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Glucose Abnormalities and Heart Failure

Epidemiological and therapeutic aspects

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Deyr fé,
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hveim er sér góðan getr

Hávamál, vers 76

Abstract

Background
The combination of heart failure and glucose abnormalities is seen with increasing frequency. The condition, which is characterised by low functional capacity and a high mortality, is very resource consuming. The link between glucose abnormalities and heart failure is complex. Improved knowledge is needed to describe the magnitude of the problem and to enable better risk stratification and patient management.

Aims
This thesis explores the relation between glucose abnormalities and heart failure from an epidemiological and a therapeutic perspective.

Studies I-III
The prevalence and incidence of glucose abnormalities and heart failure and their combination were studied in the Reykjavik Study, a large, population based cohort conducted 1967-1996. Cases were defined according to World Health Organization (WHO) criteria for type 2 diabetes mellitus/impaired glucose tolerance and the European Society of Cardiology (ESC) guidelines for heart failure. The overall prevalence of the combination of type 2 diabetes and heart failure was 0.5% in males and 0.4% in women while abnormal glucose regulation in combination with heart failure was found among 0.7% of men and 0.6% of women. The prevalence of glucose abnormalities and heart failure increased with age. The odds ratio of the association between type 2 diabetes and heart failure was 2.8 (95% CI: 2.2-3.6) and between abnormal glucose regulation and heart failure 1.7 (95% CI: 1.4-2.1). The incidence of heart failure, diabetes and abnormal glucose regulation increased with age. Body mass index and cholesterol were predictive factors for all three conditions in a multivariable model adjusting for cardiovascular risk factors and ischaemic heart disease. Moreover there was a linear association between increasing fasting glucose and incident abnormal glucose regulation or diabetes as well as with heart failure. There was a strong association between abnormal glucose regulation and heart failure (Hazard Ratio 1.8, CI: 1.5-2.3) and between diabetes and heart failure (HR 3.0, CI: 2.3-4.0). Abnormal glucose regulation, diabetes and heart failure were linked to an unfavorable vital prognosis even after adjustment for cardiovascular risk factors and ischaemic heart disease. The trend towards an unfavorable prognosis of the combination of glucometabolic perturbations and heart failure did, however, not reach statistical significance compared to the prognostic information by each of these conditions on their own.

Studies IV-V
The feasibility and safety of the administration of recombinant Glucagon Like Peptide-1 (rGLP-1) was studied in a pilot investigation in six patients with type 2 diabetes and heart failure of ischaemic origin. A continuous subcutaneous infusion of rGLP-1 was administered during three days. Blood samples, 2-dimensional echocardiograms including Tissue Doppler imaging and exercise tests were obtained prior to and at the end of the infusion. The pilot study demonstrated the safety and feasibility of rGLP-1 and indicated that favourable effects may be achieved as regards left ventricular function.
The metabolic modulator trimetazidine or placebo was added to conventional treatment in twenty patients with type 2 diabetes and heart failure of ischaemic origin in a double blind cross over study design. Trimetazidine improved left ventricular ejection fraction somewhat but there were no significant differences in myocardial tissue function measured by Tissue Doppler imaging.

Conclusion
The prevalence and incidence of glucose abnormalities and heart failure increases with increasing age. The prevalence of heart failure increases with worsening level of glucose abnormality. Glucose levels predict the occurrence of heart failure and there is a strong association between glucose abnormalities and heart failure.
Recombinant GLP-1 and trimetazidine seem to be safe to use in patients with ischaemic heart failure and diabetes. They did not improve the myocardial function significantly and further studies are needed before these metabolic modulators can be recommended in this patient group.

Contents

Abstract 5
Contents 6
List of original papers 8
List of abbreviations 9
Introduction 10
History and epidemiology 10
Heart failure and glucose abnormalities 11
Definition and classification of heart failure 11
Definition and classification of glucose abnormalities 11
Risk factors for heart failure and diabetes 12
Prevalence of heart failure and glucose abnormalities 12
Incidence of heart failure and glucose abnormalities 13
Prognostic implications of heart failure and diabetes 13
Pathogenetic considerations 15
Heart failure 15
Glucose abnormalities 16
Heart failure and diabetes 16
Management 17
Heart failure 17
Diabetes 18
Heart failure in the diabetic patient 18
GLP-1 19
Trimetazidine 19
Aims 20
Patients and methods 21
Studies I-III 21
Definitions 21
Patients and study protocol 21
Studies IV and V 23
Definitions 23
Patients and study protocols 23
Statistical analysis 24
Studies I-III 24
Study IV 24
Study V 25
Ethical considerations 25
Studies I-III 25
Studies IV-V 25

Results 26
Study I 26
Clinical data 26
Prevalence 26
Study II 27
Clinical data 27
Mortality 27
Morbidity 30
Study III 30
Clinical data 30
Incidence 31
Predictive factors 31
Study IV 31
Clinical data 31
Exercise test and echocardiography 32
Study V 33
Clinical data 33
Exercise test and echocardiography 33
General discussion 36
Epidemiology 36
Methods 36
Risk factors 36
Prevalence and incidence 37
Mortality and morbidity 38
The association of glucose abnormalities and heart failure 39
Treatment 40
Metabolic modulation 40
GLP-1 40
Trimetazidine 41
Future directions 42
Conclusions 43
Acknowledgements 44
References 46
Study I-V

List of Original Papers

This thesis is based on the following studies, which will be referred to by their Roman numerals.

I

Inga S Thrainsdottir, Thor Aspelund, Gudmundur Thorgeirsson, Vilmundur Gudnason, Thordur Hardarson, Klas Malmberg, Gunnar Sigurdsson, Lars Rydén.
The association between glucose abnormalities and heart failure in the population-based Reykjavík Study.
Diabetes Care 2005; 28: 612-616

II

IS Thrainsdottir, T Aspelund, T Hardarson, K Malmberg, G Sigurdsson, G Thorgeirsson, V Gudnason, L Rydén.
Glucose abnormalities and heart failure predict poor prognosis in the population based Reykjavík Study
European Journal of Cardiovascular Prevention and Rehabilitation 2005; in press

III

IS Thrainsdottir, T Aspelund, V Gudnason, K Malmberg, G Sigurdsson, G Thorgeirsson, T Hardarson, L Rydén.
Abnormal glucose levels - important risk factor for the development of heart failure. Experiences from the Reykjavík Study
In manuscript

IV

Inga Thrainsdottir, Klas Malmberg, Arne Olsson, Mark Gutniak, Lars Rydén.
Initial experience with GLP-1 treatment on metabolic control and myocardial function in patients with type 2 diabetes mellitus and heart failure.
Diabetes and Vascular Disease Research 2004; 1: 40-43.

V

Inga S. Thrainsdottir, Helene von Bibra, Klas Malmberg and Lars Rydén.
Effects of trimetazidine on left ventricular function in patients with type 2 diabetes and heart failure.
Journal of Cardiovascular Pharmacology 2004; 44: 101-108

List of Abbreviations

ACE	Angiotensin Converting Enzyme
ADA	American Diabetes Association
AHA	American Heart Association
ATP	Adenosine Tri Phosphate
BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Confidence Interval
CXR	Chest X-Ray
DPP-4	DiPeptidyl Peptidase-4
ECG	ElectroCardioGram
EF	Ejection Fraction
ESC	European Society of Cardiology
FFA	Free Fatty Acids
GLP-1	Glucagon Like Peptide-1
GLUT 4	GLUcose Transporter 4
HbA1c	Glycosylated haemoglobin A1c
HDL	High Density Lipoprotein
HR	Hazard Ratio
IHD	Ischaemic Heart Disease
IL-6	InterLeukin-6
LDL	Low Density Lipoprotein
MONICA	MONItoring of trends and determinants in CArdiovascular disease
NYHA	New York Heart Association
OGGT	Oral Glucose Tolerance Test
rGLP-1	recombinant Glucagon Like Peptide-1
TDI	Tissue Doppler Imaging
TNF-α	Tumor Necrosis Factor-alpha
WHO	World Health Organization
WMSI	Wall Motion Score Index
VLDL	Very Low Density Lipoprotein

Introduction

History and epidemiology

Ever since the 17th century attention has been paid to abnormal glucose levels in humans and its lethal consequences. Further research lead to the discovery of diabetes mellitus as a disease and to the detection of insulin, a discovery for which Frederick Banting and John Macleod were awarded the Nobel prize in 1923 [1]. Diabetes is classified into two major types, type 1 with no remaining insulin production and type 2 with predominantly insulin resistance and relative insulin deficiency. Type 2 diabetes is accounting for 80-90% of all cases. Impaired glucose regulation refers to a metabolic state intermediate between normal glucose homeostasis and diabetes and may be detected in the fasting state, impaired fasting glucose and post-prandially, impaired glucose tolerance. The prevalence of diabetes increases with age and is on average 4-5%. The prevalence is increasing across the world because of diet habits, physical inactivity, central obesity and aging populations. Diabetes increases the risk for cardiovascular disease and causes a high health care burden and dismal prognosis [2-5].

The potential existence of a relation between diabetes and heart failure is not a new finding. In 1954 the Danish professor Knud Lundbæk published an article on clinically important complications in patients with diabetes realizing that heart disease was common in patients with diabetes, indeed present in two thirds of elderly subjects. He was the first to suggest the presence of a diabetes specific cardiomyopathy [6, 7]. Twenty years later Rubler et al published supporting data, concluding that myocardial disease seemed to be a complication to the diabetic state by itself and not merely caused by coronary artery disease [8]. Shortly thereafter the Framingham study presented epidemiological evidence for a strong relation between heart failure and diabetes. The latter study clearly indicated that the relation between diabetes and heart failure was not only due to traditional risk factors for coronary heart disease but also involved other mechanisms [9].

The prevalence of heart failure increases in Western Societies, essentially due to ageing of the populations but also because of increased survival in ischemic heart disease, above all following myocardial infarction [10]. There are many known causes of chronic heart failure, including hypertension, coronary artery disease, valvular dysfunction, arrhythmias, anaemia, renal failure and thyroid dysfunction [10-14]. Risk factors in conjunction with heart failure include age, electro-cardiographic (ECG) signs of left ventricular hypertrophy, cardiomegaly on chest x-ray (CXR), heart rate and hypertension, decreased vital capacity, diabetes, previous myocardial infarction and valvular disease. The Framingham study used these risk factors to construct a multivariate risk formula to identify high-risk candidates for heart failure [15]. Presently ischaemic heart disease is the leading cause of heart failure in industrialised societies with diabetes as a rapidly emerging risk factor [13].

Table 1. New York Heart Association (NYHA) classification of heart failure.

NYHA Class I
No limitation of physical activities; patients without symptoms during ordinary activities.

NYHA Class II
Slight to mild limitation of physical activity; patients comfortable at rest and mild exertion.

NYHA Class III
Marked limitation of activity; patients comfortable only at rest.

NYHA Class IV
Confined to a complete rest in a bed or a chair; patients symptomatic at any physical activity and symptoms present already at rest.

Poor glucometabolic control contributes to the development of heart failure as reflected by an increase in glycosylated haemoglobin A_{1c} (HbA_{1c}) and increased risk of developing heart failure [16]. In an epidemiological study of an elderly Italian cohort 9.5% of the participants had heart failure and 14.7% diabetes. Interestingly the prevalence of diabetes among subjects with heart failure was as high as almost 30%. The association was strengthened during follow up, indicating that heart failure predicted the appearance of diabetes [17].

In summary there is a strong link between the existence of heart failure and diabetes and both conditions are becoming increasingly more common. The links between these disorders are complex and not yet fully explored. This obviates the need for further studies on this combination.

Heart failure and glucose abnormalities

Definition and classification of heart failure

The state of the art diagnosis of heart failure is based on a combination of clinical symptoms of heart failure and signs of myocardial dysfunction, most typically detected by echocardiography [10]. In clinical practice heart failure is commonly divided into systolic and diastolic myocardial dysfunction with systolic dysfunction representing an impaired capacity to eject blood from the left ventricle and diastolic dysfunction an impaired ventricular filling due to relaxation abnormalities [10]. The main clinical classification of heart failure is according to the New York Heart Association as presented in table 1. This classification is used for all patients with heart failure irrespective if seen in a hospital or outpatient setting and irrespective of etiology.

Definition and classificiation of glucose abnormalities

Diabetes and other glucose abnormalities are a group of metabolic disorders characterized by hyperglycemia due to defects in insulin secretion, insulin action or both. Diabetes is associated with damage, dysfunction and failure of various organs [2, 18]. This disease is, according to aetiology, classified as Type 1 or Type 2. Type 1 diabetes comprises patients suffering pancreatic islet β-cell destruction and these patients are prone to develop ketoacidosis. Diabetes type 2 is the most common form of diabetes, around 90%. It is caused by deficient insulin secretion almost always linked to decreased insulin sensitivity. Impaired glucose tolerance is defined as a condition in which glucose values following a glucose load increase above the normal range but remain below the range set for diabetes, while impaired fasting glucose is a state in which the fasting glucose values are above the normal range but below the diagnostic criteria for diabetes. The diagnostic criteria for different categories of glucose regulation are presented in table 2. The metabolic syndrome is an entity that has been defined in various ways [19, 20] combining

Table 2. Criteria for classification of glucose abnormalities according to WHO 1999 [19] and ADA 2004 [20].

Glucose category	Source	Classification criteria: plasma glucose in mmol/L		
		Fasting	Post load*	Casual
Normal glucose regulation	ADA 2004 WHO 1999	<5.6 <6.1	<7.8	-
Impaired fasting glucose (8 hours fasting)	ADA 2004 WHO 1999	5.6-6.9 6.1-6.9	-	-
Impaired glucose tolerance	ADA 2004 WHO 1999	-	7.8-11.0 7.8-11.0	-
Diabetes mellitus	ADA 2004 WHO 1999	≥ 7.0 ≥ 7.0	≥ 11.1 ≥ 11.1	≥ 11.1

different cardiovascular risk factors including abnormalities in the glucose homeostasis. According to the World Health Organization the diagnosis of the metabolic syndrome requires the presence of at least two of the following criteria: abnormal glucose tolerance or diabetes mellitus together with increased insulin resistance, blood pressure ≥140/90, plasma triglycerides ≥1.7 mmol/L and/or high density lipoprotein (HDL) cholesterol <1.0 mmol/L, central obesity (waist to hip ratio >0.9 in men and >0.85 in women) and/or body mass index (BMI) >30 kg/m^2 or microalbuminuria [19].

Risk factors for heart failure and diabetes

Cardiovascular disease The traditional risk factors for cardiovascular disease are well established. The most important are a family history, smoking, abnormal blood lipids, hypertension, diabetes, obesity and socio-economic factors [5].

Heart failure There are several known risk factors for heart failure, many of which by necessity are similar to those for cardiovascular disease, such as male gender, smoking, coronary artery disease, diabetes, hypertension, overweight, physical inactivity and valvular heart disease [21, 22].

Type 2 diabetes Risk factors for type 2 diabetes are family history, age, overweight, an increased waist-hip ratio and a sedentary life-style [17, 23, 24]. The morbidity increases progressively with the number of existing risk factors [25].

Particular risk factors for coronary artery disease in type 2 diabetes are lipid perturbations including small, dense easily oxidized low density lipoprotein (LDL) particles, low HDL cholesterol and increased triglycerides. Moreover poor glucometabolic control observed as high fasting plasma glucose and elevated HbA_{1c} contribute [26]. Hypertension is another important factor. The Reykjavík Study showed a strong relation between fasting and post glucose load glucose levels and the risk for hypertension, even after adjustment for age, BMI and weight gain which is interesting since hypertension is one of the main risk factors for heart failure [27, 28]. Patients with diabetes and heart failure have more ischaemic heart disease (IHD), increased systolic blood pressure, lower diastolic blood pressure and a higher HbA_{1c} than their non-diabetic counterparts [29]. This demonstrates that there are many mutual risk factors for heart failure and glucose abnormalities.

Prevalence of heart failure and glucose abnormalities

Heart failure The prevalence of heart failure varies somewhat in different studies, partly due to differences in the definition of this disease [10]. A heart failure diagnosis should, according to recent recommendations, be supported by evidence of systolic dysfunction on echocardiography. This demand may be difficult to fulfill in epidemiological studies. Modern echocardiographic techniques did not exist when several of the studies that still serve as important sources of information, were conducted [9, 30]. The prevalence of heart failure has been estimated to be 0.6-6.2% in Swedish men with an increase by age. This is similar to the overall prevalence of heart failure among both genders in the Rotterdam population [31, 32]. The prevalence of heart failure was 1-10% in outpatient populations [33]. It increases considerably when looking at elderly populations as exemplified by the Italian Campania study, in which the prevalence was 9.5%, once more underlining the impact of age [17].

Diabetes mellitus It has been estimated that up to 30% of patients with diabetes are undetected [20]. When screening a Belgian outpatient population with one known cardiovascular risk factor diabetes was detected in 11% and an additional proportion of 3% had impaired glucose tolerance [34]. The prevalence of diabetes was 7.8% in Swedish men and 5.1% in women aged 35-79 years with similar proportions reported from a Finnish middle-aged population [35-36]. The prevalence of diabetes may be considerably higher in selected high risk populations such as patients admitted to hospital because of acute coronary syndromes (31%) [37].

Considerably less is known about the prevalence

of the combination of diabetes and heart failure. Findings in previous studies have been put together in table 3. Based on Framingham data Rutter et al [38] noted that the heart is prone to changes in the form of increased left ventricular mass and wall thickness with worsening glucose tolerance. Kannel et al [9] and Gustafson et al [39] reported on the role of diabetes in heart failure from a general and a hospitalized population respectively. Their findings indicated a strong association between heart failure and diabetes. Iribarren, Bertoni and Nichols and their colleagues focused on the role of heart failure in patients with diabetes [29, 40, 41]. They noted that the prevalence of heart failure varied between 1.9 and 22.3%. Finally Amato et al found a strong association between diabetes and heart failure in a population of elderly people [17].

Incidence of heart failure and glucose abnormalities

Heart failure Recent results from the Framingham study showed a declining incidence of heart failure during the last five decades [42]. These data are unfortunately not supported by other findings [43]. On the contrary it seems that hospital admissions for heart failure are constantly increasing resulting in higher health care expenditures for patients with this diagnosis [44]. Among British outpatients the incidence of heart failure has been reported to be 4.4/1000 person-years in men and 3.9/1000 in women, rising with age in both genders [45]. The incidence in Finland is similar among men, 4.0/1000 person-years, but lower in women 1.0/1000 person-years [46].

Diabetes mellitus The age-standardized annual incidence of diabetes is rather uniform in several European countries**.** It is in the magnitude of 4.1/1000 and 3.8/1000 for Swedish men and women respectively. Corresponding numbers from the Netherlands are 2.2/1000 person-years and 2.3/1000 person-years in men and women respectively [35, 47]. However, when turning to an elderly population, as in the Italian Campania study, the incidence of type 2 diabetes was higher, 6.1% per year. This is somewhat different from the observation in the Netherlands where the incidence decreased in the oldest age-group [17, 47].

Some information is available on the incidence of the combination of diabetes and heart failure. In the Framingham study the incidence of heart failure was twice that among males and five times higher in females with diabetes during 18 years of follow-up compared to patients free from diabetes. The excessive risk of heart failure remained high even after the exclusion of patients with prior coronary heart disease. Women with diabetes had twice the risk of heart failure compared to men with diabetes [9].

Prognostic implications of heart failure and diabetes

Heart failure During the past 30 years mortality from coronary heart disease has declined markedly among patients free from diabetes. This decline has been substantially lower in men and not at all seen in women with diabetes [48]. In the presence of heart failure the prognosis becomes more deleterious. In an English population one month survival was 81% after incident heart failure, declining to 57% after 18 months [13, 49]. The annual mortality in a study of patients hospitalized for heart failure was 10-20% with mild-moderate and 40-60% with severe symptoms [33]. The mortality in an elderly population with heart failure recruited in Rotterdam was 47% during six years of follow up. This is twice that of persons without heart failure [50]. In a comparable Italian study the mortality rate was 21.3% after three years [17]. Thus heart failure is a malignant disease irrespective of the underlying reason for myocardial dysfunction. Recent reports have, however, been somewhat more encouraging. A 50 year follow up of Framingham data indicates that heart failure survival has started to improve [42]. This observation is supported by a report based on the Swedish hospital discharge registry [51]. These promising data have, however, no back up in other studies looking at time trends in mortality and morbidity in relation to heart failure [43].

Diabetes mellitus Cardiovascular mortality in men with diabetes lies between the cardiovascular mortality for men with angina and myocardial infarction [52]. Cardiovascular

Table 3. Comparison of prevalence, incidence and prediction of heart failure and diabetes in general populations and among patients

		HF in patients with diabetes			**Diabetes patients with heart failure**	
Name of study	Campania	Medicare sample	Kaiser Permantente	Kaiser Permantente	DIAMOND	Framingham
Author [ref no]	Amato et al [17]	Bertoni et al [41]	Iribarren et al [40]	Nichols et al [143]	Gustafsson et al [39]	Kannel et al [9]
Number of participants	1339	151738	48858	9591	5491	5209
Follow up time (years)	3	5	2.2	2.5	5-8	18
Period	<1997	1994-9	1995-7	<1997	1993-2003	1949-
Age	74 (mean) (all>65)	73-76 (all>65)	58 (mean)	-	52-86, (mean 73)	30-62
HF prevalence	9.5 %	22.3%	1.9%	11.8% in diabetics, 4.5% in controls	-	-
DM prevalence	14.7%	-	-	-	14.7 % (type2)	-
DM and HF association	OR 2.0 CI (1.6-2.5)	-	-	-	-	RR men 2.4 women 5.1
DM incidence	9.6%/year in heart failure patients 6.1%/year in controls	-	-	-	-	-
HF incidence	-	12.6/100 PY	-	3.3/100 PY in diabetics, 1.5/100 PY in controls	-	17.5/1000 PY among men, 18.5/1000 PY among women In diabetics 9/1000 PY in men, 14/1000 PY in women
DM predictive factors	Heart failure OR 1.4 (1.1-1.8)	-	-	-	-	-
HF predictive factors	BMI, waist-hip ratio	Men, caucasians, IHD, hypertension, stroke, PVD, nephropathy, retinopathy, neuropathy	-	Age, female DM duration, insulin, IHD, creatinine, glucose	-	DM, males
DM mortality	-	-	-	-	RR 1.5 in diabetes patients	-
Other endpoint	-	-	1% increase in HbA1c => increased risk of HF by 8%	-	-	-

PY: person years

disease is the most prevalent complication of diabetes. In the United States it has been estimated that 77% of all hospitalizations for chronic complications of diabetes are attributable to cardiovascular disease [53]. Type 2 diabetes doubles the risk of death from coronary heart disease (CHD). Type 2 diabetes, diagnosed at the age of 55 years, reduced life expectancy about five years [54]. This makes mortality from cardiovascular disease in diabetic patients without previous myocardial infarction similar to the mortality in nondiabetic patients with a history of myocardial infarction [55]. The prognosis of patients with diabetes becomes even worse in the presence of heart failure [56-59]. In the first DIGAMI study, performed in diabetic patients with acute myocardial infarction, heart failure was the most common reason for morbidity and mortality, accounting for 66% of the total mortality during the first year of follow up [60].

A worrying observation is that cardiovascular mortality has declined considerably in persons free from diabetes while the opposite has been observed among those with diabetes. Comparing the time periods 1971-1975 with the period 1982-1984 mortality in ischemic heart disease decreased by 36% in men and 27% in women without diabetes. In contrast the mortality reduction was only 13% in men with diabetes and even worse, it increased by 23% among diabetic women [48]. A recent study on 1241 patients revealed that diabetes is a serious prognostic factor for cardiovascular mortality in patients with left ventricular dysfunction due to ischaemic heart disease. This study did, however, not show any conclusive impact of diabetes on the prognosis of non-ischaemic left ventricular dysfunction [61].

The relationship between plasma glucose and mortality has been elucidated in several studies. According to UKPDS a 1% reduction in HbA1c is associated with a reduction of myocardial infarction by 14% and heart failure by 16%. In this study the prognosis improved with a decrease in HbA1c without any threshold or observed upper limit [62]. In the DECODE study a two hour post load glucose was a better predictor of mortality than fasting blood glucose [63]. This may perhaps be seen as an indicator of the importance of postprandial hyperglycemia and the potentially serious implication of impaired glucose tolerance.

Pathogenetic considerations

Heart failure

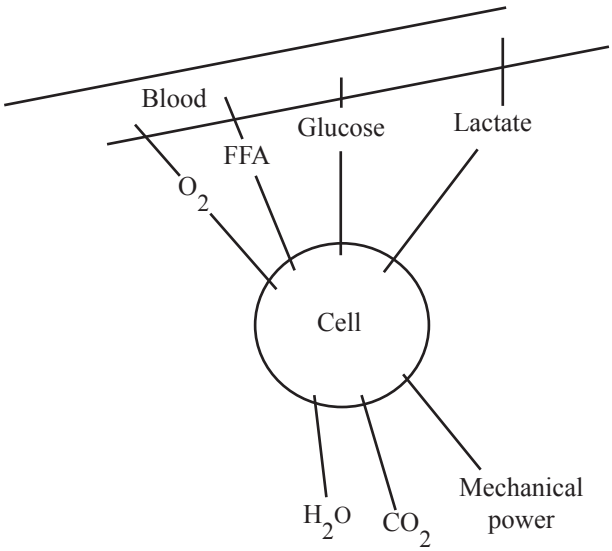
Heart failure is a clinical syndrome originally induced by myocardial damage but subsequently influenced by the induction of an untoward neurohormonal response. Thus norepinephrine, angiotensin II, endothelin and aldosterone have been linked to the vicious cycle of myocardial remodelling, which unopposed will cause successive deterioration of myocardial performance [64]. Metabolic conditions play a significant role in cardiac adaptation and remodelling. This leads to an increase of myosin heavy chain beta, altered troponin-T molecules, dimished storage of creatinine phosphatases and decreased sarcoplasmatic ATP-ase activity, which may result in myocyte hypertrophy associated with impaired contractile function and less effective energy supply [65, 66]. The dominant pathway for myocardial energy production is beta-oxidation of free fatty acids but the myocardium is also dependent on glucose oxidation. When the heart is subjected to ischemic stress or exposed to sustained enhancement of intraventricular pressure it tends to change towards a more dominant glucose oxidation [67]. This may be counteracted by a reduction of the glucose transporter 4 (GLUT4) protein concentration, which becomes reduced in heart failure, hampering glucose transport over the cell membrane. At the same time the heart is exposed to increased concentrations of free fatty acids (FFA) concentrations, released via stress influenced by an increased sympathetic tone [68]. It has been proposed that prolonged intracellular accumulation of FFA and its metabolites may cause myocardial dysfunction [69].
Besides these mechanisms alterations in gene expression and inflammatory activity have been suggested to cause metabolic and mechanical disturbances in heart failure [70-73]. All nucleated cells, including the cardiomyocyte,

can produce proinflammatory cytokines as a response to injury such as myocardial infarction, myocarditis or when the heart fails. Both tumor necrosing factor-α (TNF-α) and interleukin-6 (IL-6) levels increase proportionally to the severity and duration of heart failure [70, 71]. It has been assumed that this cytokine release may trigger a cascade of events which lead to myocardial structural alterations further deteriorating the clinical expression of heart failure.

Glucose abnormalities

Abnormalities in insulin secretion and/or insulin resistance are the causes of glucose defects which induce impaired glucose tolerance and type 2 diabetes [74]. Normally the first phase insulin secretion suppresses the endogenous glucose production [75] but in a diseased state a decline in insulin-stimulated glucose disposal and the acute insulin secretory response is associated with the development of impaired glucose tolerance [76]. Insulin binds to insulin receptors on sensitive tissues among them skeletal muscle and adipose tissue. Insulin has rapid and direct effects on hepatocytes inhibiting the glycogenolysis and gluconeogenesis. The anti-lipolytic effect of insulin in adipose tissue causes a rapid decrease in the delivery of non-esterified fatty acids to the liver and inhibition of endogenous glucose production. The early insulin response can also prime insulin sensitive tissues to increase the efficiency of glucose disposal [77].

Insulin deficiency or reduced insulin sensitivity causes hyperglycemia with several untoward effects, among them overproduction of super-oxide by the mitochondrial electron-transport chain considered to be a key harmful agent, activating the polyol pathway, and stimulating the production of advanced glycosylation end products, protein kinase C and the hexosamine pathway flux. This leads to a slowing of glycolysis, electron transport and a lower adenosine triphosphate (ATP) formation. These events are considered to contribute to the micro- and macrovascular complications that characterises diabetes [78, 79].



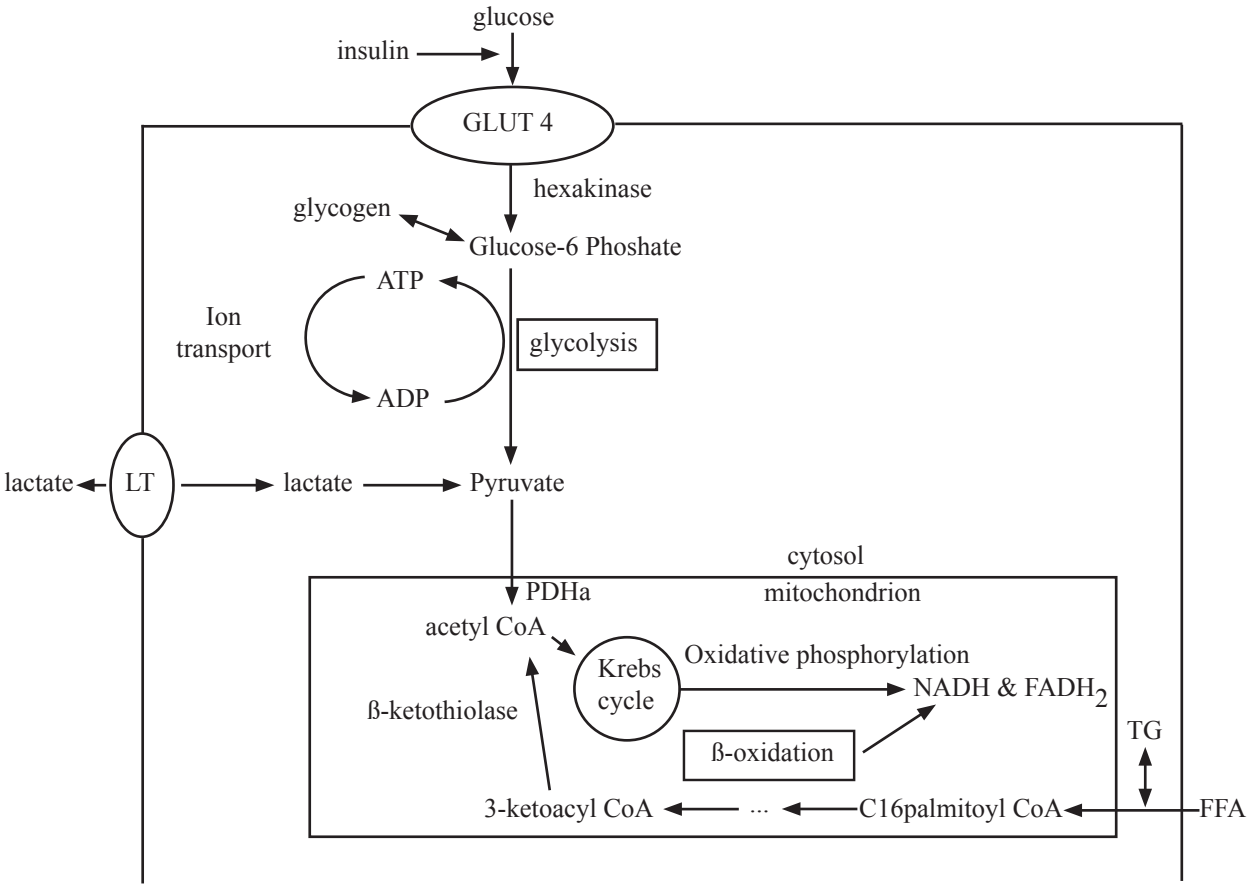
O_2: oxygen
FFA: Free Fatty Acids
H_20: water
CO_2: carbon dioxide

Figure 1a. Main substances needed for myocardial energy production

Skeletal muscles may be resistant of insulin action thus decreasing the utilization of glucose and FFA. The pancreas compensates by producing more insulin, yielding hyperinsulinemia. Not only postprandial hyperglycemia but also postprandial lipidemia is seen in subjects with diabetes. The levels of adipose tissue derived FFA are increased which lead to overproduction of triglyceride-rich lipoprotein particles, including VLDL and a reciprocal decrease in HDL. The adipocytes may also produce cytokines such as TNF-α which cause inflammation and stimulate C-reactive protein production from the liver and an increase in inhibitor of fibrinolysis plasminogen activator inhibitor-1 [80].

Heart failure and diabetes

The main myocardial energy production is based on beta-oxidation of FFA (70%) with a lesser contribution from glucose oxidation (30%) and lactate as schematically presented in figure 1a and b. Free fatty acids are produced by lipolysis of endogenous cardiac triglycerides stores or exogenous sources in the blood. If oxygen supply is sufficient, FFA oxidation is an effective supplier of energy in the form of ATP. In conditions with limited oxygen availability glucose oxidation will provide more energy per



LT: lactate transporter,
GLUT: glucose transporter

Figure 1b. Schematic overview of the myocardial cell metabolism

mole oxygen and thus support more work than fatty acids [81]. Glucose utilization for energy production is substantially lower, about 10%, in diabetes. The shift to an even more pronounced beta-oxidation of FFA causes a higher oxygen utilization than under normal circumstances [82].

The major restriction to glucose utilization in the diabetic heart is the slow rate of glucose transport across the sarcolemmal membrane in the myocardium [83, 84]. The impaired glucose oxidation in the diabetic heart can also result from a decreased rate of phosphorylation of glucose which can subsequently limit the entry of glucose into the cell. The depressed phosphorylation is triggered by the increased metabolism of FFA [85]. Insulin deficiency enhances lipolysis thereby increasing circulating FFA [82]. Diabetic patients are also known to have increased risk for other disturbances such as reduced myocardial blood flow and blunted hyperkinetic response to myocardial ischemia resulting in diminished myocardial function [86- 89]. Heart failure is indeed an insulin resistant state with an increased release of non-esterified fatty acids which are taken up in muscular tissue and down regulate glucose uptake and utilization [90]. The high levels of inflammatory cytokines in heart failure patients may also enhance insulin resistance [90, 91].

Management

Heart failure

Evidence based treatment of heart failure relies on a combination of angiotensin converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARB), β-blockers, diuretics and aldosterone antagonists [10]. ACE inhibitors, angiotensin receptor blockers and β-blockers reduce mortality and improve symptoms in moderate to severe heart failure with and without diabetes [92-95]. Diuretics are mandatory for

symptomatic treatment due to fluid overload but should not be used in excess since they induce neuro-hormonal activation [96]. The addition of aldosterone antagonists is indicated in severe forms of heart failure and may then improve longevity [97]. Many patients are, however, still symptomatic and, although improved, the vital prognosis remains unfavorable despite the best available pharmacological treatment. A search for novel treatment modalities is therefore still ongoing. One of these is metabolic modulation. Compounds used for such treatment influence the disturbed metabolic pathways in heart failure which are thought to be of a particular importance in patients with diabetes [67]. Attention has been paid to compounds that shift energy production from beta-oxidation of FFA towards the energetically more efficient glucose oxidation under such conditions as in myocardial ischaemia and heart failure [98, 99]. Examples of such drugs are trimetazidine, ranolazine, etomoxir and dichloroacetate.

Various techniques have been used to study the efficacy of pharmacological treatment in heart failure. Among them are general feeling of well being often assessed by means of different questionnaires and tests of exercise tolerance. Two-dimensional echocardiography is the most commonly applied technique for investigating myocardial function [100-103]. A relatively newly developed technique, Tissue Doppler imaging (TDI) assesses myocardial function in different myocardial segments. This technique is useful for diagnosing left ventricular dysfunction even before any symptoms or signs of heart failure appear in diabetic subjects [104-106].

Diabetes

According to the most recent European Guidelines on Cardiovascular Disease Prevention the target levels for the management of patients with diabetes should be HbA_{1c} ≤6.1%, fasting plasma glucose ≤6.0 mmol/L, blood pressure <130/80 mmHg, total cholesterol <4.5 mmol/L and LDL cholesterol <2.5 mmol/L. Although pharmacological tools are most frequently needed, treatment should always be based on dietary advice and recommendations of increased physical activity. Recommended glucose lowering treatment includes oral drugs such as sulphonylurea or biguanide or their combination and insulin [107]. Target levels for glucose and HbA_{1c} differ between European and American recommendations. The latter suggest that HbA_{1c} should be kept <7.0%, preprandial plasma glucose between 5.0-7.2 mmol/L and postprandial plasma glucose <10.0 mmol/L [20, 108]. Interestingly the scientific evidence for the recommendations on the above mentioned levels of plasma glucose and HbA_{1c} seem sparse if any, at least in type 2 diabetes.

Heart failure in the diabetic patient

Treatment of heart failure in patients with diabetes is not specifically addressed in the American Diabetes Association (ADA) and the American Heart Association (AHA) recommendations apart from comments on metformin which is recommended to be used with caution. Moreover and due to a certain risk for fluid retention use of thiazolidinediones in diabetes patients in New York Heart Associatio (NYHA) class III-IV is considered contraindicated [20, 109]. Otherwise there are no guidelines that specifically deal with diabetes and heart failure. Most data on various drugs recommended for heart failure treatment favour a proportionately similar efficacy in patients with and without diabetes. Due to a higher absolute risk in patients with diabetes the numbers needed to treat to avoid mortality and morbidity becomes less.

Unfortunately there are no studies specifically looking at the large group of patients with diabetes and heart failure. Present evidence is therefore based on subgroup analysis of patients with diabetes contained in various large clinical heart failure trials. Diabetes may have been less well defined and glucose lowering treatment not standardised in such trials making available evidence somewhat vague. No large clinical trials have so far addressed the outcome of metabolically oriented treatment. Future studies are needed to reveal if intense metabolic control and the introduction of metabolic modulation may improve the symptomatology and prognosis of patients with the combination of heart failure and diabetes.

Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is an insulinotropic hormone which under normal circumstances is produced in entero-glucagon producing L cells in the ileum and colon/rectum and secreted in response to a meal. It stimulates GLP-1 receptors on pancreatic δ and α islet cells, increasing the secretion of insulin at the same time suppressing the production of glucagon. This results in a lowering of blood glucose [110, 111]. It only acts in the presence of glucose levels above the normal range because the insulinotropic activity of GLP-1 is glucose dependent and co-regulated by glycolysis-produced ATP. Consequently the risk of inducing hypoglycaemia is considered minimal potentially making this peptide an ideal agent for the treatment of diabetes in particular in patients who are sensitive to the effects of hypoglycaemia [112, 113]. The duration of action is short and normal basal values are reached after 90-120 minutes [114]. A disadvantage with rGLP-1 is that this compound delays gastric emptying which may lead to nausea. Another concern is the short half-life, necessitating continuous parenteral administration, a drawback in clinical practice [115]. Recombinant GLP-1 improves glycemic control in diabetic subjects by enhancing the glucose-dependent pancreatic insulin secretion in response to food, inhibiting glucagon secretion, delaying gastric emptying and promoting early satiety [116].

The failing myocardium has a preference for glucose as metabolic substrate. In a study of 35 dogs with pacing induced heart failure myocardial performance was compared in animals receiving a rGLP-1 infusion and saline. Recombinant GLP-1 was associated with an increase in left ventricular contractility, stroke volume and cardiac output and a significant decrease in left ventricular end-diastolic pressure, heart rate and systemic vascular resistance. In addition rGLP-1 caused an increase in myocardial insulin sensitivity [117]. Based on these findings it is challenging to test if rGLP-1 infusion is safe in patients with diabetes and heart failure and to investigate the effect of this compound on myocardial function.

Trimetazidine

Trimetazidine is a metabolic agent with anti-ischaemic properties operating independently of any hemodynamic changes. It is suggested to reduce beta-oxidation of FFA, at the mitochondrial level, by selectively and partially inhibiting the activity of 3-ketoacyl-coenzyme-A-thiolase thereby facilitating energy production via the glycolytic pathway. This has caused this compound to be labeled a myocardial metabolic modulator with the capacity to shift the energy production from beta-oxidation of free fatty acids towards glucose oxidation. The potential benefit is that the energy production becomes less oxygen requiring [118]. Glucose utilisation is hampered in the diabetic patient, particularly during periods of stress when it is shifted almost exclusively towards beta-oxidation [82]. Thus it is of interest to study whether trimetazidine may have a beneficial influence in such patients.

In summary it has been suggested that intensive metabolic treatment or metabolic modulation may improve the prognosis in patients with diabetic cardiomyopathy [98, 108]. This assumption does, however, need confirmation in clinical trials.

Aims

To study the prevalence of glucose abnormalities and heart failure and their combination and the strength of the association of these disorders in a general population (Study I).

To determine the prognosis of subjects with glucose abnormalities and heart failure and to test if the combination of these conditions adversely affects the subsequent prognosis (Study II).

To study the incidence and prognostic factors of diabetes, abnormal glucose regulation and heart failure and to identify if there is a relation between these diseases beyond the presence of ischaemic heart disease (Study III).

To assess the feasibility and safety of three days infusion of recombinant GLP-1 in an open observational study in six patients with type 2 diabetes and heart failure (Study IV).

To assess the effect of trimetazidine on diastolic and systolic myocardial function in patients with type 2 diabetes and heart failure due to ischaemic heart disease (Study V).

Patients and Methods

Studies I - III

Definitions

Heart failure (HF) was defined according to the European Society of Cardiology guidelines as the combination of at least two symptoms, dyspnea, tiredness or ankle oedema, and one objective evidence of cardiac engagement as disclosed by ECG (Q-wave myocardial infarction according to MONICA criteria, left bundle branch block or left ventricular hypertrophy) or chest x-ray (pulmonary congestion, cardiomegaly or left ventricular enlargement) [10, 119]. Some cases were found by screening hospital records for participants with symptoms of heart failure but without any signs recorded in the Reykjavík Study database. They were accepted if they had a heart failure diagnosis and signs of heart disease as revealed by echocardiography (ejection fraction ≤40%), chest x-ray or ECG as described.

Glucose abnormalities were defined based on information from the questionnaire as previously or newly diagnosed type 2 diabetes or abnormal glucose regulation based on an abnormal oral glucose tolerance test (OGTT) or elevated fasting serum glucose. Each participant underwent an OGTT (50g glucose in 250 ml water). Blood glucose (mg/dl) was determined, in the beginning by means of a chemical method subsequently changed to a hexokinase enzymatic method, before (fasting) and 1.5 hours after the glucose load. Following a protocol amendment in 1990, classification of the glucometabolic state was based on fasting serum glucose only [120].

Glucometabolic abnormalities were categorized as:
type 2 diabetes mellitus fasting serum glucose ≥7.0 mmol/L (≥126 mg/dl) or OGTT serum glucose ≥11.1 mmol/L (≥200 mg/dl)
or
abnormal glucose regulation (impaired glucose tolerance or impaired fasting glucose); fasting serum glucose 6.1- 6.9 mmol/L (110-126 mg/dl) or OGTT serum glucose 7.8-11.0 mmol/L (140-200 mg/dl).

Myocardial infarction was defined according to the MONICA criteria [121]:
a) definite ECG changes (Minnesota codes 1:1:1-1:2:5 and 1:2:7) or b) symptoms typical or atypical or inadequately described, together with probable ECG changes and abnormal enzymes (elevation ≥double the upper normal limit) or c) typical symptoms and abnormal enzymes with ischaemic or non-codable ECG or d) coronary occlusion at necropsy and/or fresh myocardial infarction or e) typical symptoms who's ECG and enzyme results do not place them in above mentioned categories and in whom there is not good evidence for another disease/cause of death

Ischaemic heart disease was defined as a history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery or angina pectoris according to Rose questionnaire, noted at the first visit or during systematic check against hospital records. The definition of angina pectoris was a history of a chest pain located in the sternal and the left anterior areas or in the left arm when walking uphill or hurrying, with relief within 10 minutes following cessation of exertion [122].

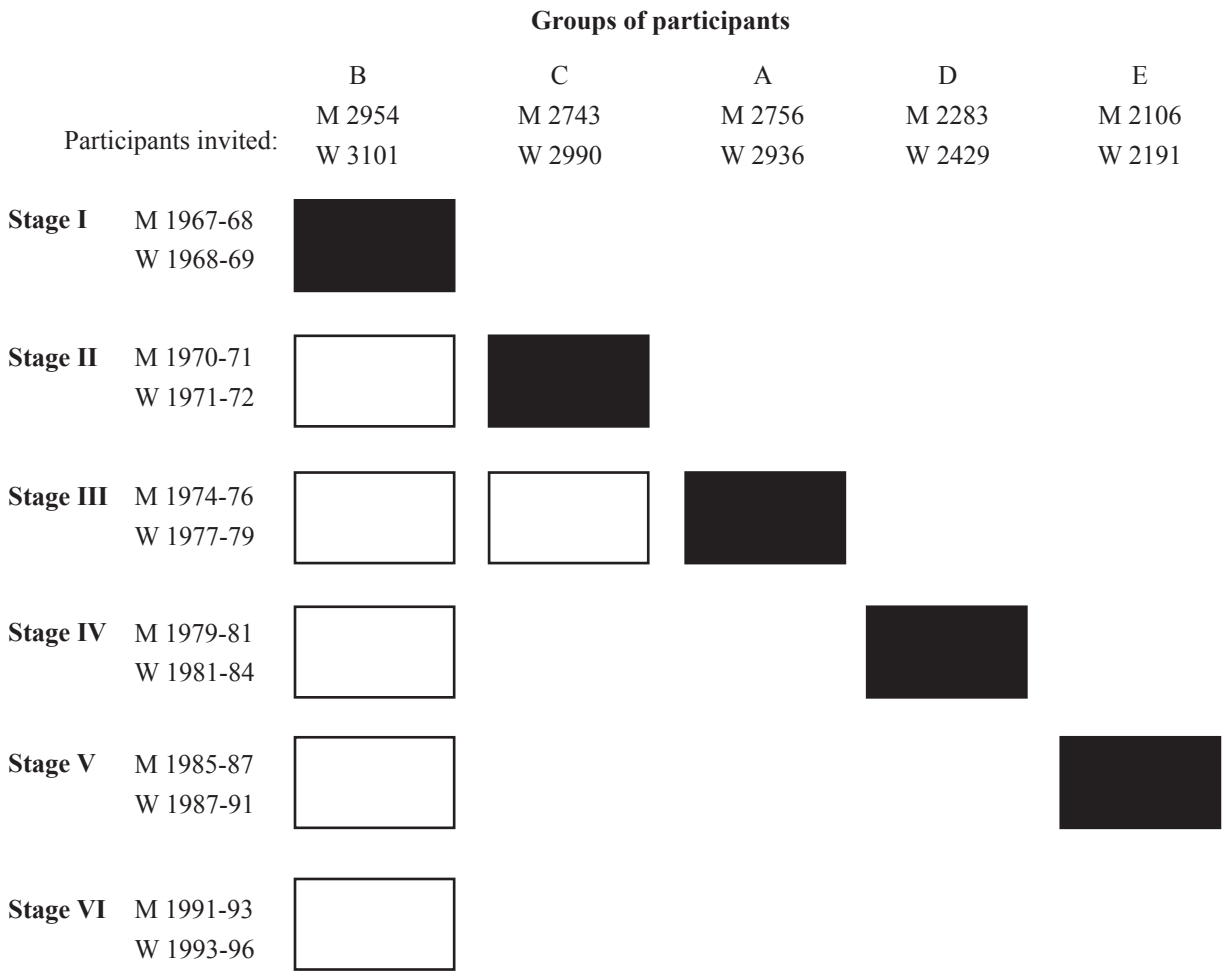
Patients and study protocol

The Reykjavík Study, a prospective population based cohort study was conducted 1967-1996. It recruited 19381 participants from the Reykjavík area aged 33-84 years, who were followed until 2002 [30, 123]. The total study population composed the study groups in the prevalence and prognosis studies (I and II).
People in two of the original study groups participated more than once in the Reykjavík Study (Figure 2; groups B and C) and these 7177 participants, out of whom 3270 (46%)

were females were the basis for the incidence study (III). The participation rate and loss to follow up are shown in Figure 3.

Every attendant to the Reykjavík Study was seen at two visits. During the first of these, baseline characteristics were registered based on a standardized questionnaire regarding current and previous health, social conditions and education [30, 119]. Information was collected on family history, risk factors for coronary artery disease, previous diseases, current medications, height, weight, blood pressure and laboratory examinations together with an ECG and a CXR [123, 124]. During the second visit a medical examination was performed, the blood pressure measurement was repeated and appropriate diagnostic codes for each participant were determined by the examining physician.

For the purpose of the current studies, all cause and cardiovascular mortality and morbidity in the form of new myocardial infarctions were registered from the date of the first study visit until January 1st 2002. Mortality information was based on the complete registry of all deaths in the Icelandic National Roster in which mortality causes were defined according to International Classification of Diseases versions 9 and 10 [125, 126]. Cardiovascular mortality was defined as deaths caused by coronary artery disease, heart failure, sudden death and stroke. The participants were divided into groups according to their glucose and heart failure status with participants free from any of these conditions serving as controls (group 1). Case groups



Black boxes: first visit
White boxes: consequent visits

Figure 2. Study plan of the Reykjavík Study, participants were divided into five groups which were invited to participate according to the figure at six different stages between 1967-1996. (M: men, W: women)

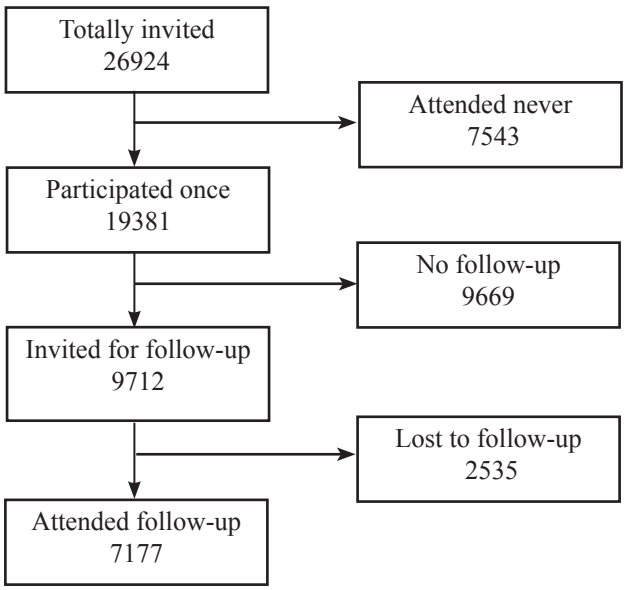


Figure 3. Flow chart of the number of participants in the Reykjavík Study.

were participants with 2) abnormal glucose regulation, 3) diabetes, 4) heart failure, 5) abnormal glucose regulation and heart failure and 6) diabetes and heart failure.

Studies IV and V

Definitions

Heart failure was defined as symptoms of heart failure in NYHA class II-III and an ejection fraction ≤40% measured by echocardiography. The underlying reason for heart failure was angiographically verified coronary artery disease, a documented history of previous myocardial infarction or an exercise test indicating myocardial ischemia.

Type 2 diabetes defined according to current criteria for diabetes from WHO or the American Diabetes Association [19, 127] or currently treated for diabetes.

Patients and study protocol

Study IV

Study IV was designed as an open, pilot investigation in six hospitalised patients with type 2 diabetes and stable heart failure. The rGLP-1 was administered as a continuous, subcutaneous infusion over a period of 72 hours following an initial echocardiographic examination including TDI and blood sampling. The dose of rGLP-1 was 4 pmol/kg/min which could be lowered to 3 pmol/kg/min in case of nausea. During the last hours of the rGLP-1 infusion the patients underwent a second echocardiographic examination, TDI and blood sampling.

The examinations before and during rGLP-1 included physical examination, a standard 2-dimensional echocardiography at rest and during sub-maximal supine exercise (approximately 50% of the predetermined exercise capacity) and myocardial Tissue Doppler imaging (TDI).

Study V

Study V was designed as a prospective, placebo controlled, cross-over trial. Twenty patients, aged 50-79 years, with type 2 diabetes and heart failure (NYHA class II-III) were recruited for the study. They were all on stable standard heart failure treatment with diuretics, ACE-inhibitors and beta-blockers. Following a two weeks long placebo run-in period, baseline data were obtained as regards exercise tolerance, echocardiography and Tissue Doppler Imaging (TDI). Thereafter the participants were randomly allocated to therapy with trimetazidine (Vastarel®, Servier, Paris, France) or to continued placebo treatment, according to a double blind cross over study design. As outlined in Figure 4 trimetazidine (20 mg three times daily) or matching placebo was administered during an initial period of four weeks. This was followed by a two weeks long washout period. Thereafter the patients switched to the alternate treatment during four weeks.

Prior to each treatment period a symptom limited, maximal bicycle exercise tolerance test was performed. The work load was increased in steps by 10 watts/minute starting at 20 watts. Supine standard 2-dimensional echocardiography and quantitative TDI were performed at rest, during moderate (25% of the maximal exercise capacity) and sub-maximal (50% of the maximal capacity) exercise. The

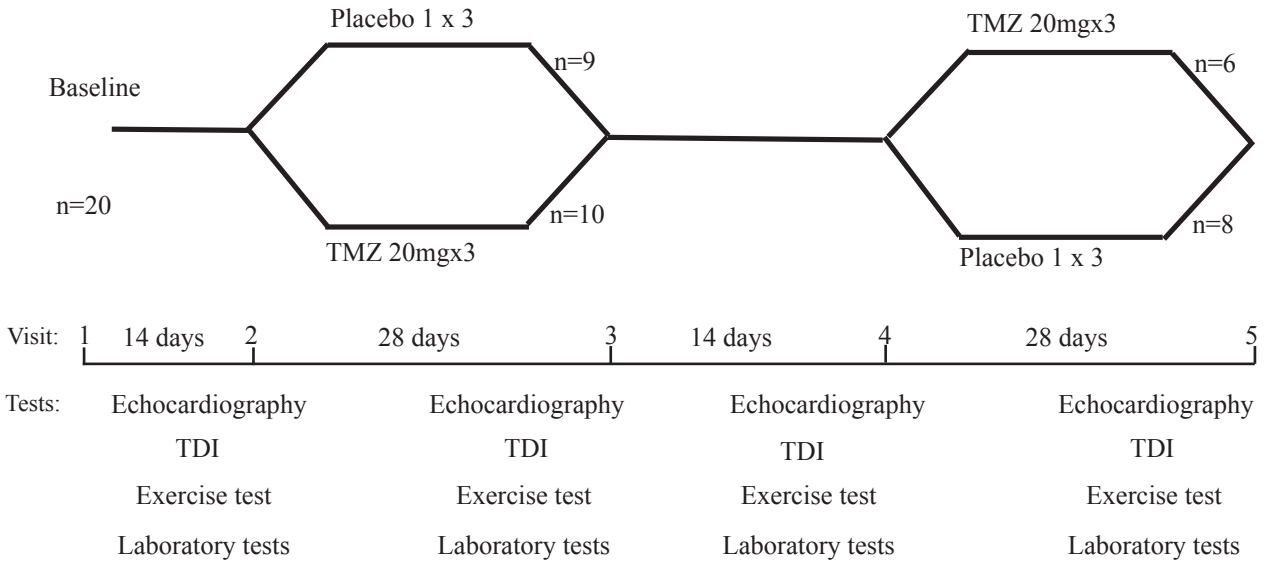


Figure 4. Schematic overview of the study V protocol including information on the number of participants in each treatment group from which all recordings were available at the end of each treatment period.

2-dimensional echocardiograms were analysed according to recommendations by the American Society of Echocardiography using a 16 segment model of the left ventricle for calculating the wall motion score index (score 1 = normal wall motion, 2 = hypokinetic wall motion; 3 = akinetic wall motion and 4 = dyskinetic wall motion) [128]. The analysis included a calculation of left ventricular ejection fraction using the mitral annulus motion method. The recordings were obtained with a commercially available ultrasound system (Vingmed System Five, GE-Vingmed, Horten, Norway). Myocardial TDI recordings were obtained at rest and stress from the apical four, two and three chamber views. Velocities were recorded from the following six myocardial segments: septal, anteroseptal, anterior, lateral, posterior and inferior walls. The following velocities were recorded as the average value (cm/sec) from three consecutive cardiac cycles: peak systolic (Vs), peak early diastolic (Vd) and late diastolic (Va). Myocardial function for each patient was expressed as the average value of tissue Doppler velocity data from all six regions described above, reported separately for systole and early and late diastole. Blood samples were obtained prior to and at the end of each treatment period.

Statistical analysis

Studies I-III

Prevalence was defined as the number of participants with type 2 diabetes mellitus or abnormal glucose regulation or heart failure at their first visit in the study divided by the total number of participants in the Reykjavík Study. The Mantel-Haenszel method and logistic regression with age adjustment were used to estimate odds ratios. Survival and incidence was estimated by means of a Cox regression model stratified by gender using age as the timescale and adjustment for smoking, cholesterol, systolic blood pressure, BMI and IHD in a multivariable analysis model. Left truncation was used to adjust for the different age at entry [129- 131]. The mortality risk was estimated and compared using both the age and time in study as time scale, with age adjustment. Hazard ratios were used to represent the effect by risk factors and membership in risk groups on morbidity and mortality.

Study IV

Values are presented as mean values. Changes from baseline to the end of the study were compared. Analysis for significance was performed using two-sided Chi-Square test with a p value <0.05 as statistically significant.

Study V

The comparison of the two treatments was set using an analysis of variance for cross-over design (sequence, period and treatment effects) considering the change in the parameter compared to baseline during each treatment period. Sequence and treatment effects were described using estimates and 95% confidence intervals of these estimates. All tests were two-sided with a p value <0.05 as statistically significant.

Ethical considerations

Studies I-III

Participants gave their informed consent and the Icelandic National Bioethics Committee approved the study as did the Icelandic Data Protection Authority.

Studies IV-V

The studies were conducted according to the revised declaration of Helsinki [132]. The protocols were approved by the Ethics committee at Karolinska Hospital and the Swedish Medical Products agency. All patients gave their written informed consent to participation.

Results

Study I

Clinical data

The median age of the participants was 53 years. A family history of diabetes mellitus was most common among participants with type 2 diabetes ($p<0.0001$). Age, weight, BMI, heart rate, systolic and diastolic blood pressure were highest ($p<0.001$) in the groups with a combination of glucose abnormalities and heart failure, and declined in those with either glucose abnormalities or heart failure to be lowest in the reference group. Smoking was most prevalent in the groups without glucose abnormalities ($p<0.03$) and previous smoking in groups with glucose abnormalities ($p<0.0001$). Cholesterol levels did not differ significantly between the groups with or without glucose abnormalities while triglycerides were highest in participants with heart failure together with diabetes or abnormal glucose regulation ($p<0.0001$) and FFA in those with heart failure and abnormal glucose regulation ($p<0.0001$). Sedimentation rate and uric acid were highest in participants with heart failure along with glucose abnormalities, gradually decreasing to the lowest level in the reference group ($p<0.0001$). ECG abnormalities, besides those included in the heart failure definition, were most common in those with the combination of heart failure and a glucose abnormality declining to the lowest level in the reference group ($p<0.0001$). Treatment with diuretic agents and/or digitalis as well as with NSAID was most frequent in the groups with heart failure ($p<0.0001$).

Prevalence

In the total population of 19381 participants, out of whom 9323 were men, the prevalence of type 2 diabetes was 3.7% and heart failure 3.8%. The prevalence of heart failure increased with the presence of abnormal glucose regulation

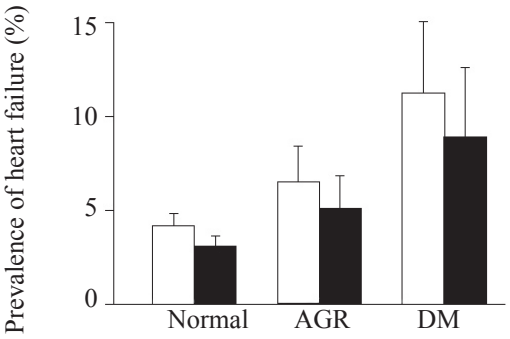


Figure 5. Age-adjusted prevalence of heart failure according to glucose abnormality in male (white bars) and female (black bars) participants in the Reykjavík Study. AGR: abnormal glucose regulation, DM: diabetes mellitus.

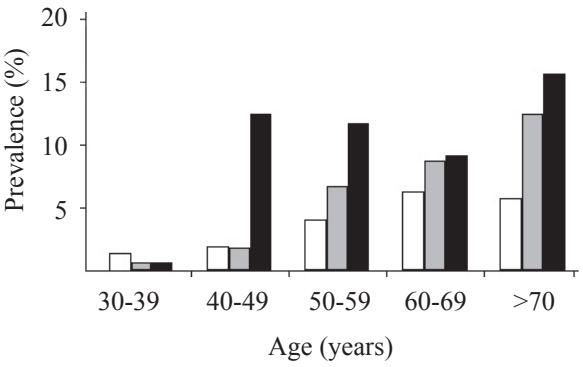


Figure 6a. The prevalence of heart failure by age and glucose abnormalities in men. Normal glucose regulation (white bars), abnormal glucose regulation (grey bars), diabetes mellitus (black bars).

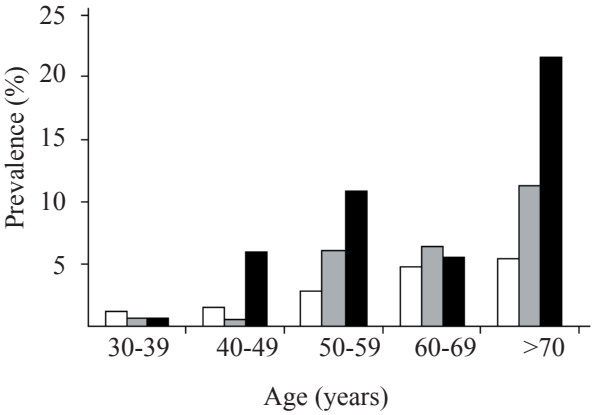


Figure 6b. The prevalence of heart failure by age and glucose abnormalities in women. Normal glucose regulation (white bars), abnormal glucose regulation (grey bars), diabetes mellitus (black bars).

Table 4. Clinical characteristics at the first visit in the Reykjavik study population divided into the six study groups, adjusted for age.

Study group	Age (years) mean (SD)	BMI (kg/m^2) mean (SD)	Cholesterol (mg/dl) mean (SD)	Smoking n (%)	Hypertension n (%)	IHD n (%)	Previous AMI n (%)
MEN							
1. Reference (n=7647)	53.2 (8.3)	25.5 (3.7)	6.3 (1.1)	4318 (56.5)	2483 (32.5)	924 (12.1)	128 (1.7)
2. Abnormal glucose regulation (n=920)	56.0 (9.0)	26.8 (3.8)	6.3 (1.1)	419 (45.5)	467 (50.8)	171 (18.6)	25 (2.7)
3. Diabetes (n=348)	58.4 (10.2)	27.4 (4.3)	6.2 (1.0)	162 (46.6)	185 (53.2)	99 (28.5)	16 (4.6)
4. Heart failure (n=281)	56.3 (8.2)	27.7 (3.7)	6.4 (1.1)	158 (56.2)	135 (48.0)	124 (44.1)	64 (22.8)
5. Abnormal glucose regulation and heart failure (n=64)	61.3 (9.4)	27.9 (4.3)	6.4 (0.9)	32 (50.0)	44 (68.8)	43 (67.2)	14 (21.9)
6. Diabetes and heart failure (n=47)	59.3 (10.4)	29.5 (5.0)	6.1 (1.2)	21 (44.7)	35 (74.5)	28 (59.6)	9 (19.2)
WOMEN							
1. Reference (n=8474)	54.6 (8.9)	24.8 (4.0)	6.5 (1.2)	3431 (40.5)	2157 (25.5)	1024 (12.1)	25 (0.3)
2. Abnormal glucose regulation (n=938)	57.3 (9.7)	26.2 (5.0)	6.6 (1.2)	317 (33.8)	429 (45.7)	177 (18.9)	7 (0.8)
3. Diabetes (n=287)	61.9(10.3)	28.2 (5.7)	6.5 (1.2)	82 (28.6)	174 (60.6)	83 (28.9)	5 (1.7)
4. Heart failure (n=248)	58.0 (9.7)	28.2 (5.2)	6.7 (1.3)	112 (45.2)	126 (51.6)	89 (35.9)	23 (9.3)
5. Abnormal glucose regulation and heart failure (n=55)	61.7 (9.4)	29.7 (5.6)	6.5 (1.2)	24 (43.6)	38 (69.1)	22 (40.0)	5 (9.1)
6. Diabetes and heart failure (n=38)	66.9 (9.4)	30.2 (4.9)	6.6 (1.0)	10 (26.3)	24 (63.2)	25 (65.8)	7 (18.4)

($p<0.0001$) and type 2 diabetes ($p<0.0001$; figure 5). Abnormal glucose regulation, type 2 diabetes and heart failure increased by age (figure 6 a,b). Looking at participants between 50-65 years the prevalence of abnormal glucose regulation remained stable during the study period ($p=0.23$) while the prevalence of type 2 diabetes ($p=0.007$) increased during the study period in both genders. The prevalence of heart failure remained stable for men 5.4 to 4.8% ($p=0.19$) but decreased among women from 4.9% among those recruited early to 3.3% (p for trend 0.004) for those recruited late in the study period. The age adjusted strength of the association (Odds Ratio) of heart failure and type 2 diabetes was 2.7 (Confidence Interval: 1.9-3.8) for men and 2.8 (1.9-4.1) for women, while the strength of the age adjusted association between abnormal glucose regulation and heart failure was 1.6 (1.2-2.1) among men and 1.7 (1.2-2.4) among women.

Study II

Clinical data

The average time of follow up for the 19381 participants was 21.5 years (range 14-30 years). The distribution of participants in groups 1 – 6 and their clinical characteristics are presented in table 4. This table also reveals the proportion of patients with ischaemic heart disease and those with a history of myocardial infarction. Participants in the reference group were younger with a lower BMI and with a less frequent history of hypertension and IHD.

Mortality

Total mortality was lowest in the reference group among both genders. It was highest in participants with the combination of any glucose abnormality and heart failure ($p<0.0001$) with cardiovascular death as the single most common cause in all groups (in males 48% and females 34%).

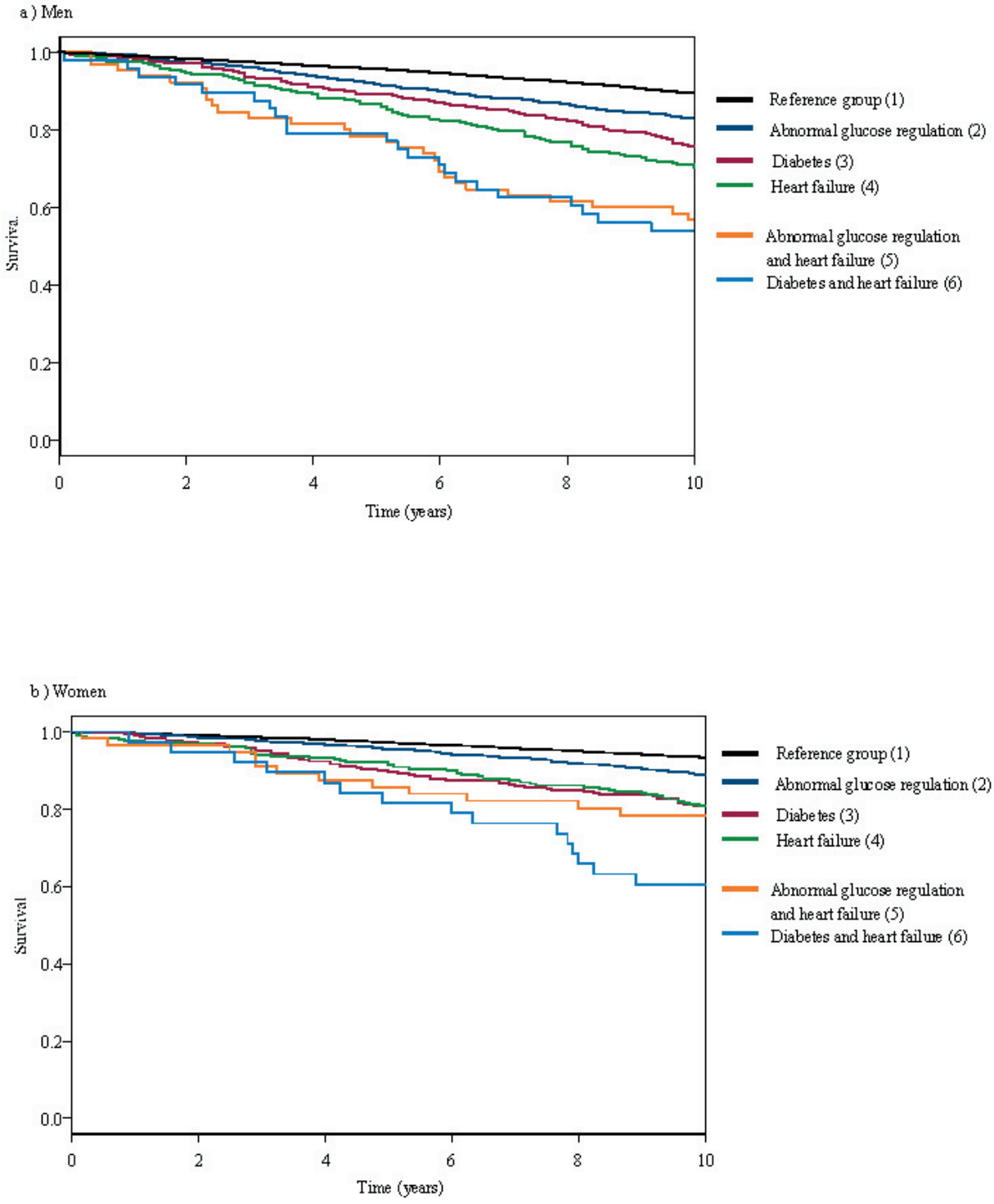


Figure 7. Survival curves during ten years of follow up for all groups of participants with/without heart failure and a glucose abnormality, a) men b) women.

Table 5. Survival analysis based on follow up until January 1st 2002 in all groups of participants. Hazard ratios and Confidence Intervals (CI) compared with the reference group with four different levels of adjustment.

	Study group	No adjustment	Age adjustment	Age and IHD adjustment	Adjustment for other major risk factors and IHD
Men	2. Abnormal glucose regulation	1.5 (1.3-1.6)	1.2 (1.0-1.3)	1.1 (1.0-1.3)	1.1 (1.0-1.2)
	3. Diabetes	2.4 (2.1-2.7)	1.7 (1.4-1.9)	1.6 (1.4-1.8)	1.6 (1.4-1.8)
	4. Heart Failure	2.5 (2.1-2.8)	1.9 (1.7-2.2)	1.7 (1.5-1.9)	1.7 (1.4-1.9)
	5. Abnormal glucose regulation and heart failure	4.6 (3.5-6.1)	2.6 (2.0-3.4)	2.0 (1.5-2.7)	1.9 (1.5-2.5)
	6. Diabetes and heart failure	4.0 (2.9-5.4)	2.7 (1.9-3.6)	2.2 (1.6-3.1)	2.1 (1.5-2.9)
Women	2. Abnormal glucose regulation	1.5 (1.4-1.7)	1.2 (1.1-1.4)	1.2 (1.1-1.4)	1.2 (1.1-1.4)
	3. Diabetes	2.8 (2.4-3.3)	1.6 (1.4-1.9)	1.5 (1.3-1.8)	1.6 (1.3-1.9)
	4. Heart Failure	2.3 (1.9-2.7)	1.8 (1.5-2.1)	1.7 (1.4-2.0)	1.6 (1.4-1.9)
	5. Abnormal glucose regulation and heart failure	2.5 (1.7-3.7)	1.4 (0.9-2.1)	1.3 (0.9-2.0)	1.3 (0.8-1.8)
	6. Diabetes and heart failure	5.1 (3.4-7.7)	2.0 (1.4-3.1)	1.8 (1.2-2.7)	1.9 (1.2-2.8)

IHD: ischaemic heart disease

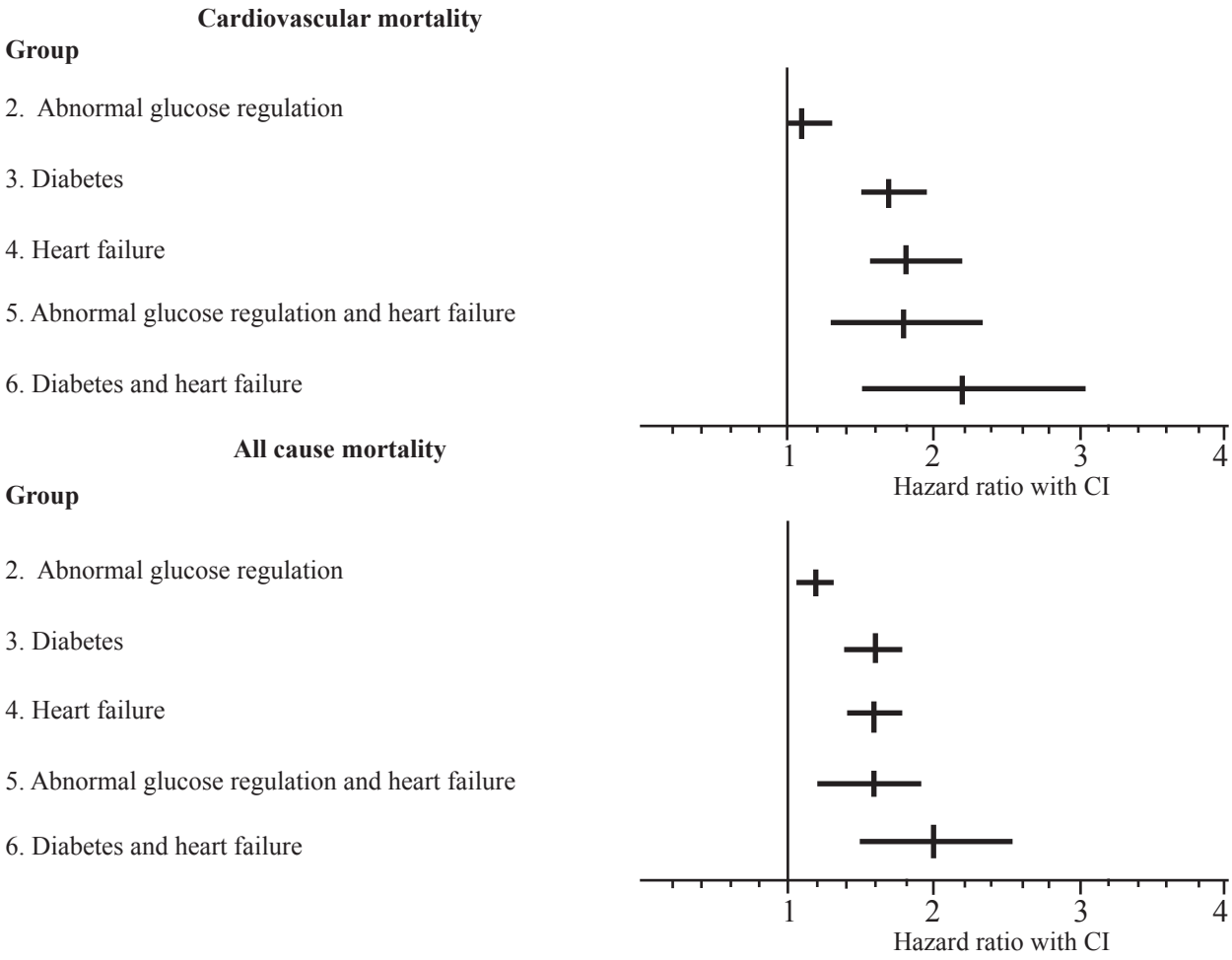


Figure 2. All cause and cardiovascular mortality during total follow up time (males and females). Adjustments are made for age, systolic blood pressure, cholesterol, body mass index, smoking and ischaemic heart disease.
Data are presented as Hazard Ratios (95% Confidence Intervals).

Table 6. New myocardial infarctions in participants, with or without a previous myocardial infarction, in the study groups in relation to the reference population (Group 1). Follow up until Jan 1st 2002. Hazards Ratios (HR) (95% Confidence Interval; CI) are stratified by birth cohort and adjusted for dissimilarities in age, body mass index, previous ischemic heart disease, systolic blood pressure, blood cholesterol and smoking habits.

Study group	Number of events (n)	New myocardial infarction and no previous infarction HR (CI)	Number of events (n)	New myocardial infarction irrespective of previous infarction HR (CI)
Men				
2. Abnormal glucose regulation (n=920)	97	1.0 (0.8-1.1)	109	1.1 (0.9-1.1)
3. Diabetes (n=348)	56	1.5 (1.2-1.8)	63	1.4 (1.2-1.7)
4. Heart failure (n=281)	28	1.2 (0.9-1.5)	66	1.9 (1.6-2.3)
5. Abnormal glucose regulation and heart failure (n=64)	10	1.1 (0.7-1.8)	20	1.5 (1.0-2.1)
6. Diabetes and heart failure (n=47)	7	1.0 (0.5-1.8)	13	1.4 (0.9-2.2)
Women				
2. Abnormal glucose regulation (n=938)	106	1.2 (0.9-1.4)	107	1.2 (1.0-1.5)
3. Diabetes (n=287)	61	1.9 (1.5-2.6)	63	1.9 (1.5-2.5)
4.Heart failure (n=248)	39	1.6 (1.1-2.1)	52	2.2 (1.7-2.9)
5. Abnormal glucose regulation and heart failure (n=55)	7	1.0 (0.5-2.2)	10	1.6 (0.9-2.9)
6. Diabetes and heart failure (n=38)	10	2.7 (1.4-5.0)	16	3.6 (2.2-5.9)

Survival curves during the first 10 years of follow up are presented in Figure 7. These, unadjusted Kaplan-Meier survival estimates demonstrate that mortality was significantly higher among participants with glucometabolic perturbations and/or heart failure compared with the reference group. In addition an impaired survival was observed in subjects with the combination of a glucose abnormality and heart failure compared to those with heart failure only ($p<0.01$). Following adjustments for age, IHD and risk factors the mortality risk remained high in all case groups. The trend towards impaired survival in the group with a combination of a glucose abnormality and heart failure did, however, not remain significant compared to the reference group after adjustment for risk factors and IHD (table 5). As presented in this table the hazard ratios for survival decreased in all case groups following adjustments with age and IHD as greatest contributors. Combining both genders and with age as the time scale, adjusted HR and 95% CI´s related to survival in the reference population are presented in Figure 8. Both heart failure and diabetes increased the mortality significantly during the follow up. Mortality was also increased among participants with abnormal glucose regulation.

Morbidity

The Hazard Ratios (HR) and 95% Confidence Intervals (CI) for developing a new MI in participants in the case and the reference groups respectively are presented in table 6. The risk was increased in men and women with diabetes and in women with heart failure. Overall there was a trend towards a higher risk among women, particularly those with the combination of diabetes and heart failure. Abnormal glucose regulation did not show an association with the development of MI.

Study III

Clinical data

The average follow up time was 13±8 years and did not differ significantly between the case and reference groups. The mean age at the diagnosis of glucose abnormalities was 61 to 64 years and that for heart failure 59 to 64 years without any significant differences between the age of the

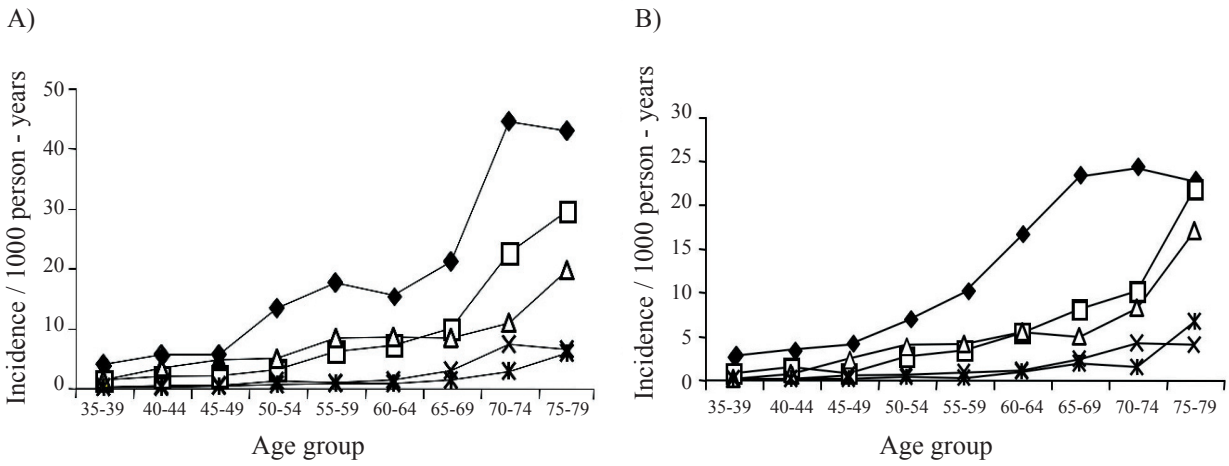


Figure 9. Incidence of abnormal glucose regulation (♦), diabetes (□), heart failure (△), abnormal glucose regulation and heart failure (×), and diabetes and heart failure (✱) expressed as number of incident cases/1000 person-years among men (panel A) and women (panel B) in different age groups.

diagnosis of these disorders. Body mass index and blood pressure were highest in participants with the combination of heart failure and a glucose abnormality. There were no significant differences in blood lipids, creatinine and haemoglobin.

Incidence

At study entry 6260 of the participants were free from abnormal glucose tolerance. New onset abnormal glucose regulation was detected in 1018 individuals (16.3%). Out of 6875 participants, who were free from diabetes at the first study visit, 460 (6.7%) developed new onset diabetes and of 6864 free from heart failure 489 (7.1%) developed heart failure during follow up. The age and gender standardized incidence of abnormal glucose regulation was 12.6/1000/year, of diabetes 4.6/1000/year and of heart failure 5.3/1000/year. The incidence of abnormal glucose tolerance, diabetes and heart failure increased by age (Figure 9).

Predictive factors

Hazards Ratios and Confidence Intervals for predictive factors for glucose abnormalities and heart failure as derived from a multivariable statistical model are presented in Table 7. A high BMI and cholesterol independently predicted each of the three conditions heart failure, diabetes and abnormal glucose regulation while hypertension and IHD predicted the development of heart failure, however, not diabetes or abnormal glucose regulation. An increase in fasting glucose level by 1 mmol/L increased the risk to develop diabetes by 220% ($p<0.0001$), abnormal glucose regulation by 66% ($p<0.0001$) and heart failure by 13% ($p=0.06$). There was a strong association between abnormal glucose regulation and heart failure (HR 1.8; CI: 1.5-2.3) and between diabetes and heart failure (HR 3.0; CI: 2.3-4.0). The relation between heart failure, diabetes and abnormal glucose regulation is outlined in Table 8 as unadjusted and adjusted hazard ratios. Heart failure, diabetes and abnormal glucose regulation did not significantly influence the risk to develop the alternate disease. An interaction was found between the presence of abnormal glucose regulation or diabetes on one hand and ischaemic heart disease and hypertension on the other ($p=0.04$). An interaction was observed for developing heart failure in these disease groups (HR 2.4; CI 1.7-3.3; $p<0.0001$), a risk markedly higher than that expected from the multiplicative effect from these conditions occurring separately.

Study IV

Clinical data

All six patients completed the study protocol. Their mean age was 69 years and the mean BMI 27 kg/m^2. The infusion rate had to be reduced by 25% (to 3 pmol/kg/min) due to nausea during the last two study days in two of the

Table 7. Predictive factors for heart failure and glucose abnormalities. Cox regression - additive model, Hazard Ratios (HR) with confidence intervals (CI).

Predictive factor	Abnormal glucose regulation HR (CI)	p-value	Diabetes HR (CI)	p-value	Heart failure HR (CI)	p-value
Body mass index +1 unit	1.0 (1.0 -1.1)	<0.0001	1.1 (1.1 -1.1)	<0.0001	1.1 (1.1-1.1)	<0.0001
Hypertension yes/no	1.0 (0.8 -1.2)	0.9	1.2 (1.0-1.6)	0.1	1.4 (1.1-1.9)	0.007
IHD yes/no	1.1 (0.9 -1.4)	0.14	1.2 (0.9-1.6)	0.3	2.2 (1.7-2.8)	<0.0001
Cholesterol 1mmol/L	0.9 (0.9-1.0)	0.005	0.9 (0.8-1.0)	0.03	1.1 (1.0-1.2)	0.05
Smoking yes/no	1.0 (1.0-1.3)	0.15	1.3 (1.1-1.6)	0.003	1.7 (1.4-2.0)	<0.0001
Fasting glucose +1mmol/L	1.7 (1.4 -1.9)	<0.0001	3.3 (2.7 - 3.9)	<0.0001	1.1 (1.0-1.3)	0.06

IHD: ischaemic heart disease

patients. Five of them spontaneously reported on subjective improvement on the second and third day of GLP-1 infusion.

The average fasting blood glucose decreased significantly on day two but increased somewhat thereafter (figure 10a). Plasma concentrations of insulin, glucagon and C-peptide are presented in table 9. There was a slight reduction of free fatty acids. Figure 10b shows GLP-1 values during the study period which raised significantly on days 2, 3 and 4.

Exercise test and echocardiography

A trend towards a reduction of resting heart rate was observed at days two and three. Similarly there was a slight trend towards decreasing systolic blood pressure and increasing diastolic blood pressure. The mean ejection fraction was 30 ± 5%. The average left ventricular end-diastolic diameter before GLP-1 was 58 ± 6 mm. The rate pressure product became somewhat lower during the study period both at rest and stress.

The results of TDI are reported in table 10. There was statistically insignificant trend towards improved global systolic and diastolic function at rest and during exercise following GLP-1. The inter-observer variations when analysing the myocardial Tissue Doppler was 20%.

Table 8. Predictive factors for heart failure and glucose abnormalities. Cox regression - comparison is made between unadjusted values and following adjustments for body mass index, hypertension, ischaemic heart disease, cholesterol, smoking and fasting glucose.

Primary disease	Secondary disease		Hazard Ratio	Confidence Interval	p-value
Abnormal glucose regulation	Heart failure	Unadjusted	1.2	0.9 - 1.6	0.1
		Adjusted	1.2	0.9 - 1.6	0.2
Diabetes	Heart failure	Unadjusted	1.5	0.9 - 2.4	0.1
		Adjusted	1.1	0.7 - 1.8	0.6
Heart failure	Abnormal glucose regulation	Unadjusted	1.2	0.8 - 1.7	0.3
		Adjusted	0.9	0.7 -1.4	0.8
Heart failure	Diabetes	Unadjusted	1.2	0.7 - 2.0	0.4
		Adjusted	0.8	0.5 - 1.3	0.4

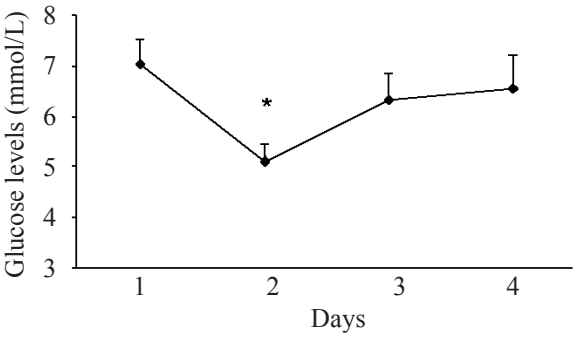


Figure 10a. Fasting blood glucose (mean ± standard deviation).
* p= 0.006

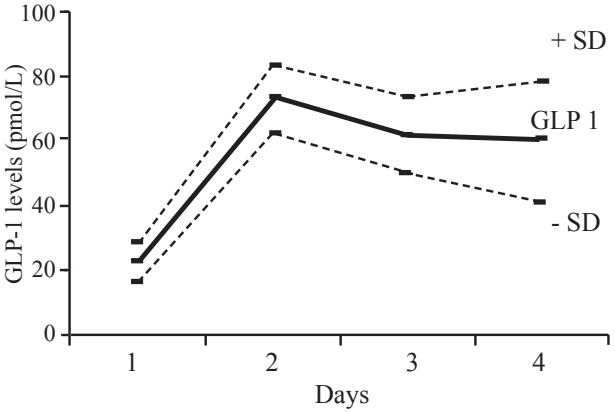


Figure 10b. Mean plasma concentration of GLP-1 during the study period ± one standard deviation.
* p<0.01

Table 9. The mean plasma concentration of glucagon (pmol/L), insulin (mE/L), c-peptide (nmol/L) and free fatty acids (mE/L) during the study period.

Metabolic parameter	Day 1	Day 4
Glucagon	20	22.2
Insulin	10.5	6.3
C-peptide	1.53	1.22
Free fatty acids	0.63	0.28

Study V

Clinical data

The 20 patients had a mean age (±SD) of 66±8 years, an average diabetes duration of 10±8 years and a mean HbA1c of 6.6±1.0%. Eighteen patients were in NYHA class II and two in class III. Baseline values for left ventricular ejection fraction was 31±10% while maximum exercise tolerance was 82±29 watts. All patients were on a rather extensive medication with beta-blockers (95%), ACE-inhibitors or angiotensin receptor blockers (75%), and diuretics (70%). At baseline there were no significant differences in clinical characteristics and risk factors between participants in the original trimetazidine and placebo groups

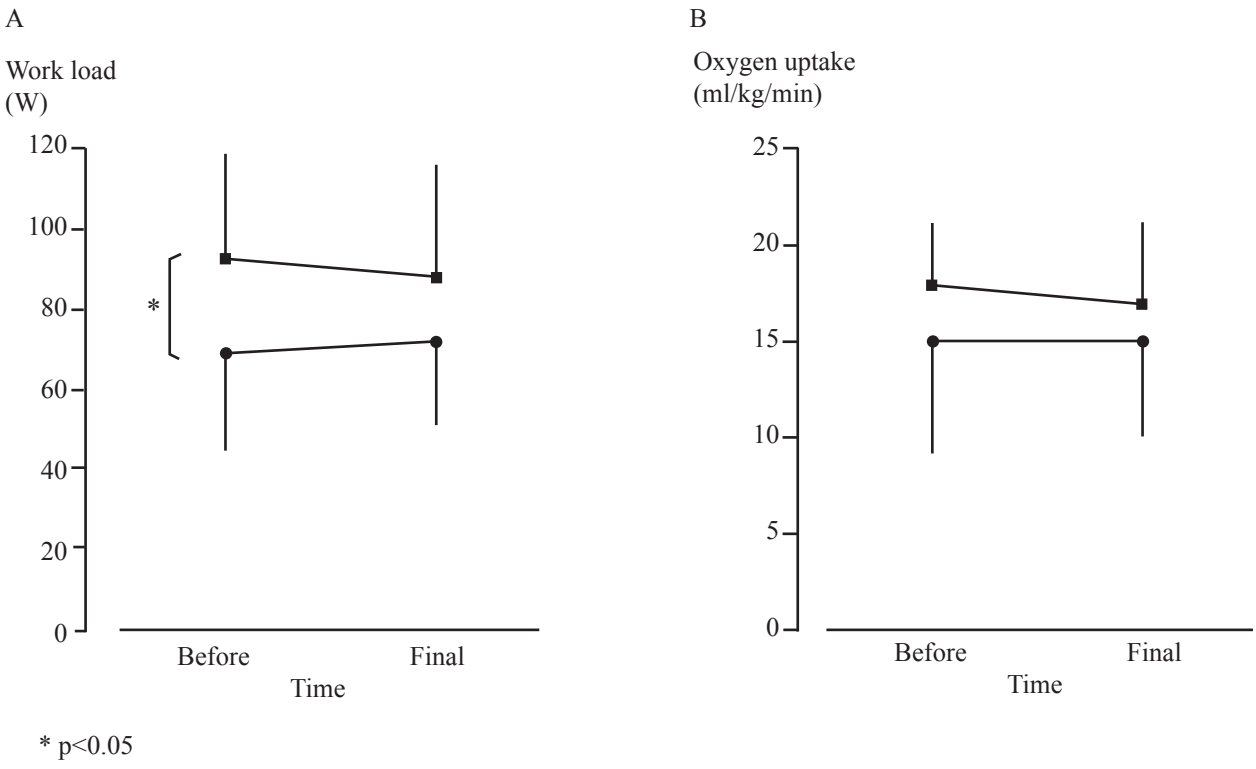
Due to a computer break down, TDI recordings from six participants (two on trimetazidine and four on placebo during the first period) were lost to analysis although they completed the study according to the protocol. Complete information from the first study period, including echocardiography, TDI, exercise tests and laboratory results, was available for 19 patients. Corresponding data for both study periods were retrieved from 14 patients. Results are presented for the participants completing the first period (n=19) and, when adding further information, separately also for patients (n=14) completing the whole study period according to the cross over design.

Exercise test and echocardiography

Participants initially randomized to trimetazidine had a significantly higher maximum exercise tolerance and time to onset of dyspnoea at baseline compared to those who initially were allocated to placebo. All patients completed the exercise tests according to the protocol.

Table 10. The effect of GLP-1 on global systolic or diastolic function at rest or during exercise, mean values (cm/s). S=systolic function, D=early diastolic function, A=late diastolic atrial contration.

	Day 1			Day 4		
Exercise level	**S**	**D**	**A**	**S**	**D**	**A**
Rest	4.75	5.25	6.86	5.07	5.58	7.13
Stress	5.0	6.67	7.29	5.33	7.17	7.85



* p<0.05

Figure 11. Exercise performance (mean ± standard deviation) during the first treatment period (n=20). Vastarel ■ ,Placebo ●

Table 11. Left Ventricular Ejection Fraction (LVEF; %) in 14 participants completing both treatment periods (LVEF±standard deviation)

	Rest		**Moderate exercise**		**Sub maximal exercise**	
	Baseline	**Final**	**Baseline**	**Final**	**Baseline**	**Final**
Placebo	38 (10)	36 (12)	42 (13)	37 (13)	34 (13)	36 (15)
Trimetazidine	35 (8)	39 (14)*	37 (14)	41 (15)**	35 (9)	38 (13)

*p=0.05; ** p<0.001 (ANOVA)

Table 12. First treatment period analysis. Tissue Doppler Imaging parameters at different exercise levels before and after treatment with trimetazidine or placebo (n=19). Values are mean ± standard deviation.

		Vs		**Vd**		**Va**	
Exercise level	**Treatment**	**Before**	**After**	**Before**	**After**	**Before**	**After**
Rest	Placebo	5.1 (1.4)	5.1 (1.4)	6.1 (1.0)	6.0 (1.2)	6.7 (1.8)	6.4 (1.4)
	Trimetazidine	5.2 (1.4)	5.1 (1.6)	7.2* (1.2)	6.8 (1.5)	6.4 (1.9)	6.2 (2.0)
Moderate	Placebo	5.6 (1.0)	5.3 (0.9)	7.0 (1.5)	6.7 (1.5)	7.3 (2.2)	6.9 (1.9)
	Trimetazidine	5.3 (1.4)	5.4 (1.5)	7.8 (1.3)	7.7 (1.9)	6.9 (1.8)	6.6 (1.7)
Submaximal	Placebo	5.7 (1.4)	5.7 (1.0)	7.1 (1.7)	7.6 (2.0)	7.5 (2.0)	7.6 (1.9)
	Trimetazidine	5.8 (1.5)	5.6 (1.5)	8.4 (1.0)	8.2 (1.6)	7.0 (1.7)	6.9 (2.1)

Vs: systolic myocardial velocity; Vd: early diastolic myocardial velocity; Va: late diastolic myocardial velocity; TDI: tissue Doppler imaging; *p=0.03.

Table 13. Tissue Doppler imaging parameters at different exercise levels in 14 patients completing both treatment periods. Values are mean (cm/s) ± standard deviation.

		Vs		Vd		Va	
Exercise level	Treatment	Before	After	Before	After	Before	After
Rest	Placebo	5.3 (1.5)	5.3 (1.5)	6.6 (1.1)	6.4 (1.3)	6.3 (2.1)	6.0 (1.9)
	Trimetazidine	5.3 (1.5)	5.5 (1.6)	7.0 (1.5)*	6.8 (1.6)	6.0 (1.7)	6.3 (1.9)**
Moderate	Placebo	5.5 (1.2)	5.4 (1.5)	7.8 (1.6)	7.5 (1.6)	6.7 (2.1)	6.3 (1.9)
	Trimetazidine	5.4 (1.4)	5.5 (1.4)	7.8 (1.5)	7.8 (1.8)	6.7 (2.2)	6.7 (1.9)
Submaximal	Placebo	5.9 (1.6)	5.9 (1.5)	8.0 (1.8)	8.4 (2.0)	7.1 (1.9)	7.1 (1.8)
	Trimetazidine	5.9 (1.5)	5.7 (1.2)	8.3 (1.4)	8.0 (1.7)	7.2 (2.1)	7.1 (1.9)

Vs: systolic myocardial velocity, Vd: early diastolic myocardial velocity, Va: late diastolic myocardial velocity.
*p=0.05 vs. placebo
** p=0.01 ANOVA

As can be seen from figure 11 the changes in the exercise parameters over time were rather small and not statistically significant in any of the two groups during the first treatment period. Dyspnea and/or leg fatigue were the consistent limiting factors for continued exercise.

Ejection fraction (EF) and wall motion score index (WMSI) at baseline did not differ significantly at rest and during exercise between patients started on trimetazidine or placebo for the first treatment period. Both EF and WMSI increased somewhat and to a similar extent in both treatment groups. The analysis of echocardiograms from the 14 individuals from whom recordings were obtained throughout the whole study period revealed that ejection fraction at rest (p=0.05) and moderate exercise (p<0.001) improved significantly during trimetazidine treatment compared to placebo (table 11). Besides a significantly better baseline early diastolic velocity in the trimetazidine treated group (p=0.03) the systolic (Vs) and diastolic (Vd, Va) myocardial velocities at rest and exercise did not show any clinically significant differences before and after treatment when analyzed separately for the 19 patients completing the first treatment period, or when looking specifically at the subset of 14 participants in whom data were complete. As can be seen in tables 12 and 13 the systolic velocity (Vs) and early diastolic velocity (Vd) increased with increasing levels of stress both during placebo and trimetazidine treatment. Late diastolic velocity (Va) increased during stress both on placebo and trimetazidine indicating worsening diastolic function during stress.

General Discussion

Epidemiology

Methods

The main strength of studies I-III is the large number of participants who were invited to repeated study visits during the period of follow up in the Reykjavík Study. They were randomly selected from the Reykjavík population and should be representative for the general Icelandic population at that time. The Icelandic population has been compared to other populations as regards risk profiles and was found to be similar to a low risk Europan population [133].

The diagnosis of heart failure is clinical and based on the combination of subjective symptoms and objective signs of myocardial dysfunction as defined by the European Society of Cardiology [10]. Echocardiography is presently the most common method to evaluate myocardial function. Studies I-III are based on data from the Reykjavík Study which was designed in 1966. By then there was no internationally accepted, uniform definition of heart failure and echocardiography was not generally available. The Reykjavík Study did, however, include a detailed questionnaire incorporating symptoms as tiredness, breathlessness and oedema. In addition ECG recordings and CXR were obtained from all participants. These data gave the opportunity to define heart failure in concordance with the ESC guidelines [10], recommendations which were also used in the Rotterdam Study, another prospective population based investigation [134]. The method applied does still carry some risk for a false positive or negative diagnosis. In the Framingham Study, signs of cardiac dysfunction, such as heart enlargement on CXR and left ventricular hypertrophy on ECG, were highly predictive for deteriorating cardiac function [135]. Moreover, systolic dysfunction is found in 8-15% of asymptomatic patients with hypertension, diabetes mellitus, coronary artery disease or previous myocardial infarction by screening with echocardiography [136]. Thus it is more likely that the true number of heart failure cases was underestimated rather than over exaggerated in studies I-III causing if anything an underestimation of the impact of heart failure.

A crucial feature for studies I-III is that the protocol of the Reykjavík study, until 1990, requested an OGTT to be performed on each participant offering the opportunity not only to study people with established type 2 diabetes mellitus but also to identify those with newly detected diabetes or abnormal glucose regulation. The present definitions of glucose abnormalities were based on a history of diabetes or a newly diagnosed abnormal glucose regulation detected by the OGTT until 1990 and thereafter on history in combination with fasting plasma glucose. The OGTT differed somewhat from current WHO recommendations which are 75g glucose in 250-300 ml water ingested within 5 minutes, after an overnight fast, and with blood samples obtained in the fasting state and 2 hours after the glucose load [19]. In studies I-III the OGTT used 50g glucose in 250 ml water. This is compensated for by post load sampling after 1.5 rather than 2 hours. More of a concern is that the glucometabolic state had to be based on fasting glucose from 1990. As demonstrated by for example the GAMI and DECODE studies fasting blood glucose will not disclose people with impaired glucose tolerance and leave some cases of diabetes mellitus undetected [137, 138]. Thus, studies I-III may to some extent underestimate the true prevalence, incidence and impact of these conditions.

Risk factors

It is well established that life style influences future health, increasing or decreasing the risk for several diseases. Smoking, hyperlipidemia and

hypertension are risk factors for cardiovascular disease while daily consumption of fruits, vegetables and a modest amount of alcohol are protective as is regular physical activity [5].

Heart failure

Risk factors for heart failure in studies I and III were increasing age, overweight and hypertension. Ischaemic heart disease was another important predictor together with hypercholesterolaemia. A trend was observed towards a linear association between fasting glucose and heart failure (Study III). These findings are concordant with previous findings. Hypertension and coronary artery disease are known as important risk factors for heart failure [41, 135]. Increasing age, diabetes, impaired glucose tolerance, dyslipidemia, obesity, a high BMI, smoking and IHD do also increase the risk in people in all ages [21, 139-141].

Glucose abnormalities

Similarly high age, hypertension, increasing BMI, previous smoking and IHD were more frequent in patients with glucose abnormalities than in their normal counterparts (study I). Predictive factors for subsequent glucose abnormalities were age, BMI, fasting glucose and cholesterol (Study III). These results are once more in accordance with previous findings [17, 25, 39].

Heart failure and glucose abnormalities

Studies I and III reveal that age, BMI, smoking, hypertension, increased FFA, triglycerides, uric acid and fasting glucose are all risk factors for the combination of glucose abnormalities and heart failure. As outlined most of these variables are known risk factors for diabetes and heart failure as separate conditions. Although perhaps predictable the present findings are of interest considering the limited number of previous reports on this subject. The relation between hypertension and blood glucose was acknowledged in a previous report from the Reykjavík study underlining the strong relation between elevated levels of blood glucose and hypertension [27, 41]. In the Kaiser Permanente diabetes registry the risk for heart failure was higher in patients on insulin treatment compared to those treated with oral glucose lowering agents [142]. Insulin is ordinarily used later in the development of diabetes after attempts with oral treatment has failed. It is therefore difficult to know whether, insulin in itself or the severity of the disease determines the increased risk for heart failure, that remains to be tested.

We were unable to identify other studies that systematically looked for risk factors for the combination of glucose abnormalities and heart failure, which makes further comparisons with the outcome of studies I and III difficult.

Prevalence and incidence

In study I the prevalence of diabetes was 3.7% which is similar to the prevalence of heart failure 3.8%, with no significant gender related differences. The mean incidence of abnormal glucose regulation was 12.6/1000/year, for diabetes 4.6/1000/year and for heart failure 5.3/1000/year. The mean age at the diagnosis of heart failure and glucose abnormalities was about the same, 59-64 years. Not surprisingly the prevalence and incidence of glucose abnormalities and heart failure increased with age (Studies I, III). The present prevalence of *heart failure* is similar to the prevalence reported from the Rotterdam study, recruiting participants in similar age intervals and also comparable to the prevalence in non-diabetics in a study from the United States [32, 143]. The prevalence of *diabetes* in Study I is slightly lower than the average estimated prevalence 4.0-4.5% in developed countries [4]. Few studies did, however, estimate the incidence of diabetes in a general population. One study was performed in the Netherlands reporting an incidence of diabetes as 2.3/1000 person-years [47], compared to the present finding of 4.6/1000/year (Study III).

Study I confirms the observations by King et al [4] that the prevalence of diabetes is increasing over time. More surprisingly was perhaps that study I revealed that the prevalence of abnormal glucose regulation was stable as was the prevalence of heart failure for men and indeed decreasing for women. The Rotterdam

and Framingham studies show, for comparison, an increase in the prevalence of heart failure, a finding more in concordance with current opinion of this trend [134, 139]. In contrast study I does not support that the burden of heart failure is increasing in the general population in Iceland. The discrepant findings may, as already emphasised, to some extent be explained by a potential underestimation of the true number of people with heart failure based on definition inaccuracy. This is, however, unlikely to be the only reason. Another contributing factor may very well be a low risk profile of the Icelandic population, making them less prone to develop heart failure [133]. A third contributing explanation for potential underestimation of the time trends in heart failure prevalence in study I might be relatively long intervals between study stages causing missing cases due to hospitalization and fatality.

An interesting question is whether there is a relation between heart failure and glucometabolic abnormalities. The prevalence of diabetes was higher in people with heart failure, 30% versus 15%, than in a general population of elderly Italians and in that study heart failure turned out as an independent predictor for subsequent diabetes [17]. Study I shows a significant increase in the prevalence of heart failure with increasing level of glucose abnormalities being lowest (3.2%) among control subjects, higher (6.0%) in participants with abnormal glucose regulation and highest (11.8%) in those with established diabetes. Previous studies in patients with heart failure revealed that glucose abnormalities are common in patients with heart failure and that heart failure is associated not only with hyperglycemia but also hyperinsulinemia, a marker of insulin resistance [90, 144]. The findings in study I underline that hyperglycaemia does not start as a risk factor at the levels used as a cut off for the diagnosis of type 2 diabetes. It supports the conclusion that glucometabolic abnormalities should be looked upon as a continuous risk factor for heart failure as for cardiovascular disease in a general sense [145, 146].

Mortality and morbidity

Diabetes and heart failure are linked to an unfavourable vital prognosis apparent already among people with less pronounced glucometabolic perturbations (Study II). This is unrelated to gender and remains after adjustments not only for traditional risk factors for coronary artery disease but also for previously known IHD. The trend towards added unfavourable prognostic influence of the combination of glucometabolic perturbation and heart failure did, however, not reach statistical significance when compared to the prognostic information by each of the two conditions on their own. It is likely that a limited number of participants in these groups, is a partial explanation. That mortality is high in male patients with diabetes, cardiovascular disease and coronary heart disease is known [25]. Likewise, it is known that the prognosis is impaired in diabetic patients with heart failure [39, 41]. New is, however, the present information that this pattern is seen also in a truly population based study

The most common underlying factor increasing mortality risk in heart failure patients is IHD, both in the presence or absence of diabetes [61]. This is in concordance with results from study II in which survival improved after adjustment for ischaemic heart disease in participants with heart failure, with or without glucose abnormalities. Thus, IHD remains as an important prognostic factor in subjects with heart failure. The fact that there still were mortality differences following adjustments does, however, make IHD less likely as the single reason for increased mortality. Indeed it indicates that the relation between glucose abnormalities and myocardial performance is more direct. The prognosis in participants with glucose abnormalities combined with heart failure was, however, not markedly worse when compared to participants with either disease separately. The present results can therefore not be taken as evidence for the existence of a specific diabetic cardiomyopathy. Further information, supporting the existence of such condition, would be that improved glucose control would improve the prognosis irrespective of ischaemic heart disease. Such study would be of major interest to test the hypothesis if there is a link between metabolic control and myocardial injury.

Patients with diabetes are at a high risk for cardiovascular disease, especially in the presence of other risk factors [5, 62, 147]. This was confirmed by study II in which the risk for a future myocardial infarction was increased in participants with diabetes and heart failure separately or combined. Of interest is also if heart failure may increase the risk for myocardial infarction. Observations in that direction were reported from the Rotterdam study. Participants with heart failure had an increased number of non-fatal cardiovascular events including myocardial infarctions and increased demand for percutaneous coronary intervention or bypass surgery [50]. Melchior et al [148] studied how patients with myocardial infarction and type 2 diabetes differed from patients with myocardial infarction without diabetes with respect to subsequent heart failure and mortality. The incidence of heart failure was higher among the diabetic patients. Two percent of those with type 2 diabetes and heart failure survived 10 years compared with 15% of those with heart failure but no diabetes [148]. These findings are in accordance with the present observation that previous myocardial infarction is more prevalent in participants with heart failure and diabetes than in those with heart failure only. The present finding that heart failure carries an increased risk for myocardial infarction in diabetic women is interesting. That participants with diabetes had an increased risk for a new myocardial infarction further illustrates the relation between glucometabolic perturbations and ischaemic heart disease.

The association of glucose abnormalities and heart failure

Diabetes has been claimed to be an independent risk factor for heart failure and vice versa [17, 29, 33, 89, 140]. Study III does not provide support to this, showing a strong association between these two conditions but no indications of a causal relationship. A potential explanation is that previous studies focused on elderly populations or were selected from patients in health maintenance organizations. Moreover the occurrence of new onset diabetes was unusually high in one of these reports, the Campania study [17, 29]. Besides a strong association between diabetes and heart failure and abnormal glucose regulation and heart failure in studies I and III there was an interaction between glucose abnormalities and IHD or hypertension that increased the risk for heart failure, indicating a stronger connection between glucose abnormalities and heart failure than could be expected by a simple additive association. This is further underlined by the linear relationship between fasting plasma glucose and risk for heart failure supported by a previous observation that an increase in HbA_{1c} by 1% increased the risk for heart failure by 8% [40].

A causal relationship between different diseases may be hypothesised, however, not proven based on epidemiological data. The Reykjavik study, which includes a 30 year period of follow up, a standardised exploration of the glucometabolic state and reasonably accurate possibilities to confirm suspect heart failure provided excellent possibilities to study the time relationship between these disorders in a large and truly population based cohort. The hypothesis that there may be a causal relationship is hardly supported by the current data, which rather indicate the existence of a common denominator between glucometabolic abnormalities and heart failure, conditions that indeed appeared close to each other in time. Insulin resistance has been suggested as a potential common denominator. From the Framingham study it was reported that ventricular mass increased with increasing insulin resistance [38] and an association of left ventricular structure and diabetes has also been established [149, 150]. Heart failure is associated with endothelial dysfunction leading to impaired endothelial dependent peripheral vasodilatation a condition that affects diabetics as well [151, 152]. It may therefore be assumed that patients with the combination of heart failure and diabetes may be at a particular risk for severe endothelial dysfunction. It remains to be studied if good metabolic control of patients with diabetes and heart failure will diminish the effect of insulin resistance and improve endothelial function increasing the possibilities to preserve myocardial function.

Treatment

Studies IV and V were conducted to explore new treatment modalities of heart failure in association with diabetes. Recombinant GLP-1, a peptide causing glucose-dependent secretion of insulin, and trimetazidine, an inhibitor of fatty acid beta-oxidation, were added to traditional treatment. The objectives with these trials, of pilot character, were to test if they are safe treatment options with beneficial effects on the metabolic control and myocardial function.

Metabolic modulation

The aim of heart failure treatment is to prevent further cardiac dysfunction, maintain and improve the quality of life and increase longevity. Traditional treatment of heart failure in diabetic patients is based on diuretics, ACE-inhibitors or angiotensin receptor blockers and β-blockers as outlined in current guidelines [10, 153]. Betablockers are indicated since they decrease the mortality in patients with heart failure and diabetes [154-156]. The use of ACE inhibitors is indicated both in asymptomatic myocardial dysfunction and heart failure [157-159] since they improve heart failure symptoms and reduce the mortality [93]. Insulin treatment in patients with diabetes and heart failure is under debate since it has been shown to have both beneficial effects on the myocardial function and to be a predictor of mortality [160, 161]. Obviously further studies are needed to find concrete evidence about insulin treatment in patients with diabetes and heart failure. In general it has been assumed that meticulous metabolic control should be beneficial in heart failure patients [3]. There are several metabolic impairments observed in the diabetic heart which may be subjected to medical treatment. The target is to modulate both the glucose and myocardial metabolism, thus shifting the myocardial metabolism from the unfavourable fatty acid oxidation to oxygen sparing ATP production through glycolysis. The purpose of this treatment is to improve the myocardial function in patients with diabetes and heart failure.

Before the institution of the novel drugs tested it was ascertained that the patients in studies IV and V were treated appropriately according to these recommendations. The glucose lowering treatment was also monitored to be stable and well balanced.

GLP-1

The assumption that left ventricular dysfunction may improve by the metabolic shift induced by glucose-insulin has been verified in experimental animal models and similar effects have been observed with rGLP-1 treatment in dogs with experimentally induced cardiomyopathy [117, 162, 163]. Another study, performed in pigs subjected to myocardial ischaemia, indicated that myocardial preservation during rGLP-1 infusion may be related to a shift of myocardial mitochondrial function, decreasing the interstitial levels of pyruvate and lactate during ischaemia [164]. Study IV is to the best of our knowledge the first attempt to administer rGLP-1 in patients with heart failure related to diabetes. The study was primarily performed to test safety and feasibility.

The rGLP-1 infusion was in general well tolerated although dose adjustments were required in two of the six patients due to nausea. This is a well known side effect related to delayed gastric emptying [115]. As could be expected rGLP-1 improved metabolic control reflected as lower values of fasting glucose and FFA. A trend towards improved myocardial velocities was observed, but this change did not reach statistical significance. As always in an uncontrolled pilot investigation the outcome has to be interpreted with great caution. The number of patients that were accepted in this early investigation was small causing difficulties to perform standard statistical calculations. The study did not have a control group. Accordingly no conclusions can at this stage be drawn regarding the efficacy of rGLP-1 in diabetic patients with heart failure. A recent literature search indicates that there are still no other studies testing the effect of rGLP-1 in this patient category. New studies are certainly warranted to test the hypothesis that rGLP-1 may be useful in this setting and may be expanded considering the outcome of this pilot investigation that proved reasonable feasibility and safety. In future studies it may, however, be

better and easier to increase circulating rGLP-1 by inhibiting dipeptidyl peptidase-4 (DPP-4). This drug improves metabolic control in type 2 diabetes, an improvement seen in association with reduced glucagon and, despite lower glycemia, unaltered insulin levels. A great advantage is that DDP-4 inhibitors are orally active [165, 166].

Trimetazidine

Trimetazidine is one of several metabolic modulators in clinical testing with the ability to shift myocardial metabolism from oxidation of FFA towards glycolysis as reviewed by Stanley and Marzilli [167]. Trimetazidine improves angina pectoris and increases exercise time when added to conventional treatment in patients with stable coronary artery disease without heart failure [168, 169]. Trimetazidine has also been tested in patients with heart failure with beneficial effects such as symptomatic improvement and enhancement of left ventricular function and also improved glucose metabolism [170-171]. These results were indeed more beneficial than those in study V showing a slight, however, statistically not proven, improvement of left ventricular EF in patients with type 2 diabetes and heart failure. Moreover there were no, differences in wall motion score index and in myocardial velocities measured by TDI.

Loss of data in six patients, due to a computer break down, diminished the power of the study to detect differences between trimetazidine and placebo treatment in study V. This can, however, not be the only explanation to the lack of clear differences between placebo and trimetazidine. Patients in study V had rather severe heart failure, with a low average ejection fraction. If trimetazidine had been as effective as expected from previous reports it should have induced a more marked improvement in myocardial function. The TDI technique that was used for the study of systolic and diastolic myocardial function has the capacity to disclose myocardial functional impairment in diabetic patients free from clinical signs of heart failure and with normal traditional echocardiograms [106]. It is therefore unlikely that the lack of obvious improvements in study V is related to a methodological lack of sensitivity.

Most studies of the metabolic modulators, dichloroacetate, etomoxir and trimetazidine, were designed as open trials which include a definite risk to over exaggerate beneficial effects on the myocardial function [99, 172, 173]. Besides differences in trial design there may, however, be other and important reasons for discrepancies in effectiveness as reflected by previous and present experiences. Factors of potential influence may be patient condition, background medication and the possibility of a pre-existing down regulation of FFA beta oxidation in the failing heart. In the study by Bellardinelli and Purcaro [171] treatment duration was longer and dobutamine rather than physical exercise was used to stress the heart. Moreover none of their patients had type 2 diabetes. Fragasso et al [170] treated diabetic patients with ischaemic cardiomyopathy in a double blind placebo controlled, cross-over study design. Trimetazidine improved left ventricular ejection fraction by 20% after six months. Compared to their study population patients in study V had lower ejection fraction and a lower HbA_{1c} indicating more severe heart failure but better diabetic control. It may be, but remains to be further explored, that a careful glucometabolic control accomplished by traditional glucose lowering treatment leaves less space for further metabolic interventions. Thus, improved metabolic care, in particular by means of insulin, seems to improve diastolic function in diabetic patients [175]. Diet was the only glucose lowering treatment in the single study that, so far, specifically addressed diabetic patient. Thus none of the patients in the study by Fragasso et al [170] were on insulin and their baseline HbA_{1c} was rather high, 7.8%, as an indication of a rather poor metabolic control. Almost all patients in study V were on β-blockers, a proportion much higher than in the studies referred to as positive. Betablockade decreases myocardial FFA exposure thereby changing that metabolic pathway in type 2 diabetes [175, 176]. Betablockers should, based on recent successful clinical trials including sub groups with diabetes, be first hand treatment in

heart failure [177, 178]. Supporting that presence and absence of β-blockade is an important reason for the discrepant findings in study V and previous reports is that in the latter studies on trimetazidine, etomoxir and dichloroacetate β-blockers were either withdrawn prior to study start or present only in a limited proportion of the patients [44, 170-172, 179]. Accordingly the ideal candidate for metabolic modulation with trimetazidine and similar compounds is perhaps a patient in a fairly poor metabolic state and not on treatment with insulin or a β-blocker.

An alternate explanation to the negative outcome of the present study may be that FFA oxidation in the failing myocardium as well as the enzymes for beta oxidation are down regulated while the reverse is true for glucose oxidation [72, 176]. In that case further attempts to inhibit beta oxidation by means of trimetazidine may be less successful. The present study is not the only with a rather neutral effect of metabolic modulation. Lewis et al [180], did not find any non-invasively detectable improvement in left ventricular function following intravenous dichloroacetate in 25 heart failure patients with a left ventricular EF ≤40%. This may also explain why trimetazidine and similar metabolic modulators may have a better effect relieving symptoms and improving exercise capacity in stable coronary artery disease, devoid of such down regulation, than in heart failure which in itself may induce the down regulation. Presently it has to be acknowledged that no conclusive evidence is available showing the benefit of metabolic modulation in patients with diabetes and heart failure. The subject is of high interest for further studies. These should preferably include detailed myocardial metabolic investigations for example by looking at myocardial glucose oxidation and FFA consumption by means of positron emission tomography or magnetic resonance spectroscopy.

Future directions

In order to establish causal evidence for the relationship between glucose abnormalities and heart failure, epidemiological evidence are needed as well as established time relationship between these disorders. A possible biological explanation of the relationship should be established, surrogate markers in support of the relationship identified followed by clinical trials designed to prove the concept. There are strong indications that these disorders are linked from an epidemiological perspective and evidence has been provided on the time relationship between glucose abnormalities and heart failure. Glucose levels relate to the appearance of both disorders and interventions indicate a relation between improvement in glucose status and myocardial function. Thus there are some indications for a causal relationship between these diseases. It is, however, obvious that further attempts must aim to more precisely identify suitable candidates for metabolic modulation in order to show potential beneficial effects of such treatment. It may be that the "patient model" is to be found among subjects with difficulties to accept β-blockade and among those with a poor glucometabolic state. Another option would be to test the hypothesis that tight metabolic control may delay or perhaps prevent progressive deterioration of first diastolic and subsequently systolic myocardial function in patients with type 2 diabetes.

The present findings support that initiation of screening for glucose abnormalities in heart failure patients and for heart failure in people with diabetes or abnormal glucose regulation should be performed already at an early stage of the respective disorder. The prognosis of patients with these disorders separately or in combination is poor. Thus implementation of already available treatment and a search for novel therapeutic options are important. Physicians must link the most specialized treatment of two common diseases across the borders of two specialties, diabetology and cardiology, not only in clinical practice but also in research aiming to improve the prognosis of patients with glucose abnormalities and heart failure.

Conclusion

Study I
The prevalence of glucose abnormalities and heart failure increases with age. The prevalence of heart failure is doubled in participants with abnormal glucose regulation and again doubled in type 2 diabetes. The association of glucose abnormalities and heart failure is strong.

Study II
Heart failure or glucose abnormalities occurring separately are related to an increased morbidity and mortality, but the combination of these disorders did not significantly worsen the prognosis. Already abnormal glucose regulation is linked to an unfavorable prognosis unrelated to the presence of ischaemic heart disease and to the best of our knowledge shown for the first time in such a large, truly population based study.

Study III
The incidence of heart failure and glucose abnormalities increases with age. There is a linear relationship between fasting glucose levels and future development not only of diabetes but also heart failure. This favours the concept of a closer relation between two common diseases than previously thought. The link between these diseases is supported by a strong association between glucose abnormalities and heart failure. A causal relationship between heart failure and diabetes is, however, not obvious since glucose abnormalities and heart failure did not predict each other independently.

Study IV
GLP-1 seems to be a safe and feasible treatment worth further studies in heart failure patients with type 2 diabetes. Such studies are of great interest in extended attempts to find pharmacological tools improving myocardial metabolism as an alternate supplementary treatment in heart failure management.

Study V
There were only weak signs of improved systolic myocardial function at rest and exercise following the addition of trimetazidine to standard treatment in heart failure patients with type 2 diabetes. The present observations indicate the need of further and mechanistically more detailed research to understand the possible potential with trimetazidine and other metabolic modulators in patients with diabetes and heart failure.

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