41 Congestive Heart Failure

Inga S. Thrainsdottir[1] & Lars Rydén[2]

[1] Department of Cardiology, Landspitali University Hospital, Reykjavik, Iceland
[2] Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden

Keypoints

- There is a strong link between congestive heart failure (CHF), and diabetes and both conditions are becoming increasingly more common.
- The prevalence of the combination of CHF and diabetes was 0.5% in men and 0.4% in women increasing by age in a recent population-based study. Diabetes was found in 12% of those with CHF compared with only 3% of the controls without CHF.
- Diabetes is a serious prognostic factor for cardiovascular mortality in patients with left ventricular dysfunction caused by ischemic heart disease.
- A 1% (11 mmol/mol) reduction in glycated hemoglobin (HbA_{1c}) has been found to reduce CHF by 16%. In this study, the prognosis improved with a decrease in HbA_{1c} without any threshold or observed upper limit.

- Available data favor a proportionately similar efficacy of evidence-based CHF therapy in patients with and without diabetes. The impact expressed as number of patients needed to treat to avoid one event is lower among people with diabetes because of their higher absolute risk.
- Further studies have to be conducted before an aggressive glucose normalization can be recommended as a possibility to improve the prognosis in patients with diabetes and CHF.
- Thiazolidinediones can provoke or worsen CHF. These drugs should be used with great caution in patients with diabetes and heart failure.

Introduction

The concept that there may be a direct relation between diabetes and congestive heart failure (CHF) is not new. In 1954, Lundbaek [1,2] published an article on clinically important complications in patients with diabetes underlining that heart disease was common in patients with diabetes; indeed, it was present in two-thirds of elderly subjects. He was the first to suggest the presence of a diabetes-specific cardiomyopathy. Twenty years later, Rubler *et al.* [3] published supporting data, concluding that myocardial disease seemed to be a complication of the diabetic state and not merely caused by coronary artery disease (CAD). Shortly there-after, the Framingham study presented epidemiologic evidence for a strong relation between CHF and diabetes. The latter study clearly indicated that the relation between diabetes and CHF was not only caused by traditional risk factors for coronary heart disease (CHD), but also involved other mechanisms [4].

The prevalence of CHF is increasing in Western societies because of an aging population and also because of increased survival following ischemic heart disease (IHD), and in particular myocardial infarction (MI) [5]. There are many known causes of CHF, including hypertension, CAD, valvular dysfunction, arrhythmias, anemia, renal failure and thyroid dysfunction [5–9]. Risk factors for the development of CHF include increasing age, valvular heart disease and IHD, particularly previous MI, electrocardiographic signs of left ventricular hypertrophy, cardiomegaly detected by chest X-ray, increased heart rate, hypertension and decreased pulmonary vital capacity; diabetes should be added to this list as a strong risk factor. The Framingham study used several of these risk factors to construct a multivariate risk formula to identify high-risk candidates for CHF [10].

Currently, IHD is the leading cause of CHF in industrialized societies with diabetes as a rapidly emerging risk factor for both CHF and IHD [8,11]. Considering the rapidly growing prevalence of diabetes [12], this means that the combination of diabetes and CHF will become increasingly more common in the future. Poor glucose control contributes to the development of CHF as reflected by the relation between an increase in glycated hemoglobin (HbA_{1c}) and the risk of developing CHF [13]. In an epidemiologic study of an elderly Italian cohort, 9.5% of the participants had CHF and 14.7% diabetes. Interestingly, the prevalence of diabetes among subjects with CHF was high, almost 30%. The association was strengthened

during follow-up, indicating that CHF predicted the appearance of diabetes [14].

In summary, there is a strong link between the existence of CHF and diabetes, and both conditions are becoming increasingly more common. The links between these disorders are complex and not yet fully explored.

Symptoms and diagnosis

Diagnosis and definition of congestive heart failure

The state of the art diagnosis of CHF is based on a combination of clinical symptoms combined with characteristic signs of myocardial dysfunction [5]. In clinical practice, CHF is commonly divided into systolic and diastolic myocardial dysfunction, the latter also being known as heart failure with preserved left ventricular function, with systolic dysfunction representing an impaired capacity to eject blood from the left ventricle and diastolic dysfunction an impaired ventricular filling caused by relaxation abnormalities. Echocardiography is the preferred method for documentation of such dysfunction, and left ventricular ejection fraction is the most commonly used expression for impaired systolic dysfunction. Evidence of abnormal left ventricular relaxation, reduced diastolic distensibility or diastolic stiffness are the echocardiographic signs of diastolic dysfunction. Echocardiography, including tissue Doppler imaging (TDI), is useful in detecting myocardial diastolic dysfunction in people with diabetes as well as in the non-diabetic population [15,16]. Plasma concentrations of natriuretic peptides or their precursors are also helpful for diagnosing CHF in patients, including those with diabetes [5,17]. The main clinical classification of the severity of CHF is that presented by the New York Heart Association (Table 41.1). This classification is used for all patients with CHF irrespective if seen in a hospital or outpatient setting and irrespective of etiology.

Diagnosis and definition of glucose abnormalities

Diabetes and other glucose abnormalities are a group of metabolic disorders characterized by hyperglycemia caused by defects in insulin secretion, insulin action or both. Diabetes is associated with damage, dysfunction and failure of various organs [18]. The metabolic syndrome is an entity that has been defined in various ways [19,20], combining different cardiovascular risk factors including abnormalities in glucose homeostasis. Further details on the classification and diagnosis of different glucose abnormalities are given elsewhere in this book.

Epidemiology

Risk factors for CHF and diabetes

The most important risk factors for cardiovascular disease (CVD) and MI are family history, smoking, abnormal blood lipids, hypertension, diabetes, obesity and socioeconomic factors [21]. Many of the risk factors for CHF are by necessity similar to those for CVD, with IHD and hypertension as leading causes. Other common factors influencing the occurrence of CHF are male gender, smoking, overweight, physical inactivity and valvular heart disease [5]. Type 2 diabetes mellitus (T2DM) as well as poor glucose control observed as high fasting plasma glucose and elevated HbA_{1c} are also of considerable importance [22–27].

Risk factors for T2DM are family history, age, overweight or increased waist:hip ratio and a sedentary lifestyle [28,29]. The morbidity is known to increase progressively with the number of existing risk factors [30]. Particular risk factors for CAD in T2DM are lipid perturbations, including small, dense, easily oxidized low density lipoprotein (LDL) particles, low high density lipoprotein (HDL) cholesterol and increased triglycerides. Moreover, poor glucometabolic control observed as high fasting plasma glucose and elevated HbA_{1c} contribute [31]. Hypertension is another important factor. The Reykjavík Study showed a strong relation between fasting and post load glucose levels and subsequent risk for hypertension, even after adjustment for age, body mass index (BMI) and weight gain, which is interesting because hypertension is one of the main risk factors for CHF [24,25]. Patients with diabetes and CHF have more IHD, increased systolic blood pressure (BP), lower diastolic BP and a higher HbA_{1c} than their counterparts without diabetes [26]. Accordingly, there are many mutual risk factors for CHF and glucose abnormalities.

Prevalence of CHF and glucose abnormalities

The prevalence of CHF varies somewhat in different studies, partly because of differences in the definition of this disease [5]. The demand that a heart failure diagnosis should be supported by evidence of systolic dysfunction on echocardiography may be difficult to fulfill in epidemiologic studies. Modern echocardiographic techniques did not exist when several of the studies, still serving as important sources of information, were conducted [4,32]. The prevalence of CHF has been estimated to be 0.6–6.2% in Swedish men with an increase by age [32]. This is similar to the overall prevalence of CHF among both genders in the Rotterdam population and in the Reykjavík Study [33,34]. The prevalence of CHF was 1–10% in a British outpatient population [35]. 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 [14].

Table 41.1 Classification of congestive heart failure (CHF) according to New York Heart Association (NYHA).

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 complete rest in a bed or a chair

It has been estimated that at least 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 (IGT) [36]. 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 [37,38]. The prevalence of diabetes may be considerably higher in selected high risk populations not the least those with CAD. In the Euro Heart Survey Diabetes and the Heart, patients admitted to hospital because of acute and stable CAD were investigated for the presence of diabetes and IGT. Only 29% of the 4961 patients had a normal glucose metabolism while 31% had known and 12% previously unknown diabetes. The remaining 28% of the patients had IGT [39]. Similar proportions were detected in patient populations with cerebral and peripheral vascular disease [40]. Thus, the combination of CVD and glucose perturbations is very common but underestimated in many previous studies because of lack of diagnostic accuracy in combination with a thorough investigation of the glucometabolic state.

Considerably less is known about the prevalence of the combination of diabetes and CHF. The most recent and extensive study of the prevalence of diabetes and CHF is that from the Reykjavík population [34], in which the prevalence of the combination of CHF and diabetes was 0.5% in men and 0.4% in women, increasing by age. Diabetes was found in 12% of those with CHF compared to only 3% of the controls without CHF. Thus, there was a strong association between diabetes and CHF (Figure 41.1).

Based on Framingham data, Rutter et al. [41] 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. [4] and Gustafsson et al. [42] reported on the role of diabetes in CHF from a general and a hospitalized population, respectively. Their findings indicated a strong association between CHF and diabetes. Iribarren et al. [43], Bertoni et al. [44] and Nichols et al. [26], focusing on the role of CHF in patients
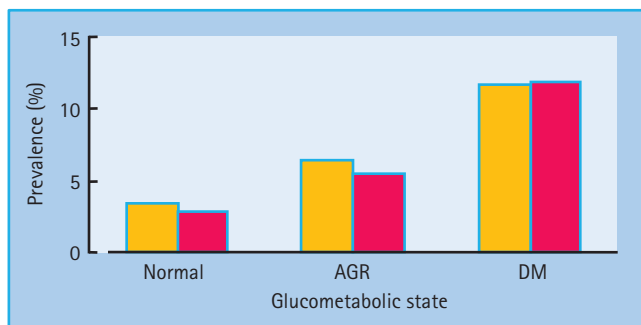
with diabetes, noted that the prevalence of CHF varied between 1.9 and 22.3%. Finally, Amato et al. [14] found a strong association between diabetes and CHF in a population of elderly people. The outcomes of these studies have been summarized in Table 41.2.

Incidence of CHF and glucose abnormalities

Recent results from the Framingham study indicate that the incidence of CHF has declined during the last five decades [45], but these data are not supported in other studies [46]. On the contrary, it seems that hospital admissions for CHF are increasing, resulting in higher health care expenditures for patients with this diagnosis [47]. Among British outpatients, the incidence of CHF has been reported to be 4.4/1000 person-years in men and 3.9/1000 in women, rising with age in both genders [48]. The incidence in Finland is similar among men, 4.0/1000 person-years, but lower in women 1.0/1000 person-years [49].

The age-standardized annual incidence of diabetes, reported to be 2.2 and 2.3/1000 person-years in Dutch men and women, respectively, is rather uniform in several European countries [50]. When turning to an elderly population, however, as in the Italian Campania study, the incidence was considerably higher at 6.1% per year. This is somewhat different from the observation in the Netherlands where the incidence decreased in the oldest age group [14,50].

Considerably less is known about the incidence of the combination of diabetes and CHF. Once more it seems as if the most recent and extensive study originates from the Reykjavík population. In this study, the age and gender standardized incidence of abnormal glucose regulation was 12.6/1000/year, diabetes 4.6/1000/year and CHF 5.3/1000/year (Figure 41.2). In addition, there was a strong association between the incidence of glucose abnormalities and CHF [51].

In the Framingham study, the incidence of CHF was twice that among males and five times higher in females with diabetes during 18 years of follow-up than patients free from diabetes. The excessive risk of CHF remained high even after the exclusion of patients with prior CAD [4]. In a general population of elderly Italians, the prevalence of diabetes was 9.6% per year in CHF patients [14].

Pathophysiology

Myocardial structural and biochemical alterations can be identified in the failing heart, and many of them seems to be independent of the etiology of myocardial dysfunction. They include changes in myocardial energy production, altered expression of contractile proteins, a desynchronized excitation–contraction coupling, β-adrenergic receptor stimulation, myocyte depletion and increased activity of a number of cytokines. Many of these aberrations are found in diabetic heart. Here, some general features of the pathophysiology are followed by a discussion of more diabetes-specific factors.

Figure 41.1 Prevalence of congestive heart failure (CHF) in relation to glucometabolic state. Yellow bars, males; red bars, females; AGR, abnormal glucose regulation; DM, diabetes. Reproduced from Thrainsdottir et al. [34], with permission from American Diabetes Association.

Table 41.2 Comparison of the prevalence, incidence and prediction of heart failure and diabetes in general populations and among patients.

Study name	Campania	Heart failure in patients with diabetes			Patients with diabetes and heart failure	
		Medicare sample	Kaiser Permanente	Kaiser Permanente	DIAMOND	Framingham
Authors [ref]	Amato *et al.* [14]	Bertoni *et al.* [44]	Iribarren *et al.* [43]	Nichols *et al.* [26]	Gustafsson *et al.* [42]	Kannel *et al.* [4]
Participants (no)	1339	151738	48858	9591	5491	5209
Follow-up (years)	3	5	2.2	2.5	5–8	18
Period	<1997	1994–1999	1995–1997	<1997	1993–2003	1949–
Age	74 (mean) (all >65)	73–76 (all >65)	58 (mean)		52–86, (mean 73)	30–62
CHF prevalence	9.5 %	22.3%	1.9%	11.8% in people with DM, 4.5% in controls	–	–
Diabetes prevalence	14.7	–	–	–	14.7% (T2DM)	–
Diabetes and CHF association	OR 2.0 CI (1.6–2.5)	–	–	–	–	RR men 2.4 women 5.1
Diabetes incidence	9.6%/year in CHF patients 6.1%/year in controls	–	–	–	–	
CHF incidence	–	12.6/100 PY	–	3.3/100 PY in people with DM, 1.5/100 PY in controls	–	17.5/1000 PY among men, 18.5/1000 PY among women In people with DM 9/1000 PY in men, 14/1000 PY in women
Diabetes predictive factors	CHF OR 1.4 (1.1–1.8)	–	–	–	–	–
CHF predictive factors	BMI, Waist:hip ratio	Men, Caucasians, IHD, hypertension, stroke, PVD, nephropathy, retinopathy, neuropathy	–	Age, female, diabetes duration, insulin, IHD, creatinine, glucose	–	Diabetes, males
Diabetes mortality	–	–		–	RR 1.5 in diabetes patients	–
Other endpoint	–	–	1% (11 mmol/mol) increase in HbA$_{1c}$ => increased risk of CHF by 8%	–	–	–

BMI, body mass index; CHF, congestive heart failure; CI, confidence interval; DM, diabetes mellitus; IHD, ischemic heart disease; OR, odds ratio; PVD, peripheral vascular disease; PY, person-years; RR, relative rate.
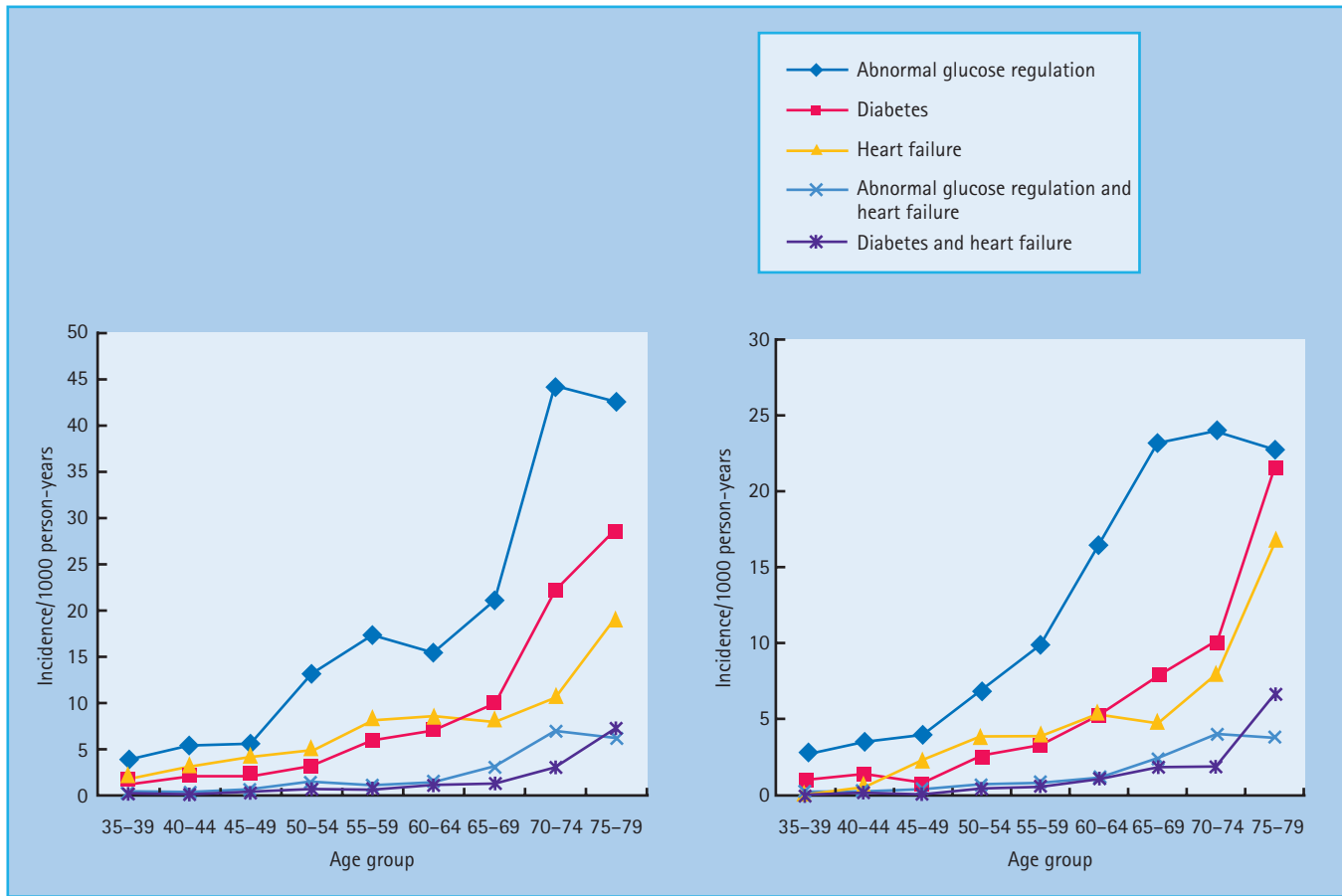
Congestive heart failure

CHF 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 are all linked to the vicious cycle of myocardial remodeling (Figure 41.3) which unopposed will cause successive deterioration of myocardial performance [52].

Metabolic conditions have a significant role in cardiac adaptation and remodeling. This leads to an increase of myosin heavy chain beta, altered troponin T (TnT) molecules, diminished storage of creatinine phosphatases, and decreased sarcoplasmatic ATPase activity, which may result in myocyte hypertrophy associated with impaired contractile function and less effective energy supply [53,54].

The myocardium has a high energy turnover with ATP as an important source of energy. The two pathways for energy supply are via the breakdown of free fatty acids (FFA) and of carbohydrates (Figure 41.4). The lipolytic pathway transfers FFA via β-oxidation to acetyl co-enzyme A (ACA), which enters the citric acid or Krebs cycle. The carbohydrate pathway produces pyruvate via glycolysis, glycogenolysis and lactate oxidation. Pyruvate is

Figure 41.2 Incidence of abnormal glucose regulation, diabetes, congestive heart failure (CHF), abnormal glucose regulation and CHF, and diabetes and CHF expressed as number of incident cases/1000 person years among men (left) and women (right) by age. Reproduced from Thrainsdottir *et al.* [51], with permission from Oxford University Press.
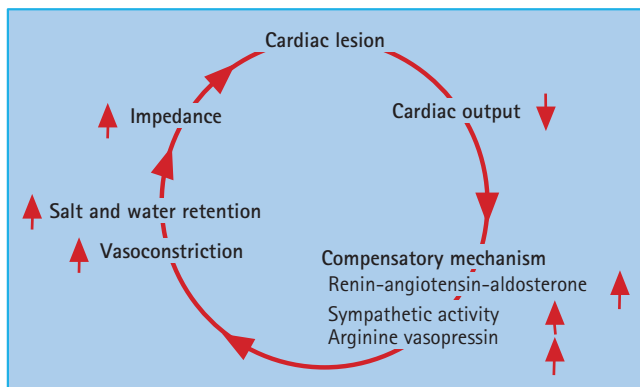

Figure 41.3 Neurohormonal activation caused by depressed myocardial function leads to a vicious circle further compromising the already compromised myocardial function.

decarboxylated via pyruvate dehydrogenase to ACA, which enters the Krebs cycle. The dominant pathway for myocardial energy production is β-oxidation of FFA, but the myocardium is also dependent on glucose oxidation [55].

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 [56]. This may be counteracted by a reduction of the glucose transporter 4 (GLUT-4), which becomes reduced in CHF, hampering glucose transport over the cell membrane. At the same time, the heart is subjected to increased FFA concentrations, released via stress influenced by an increased sympathetic tone [57]. It is assumed that prolonged intracellular accumulation of FFA and its metabolites may cause myocardial dysfunction [58].

Besides these mechanisms, alterations in gene expression and inflammatory activity have been suggested to cause metabolic and mechanical disturbances in CHF [59–62]. All nucleated cells, including the cardiomyocyte, can produce pro-inflammatory cytokines as a response to injury such as MI, myocarditis or when the heart fails. Both tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) levels increase in proportion to the severity and duration of CHF [59,60]. This cytokine release may trigger a cascade of events leading to myocardial structural alterations further deteriorating the clinical picture of CHF.

Figure 41.4 Schematic illustration of myocardial energy production of relevance for congestive heart failure (CHF) patients with and without diabetes. The site of action for metabolic modulators are indicated. See text for further information. CoA, co-enzyme A; FFA, free fatty acids; PDH, pyruvate dehydrogenase.
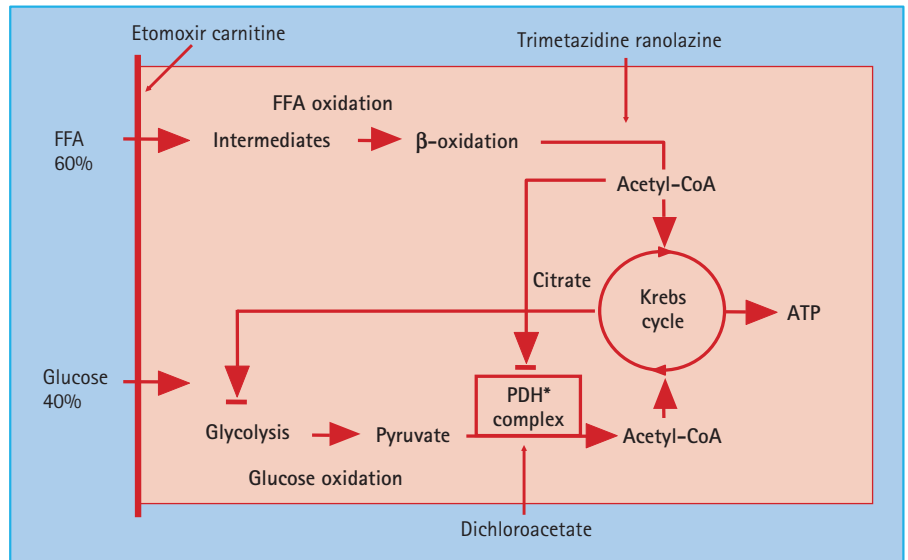
Figure 41.5 Metabolic effects of hyperglycemia induced activation of protein kinase C (PKC) and diacyloglycerol (DAG). See text for further explanation. ANP and BNP, atrial and brain natriuretic peptide; eNOS, endothelial nitrous oxide synthase; ET-1, endothelin 1; PAI-1, plasminogen activating inhibitor 1; PG, prostaglandin; PLA$_2$, phospholipase A$_2$; TGF-β, transforming growth factor β; VEGF, vascular endothelial growth factor.
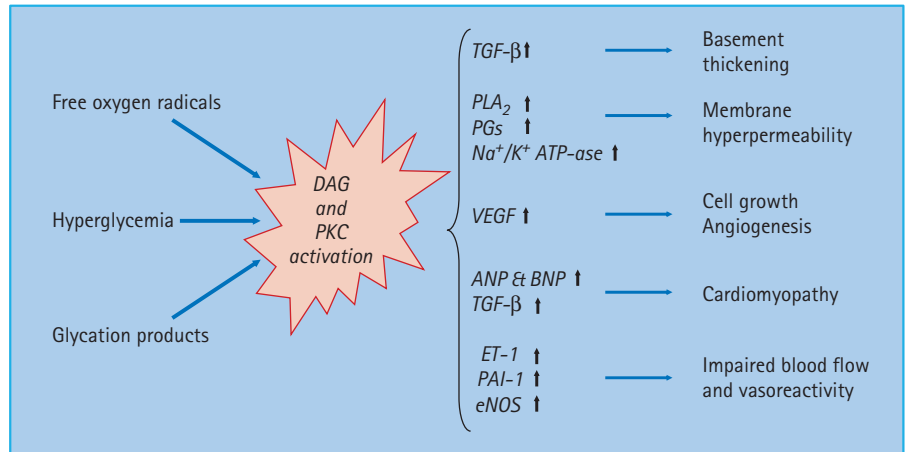
CHF and diabetes

The main myocardial energy production is normally based on β-oxidation of FFA (70%) with a smaller contribution from glucose oxidation (30%) and lactate. FFA are produced by lipolysis of endogenous cardiac or exogenous stores of triglycerides. Oxidation of FFA is an effective supplier of energy in the form of ATP if the oxygen supply is sufficient. In conditions with limited oxygen availability, glucose oxidation will provide more energy per mole oxygen and support more work than FFA [63]. In the person with diabetes, glucose utilization for energy production is substantially lower, about 10% (Figure 41.4). The shift to an even more pronounced β-oxidation of FFA causes a higher oxygen utilization than under normal circumstances [64]. The major restriction to glucose utilization in the diabetic heart is the slow rate of glucose transport across the sarcolemmal membrane in the myocardium [65,66]. The impaired glucose oxidation in the diabetic heart can also result from a decreased rate of phosphory-

lation of glucose which subsequently limits the entry of glucose into the cell. The depressed phosphorylation is triggered by the increased metabolism of FFA [64]. Insulin deficiency enhances lipolysis thereby increasing circulating FFA [67]. People with diabetes 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 [68–71]. Indeed, CHF is an insulin-resistant state with an increased release of non-esterified fatty acids which are taken up in muscular tissue and downregulate glucose uptake and utilization [72].

Another consequence of hyperglycemia is oxidative stress and activation of processes triggered by an increased level of diacylglycerol and protein kinase C as depicted in Figure 41.5. Besides, many other unfavorable effects of the increased levels of inflammatory cytokines in heart failure patients may enhance insulin resistance [71,72].

Prognosis

CHF in general

During the past 30 years, mortality from CHD has declined markedly among patients free from diabetes. This decline has been substantially lower in men but is not seen in women with diabetes [73]. In the presence of CHF, the prognosis becomes poor [74]. In an English population, 1 month survival was 81% after incident CHF, declining to 57% after 18 months [8,75]. The annual mortality in a study of patients hospitalized for CHF was 10–20% with mild–moderate and 40–60% with severe symptoms [35]. The mortality in an elderly population with CHF recruited in Rotterdam was 47% during 6 years of follow-up. This is twice that of persons without CHF [74]. In a comparable Italian study, the mortality rate was 21.3% after 3 years [14]. Thus, CHF is a malignant disease irrespective of the underlying reason for myocardial dysfunction. Recent reports have been somewhat more encouraging. A 50-year follow-up of the Framingham data indicates that CHF survival has improved to some extent [45]. This observation is supported by a report based on the Swedish hospital discharge registry [76].

Diabetes and CHF

CVD is the most prevalent complication of diabetes and is of major importance. Cardiovascular mortality in men with diabetes lies between the mortality for men with angina and MI [77]. In the USA, it has been estimated that 77% of all hospitalizations for chronic complications of diabetes are attributable to CVD [78]. T2DM doubles the risk of death from CHD, and T2DM diagnosed at the age of 55 years reduces life expectancy by about 5 years [79]. This makes mortality from CVD in people with diabetes but without previous MI similar to the mortality in patients with a history of MI but without diabetes [80].

The prognosis of patients with diabetes becomes even worse in the presence of CHF [81–84]. In the first DIGAMI study, performed in patients with diabetes and acute MI, CHF was the most common reason for morbidity and mortality, accounting for 66% of the total mortality during the first year of follow-up [85]. Diabetes is a serious prognostic factor for cardiovascular mortality in patients with left ventricular dysfunction caused by IHD [86]. In a general population in Reykjavík, the survival decreased significantly with the concomitant presence of both CHF and glucose abnormality even after adjustment for cardiovascular risk factors and IHD [87], which may serve as an indicator of the serious implication of the presence of diabetes along with CHF.

Hyperglycemia and prognosis

The relationship between plasma glucose and mortality has been elucidated in several studies. According to the UK Prospective Diabetes Study (UKPDS), a 1% (11 mmol/mol) reduction in HbA_{1c} is associated with a reduction of MI by 14% and CHF by 16%. In this study, the prognosis improved with a decrease in HbA_{1c} without any threshold or observed upper limit [88]. In the DECODE study, a 2-hour post load glucose was a better predictor of mortality than fasting blood glucose [89]. This may perhaps be seen as an indicator of the importance of post-prandial hyperglycemia and the potentially serious implication of IGT for myocardial function.

Treatment

General aspects

Evidence-based treatment of CHF relies on a combination of angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs), beta-blockers, diuretics and aldosterone antagonists [5]. ACE inhibitors, ARBs and beta-blockers reduce mortality and improve symptoms in moderate to severe CHF with or without diabetes [90–93]. Diuretics are mandatory for symptomatic treatment of fluid overload, but should not be used in excess because they induce neurohormonal activation [94]. The addition of aldosterone antagonists is indicated in severe forms of CHF and may then improve longevity [95]; however, many patients are, although symptomatically improved, left with an unfavorable vital prognosis despite the best available pharmacologic treatment. A search for novel treatment modalities is therefore still ongoing. One of these is metabolic modulation with compounds that influence the disturbed metabolic pathways in CHF and which are thought to be of particular importance in patients with diabetes [55]. Attention has been paid to compounds that shift energy production from β-oxidation of FFA towards the energetically more efficient glucose oxidation under such conditions as in myocardial ischemia and CHF. Examples of such drugs are trimetazidine, ranolazine, etomoxir and dichloroacetate [96,97].

Various techniques have been used to study the efficacy of pharmacologic treatment in CHF. Among them are the general feeling of well-being as assessed by means of different questionnaires, and an estimation of physical capacity tested by exercise tolerance on a bicycle ergometer or treadmill. Two-dimensional echocardiography is the most commonly applied technique for investigating myocardial function [98–101]. A relatively newly developed technique, TDI assesses myocardial function in different myocardial segments. This technique is useful for diagnosing left ventricular dysfunction even before any symptoms or signs of CHF appear in subjects with diabetes [102–104].

Guidelines that specifically deal with diabetes and CVD including CHF have not been available until recently. Through a combined initiative by the European Society of Cardiology (ESC) and the European Association of the Study of Diabetes (EASD), guidelines on the management of diabetes, pre-diabetes and CVD were published in 2007 [105]. As outlined in this document, there are few trials that specifically address the treatment of patients with the combination of glucose abnormalities and CHF, causing a lack of specific evidence regarding the management of such patients. Current data are mostly based on analyses of subgroups

Table 41.3 The effect of inhibition of the renin angiotensin system in congestive heart failure (CHF) trials by diabetic state.

Study [ref]	Participants (no)	Diabetes (%)	Outcome
CONSENSUS [109]	253	18	31% reduction of 1-year mortality
SAVE [114]	2231	22	19% all cause mortality risk reduction
			21% risk reduction of cardiovascular morbidity
ATLAS [112]	3164	19	14% mortality risk reduction with high dose ACE inhibitor treatment
GISSI 3 [115]	18 131	15	30% reduction in mortality after 6 weeks

ACE, angiotensin-converting enzyme.

Figure 41.6 The impact of the beta-blocker metoprolol on the combined end-point mortality or hospitalization in congestive heart failure (CHF) patients with and without diabetes participating in the MERIT-HF trial [124,125]. Note that the relative risk reduction (given in % above bars) is independent of diabetic state but that the absolute mortality even with metoprolol treatment is considerably higher in the diabetic subgroup. Dark green bars, placebo; light green bars, metoprolol.
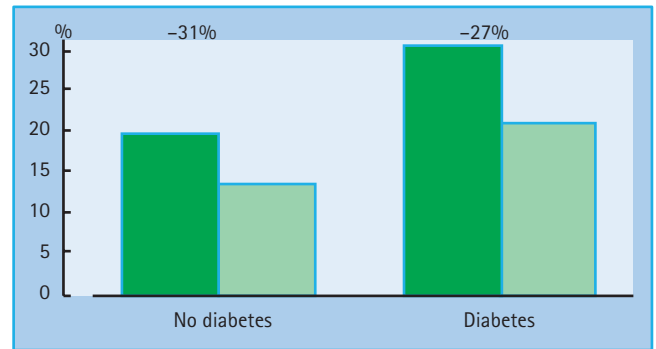
of patients with diabetes in large CHF trials. This results in potential shortcomings related to a poor definition of diabetes and hidden diabetes, actual glucose lowering therapy and also a risk for selection biases with an overrepresentation of less severe diabetes. With these limitations in mind, available data favor a proportionately similar efficacy in patients with and without diabetes. Because the absolute prognosis is considerably worse in patients with diabetes, the impact of therapy expressed as number of patients needed to treat to avoid an event (e.g. hospitalization for CHF or death) is considerably lower among these patients than their counterparts without diabetes.

Pharmacologic therapy of CHF
ACE inhibition
ACE inhibitors are recommended both in asymptomatic myocardial dysfunction and overt CHF. As shown in Table 41.3, they reduce mortality and improve symptoms in moderate to severe CHF with and without diabetes [106–110]. Patients with diabetes represent rather large subgroups in several trials. In SOLVD, the effect of enalapril on compromised left ventricular function was similar in patients with and without diabetes [111]. In ATLAS, comparing a high and a low dose lisinopril treatment strategy, mortality reduction was at least as good in patients with as in those without diabetes [112]. The GISSI 3 and the SAVE trials reported beneficial effects on morbidity and mortality of ACE inhibitor treatment in post-MI patients with diabetes [113–115].

Because hypoglycemic episodes may be provoked by ACE inhibitor therapy in patients on glucose lowering therapy, it is recommended that plasma glucose is monitored in the early phase of the institution of an ACE inhibitor in patients on glucose lowering treatment [116,117].

Angiotensin receptor blockers
The use of ARBs is an alternative to ACE inhibition and may even be used in combination with ACE inhibition in severe CHF. ARBs improve morbidity and mortality in CHF patients with and without diabetes [118,119].

Beta-blockers
Beta-blockade decreases myocardial FFA exposure and therefore such treatment has the capacity to influence the metabolic pathway favorably in patients with T2DM and CHF [120,121]. Subgroup analyses of patients with diabetes and moderate to severe CHF participating in large trials reveal that beta-blockers reduce mortality and improve symptoms. Therefore, beta-blockers are indicated as first-line treatment in patients with the combination of CHF and diabetes [122–126]. An example of the impact of beta-blockade (metoprolol) added to treatment with ACE inhibitors and diuretics in CHF patients with and without diabetes is given in Figure 41.6. It is worthy of note that the relative risk reduction following metoprolol is similar in the two groups. The remaining event rate is still substantially higher in the diabetic cohort than among those without diabetes.

Diuretics and aldosterone antagonists
Diuretics are mandatory for symptomatic relief of fluid overload. As already underlined, they should not be used in excess because they induce neurohormonal activation [94]. Loop diuretics are recommended rather than diuretics that may further impair glucose metabolism. The addition of aldosterone antagonists is indicated in severe forms of CHF and may improve longevity [127]; however, no information is available on the administration of aldosterone antagonists in patients with diabetes and CHF.

Statins

It has been debated for some time whether statin treatment may impact morbidity and longevity in patients with CHF. Two recent clinical trials, the Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) and GISSI Heart Failure (GISSI-HF), were both negative in this respect [128,129]. It is therefore not indicated to include statin therapy as part of the management of CHF if not needed for other reasons.

Glucose lowering treatment

General aspects

In accordance with the pathophysiologic aspects on CHF in patients with diabetes, it has been postulated that meticulous metabolic control may have beneficial effects on progress and prognosis. The European guidelines for the management of diabetes recommend that HbA_{1c} should be <6.5% (48 mmol/mol) and plasma glucose fasting <6 mmol/L (<108 mg/dL) and postprandial <7.5 mmol/L (<135 mg/dL) [105]. The scientific evidence, as derived from properly designed clinical trials, behind these recommendations seem sparse even if they are somewhat more solid for type 1 diabetes (T1DM) than T2DM [130]. The negative outcome of some recent trials on aggressive glucose lowering have further underlined the uncertainty in this respect [131,132]; however, these trials did not specifically look at patients with CHF. Further studies are yet to be conducted on this category of patient before aggressive glucose normalization can be recommended as a possibility to improve their situation. Currently, it seems as if such assumptions reflect information from epidemiologic studies showing increased risk with increasing levels of plasma glucose and HbA_{1c} starting well below what has currently been labeled as normal.

Glucose lowering agents

Regarding specific glucose lowering agents, there is some information available of importance for the choice of treatment in patients with or at risk for heart failure. The insulin sensitizers thiazolidinediones can provoke or worsen CHF because of their propensity to induce fluid retention. These drugs should be used with great caution in patients in New York Heart Association class I–II and are considered contraindicated in those in class III–IV [133–136]. Metformin is also contraindicated in CHF because of the risk of lactic acidosis.

Insulin treatment in patients with diabetes and CHF is under debate. The main effect of insulin is to decrease blood glucose, but it may also increase myocardial blood flow, decrease heart rate and cause a modest increase in cardiac output [137,138]. Beneficial effects on myocardial function have been reported, but also that insulin may be associated with increased morbidity [139] and mortality [140,141]. Further studies are needed to establish the specific role of insulin beyond the role as a glucose lowering agent in patients with diabetes and CHF.

In general, it may be summarized that there is very little information available of importance for the choice of agents for glycemic control in patients with diabetes and CHF. Thus, generally accepted management rules should apply [142].

Diastolic congestive heart failure

Impaired myocardial diastolic function and endothelial dysfunction are early expressions of diabetes-related cardiovascular involvement causing a decreased myocardial blood flow reserve. It has been suggested that hyperglycemia-related early myocardial and microcirculatory disturbances are dynamic and that they may be reversed by improved metabolic control [143]. An observational study by von Bibra *et al.* [144], on patients subjected to intensified glucose control in clinical routine, gave support to the assumption that particularly insulin-based glycemic control may be useful. Unfortunately, these observations were not verified in a recent prospective study, the Diabetes mellitus And Diastolic Dysfunction (DADD) trial, randomly distributing patients with T2DM and early signs of diastolic dysfunction to insulin or oral based glucose normalization. The patients were selected to be free from previous cardiovascular events and signs of CHF or CAD [145]. It should be underlined that it is still too early to abandon the hypothesis of a favorable relation between glycemic control and myocardial diastolic dysfunction. It may be that the DADD patients were too healthy to react to normalization of glucose control. Thus, it would be of value to study new agents, such as incretins, in future trials and to recruit patients at a more advanced disease stage than those selected for the DADD study. The problem is then the obvious risk for biases caused by hypertension and CAD and other complications to diabetes. Accordingly, such protocols must include detailed examinations of the patients with this in mind.

Metabolic modulators

Drugs, such as trimetazidine, etomoxir and dichloroacetate, whose mode of action is to shift myocardial metabolism from oxidation of FFA towards glycolysis have been tested in patients with myocardial dysfunction and diabetes. They act on different parts of the metabolic pathways as indicated in Figure 41.4. Their usefulness must be further explored in clinical trials of appropriate design until their therapeutic role can be considered established despite some recent promising results [146–148].

References

1 Lundbaek K. Diabetic angiopathy: a specific vascular disease. *Lancet* 1954; **263**:377–379.

2 Lundbaek K. Is there a diabetic cardiopathy? In: Schettler G, ed. *Pathogenetishe Faktoren des Myokardinfarkts*. Stuttgart: Schattauer, 1969: 63–71.

3 Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* 1972; **30**:595–602.

4 Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974; **34**:29–34.

5 Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, *et al.*; Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of

Cardiology. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008; **29**:2388–2442.

6 Eriksson H, Svärdsudd K, Larsson B, Ohlson LO, Tibblin G, Welin L, *et al.* Risk factors for heart failure in the general population: the study of men born in 1913. *Eur Heart J* 1989; **10**:647–656.

7 Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol* 1992; **20**:301–306.

8 Massie BM, Shah NB. Evolving trends in the epidemiologic factors of heart failure: rationale for preventive strategies and comprehensive disease management. *Am Heart J* 1997; **133**:703–712.

9 Chae CU, Pfeffer MA, Glynn RJ, Mitchell GF, Taylor JO, Hennekens CH. Increased pulse pressure and risk of heart failure in the elderly. *JAMA* 1999; **281**:634–639.

10 Kannel WB, D'Agostino RB, Silbershatz H, Belanger AJ, Wilson PW, Levy D. Profile for estimating risk of heart failure. *Arch Intern Med* 1999; **159**:1197–1204.

11 Soläng L, Malmberg K, Rydén L. Diabetes mellitus and congestive heart failure. *Eur Heart J* 1999; **20**:789–795.

12 King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998; **21**:1414–1431.

13 Chae CU, Glynn RJ, Manson JE, Guralnik JM, Taylor JO, Pfeffer MA. Diabetes predicts congestive heart failure risk in the elderly. *Circulation* 1998; **98**(Suppl 1):721.

14 Amato L, Paolisso G, Cacciatore F, Ferrara N, Ferrara P, Canonico S, *et al.*; Osservatorio Geriatrico Regione Campania Group. Congestive heart failure predicts the development of non-insulin-dependent diabetes mellitus in the elderly. *Diabetes Metab* 1997; **23**:213–218.

15 Hatle L. How to diagnose diastolic heart failure a consensus statement. *Eur Heart J* 2007; **28**:2421–2423.

16 Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, *et al.* How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007; **28**:2539–2550.

17 Epshteyn V, Morrison K, Krishnaswamy P, Kazanegra R, Clopton P, Mudaliar S, *et al.* Utility of B-type natriuretic peptide (BNP) as a screen for left ventricular dysfunction in patients with diabetes. *Diabetes Care* 2003; **26**:2081–2087.

18 Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; **15**:539–553.

19 WHO. *Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1: Diagnosis and classification of diabetes mellitus.* Geneva: World Health Organization, Department of Noncommunicable Disease Surveillance, 1999.

20 American Diabetes Association. Clinical practice recommendations 2004. *Diabetes Care* 2004; **27**(Suppl 1):5–19.

21 Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, *et al.*; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. *Lancet* 2004; **364**:937–952.

22 He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women. NHANES I. Epidemiologic follow-up study. *Arch Intern Med* 2001; **161**:996–1002.

23 Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, *et al.* Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *Br Med J* 2000; **321**:405–412.

24 Kristiansson K, Sigfusson N, Sigvaldason H, Thorgeirsson G. Glucose tolerance and blood pressure in a population-based cohort study of males and females: the Reykjavik Study. *J Hypertens* 1995; **13**:581–586.

25 McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham Study. *N Engl J Med* 1971; **285**:1441–1446.

26 Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care* 2004; **27**:1879–1884.

27 Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, *et al.* Obesity and the risk of heart failure. *N Engl J Med* 2002; **347**:305–313.

28 Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, *et al.*; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; **344**:1343–1350.

29 Simpson RW, Shaw JE, Zimmet PZ. The prevention of type 2 diabetes: lifestyle change or pharmacotherapy? A challenge for the 21st century. *Diabetes Res Clin Pract* 2003; **59**:165–180.

30 Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; **16**:434–444.

31 Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, *et al.*; UK Prospective Diabetes Study Group. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: UK Prospective Diabetes Study (UKPDS: 23). *Br Med J* 1998; **316**:823–828.

32 Wilhelmsen L, Rosengren A, Eriksson H, Lappas G. Heart failure in the general population of men: morbidity, risk factors and prognosis. *J Intern Med* 2001; **249**:253–261.

33 Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A, *et al.* Prevalence of heart failure and left ventricular dysfunction in the general population: the Rotterdam Study. *Eur Heart J* 1999; **20**:447–455.

34 Thrainsdottir IS, Aspelund T, Thorgeirsson G, Gudnason V, Hardarson T, Malmberg K, *et al.* The association between glucose abnormalities and heart failure in the population based Reykjavík study. *Diabetes Care* 2005; **28**:612–616.

35 Dargie HJ, McMurray JJ, McDonagh TA. Heart failure: implications of the true size of the problem. *J Intern Med* 1996; **239**:309–315.

36 Buysschaert M, Vandenbroucke C, Barsoum S. A type 2 diabetes screening program by general practitioners in a Belgian at risk population. *Diabetes Metab* 2001; **27**:109–114.

37 Andersson DK, Svardsudd K, Tibblin G. Prevalence and incidence of diabetes in a Swedish community 1972–1987. *Diabet Med* 1991; **8**:428–434.

38 Tuomilehto J, Korhonen HJ, Kartovaara L, Salomaa V, Stengård JH, Pitkänen M, *et al.* Prevalence of diabetes mellitus and impaired glucose tolerance in the middle-aged population of three areas in Finland. *Int J Epidemiol* 1991; **20**:1010–1017.

39 Bartnik M, Rydén L, Ferrari R, Malmberg K, Pyörälä K, Simoons M, *et al.*; Euro Heart Survey Investigators. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe: the Euro Heart Survey on diabetes and the heart. *Eur Heart J* 2004; **25**:1880–1890.

40 Johansen OE, Birkeland KI, Brustad E, Aaser E, Lindahl AK, Midha R, *et al.* Undiagnosed dysglycaemia and inflammation in cardiovascular disease. *Eur J Clin Invest* 2006; **36**:544–551.

41 Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, *et al.* Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. *Circulation* 2003; **107**:448–454.

42 Gustafsson I, Brendorp B, Seibaek M, Burchardt H, Hildebrandt P, Kober L, *et al.*; DIAMOND Study Group. Influence of diabetes and diabetes–gender interaction on the risk of death in patients hospitalized with congestive heart failure. *J Am Coll Cardiol* 2004; **43**:771–777.

43 Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, *et al.* Glycemic control and heart failure among adult patients with diabetes. *Circulation* 2001; **103**:2668–2673.

44 Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care* 2004; **27**:699–703.

45 Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, *et al.* Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002; **347**:1397–1402.

46 Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, *et al.* Congestive heart failure in the community: trends in incidence and survival in a 10-year period. *Arch Intern Med* 1999; **159**:29–34.

47 Dominguez LJ, Parrinello G, Amato P, Licata G. Trends of congestive heart failure epidemiology: contrast with clinical trial results. *Cardiologia* 1999; **44**:801–808.

48 Johansson S, Wallander MA, Ruigómez A, Garcia Rodríguez LA. Incidence of newly diagnosed heart failure in UK general practice. *Eur J Heart Fail* 2001; **3**:225–231.

49 Remes J, Reunanen A, Aromaa A, Pyörala K. Incidence of heart failure in eastern Finland: a population-based surveillance study. *Eur Heart J* 1992; **13**:588–593.

50 Ubink-Veltmaat LJ, Bilo HJ, Groenier KH, Houweling ST, Rischen RO, Meyboom-de Jong B. Prevalence, incidence and mortality of type 2 diabetes mellitus revisited: a prospective population-based study in the Netherlands (ZODIAC-1). *Eur J Epidemiol* 2003; **18**:793–800.

51 Thrainsdottir I, Aspelund T, Gudnason V, Malmberg K, Sigurdsson G, Thorgeirsson G, *et al.* Increasing glucose levels and BMI predict future heart failure: experiences from the Reykjavik Study. *Eur J Heart Fail* 2007; **9**:1051–1057.

52 Mann DL. Mechanisms and models in heart failure: a combinatorial approach. *Circulation* 1999; **100**:999–1008.

53 Young ME, McNulty P, Taegtmeyer H. Adaptation and maladaptation of the heart in diabetes. Part II: potential mechanisms. *Circulation* 2002; **105**:1861–1870.

54 Guzik TJ, Mussa S, Gastaldi D, Sadowski J, Ratnatunga C, Pillai R, *et al.* Mechanisms of increased vascular superoxide production in human diabetes mellitus: role of NAD(P)H oxidase and endothelial nitric oxide synthase. *Circulation* 2002; **105**:1656–1662.

55 Stanley WC. Metabolic dysfunction in the diabetic heart. In: Stanley WC, Rydén L, eds. *The Diabetic Coronary Patient*. London: Science Press, 1999: 13–28.

56 Taegtmeyer H. Cardiac metabolism as a target for the treatment of heart failure. *Circulation* 2004; **110**:894–896.

57 Murray AJ, Anderson RE, Watson GC, Radda GK, Clarke K. Uncoupling proteins in human heart. *Lancet* 2004; **364**:1786–1788.

58 Pogatsa G: Metabolic energy metabolism in diabetes: therapeutic implications. *Coron Artery Dis* 2001; **12**(Suppl 1):S29–S33.

59 Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol* 1996; **27**:1201–1206.

60 Dibbs Z, Thornby J, White BG, Mann DL. Natural variability of circulating levels of cytokines and cytokine receptors in patients with heart failure: implications for clinical trials. *J Am Coll Cardiol* 1999; **33**:1935–1942.

61 Sack MN, Rader TA, Park S, Bastin J, McCune S, Kelly DP. Fatty acid oxidation enzyme gene expression is downregulated in the failing heart. *Circulation* 1996; **94**:2837–2842.

62 Razeghi P, Young ME, Alcorn JL, Moravec CS, Frazier OH, Taegtmeyer H. Metabolic gene expression in fetal and failing human heart. *Circulation* 2001; **104**:2923–2931.

63 Wolff AA, Rotmensch HH, Stanley WC, Ferrari R. Metabolic approaches to the treatment of ischemic heart disease: the clinicians' perspective. *Heart Fail Rev* 2002; **7**:187–203.

64 Rodrigues B, Cam MC, McNeill JH, Metabolic disturbances in diabetic cardiomyopathy. *Mol Cell Biochem* 1998; **180**:53–57.

65 Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* 1963; **1**:785–789.

66 Garvey WT, Huecksteadt TP, Birnbaum MJ. Pretranslational suppression of an insulin-responsive glucose transporter in rats with diabetes mellitus. *Science* 1989; **245**:60–63.

67 Rodrigues B, McNeill JH. The diabetic heart: metabolic causes for the development of a cardiomyopathy. *Cardiovasc Res* 1992; **26**:913–922.

68 Williams SB, Goldfine AB, Timimi FK, Ting HH, Roddy MA, Simonson DC, *et al.* Acute hyperglycemia attenuates endothelium-dependent vasodilation in humans *in vivo*. *Circulation* 1998; **97**:1695–1701.

69 Yokoyama I, Momomura S, Ohtake T, Yonekura K, Nishikawa J, Sasaki Y, *et al.* Reduced myocardial flow reserve in non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol* 1997; **30**:1472–1477.

70 Woodfield SL, Lundergan CF, Reiner JS, Greenhouse JS, Thompson MA, Rohrbeck SC, *et al.* Angiographic findings and outcome in diabetic patients treated with thrombolytic therapy for acute myocardial infarction: the GUSTO-I experience. *J Am Coll Cardiol* 1996; **28**:1661–1669.

71 Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. *JAMA* 1979; **241**:2035–2038.

72 Swan JW, Anker SD, Walton C, Godsland IF, Clark AL, Leyva F, *et al.* Insulin resistance in chronic heart failure: relation to severity and etiology of heart failure. *J Am Coll Cardiol* 1997; **30**:527–532.

73 Gu K, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. *JAMA* 1999; **281**:1291–1297.

74 Mosterd A, Cost B, Hoes AW, de Bruijne MC, Deckers JW, Hofman A, *et al.* The prognosis of heart failure in the general population: the Rotterdam Study. *Eur Heart J* 2001; **22**:1318–1327.

75 Cowie MR, Wood DA, Coats AJ, Thompson SG, Suresh V, Poole-Wilson PA, *et al.* Survival of patients with a new diagnosis of heart failure: a population based study. *Heart* 2000; **83**:505–510.

76 Schaufelberger M, Swedberg K, Koster M, Rosen M, Rosengren A. Decreasing one-year mortality and hospitalization rates for heart failure in Sweden: data from the Swedish Hospital Discharge Registry 1988 to 2000. *Eur Heart J* 2004; **25**:300–307.

77 Wannamethee SG, Shaper AG, Lennon L. Cardiovascular disease incidence and mortality in older men with diabetes and in men with coronary heart disease. *Heart* 2004; **90**:1398–1403.

78 Wingard DL, Barrett-Connor E. Heart disease and diabetes. In: Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennet PH, eds. *Diabetes in America*, 2nd edn. Washington DC: US Government Office, 1995: 429–448.

79 Vilbergsson S, Sigurdsson G, Sigvaldason H, Sigfusson N. Coronary heart disease mortality amongst non-insulin-dependent diabetic subjects in Iceland: the independent effect of diabetes. The Reykjavik Study 17-year follow up. *J Intern Med* 1998; **244**:309–316.

80 Haffner SM, Lehto S, Ronnemaa T, Pyörala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; **339**:229–234.

81 Stone PH, Muller JE, Hartwell T, York BJ, Rutherford JD, Parker CB, *et al.*; MILIS Study Group. The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis. *J Am Coll Cardiol* 1989; **14**:49–57.

82 Gwilt DJ, Petri M, Lewis PW, Nattrass M, Pentecost BL. Myocardial infarct size and mortality in diabetic patients. *Br Heart J* 1985; **54**:466–472.

83 Singer DE, Moulton AW, Nathan DM. Diabetic myocardial infarction: interaction of diabetes with other preinfarction risk factors. *Diabetes* 1989; **38**:350–357.

84 Melchior T, Gadsboll N, Hildebrandt P, Kober L, Torp-Pedersen C. Clinical characteristics, left and right ventricular ejection fraction, and long-term prognosis in patients with non-insulin-dependent diabetes surviving an acute myocardial infarction. *Diabet Med* 1996; **13**:450–456.

85 Malmberg K, Rydén L, Hamsten A, Herlitz J, Waldenström A, Wedel H; DIGAMI study group. Effects of insulin treatment on cause-specific one-year mortality and morbidity in diabetic patients with acute myocardial infarction. Diabetes Insulin-Glucose in Acute Myocardial Infarction. *Eur Heart J* 1996; **17**:1337–1344.

86 De Groote P, Lamblin N, Mouquet F, Plichon D, McFadden E, Van Belle E, *et al.* Impact of diabetes mellitus on long-term survival in patients with congestive heart failure. *Eur Heart J* 2004; **25**:656–662.

87 Thrainsdottir IS, Aspelund T, Hardarson T, Malmberg K, Sigurdsson G, Thorgeirsson G, *et al.* Glucose abnormalities and heart failure predict poor prognosis in the population-based Reykjavík Study. *Eur J Cardiovasc Prev Rehab* 2005; **12**:465–471.

88 Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, *et al.*; UK Prospective Diabetes Study Group. Association of glycae-mia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *Br Med J* 2000; **321**:405–412.

89 DECODE Study Group, European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 2001; **161**:397–405.

90 CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; **353**:9–13.

91 CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; **316**:1429–1435.

92 Haas SJ, Vos T, Gilberg RE, Krum H. Are β-blockers as efficacious in patients with diabetes mellitus as in patients without diabetes mellitus who have chronic heart failure? A meta-analysis of large-scale clinical trials. *Am Heart J* 2003; **146**:848–853.

93 Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, *et al.*; ELITE II investigators. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial – the Losartan Heart Failure Survival Study ELITE-II. *Lancet* 2000; **355**:1582–1587.

94 Vargo DL, Kramer WG, Black PK, Smith WB, Serpas T, Brater DC. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. *Clin Pharmacol Ther* 1995; **57**:601–609.

95 Van Vliet AA, Donker AJ, Nauta JJ, Verheugt FW. Spironolactone in congestive heart failure refractory to high-dose loop diuretic and low-dose angiotensin-converting enzyme inhibitor. *Am J Cardiol* 1993; **71**:21A–28A.

96 Vitale C, Wajngaten M, Sposato B, Gebara O, Rossini P, Fini M, *et al.* Trimetazidine improves left ventricular function and quality of life in elderly patients with coronary artery disease. *Eur Heart J* 2004; **25**:1814–1821.

97 Bersin RM, Wolfe C, Kwasman M, Lau D, Klinski C, Tanaka K, *et al.* Improved hemodynamic function and mechanical efficiency in congestive heart failure with sodium dichloroacetate. *J Am Coll Cardiol* 1994; **23**:1617–1624.

98 Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG. Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. *Diabetes Care* 2001; **24**:5–10.

99 Sánchez-Barriga JJ, Rangel A, Castaneda R, Flores D, Frati AC, Ramos MA, *et al.* Left ventricular diastolic dysfunction secondary to hyperglycemia in patients with type II diabetes. *Arch Med Res* 2001; **32**:44–47.

100 Di Bonito P, Cuomo S, Moio N, Sibilio G, Sabatini D, Quattrin S, *et al.* Diastolic dysfunction in patients with non-insulin-dependent diabetes mellitus of short duration. *Diabet Med* 1996; **13**:321–324.

101 Annonu AK, Fattah AA, Mokhtar MS, Ghareeb S, Elhendy A. Left ventricular systolic and diastolic functional abnormalities in asymptomatic patients with non-insulin-dependent diabetes mellitus. *J Am Soc Echocardiogr* 2001; **14**:885–891.

102 Henein M, Lindqvist P, Francis D, Mörner S, Waldenström A, Kazzam E. Tissue Doppler analysis of age-dependency in diastolic ventricular behaviour and filling: a cross-sectional study of healthy hearts (the Umea General Population Heart Study). *Eur Heart J* 2002; **23**:162–171.

103 Holzmann M, Olsson A, Johansson J, Jensen-Urstad M. Left ventricular diastolic function is related to glucose in a middle-aged population. *J Intern Med* 2002; **251**:415–420.

104 von Bibra, Thrainsdottir IS, Hansen A, Dounis V, Malmberg K, Rydén L. Tissue Doppler imaging for the detection and quantification of myocardial dysfunction in patients with type 2 diabetes mellitus. *Diabetes Vasc Dis Res* 2005; **2**:24–30.

105 Rydén L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, *et al.*; Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. *Eur Heart J* 2007; **28**:88–136.

106 Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993; **342**:821–828.

107 Konstam MA, Rousseau MF, Kronenberg MW, Udelson JE, Melin J, Stewart D, *et al.*; SOLVD Investigators. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. *Circulation* 1992; **86**:431–438.

108 Konstam MA, Patten RD, Thomas I, Ramahi T, La Bresh K, Goldman S, *et al.* Effects of losartan and captopril on left ventricular volumes in elderly patients with heart failure: results of the ELITE ventricular function substudy. *Am Heart J* 2000; **139**:1081–1087.

109 CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; **316**:1429–1435.

110 Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, *et al.*; ELITE II Investigators. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial – the Losartan Heart Failure Survival Study ELITE-II. *Lancet* 2000; **355**:1582–1587.

111 SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. *N Engl J Med* 1991; **325**:293–302.

112 Rydén L, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Packer M, *et al.* Efficacy and safety of high-dose lisinopril in chronic heart failure patients at high cardiovascular risk, including those with diabetes mellitus: results from the ATLAS trial. *Eur Heart J* 2000; **21**:1967–1978.

113 Pfeffer M, Braunwald E, Moyé LA, Basta L, Brown EJ Jr, Cuddy TE, *et al.*; SAVE investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1992; **327**:669–677.

114 Moyé LA, Pfeffer MA, Wun CC, Davis BR, Geltman E, Hayes D, *et al.* Uniformity of captopril benefit in the SAVE study: subgroup analysis. Survival and ventricular enlargement study. *Eur Heart J* 1994; **15**(Suppl B):2–8.

115 Zuanetti G, Latini R, Maggiono AP, Franzosi MG Santoro L, Tognoni G; GISSI 3 Investigators. Effect of the ACE inhibitor lisinopril on mortality in diabetic patients with acute myocardial infarction: data from the GISSI 3 study. *Circulation* 1997; **96**:4239–4245.

116 Herings RMC, deBoer A, Stricker BHC, Leufkens HGM, Porsius A. Hypoglycemia associated with the use of inhibitors of angiotensin-converting enzyme. *Lancet* 1996; **345**:1195–1198.

117 Morris AD, Boyle DIR, McMahon AD, Pearce H, Evans JM, Newton RW, *et al.* ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. *Diabetes Care* 1997; **20**:1363–1379.

118 Pfeffer MA, Swedberg K, Granger CB, Granger CB, Held P, McMurray JJ, *et al.*; CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003; **362**:759–766.

119 MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, *et al.*; CHARM Investigators. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the candesartan in Heart failure: assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J* 2008; **29**:1377–1385.

120 Opie LH, Thomas M. Propranolol and experimental myocardial infarction: substrate effects. *Postgrad Med J* 1976; **52**(Suppl 4):124–133.

121 Dávila-Román VG, Vedala G, Herrero P, de las Fuentes L, Rogers JG, Kelly DP, *et al.* Altered myocardial fatty acid and glucose metabolism in idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 2002; **40**:271–277.

122 CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; **353**:9–13.

123 Haas SJ, Vos T, Gilberg RE, Krum H. Are β-blockers as efficacious in patients with diabetes mellitus as in patients without diabetes mellitus who have chronic heart failure? A meta-analysis of large-scale clinical trials. *Am Heart J* 2003; **146**:848–853.

124 Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, *et al.*; for the MERIT-HF Study Group. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *JAMA* 2000; **283**:1295–1302.

125 Deedwania PC, Giles TD, Klibaner M, Ghali JK, Herlitz J, Hildebrandt P, *et al.*; MERIT-HF Study Group. Efficacy, safety and tolerability of metoprolol CR/XL in patients with diabetes and chronic heart failure: experiences from MERIT-HF. *Am Heart J* 2005; **149**:159–167.

126 Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, *et al.*; Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001; **344**:1651–1658.

127 Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, *et al.*; Randomized Aldactone Evaluation Study Investigators. The effects of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; **341**:709–717.

128 Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, *et al.*; CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007; **357**:2248–2261.

129 Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, *et al.*; GISSI-HF Investigators. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **372**:1231–1239.

130 Stettler C, Allemann S, Jüni P, Cull CA, Holman RR, Egger M, *et al.* Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials. *Am Heart J* 2006; **152**:27–38.

131 Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**:2545–2559.

132 Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, *et al.*; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**:2560–2572.

133 Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, *et al.* Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (Prospective Pioglitazone Clinical Trial in Macrovascular Events): a randomised controlled trial. *Lancet* 2005; **366**:1279–1289.

134 Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 2007; **298**: 1189–1195.

135 Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007; **298**:1180–1188.

136 Lipscombe LL, Gomes T, Lévesque LE, Hux JE, Juurlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. *JAMA* 2007; **298**:2634–2643.

137 Parsonage WA, Hetmanski D, Cowley AJ. Beneficial haemodynamic effects of insulin in chronic heart failure. *Heart* 2001; **85**:508–513.

138 McNulty PH, Pfau S, Deckelbaum LI. Effect of plasma insulin level on myocardial blood flow and its mechanism of action. *Am J Cardiol* 2000; **85**:161–165.

139 Mellbin L G, Malmberg K, Norhammar A, Wedel H, Rydén L; DIGAMI 2 Investigators. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. *Europ Heart J* 2008; **29**:166–176.

140 Smooke S, Horwich TB, Fonarow GC. Insulin-treated diabetes is associated with a marked increase in mortality in patients with advanced heart failure. *Am Heart J* 2005; **149**:168–174.

141 Khoury VK, Haluska B, Prins J, Marwick TH. Effects of glucose–insulin–potassium infusion on chronic ischaemic left ventricular dysfunction. *Heart* 2003; **89**:61–65.

142 Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, *et al.* Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes Trials: a position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association. *Circulation* 2009; **53**:298–304.

143 Rask-Madsen C, Ihlemann N, Krarup T, Christiansen E, Kober L, Nervil Kistorp C, *et al.* Insulin therapy improves insulin-stimulated endothelial function in patients with type 2 diabetes and ischemic heart disease. *Diabetes* 2001; **50**:2611–2618.

144 von Bibra H, Hansen A, Dounis V, Bystedt T, Malmberg K, Ryden L. Augmented metabolic control improves myocardial diastolic function and perfusion in patients with non-insulin dependent diabetes. *Heart* 2004; **90**:1483–1484.

145 Jarnert C, Landstedt-Hallin L, Malmberg K, Melcher A, Ohrvik J, Persson H, *et al.* A randomized trial on the impact of strict glycaemic control on myocardial diastolic function and perfusion reserve: a report from the DADD (Diabetes mellitus And Diastolic Dysfunction) study. *Eur J Heart Fail* 2009; **11**:39–47.

146 Thrainsdottir IS, von Bibra H, Malmberg K, Ryden L. Effects of trimetazidine on left ventricular function in patients with type 2 diabetes and heart failure. *J Cardiovasc Pharmacol* 2004; **44**:101–108.

147 Schmidt-Schweda S, Holubarsch C. First clinical trial with etomoxir in patients with chronic congestive heart failure. *Clin Sci (Lond)* 2000; **99**:27–35.

148 Tuunanen H, Engblom E, Naum A, Någren K, Scheinin M, Hesse B, *et al.* Trimetazidine, a metabolic modulator, has cardiac and extracardiac benefits in idiopathic dilated cardiomyopathy. *Circulation* 2008; **118**:1250–1258.