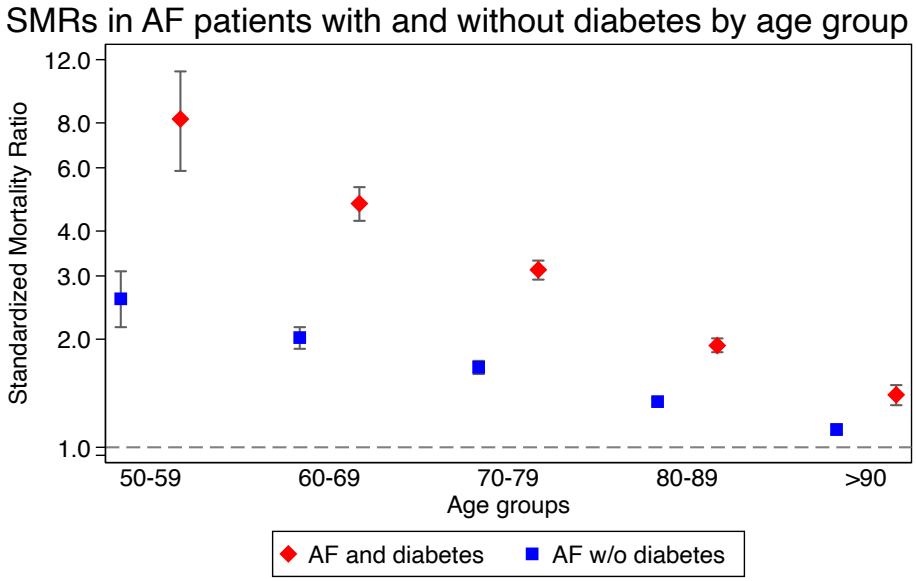

Figure 25: Standardised mortality ratio in AF patients with and without diabetes stratified by 10-year age groups.

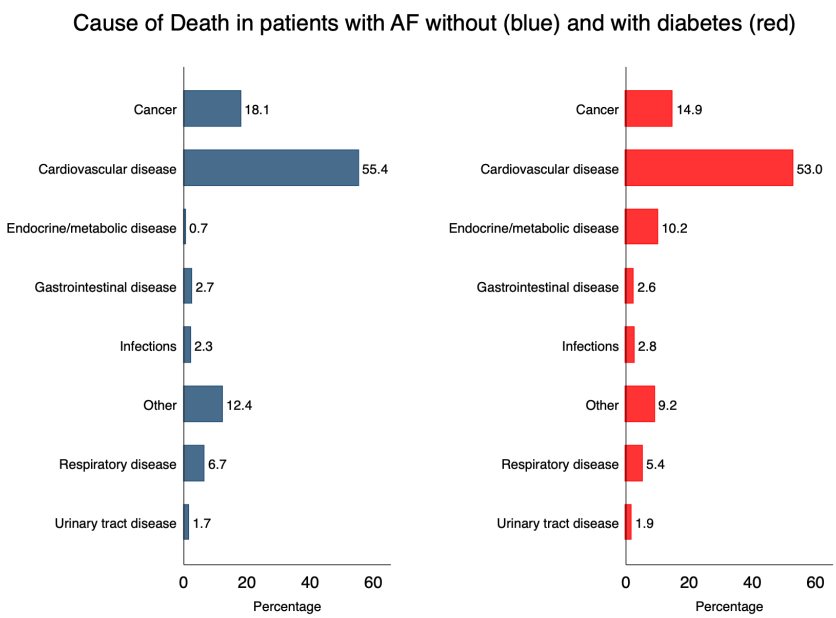

Figure 26: Cause of death as listed in the Cause of Death Register for our study population in those with (red bars) and without diabetes (blue bars).

4.4 STUDY IV

Our study population comprised 309,611 individuals with AF, of whom 60,294 (19.5%) had diabetes mellitus. Among those with diabetes, 2,221 (3.7%) were classified as having type 1 diabetes and 58 073 (96.3%) as having type 2. In general, patients with diabetes had more comorbidities and were more frequently treated with cardiovascular medication than those without diabetes. Patients with type 1 diabetes were younger (median: 70 vs. 77 years) and had generally a longer diabetes duration (77.0% vs. 23.6% with duration >10 years) than those with type 2 diabetes. Patients with type 1 diabetes had chronic kidney disease (22.2% vs. 10.1%; p<0.001), peripheral artery disease (22.3% vs. 11.3%; p<0.001), previous myocardial infarction (29.2% vs. 26.8%; p=0.013) and hypothyroidism (14.7% vs. 7.9%; p<0.001) to a greater extent and were more frequently treated with aspirin (50.6% vs. 43.4%; p<0.001) and statins (68.3% vs. 59.7%; p<0.001) than those with type 2 diabetes. Patients with type 2 diabetes more frequently had heart failure (38.6% vs. 34.9%; p<0.001), dementia (4.6% vs. 2.2%; p<0.001) and previous stroke (23.4% vs. 21.1%; p=0.011) and were more frequently treated with beta-blockers (73.3% vs. 68.9%; p<0.001), diuretics (58.6% vs. 54.7%; p<0.001) and warfarin (44.8% vs. 35.1%; p<0.001) than those with type 1 diabetes (**Table 9**).

Outcomes

Incidence rates for different events in patients with AF and diabetes

Patients with diabetes type 2 had a higher mortality rate and a higher event rate for incident dementia than patients with type 1 diabetes. The incidence rate of myocardial infarction was higher in those with type 1 compared to those with type 2 diabetes. The event rate for incident heart failure and ischaemic stroke was similar in type 1 and type 2 diabetes (**Figure 27**).

When comparing within the diabetes groups, between those with and without previous severe hypoglycaemia, we found that the mortality rate was almost doubled and the incidence rate of heart failure, ischaemic stroke and dementia was higher in those with type 2 diabetes and previous severe hypoglycaemia than in those with type 2 diabetes and no documented previous severe hypoglycaemia. On the other hand, among those with type 1 diabetes, those with a history of severe hypoglycaemia did not have significantly higher event rates compared with those without previous severe hypoglycaemia (**Figure 27**).

Hazard ratios after adjustments stratified by type of diabetes compared with those without diabetes (HR=1)

The observed risks for mortality, heart failure, myocardial infarction and ischaemic stroke were significantly increased in both type 1 and type 2 diabetes, compared to those without diabetes. Those with type 1 diabetes had a higher risk of all-cause mortality [HR: 1.87 (CI 1.73-2.02) vs. 1.51 (CI 1.47-1.55)] and myocardial infarction [HR: 2.49 (CI 2.17-2.85) vs. 1.70 (CI 1.59-1.81)] than those with type 2 diabetes, when using as baseline (HR=1) those without diabetes. The risk of dementia was significantly higher in both type 1 [HR 1.46 (1.15-1.85)] and type 2 diabetes [HR 1.28 (1.18-1.40)] (**Figure 28**).

Hazard ratios after adjustments in those with a history of severe hypoglycaemia in type 1 and type 2 diabetes compared with those without a history of severe hypoglycaemia (HR=1)

A history of severe hypoglycaemia in those with type 2 diabetes was associated with a higher risk of mortality [HR; 95% CI: 1.26; (1.17-1.36)] and dementia [1.37; (1.08-1.73)] but with a lower risk of myocardial infarction [0.79; (0.63-0.99)], compared with type 2 diabetes individuals without hypoglycaemia. When we limited the analysis only to those patients without a previous myocardial infarction and adjusted only for age and sex, the association between severe hypoglycaemia and myocardial infarction disappeared (HR: 1.03; 95% CI: 0.75–1.43).

In type 1 diabetes, a history of severe hypoglycaemia was not significantly associated with an increased risk of mortality, cardiovascular events or dementia (**Figure 29**).

Table 9: Baseline characteristics of the study population stratified by presence and type of diabetes.

Characteristic	No diabetes [N= 249,317 (80.5%)]	Diabetes mellitus [N=60,294 (19.5%)]		
All patients with diabetes N=60,294 (100%)		Diabetes mellitus type 1 [N=2,221 (3.7%)]	Diabetes mellitus type 2 [N=58,073 (96.3%)]	p-value (T1DM vs. T2DM)
Female sex - no. (%)	110,866 (44.5)	822 (37.0)	23,083 (39.7)	0.01
Age - yr [median (IQR)]	76 (67-84)	70 (63-77)	77 (70-83)	<0.001
Diabetes duration >10 years	n/a	1,711 (77.0)	13,690 (23.6)	<0.001
CHA2DS2-VASc score, [median (IQR)]	3 (2-4)	4 (3-6)	5 (4-6)	<0.001
Previous diseases				
Hypertension - no. (%)	133,031 (53.4)	1,764 (79.4)	45,523 (78.4)	0.245
Previous MI - no. (%)	37,495 (15.0)	648 (29.2)	15,562 (26.8)	0.013
Previous PCI or CABG - no. (%)	25,754 (10.3)	531 (23.9)	11,704 (20.2)	<0.001
Previous any stroke - no. (%)	44,524 (17.9)	468 (21.1)	13,580 (23.4)	0.011
Previous heart failure - no. (%)	60,991 (24.5)	775 (34.9)	22,412 (38.6)	<0.001
Peripheral artery disease - no. (%)	17,054 (6.8)	496 (22.3)	6,538 (11.3)	<0.001
Chronic kidney disease - no. (%)	9,882 (4.0)	494 (22.2)	5,851 (10.1)	<0.001
Dementia - no. (%)	9,580 (3.8)	49 (2.2)	2,650 (4.6)	<0.001
Cancer within 3 years before inclusion - no. (%)	26,043 (10.4)	255 (11.5)	6,625 (11.4)	0.915
Hypothyroidism - no. (%)	16,058 (6.4)	326 (14.7)	4,571 (7.9)	<0.001
Medication at inclusion				
Aspirin - no. (%)	84,287 (33.8)	1,124 (50.6)	25,228 (43.4)	<0.001
ACEI or ARB - no. (%)	117,053 (46.9)	1,622 (73.0)	42,315 (72.9)	0.864
Beta blockers - no. (%)	150,259 (60.3)	1,530 (68.9)	42,585 (73.3)	<0.001
Statins - no. (%)	74,671 (29.9)	1,517 (68.3)	34,684 (59.7)	<0.001
Diuretics - no. (%)	95,344 (38.2)	1,216 (54.7)	34,018 (58.6)	<0.001
Anticoagulants				
Warfarin - no. (%)	91,684 (36.8)	780 (35.1)	26,016 (44.8)	<0.001
NOACs - no. (%)	4,507 (1.8)	37 (1.7)	907 (1.6)	0.698
Digoxin - no. (%)	25,669 (10.3)	222 (10.0)	9,598 (16.5)	<0.001

MI=Myocardial infarction; PCI=Percutaneous coronary intervention; CABG=Coronary artery bypass grafting; ACE=Angiotensin converting enzyme; ARB=Angiotensin II receptor blocker; NOACs=Non-vitamin K oral anticoagulants.

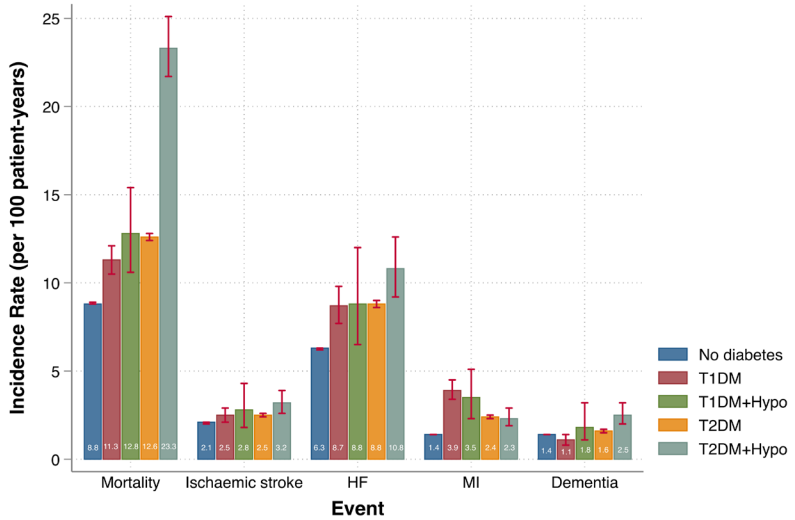

Figure 27: Incidence rates per 100 person-years and their 95% confidence intervals for mortality, cardiovascular events and dementia stratified by the type of diabetes and a history of severe hypoglycaemia.

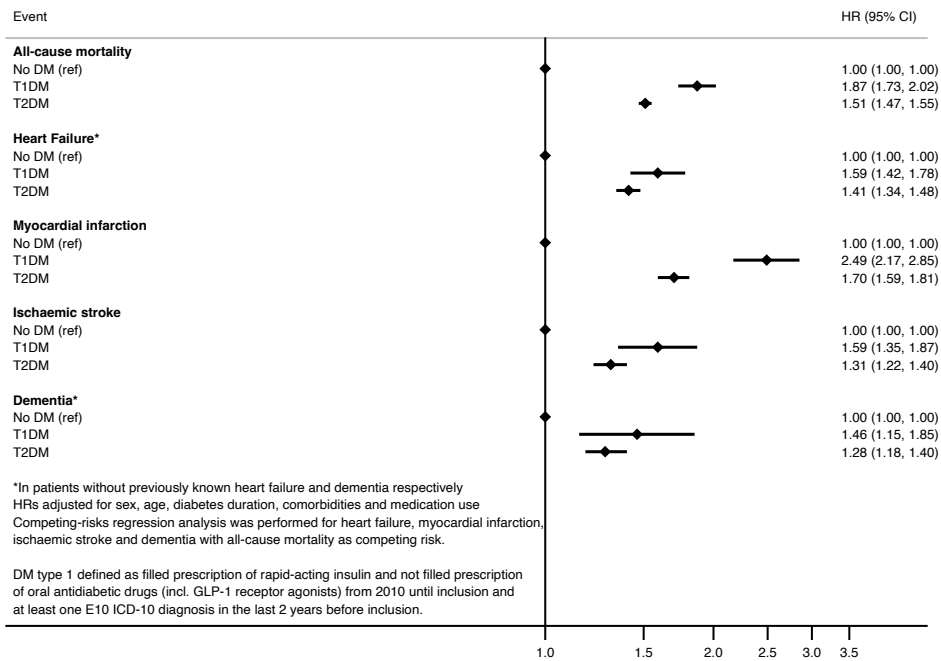

Figure 28: Forest plot with hazard ratios and their 95% confidence intervals for all-cause mortality, cardiovascular events and dementia stratified by the type of diabetes. HRs adjusted for age, sex, diabetes duration (<5 years, 5-10 years, >10 years), the presence of hypertension, previous stroke, transient ischaemic attack (TIA) or systemic embolism, heart failure, chronic kidney disease, peripheral artery disease, dementia, valvular disease, presence of pacemaker/ICD, previous myocardial infarction, cancer diagnosis within three years from inclusion, overconsumption of alcohol, use of anticoagulants, antiplatelets, statins, beta-blockers, ACE inhibitors, angiotensin II-receptor blockers, antiarrhythmics, diuretics and digoxin at baseline.

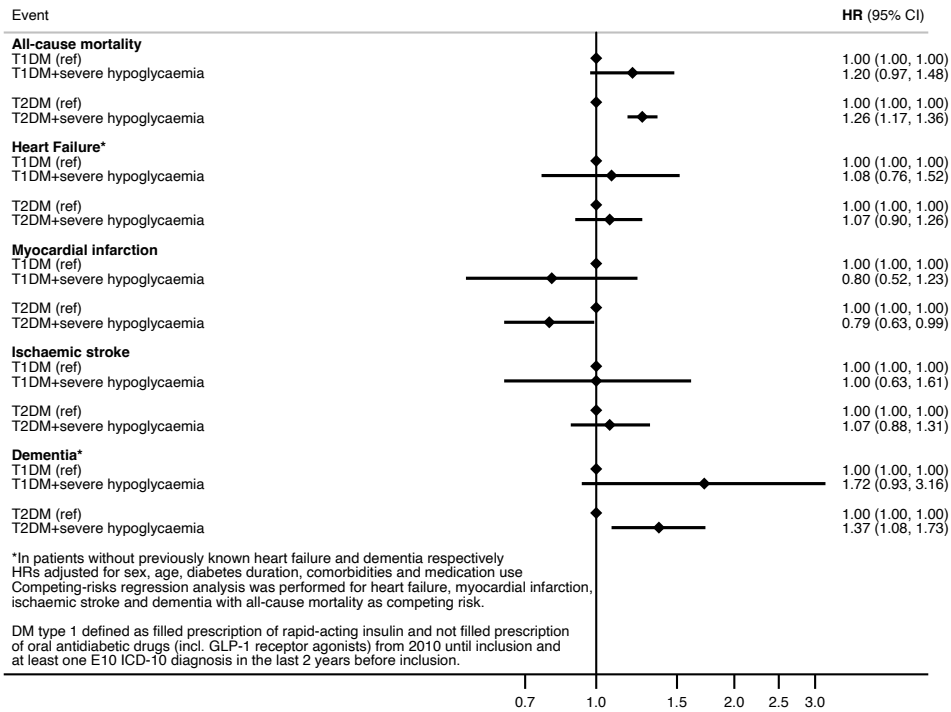

Figure 29: Forest plot with hazard ratios and their 95% confidence intervals for different events and mortality stratified by a history of severe hypoglycaemia. HRs adjusted for age, sex, diabetes duration (<5 years, 5-10 years, >10 years), the presence of hypertension, previous stroke, transient ischaemic attack (TIA) or systemic embolism, heart failure, chronic kidney disease, peripheral artery disease, dementia, valvular disease, presence of pacemaker/ICD, previous myocardial infarction, cancer diagnosis within three years from inclusion, overconsumption of alcohol, use of anticoagulants, antiplatelets, statins, beta-blockers, ACE inhibitors, angiotensin II-receptor blockers, antiarrhythmics, diuretics and digoxin at baseline.

4.5 STUDY V

In total, our study population (n=119) had a median age of 65 (59-72) years and among them we had 78 (65.6%) men and 41 (34.4%) women. They were a relatively healthy cohort with a dominant comorbidity of hypertension in 56 (47.1%) of these patients.

According to the ADA criteria, 67 (56.3%) of the 119 patients screened had prediabetes (IFG/IGT) and nine (7.6%) had diabetes if the OGTT was used, whereas the respective numbers using HbA1c were 52 (43.7%) with prediabetes and six (5%) with diabetes. The absolute numbers and percentages of patients that had a normal glycaemic status and prediabetes or diabetes according to the OGTT and HbA1c results are presented in **Figure 30**.

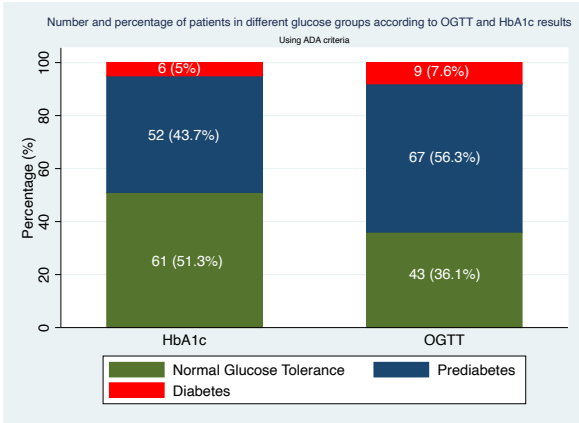

Figure 30: Number and percentage of patients in different glycaemic groups in our study population of patients with atrial fibrillation undergoing electric cardioversion according to OGTT and HbA1c results using ADA criteria.

Using the WHO criteria identified fewer patients with glucose abnormalities (n=54, 45.4%). Of those patients, 35 (29.4%) had prediabetes (IFG/IGT) and nine (7.6%) had diabetes according to OGTT results and 18 (15.1%) had prediabetes and six (5.0%) had diabetes according to HbA1c values (**Figure 31**).

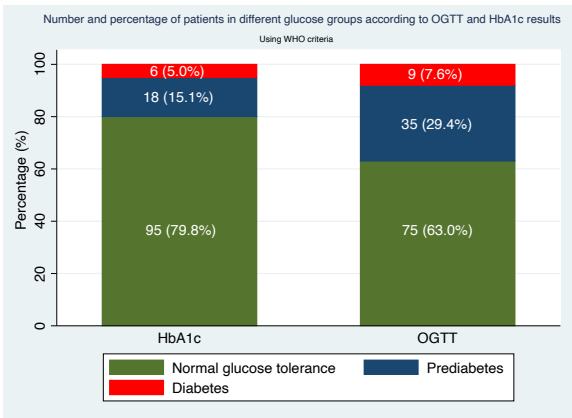

Figure 31: Number and percentage of patients in different glycaemic groups in our study population of patients with atrial fibrillation undergoing electric cardioversion according to OGTT and HbA1c results using WHO criteria.

Patients with undiagnosed glucose abnormalities (IFG/IGT or diabetes) according to the OGTT had a significantly higher median weight, waist circumference, hip circumference and body mass index, i.e., features of the metabolic syndrome, compared with those without glucose abnormalities, regardless of whether the ADA or WHO criteria were used for classification (**Table 10**).

These differences were not observed in those with undiagnosed glucose abnormalities screened with HbA1c compared with those with normal glycaemic status (**Table 11**).

Of the 119 patients screened using the ADA criteria for the diagnosis of diabetes, only 27 (22.7%) had a normal glycaemic status with both screening methods (OGTT and HbA1c), i.e. had normal fasting plasma glucose (fPG), normal 2-hour postload plasma glucose (2hPG) and normal HbA1c. Of the 92 patients with identified glucose abnormalities according to either the OGTT or HbA1c, 88 (96%) would have been identified using the combination of fPG and HbA1c. A Venn diagram showing proportions and their overlap between fPG, 2hPG and HbA1c when classifying glucose abnormalities (prediabetes or diabetes) in the 92 of 119 patients who had glucose abnormalities according to either OGTT or HbA1c result is presented in **Figure 32**.

When the WHO criteria were used, the combination of fPG and HbA1c would have identified 44 of 54 patients (81%) with glucose abnormalities, illustrated by a Venn diagram in **Figure 33**.

The overall agreement between the OGTT and HbA1c when categorising glucose abnormalities was low, with an observed agreement at 51.3% and a Cohen's kappa coefficient at 0.137. The respective figures using the WHO criteria were slightly better, but still low, with an observed agreement between the OGTT and HbA1c at 62.2% and a Cohen's kappa coefficient at 0.157.

Table 10: Baseline characteristics stratified by glycaemic status according to OGTT results (ADA criteria).

	Normoglycaemia N=43	Prediabetes (IFG/IGT) N=67	Diabetes N=9	p-value
Age (years), [median (IQR)]	67.0 (59.0-72.0)	64.0 (59.0-70.0)	68.0 (63.0-71.0)	0.78
Female sex, no. (%)	21 (48.8%)	19 (28.4%)	1 (11.1%)	0.027
Height (cm), mean ± SD	175.9±9.3	178.4±9.6	179.6±11.0	0.34
Weight (kg), mean ± SD	80.9±15.1	92.3±16.0	105.3±19.7	<0.001
Waist circumference (cm), mean ± SD	92.3±14.0	103.1±11.3	118.2±9.0	<0.001
BMI (kg/m^2), [median (IQR)]	25.7 (23.3-27.8)	28.3 (26.0-31.0)	32.5 (30.5-35.1)	<0.001
Smoking, no. (%)	0 (0.0%)	2 (3.0%)	0 (0.0%)	0.82
Snuff use, no. (%)	4 (9.3%)	12 (17.9%)	4 (44.4%)	0.14
Education (university/college), no. (%)	24 (55.8%)	32 (47.8%)	4 (44.4%)	0.83
Exercise (3-5 times/week), no. (%)	19 (44.2%)	27 (40.3%)	2 (22.2%)	0.003
Estimation of physical health (0-100), [median (IQR)]	75.0 (60.0-75.0)	70.0 (50.0-75.0)	57.5 (37.5-72.5)	0.28
AF symptoms according to EHRA scale				0.018
No symptoms, no. (%)	2 (4.7%)	14 (20.9%)	2 (22.2%)	
Mild symptoms, no. (%)	13 (30.2%)	27 (40.3%)	4 (44.4%)	
Severe symptoms, no. (%)	22 (51.2%)	16 (23.9%)	1 (11.1%)	
Disabling symptoms, no. (%)	3 (7.0%)	7 (10.4%)	1 (11.1%)	
Missing, no. (%)	3 (7.0%)	3 (4.5%)	1 (11.1%)	
Hypertension, no. (%)	16 (37.2%)	33 (49.3%)	7 (77.8%)	0.078
Previous myocardial infarction, no. (%)	1 (2.3%)	2 (3.0%)	1 (11.1%)	0.49
Previous PCI/CABG, no. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Heart failure, no. (%)	4 (9.3%)	3 (4.5%)	2 (22.2%)	0.10
Previous any stroke/TIA, no. (%)	1 (2.3%)	4 (6.0%)	2 (22.2%)	0.11
ECG rhythm (at OGTT visit)				0.015
Sinus rhythm, no. (%)	28 (65.1%)	30 (44.8%)	3 (33.3%)	
Atrial fibrillation/flutter, no. (%)	11 (25.6%)	34 (50.7%)	6 (66.7%)	
Other, no. (%)	4 (9.3%)	1 (1.5%)	0 (0.0%)	
Missing, no. (%)	0 (0.0%)	2 (3.0%)	0 (0.0%)	
Use of anticoagulants				0.16
No anticoagulants, no. (%)	0 (0.0%)	4 (6.0%)	0 (0.0%)	
NOACs, no. (%)	39 (90.7%)	62 (92.5%)	9 (100.0%)	
Warfarin, no. (%)	4 (9.3%)	1 (1.5%)	0 (0.0%)	
Statins, no. (%)	5 (11.6%)	16 (23.9%)	1 (11.1%)	0.24
Beta-blockers, no. (%)	37 (86.0%)	54 (80.6%)	8 (88.9%)	0.80
ACEi or ARBs, no. (%)	12 (27.9%)	35 (52.2%)	6 (66.7%)	0.017
Dihydropyridine calcium channel antagonists, no. (%)	4 (9.3%)	14 (20.9%)	4 (44.4%)	0.037
Diuretics, no. (%)	9 (20.9%)	9 (13.4%)	4 (44.4%)	0.053
Antiarrhythmics, no. (%)	10 (23.3%)	16 (23.9%)	2 (22.2%)	1.00

EHRA=European Heart Rhythm Association; PCI=Percutaneous coronary intervention; CABG=Coronary artery bypass grafting; OGTT=Oral glucose tolerance test; NOAC=Non-vitamin K oral anticoagulants; ACEi=Angiotensin-converting enzyme inhibitors; ARB=Angiotensin II receptor blockers.

Table 11: Baseline characteristics stratified by glycaemic status according to HbA1c results (ADA criteria).

	Normoglycaemia N=61	Prediabetes N=52	Diabetes N=6	p-value
Age (years), [median (IQR)]	64.0 (56.0-70.0)	67.5 (60.0-74.5)	69.5 (63.0-71.0)	0.076
Female sex, no. (%)	18 (29.5%)	21 (40.4%)	2 (33.3%)	0.48
Length (cm), mean ± SD	179.4±9.2	174.9±9.5	182.2±10.8	0.022
Weight (kg), mean ± SD	90.1±17.7	88.3±16.4	87.4±24.0	0.83
Waist circumference (cm), mean ± SD	100.4±14.5	100.6±13.7	98.0±15.6	0.92
BMI (kg/m^2), [median (IQR)]	27.7 (25.1-30.0)	27.8 (25.7-31.6)	25.0 (22.9-25.6)	0.14
Smoking, no. (%)	1 (1.6%)	1 (1.9%)	0 (0.0%)	0.75
Snuff use, no. (%)	11 (18.0%)	9 (17.3%)	0 (0.0%)	0.34
Education (University/college), no. (%)	27 (44.3%)	29 (55.8%)	4 (66.7%)	0.015
Exercise (3-5 times/week), no. (%)	28 (45.9%)	20 (38.5%)	0 (0.0%)	0.34
Estimation of physical health (0-100), [median (IQR)]	75.0 (50.0-75.0)	72.5 (50.0-75.0)	50.0 (50.0-50.0)	0.040
AF symptoms according to EHRA scale				0.34
No symptoms, no. (%)	9 (14.8%)	7 (13.5%)	2 (33.3%)	
Mild symptoms, no. (%)	23 (37.7%)	21 (40.4%)	0 (0.0%)	
Severe symptoms, no. (%)	19 (31.1%)	16 (30.8%)	4 (66.7%)	
Disabling symptoms, no. (%)	5 (8.2%)	6 (11.5%)	0 (0.0%)	
Missing, no. (%)	5 (8.2%)	2 (3.8%)	0 (0.0%)	
Hypertension, no. (%)	29 (47.5%)	25 (48.1%)	2 (33.3%)	0.83
Previous myocardial infarction, no. (%)	2 (3.3%)	1 (1.9%)	1 (16.7%)	0.29
Previous PCI/CABG, no. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Heart failure, no. (%)	2 (3.3%)	5 (9.6%)	2 (33.3%)	0.034
Previous any stroke/TIA, no. (%)	1 (1.6%)	6 (11.5%)	0 (0.0%)	0.097
ECG-rythm (at OGTT visit)				0.049
Sinus rhythm, no. (%)	33 (54.1%)	23 (44.2%)	5 (83.3%)	
Atrial fibrillation/flutter, no. (%)	24 (39.3%)	27 (51.9%)	0 (0.0%)	
Other, no. (%)	3 (4.9%)	1 (1.9%)	1 (16.7%)	
Missing, no. (%)	1 (1.6%)	1 (1.9%)	0 (0.0%)	
Use of anticoagulants				0.48
No anticoagulants, no. (%)	3 (4.9%)	1 (1.9%)	0 (0.0%)	
NOACs, no. (%)	56 (91.8%)	49 (94.2%)	5 (83.3%)	
Warfarin, no. (%)	2 (3.3%)	2 (3.8%)	1 (16.7%)	
Statins, no. (%)	6 (9.8%)	13 (25.0%)	3 (50.0%)	0.013
Beta-blockers, no. (%)	52 (85.2%)	42 (80.8%)	5 (83.3%)	0.84
ACEi or ARBs, no. (%)	23 (37.7%)	28 (53.8%)	2 (33.3%)	0.19
Dihydropyridine calcium channel antagonists, no. (%)	11 (18.0%)	9 (17.3%)	2 (33.3%)	0.58
Diuretics, no. (%)	9 (14.8%)	10 (19.2%)	3 (50.0%)	0.12
Antiarrhythmics, no. (%)	16 (26.2%)	11 (21.2%)	1 (16.7%)	0.87

EHRA=European Heart Rhythm Association; PCI=Percutaneous coronary intervention; CABG=Coronary artery bypass grafting; OGTT=Oral glucose tolerance test; NOAC=Non-vitamin K oral anticoagulants; ACEi=Angiotensin-converting enzyme inhibitors; ARB=Angiotensin II receptor blockers.

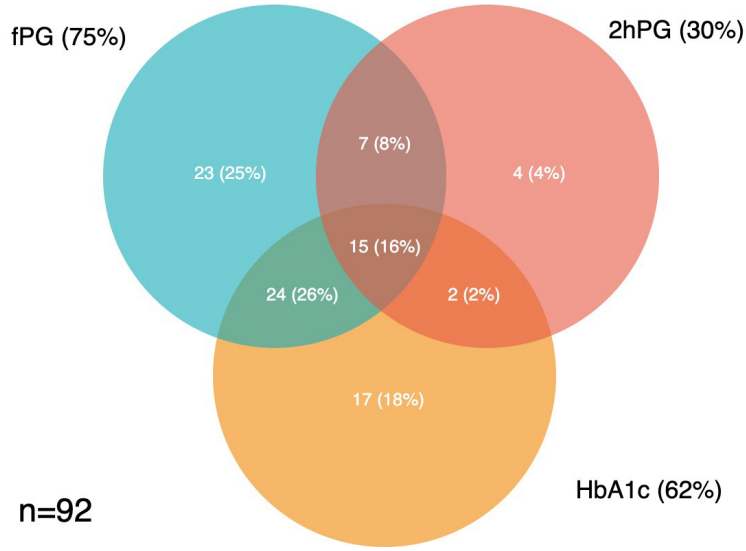

Figure 32: Venn diagram showing proportions and their overlap between the fPG, 2hPG and HbA1c in classifying glucose abnormalities (prediabetes or diabetes) in the 92 of 119 patients who had glucose abnormalities according to either the OGTT or HbA1c result when using the ADA criteria for the diagnosis of diabetes.

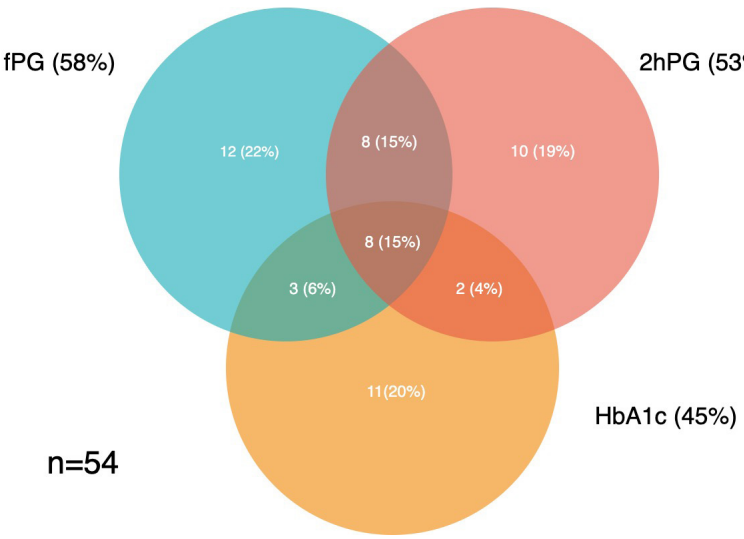

Figure 33: Venn diagram showing proportions and their overlap between fPG, 2hPG and HbA1c in classifying glucose abnormalities (prediabetes or diabetes) in the 54 of 119 patients who had glucose abnormalities according to either the OGTT or HbA1c result when using the WHO criteria for the diagnosis of diabetes.

5. DISCUSSION

The overall aim of this thesis was to study the prevalence and prognosis in patients with different types of cardiovascular disease and established diabetes or newly detected glucose abnormalities. From the studies in this thesis, it can be summarised that the proportion of established diabetes is around 14% and 18% in ST-elevation myocardial infarction and atrial fibrillation, respectively, but in addition to that up to 70-80% of the patients, depending on which screening method used, have previously unknown glucose abnormalities. Further, there is an increased risk of cardiovascular events in those with newly detected glucose abnormalities. The presence of diabetes in individuals with atrial fibrillation, not only puts the patients in risk of future stroke, but also increases the risk of heart failure and other cardiovascular events and mortality. This is also true for type 1 diabetes. Below these results will be discussed in more detail.

In **Study I,** we showed that, in a population with ST-elevation myocardial infarction receiving contemporary treatment, diabetes was still an independent adverse prognostic risk factor, resulting in an almost doubled one-year mortality. This mortality risk was more pronounced in insulin-treated patients who also ran an increased risk of a new MI, while non-insulin-treated patients did not have a higher complication risk at one year.
In **Study II**, we showed that more than two thirds of patients with AMI have undiagnosed glucose abnormalities and that the available screening methods for glucose abnormalities (OGTT and HbA1c) identify different at-risk populations. We found that the HbA1c values in the prediabetes range (39-47 mmol/mol) had prognostic value regarding the risk of premature death and cardiovascular events.
In **Study III**, we found that, in a nationwide unselected cohort with atrial fibrillation**,** the presence of diabetes was associated with an increased morbidity and mortality risk, especially in those with insulin treatment.
In **Study IV,** we investigated the prognostic effect of different types of diabetes and severe hypoglycaemia in patients with atrial fibrillation and we found that both type 1 and type 2 diabetes were associated with a higher risk of premature death, cardiovascular events and dementia. This increased risk was generally more pronounced in those with type 1 diabetes, especially for premature death and myocardial infarction. A history of severe hypoglycaemia was associated with a higher risk of premature death and dementia among those with type 2 diabetes.
In **Study V,** we showed that, even in a selected, generally healthy population with atrial fibrillation, the proportion of patients with undiagnosed glucose abnormalities is high, with the criteria for the diagnosis of diabetes from the American Diabetes Association identifying a larger proportion than the criteria from the World Health Organisation (75% vs. 45%). As in the population with myocardial infarction, OGTT and HbA1c identify different at-risk populations and have low agreement.

5.1 PROGNOSIS IN PATIENTS WITH DIABETES AFTER A MYOCARDIAL INFARCTION

Our findings are in line with previous reports on an excess mortality risk after an MI in patients with diabetes compared with those without diabetes (67,92), despite decreasing cardiovascular mortality in the western world in the last few decades (93,94). The current European Society of Cardiology guidelines for the management of STEMI highlight the fact that patients with diabetes have a higher mortality risk and more complications post-STEMI and that they should receive special consideration (95).

We observed no difference in thrombus grade or thrombus burden in patients with diabetes when compared with those without diabetes in **Study I**. These results corroborate the findings of a previous study by Sebben et al. in patients with STEMI, where thrombus material was obtained by aspiration thrombectomy, and the morphological and histopathological characteristics of coronary thrombi were not found to be significantly different in those with diabetes compared with those without (96).
Furthermore, a higher rate of stent thrombosis associated with diabetes or insulin use after one year was not observed. This contradicts the findings reported by Dangas et al. (100% STEMI) and Ritsinger et al. (34% STEMI) where the risk of stent thrombosis in insulin-treated patients was increased by around three times (97) and 1.6 times (61) respectively. One possible explanation might be the low absolute number of stent thromboses observed in the TASTE study, the use of only first-generation DES in the study by Dangas et al. and the fact that our cohort included only STEMI patients. As a result, the diabetes-associated excess mortality risk following STEMI is unlikely to be explained by an increased risk of stent thrombosis and possible mechanistic explanations consequently need to be sought elsewhere.

Suggested mechanisms for the high event rates in patients with diabetes and ACS are more widespread coronary artery disease (59), incomplete revascularisation (59,61) and a tendency towards increased thrombosis and platelet dysfunction (63), with resistance to platelet-stabilising drugs such as aspirin (64,65) and clopidogrel (66).

Our findings suggest that, despite the improved prognosis in recent years for patients with a myocardial infarction due to advances in available treatments, those with diabetes still run an excess risk of adverse outcomes. This illustrates the need for further improved and novel treatment strategies in patients with diabetes after a myocardial infarction. The inclusion of our study population took place before newer diabetes medications, such as SGLT2-inhibitors and GLP-1 receptor agonists, which have been shown to have a cardioprotective effect, were made available. Their wider use, as well as improved secondary prevention with multifactorial risk factor control, will hopefully improve the prognosis in these patients. As discussed in the limitation section, we lacked information on type of diabetes, diabetes duration and presence of microvascular complications. Therefore, we cannot rule out that some of the observed increased risk is attributed to these factors.

5.2 SCREENING FOR GLUCOSE ABNORMALITIES IN PATIENTS AFTER A MYOCARDIAL INFARCTION – CHOICE OF SCREENING STRATEGY

Both diabetes and prediabetes are associated with a higher risk of cardiovascular events and mortality in individuals with and without established cardiovascular disease (98–101). The current ESC guidelines on diabetes and cardiovascular disease that were developed in collaboration with the European Association for the Study of Diabetes recommend screening all patients with established cardiovascular disease for unknown glucose abnormalities using HbA1c and/or fasting glucose and only when in doubt completing the screening process with an OGTT (46). While there is consensus that it is important to screen this high-risk population for undiagnosed glucose abnormalities, the choice of screening method has been, and still is, a matter of debate (16,47).

As using the HbA1c is less time consuming and simpler for both the patient and the healthcare personnel, the question of whether the use of the OGTT is still justified has arisen. One important aspect when answering that question is which of these two screening methods gives the most prognostic information, since the purpose of the screening is to identify high-risk individuals and initiate timely interventions to mitigate future risks of morbidity and mortality.

In **Study II**, we sought to add some information to the current state of knowledge regarding this question, as the results from previous published studies regarding the prognostic value of these two screening methods have been conflicting. We showed that, in our single-centre cohort of patients with AMI, only the HbA1c in the prediabetes range was of prognostic importance for the combined endpoint of all-cause mortality, myocardial infarction, heart failure or ischaemic stroke. Strengths of our study include that the patients were screened early after a myocardial infarction, we had no individuals lost to follow-up for our outcomes of interest and the study was performed in a more recent time period than other studies. Mahendran et al. reported that, in a similar population of individuals with acute coronary syndrome, the HbA1c in the prediabetes range according to ADA criteria (39-47 mmol/L) was not associated with an increased risk of recurrent acute coronary syndrome or premature death, however during only 12 months of follow-up (102). In a report from EUROASPIRE IV in patients with stable coronary disease, it was shown that, when comparing the fPG, 2h-PG and HbA1c, only the 2h-PG played an important part in the prognosis regarding the risk of future cardiovascular events (55). Chattopadhyay et al. showed that the 2h-PG, but not the fPG, had predictive value for the risk of reinfarction and mortality in patients with AMI, although the HbA1c was not compared (103). On the other hand, studies of both a general population and patients with established coronary artery disease have suggested that the HbA1c is a better predictor of mortality compared with the fPG (50,52).

It should be noted that one important limitation of our study is that, according to clinical practice at our hospital during that time, individuals with prediabetes according to the OGTT were referred to their general practitioner for follow-up with a new OGTT and risk factor optimisation. This intervention was not offered consistently to patients with prediabetes according to the HbA1c, which could have affected our results, although a recently published study has shown that individuals who were made aware that they had prediabetes did not make any changes to their diet or physical activity patterns (104). During our inclusion period (2006-2013), the HbA1c had not yet been established as a diagnostic criterion for diabetes and, as a result, HbA1c values in the prediabetes range probably received less attention than OGTT values in the prediabetes range.

The answer to the question of which screening strategy gives the best prognostic information regarding the future risk for cardiovascular events in patients is yet not fully answered and further studies are needed.

5.3 PROGNOSIS IN PATIENTS WITH CONCOMITANT ATRIAL FIBRILLATION AND DIABETES

In patients with atrial fibrillation, the presence of diabetes is an independent adverse prognostic factor (105). Several previous studies, most using register-based data, from

different continents such as the USA (79), Europe (106,107) and Asia (108–110) have consistently shown that the presence of diabetes is associated with an increased risk of all-cause and cardiovascular mortality. Results relating to other studied endpoints were not consistent with some of these studies, even showing an increased risk of ischaemic stroke/TIA (107,108), major bleeding (108) and heart failure (108,109) in those with diabetes compared with patients without diabetes and some showing similar risks of thromboembolic events (79,109,110), heart failure (107) and bleeding (107). These discrepancies could be partially explained by short follow-up periods and the low number of studied patients not giving enough statistical power to study these events, but they could also be due to differences in baseline characteristics in the studied cohorts. For example, the utilisation of oral anticoagulants in these studies ranged from around 12% to 85%.

In **Study III**, as we used unselected data from a nationwide register and had a longer follow-up period than most of the other studies, we had enough statistical power and were able to show that the presence of diabetes in patients with atrial fibrillation is associated not only with a higher risk of mortality and stroke but also with a higher risk of myocardial infarction, heart failure and bleeding, thereby adding to the current state of knowledge on the subject of prognosis in patients with atrial fibrillation and diabetes.

Suggested mechanisms for the poorer prognosis in patients with diabetes are the increased burden of atrial fibrillation and the clustering of comorbidities such as ischaemic heart disease, hypertension, heart failure and chronic kidney disease in these patients (105)

We were also able to show that insulin-treated patients with diabetes had the poorest prognosis among those with diabetes. This result was partially replicated in a recent analysis of the ARISTOTLE trial which showed that, in patients with atrial fibrillation receiving anticoagulation, regardless of type, patients with diabetes treated with insulin ran a higher risk of myocardial infarction and CV mortality compared with patients without diabetes, while the risk in non-insulin-treated patients with diabetes was not significantly increased (111).
This poorer prognosis could be explained by different mechanisms. Patti et al. showed that insulin treatment in patients with atrial fibrillation and type 2 diabetes treated with anticoagulants led to increased thrombin formation (112). Moreover, the use of insulin confers a risk of hypoglycaemia and is a proxy for longer diabetes duration. Andersen et al. showed that cardiac arrhythmias were frequent in insulin-treated patients with diabetes mellitus type 2 and were associated with the glycaemic variability in these patients (113). Longer diabetes duration was found to be associated with a higher risk of mortality and thromboembolism in patients with atrial fibrillation (76). The question remains if the excess risk in insulin-treated individuals with diabetes is an effect of insulin itself or if insulin use is a proxy for frailty, more progressive diabetes disease with longer duration, more diabetes complications and more comorbidities.

Most of the published studies regarding atrial fibrillation and diabetes investigated diabetes as one group of patients and did not make a distinction between type 1 and type 2 diabetes. We attempted to address this knowledge gap in **Study IV,** where we showed that both types of diabetes are associated with a higher risk of premature death, myocardial infarction, heart failure, stroke and dementia. Patients with type 1 diabetes have a more pronounced increase in the risk of premature death and myocardial infarction than patients with type

2 diabetes. To our knowledge, only one other study (114) has assessed the differences in risk between patients with type 1 and type 2 diabetes in patients with atrial fibrillation, although that study evaluated only the risk of thromboembolism and did not include other endpoints. Fangel et al. showed that, in a Danish cohort of patients with atrial fibrillation, those with type 1 and type 2 diabetes had a similar risk of thromboembolism, which we also showed in our study (114). However, we also assessed differences between type 1 and type 2 diabetes regarding other endpoints such as premature death, heart failure, myocardial infarction and dementia, which adds to the current state of knowledge of the prognosis of patients with atrial fibrillation and diabetes. Regarding dementia, a recently published study using the Atherosclerosis Risk in Communities (ARIC) cohort assessed the risk of dementia in a similar setting, i.e., risk in those with concomitant atrial fibrillation and diabetes compared with those with only atrial fibrillation and found that the presence of diabetes increases the risk of dementia by 45% even after adjustments for cofactors, a result similar to that in our study (115). It should be noted, however, that, in that study when adjusting for the competing risk of death, the association between the presence of diabetes and an increased risk of dementia disappeared.

The mechanisms behind the excess cardiovascular risk in type 1 diabetes are not completely understood. One proposed model is a combination of autoimmune factors with the formation of cardiac autoantibodies that contribute to increased inflammation and atherosclerosis (116) and long-lasting hyperglycaemia which leads to increased oxidative stress which, in turn, leads to tissue hypoxia, inflammation and microcirculatory damage (117). These effects are augmented by the presence of traditional risk factors such as hypertension and chronic kidney disease.

In **Study IV,** we also showed that a history of severe hypoglycaemia among individuals with type 2 diabetes is associated with an increased risk of premature death and dementia. Our results agree with several previous published studies that showed that severe hypoglycaemia is associated with adverse events and mortality (118–120). Due to the observational design of these studies, it is difficult to draw inferences relating to causality and the question of whether hypoglycaemia is the causal factor or merely a risk marker identifying frail, high-risk individuals has not been completely answered. Regardless of this, it could be valuable for the clinicians treating patients with diabetes to consider treatment strategies that minimise the risk of hypoglycaemia, especially in patients with a high cardiovascular risk (120). Indeed, in the very recently published guidelines for the management of hyperglycaemia by European Association for the Study of Diabetes and ADA, the avoidance of hypoglycaemia is identified as one of the variables that should be considered in the choice of pharmacological therapy for high-risk individuals in type 2 diabetes (121).

5.4 SCREENING FOR GLUCOSE ABNORMALITIES IN PATIENTS WITH ATRIAL FIBRILLATION – CHOICE OF SCREENING STRATEGY

In **Study V,** we show that there is a high prevalence of glucose abnormalities, mainly prediabetes, among individuals with atrial fibrillation undergoing electrical cardioversion. More than two thirds of our patients had undiagnosed glucose abnormalities (prediabetes or diabetes) according to either the OGTT or HbA1c. Our results agree with the results of previously published studies that reported a high prevalence of glucose abnormalities in different populations with cardiovascular disease (45,122,123) and confirm the current guideline recommendation of screening for diabetes in patients with cardiovascular disease (46).

Regarding the screening method used to detect glucose abnormalities, the current recommendation is to use a combination of the fPG and HbA1c and when in doubt to continue with the OGTT (46), which is a recommendation supported by our data, as, in our AF study population, a combination of the fPG and HbA1c identified 96% of patients with glucose abnormalities if the ADA criteria were used and 81% if the WHO criteria were applied. Other published studies of patients with ischaemic heart disease suggest that the OGTT should be used as a screening method, as we would have failed to identify many patients with glucose abnormalities by using only the fPG and HbA1c (124,125).

To our knowledge, there is only one other study from Norway that has assessed the prevalence of undiagnosed glucose abnormalities in patients with atrial fibrillation (80). In that study, Johansen et al. showed that, among 46 screened 75-year-old individuals with atrial fibrillation, 13% had diabetes and 26.1% had prediabetes, according to OGTT results using the WHO diagnostic criteria (80). The number of individuals with prediabetes was similar to that in our cohort, but the percentage of patients with diabetes was almost doubled. This difference could depend on the fact that our cohort was much younger, with a median age of 65 years. Age is one of the most important risk factors for diabetes, as glucose intolerance increases progressively with advancing age (126).

5.5 ADA VS. WHO CRITERIA FOR THE DIAGNOSIS OF PREDIABETES

The ADA has decided on lower cut-offs for the diagnosis of prediabetes, for both fasting plasma glucose (5.6-6.9 mmol/L) (127) and HbA1c (39-42 mmol/mol) (128) compared with the WHO prediabetes criteria for fasting plasma glucose (6.1-6.9 mmol/L) (129) and the HbA1c criteria for prediabetes suggested by the International Expert Committee in 2009 (42-47 mmol/mol) (10). It is thus understandable that, using the ADA criteria for the diagnosis of prediabetes results in many more individuals being classified as having prediabetes and thus becoming eligible for a follow-up/intervention. When applying the lower ADA cut-offs to the NHANES 2009-2010 cohort, the prevalence of prediabetes increases three-fold when using the lower cut-off for fasting plasma glucose and five-fold when using the lower cut-off for HbA1c (130). In **Study II**, we found that only HbA1c in the prediabetes range with both ADA (39-47 mmol/mol) and the criteria recommended by the IEC (42-47 mmol/mol) was predictive of premature death and cardiovascular events in a post-myocardial infarction population.

Davidson and Kahn reported on the predictive value of the lower and upper intervals for prediabetes in terms of the incidence of cardiovascular disease (130). They reported that, in 13 studied cohorts, there was no increase in incident cardiovascular disease with fasting plasma glucose values of 5.6-6.0 mmol/L compared with persons with values of < 5.6 mmol/L (130). Regarding the HbA1c, they reported that HbA1c values of 37-41 mmol/L were not predictive of incident cardiovascular disease in nine of 12 studied cohorts and were predictive in three compared with persons with an HbA1c of < 37mmol/mol. Lind et al. reported that in almost 300,000 subjects without previous cardiovascular disease who had a mean follow-up time of more than 19 years, increased fasting glucose at prediabetes levels according to the WHO criteria, i.e., 6.1-6.9 mmol/L, was associated with an increased risk of heart failure and atrial fibrillation (131).

Another important aspect is the risk of progression from prediabetes to diabetes. This risk increases in a curvilinear fashion as the values for fasting plasma glucose and HbA1c approach the cut-off for diabetes, with an almost five-fold increase in risk in individuals with fasting plasma glucose of 6.1-6.9 mmol/L compared with those with values of 5.6-6.0 mmol/L and an almost four-fold increase in those with an HbA1c of 42-46 mmol/mol compared with those with an HbA1c of 37-42 mmol/mol (13).

When considering all the above, concentrating our preventive efforts in those individuals with fasting plasma glucose and HbA1c values closer to the cut-off for diabetes, i.e. use the WHO criteria for the diagnosis of prediabetes, would perhaps constitute a more efficient use of healthcare resources.

5.6 STRENGTHS AND LIMITATIONS

The main strength of **Study I** is the large number of diabetes patients from all the hospitals in Sweden performing PCI, all with a STEMI diagnosis, and the inclusion of detailed information on coronary angiography findings, coronary artery disease distribution, thrombus grade, ejection fraction, type of intervention and pharmacological treatment. The study cohort is consequently unselected and likely to be highly representative of a contemporary diabetes-STEMI population. In **Study II**, we used a standardised method of performing the OGTT and all the samples were analysed in one accredited laboratory, thereby helping to improve the internal validity of our results. Moreover, the patients were screened early after the myocardial infarction, and we had no subjects lost to follow-up. The main strength of **Studies III and IV** is the use of high-quality, Swedish, nationwide data registers, allowing for the inclusion of all AF patients in Sweden and essentially a complete follow-up, thereby reducing the risk of selection and misclassification bias and allowing a high level of generalisability in our results. The prospective nature of **Study V** makes it less susceptible to bias and improves the quality of our collected data regarding data on exposure, outcome and confounding variables.

There are also important limitations that should be mentioned. Because of the observational design of our studies, we are unable totally to exclude residual confounding and we are only able to show associations between exposure and outcome and not draw any inferences on causality. Another limitation in **Studies I-IV** is the lack of information on diabetes-related metabolic variables, such as the values of HbA1c and information on the presence of diabetes microvascular complications. In addition, we do not have any information on exposure to medication during follow-up, which could modify the effect on outcomes that depend on exposure to specific medications, such as anticoagulants. Moreover, the Prescribed Drug Register gives information on filled prescriptions and not actual adherence to medication. Specific limitations in **Study I** are the lack of information on mortality causes and events, such as heart failure or severe hypoglycaemia, which in themselves are known to be associated with increased mortality in patients with diabetes, the lack of information on the type of diabetes and the fact that this is a post-hoc analysis where the original trial was not powered for event analysis in patients with diabetes. In **Study II**, a follow-up via the primary care physician was offered to all patients with prediabetes according to the OGTT but not to patients with prediabetes according to the HbA1c, which could have helped to improve the secondary prevention in these patients and could have affected our results. An

even more structured intervention was offered to individuals with diabetes according to the OGTT but not to those with diabetes according to the HbA1c, as the HbA1c had not been implemented as a diagnostic criterion for diabetes in Sweden during our inclusion period. In **Study III,** we lacked information on type of diabetes. Our results showed that insulin-treated patients have a more pronounced increase in risk of cardiovascular events which raised the question if some this excess risk could be explained by the presence of individuals with type 1 diabetes among the insulin-treated patients. Indeed, the presence of persons with type 1-diabetes among the insulin-treated population could partly explain the excess cardiovascular risk because **Study IV** showed that individuals with type 1 diabetes have a more pronounced increase in risk for premature death and myocardial infarction than individuals with type 2 diabetes. In **Study IV**, the definition of type 1 diabetes was arbitrary and was based on ICD-10 diagnoses and prescribed medication instead of clinical judgment. In **Study IV**, we used hospital ICD-10 hypoglycaemia diagnoses to identify patients with a history of severe hypoglycaemia and may thus have missed patients with episodes of severe hypoglycaemia outside hospital. Further, we also lack information on the severity or total number of hypoglycaemia episodes.

6 CONCLUSIONS

Based on the studies included in this thesis, the following conclusions can be drawn:

- Despite the advances in medical and interventional treatments in recent decades that have led to the continuously improving one-year survival after STEMI, diabetes is still independently associated with an increased risk of premature death.

- A large proportion of patients with acute myocardial infarction have undiagnosed glucose abnormalities, necessitating the need for screening in this population. The available screening methods, the fPG, 2hPG and HbA1c, identify different at-risk populations and which of these tests gives the most valuable prognostic information is still an unanswered question. In our single-centre study cohort, where patients were informed of the OGTT results, only HbA1c values in the prediabetes range (39-47 mmol/mol) were associated with an increased risk of mortality and cardiovascular morbidity.

- The presence of diabetes in patients with atrial fibrillation is associated with an increased risk of heart failure, myocardial infarction, stroke and mortality, especially in insulin-treated individuals with diabetes. Therefore, we believe that it is important for these individuals to be carefully followed-up, treated with evidence-based therapy, actively screened for undiagnosed heart failure and to achieve their treatment targets.

- Among individuals with atrial fibrillation, type 1 diabetes confers risks of adverse events similar to those in type 2 diabetes and an even higher risk than type 2 diabetes of the events of premature death and myocardial infarction.

- Severe hypoglycaemia appears to be an important risk factor for adverse events, such as premature death and dementia in patients with atrial fibrillation and diabetes type 2. The treating physician of these patients may consider a treatment strategy that minimizes the risk of hypoglycaemia in this group.

- There is a large proportion of undiagnosed glucose abnormalities not only in patients with ischaemic heart disease but also in patients with atrial fibrillation undergoing electric cardioversion, raising the question of whether screening for diabetes should be included in standard care for this group of patients.

7 FUTURE PERSPECTIVES

Diabetes is still an independent risk factor for adverse cardiovascular events and mortality, despite advances in cardiovascular treatment during the last few decades. Novel diabetes medications, such as SGLT2-inhibitors and GLP-1 receptor agonists, have, in addition to glucose-lowering effects, been shown to have a cardioprotective and nephroprotective effect on specific subsets of patients with diabetes mellitus type 2 (132). In a post-hoc analysis of patients with heart failure, SGLT2-inhibitors have been shown to reduce the atrial fibrillation burden in patients with diabetes mellitus type 2 (133). Prospective studies are needed to explore whether SGLT2-inhibitors have a preventive effect on recurrent atrial fibrillation in patients with atrial fibrillation and diabetes. Since undetected glucose abnormalities are common in patients with atrial fibrillation, it would also be of interest to study this concept in individuals without established diabetes and perhaps even in patients with normoglycaemia.

The LEGACY study has shown that weight loss in patients with atrial fibrillation may reduce the recurrence of atrial fibrillation (137), while the Steno-2 study has shown that multifactorial intervention in patients with diabetes may reduce the risk of developing diabetes complications (134). For this reason, it would be interesting to study the effect of lifestyle and multifactorial interventions in patients with atrial fibrillation and diabetes, including the use of medication such as GLP-1 receptor agonists, which have been shown to facilitate weight loss (135). Moreover, since we showed that the standardised mortality ratio is much higher in younger patients with atrial fibrillation and diabetes, it is important that the young, high-risk population of patients with atrial fibrillation and diabetes is prioritised in intervention studies in order to improve their prognosis.

Our results suggest that episodes of severe hypoglycaemia are an adverse risk factor which could be associated with an increased risk of premature death and cognitive impairment. The technological advances of recent years, with the availability of glucose sensor technology, could enable the design of studies looking into the effect of the avoidance of hypoglycaemia in the preservation of cognition or prevention of other adverse outcomes. It would also be interesting to test the prognostic value of measures for glycaemic control other than the HbA1c, such as time in range (TIR), i.e., the amount of time with glucose values within the target range between 4-10 mmol/L, not only in diabetes type 1 but also in diabetes type 2.

We show that there are significant differences in prognosis in patients with atrial fibrillation and different types of diabetes. Further research is needed to explore the mechanisms behind this unfavourable prognosis in patients with atrial fibrillation and type 1 and type 2 diabetes (136), in order to implement timely preventive measures.

There are significant differences in predisposing factors, clinical presentation, epidemiology and prognosis, as well as structural and electrophysiological differences, between men and women with atrial fibrillation (137). Regarding prognosis, it is suggested that female sex is associated with an increased risk of stroke, and this is reflected in the CHA_2DS_2-VASc score. Previous studies have shown conflicting results for the sex-specific mortality risk in atrial fibrillation, but a meta-analysis, which included 30 studies, showed that women have a 12%

higher relative mortality risk than men (138). Because of the conflicting results relating to the sex-specific prognostic differences in patients with atrial fibrillation and the lack of this information in an unselected population with concomitant atrial fibrillation and diabetes, further studies are needed to help offer sex-targeted care to patients with atrial fibrillation and diabetes and possibly improve outcomes.

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