Journal of Clinical & Experimental Cardiology

Li YW and Aronow. J Clinic Experiment Cardiol 2011, 2:1
DOI: 10.4172/2155-9880.1000114

Review Article Open Access

Diabetes Mellitus and Cardiovascular Disease

Yat Wa Li and Wilbert S Aronow*

Cardiology Division, Department of Medicine, New York Medical College, Valhalla, NY, USA

Abstract

Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes mellitus. Patients with diabetes mellitus have a 2 to 4 time's higher risk of cardiovascular disease and up to a 3 times increase in mortality than non diabetics. The accelerated rate of atherosclerosis seen in diabetes mellitus predisposes patients to coronary artery disease and to higher rates of myocardial infarction and death. This review article discusses cardiovascular disease in diabetics and the management of these patients.

Introduction

The prevalence of diabetes mellitus is rising at an alarming rate. In the United States, 23.6 million people, or 7.8% of the population, have diabetes mellitus, with 1.6 million new cases diagnosed annually [1]. Over 200 million people are affected worldwide with diabetes mellitus [2]. Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes mellitus. Despite a marked decline in cardiovascular disease related deaths over the past several decades, a smaller reduction has occurred in diabetics compared to non diabetics [3]. Diabetes mellitus remains a key risk factor for cardiovascular disease and is widely recognized as a coronary artery disease risk equivalent [4]. It is associated with a 2 to 4 times higher risk of cardiovascular disease, as well as an increased risk of mortality by up to 3 times [5,6].

Epidemiology

Epidemiological studies of diabetes mellitus have shown that gender, age, and ethnic background are important factors when considering the development of diabetes mellitus and its complications. Given similar levels of fasting glucose and proteinuria, women with diabetes mellitus at diagnosis tend to be older and more likely hypertensive. Among those diagnosed at younger ages, women are more likely than men to be obese [7]. Compared to the non-diabetic population, the overall mortality from acute myocardial infarction in the diabetic population was 4 times higher among men and 7 times higher among women [8]. Despite a similar rate of myocardial infarction and chronic heart disease, the rate of transluminal coronary angioplasty and coronary bypass grafting was doubled in diabetic male patients [9].

According to the National Diabetes Information Clearinghouse (NDIC), after adjusting for population age differences, 2004-2006 national survey data for people aged 20 years or older indicate that 6.6% of whites, 7.5% of Asians, 10.4% of Hispanics, and 11.8% of African-Americans had diagnosed diabetes mellitus [10]. Interestingly, a study by McWilliams et al. [11] showed Medicare coverage after age 65 years is associated with reductions in racial, ethnic, and socioeconomic differences in patients with cardiovascular disease and diabetes [11].

The clinical and economic burden of diabetes mellitus and its sequelae are immense. According to the American Diabetes Association (ADA), the actual national burden of diabetes mellitus is estimated to exceed $174 billion; excluding indirect costs such as disability, work loss, and premature mortality [12]. These costs are primarily due to the macro vascular and micro vascular complications of diabetes mellitus. In addition to heart disease (68%) and stroke (16%) being the biggest contributors to diabetes-related deaths, other complications include hypertension, retinopathy, end-stage renal disease, neuropathy, peripheral vascular disease, electrolyte imbalance, immune suppression, erectile dysfunction, and complications of pregnancy [13].

Patients with diabetes mellitus continue to remain at a higher risk of all-cause and cardiovascular disease mortality than those without diabetes. Diabetics are more likely to have coronary artery disease, which is more often multi vessel, and to have episodes of silent myocardial ischemia. Traditional coronary heart disease risk factors such as hypertension, dyslipidemia, and obesity cluster in patients with diabetes mellitus, but this clustering does not account for all of the increased risk in these patients [14]. Research has shown a number of diabetes-specific risk factors contributing to the acceleration of atherosclerosis and increased morbidity and mortality of coronary artery disease. For example, the coronary arteries of patients with diabetes mellitus exhibit a larger content of lipid-rich, inflamed atheromas, with macrophage infiltration, and subsequent thrombosis that is more vulnerable to rupture than plaque found in patients without diabetes [15].

Pathogenesis

Diabetes mellitus promotes the accumulation of foam cells in the sub endothelial space by increasing the production of leukocyte adhesion molecules and pro inflammatory mediators [16]. This augmented vascular inflammatory reaction may result from over-expression of receptor for advanced glycation end products, which correlates linearly with hemoglobin A1c levels. Receptors for advanced glycation end products enhance matrix metalloproteinase activity that can destabilize plaques [17].

Endothelial dysfunction has been documented in diabetic patients who have normal coronary arteries and no other risk factors for coronary disease. The presence of insulin resistance alone may be associated with coronary endothelial dysfunction. In a prospective, open-label

***Corresponding author:** Wilbert S. Aronow, Cardiology Division, New York Medical College Macy Pavilion, Room 138, Valhalla, NY 10595, USA, Tel: 914-493-5311; Fax: 914-235-6274; E-mail: wsaronow@aol.com

Received December 09, 2010; **Accepted** January 20, 2011; **Published** January 22, 2011

Citation: Li YW, Aronow WS (2011) Diabetes Mellitus and Cardiovascular Disease. J Clinic Experiment Cardiol 2:114. doi:10.4172/2155-9880.1000114

treatment study of 50 insulin-resistant and 22 insulin-sensitive subjects without glucose intolerance or traditional risk factors for or evidence of coronary artery disease, endothelium-dependent coronary vasomotor function is abnormal (as assessed by myocardial blood flow response to a cold pressor test) in the insulin-resistant compared to the insulin-sensitive group. After 3 months of thiazolidinedione therapy in the insulin-resistant subjects, insulin sensitivity improved, fasting plasma insulin levels decreased, and myocardial blood flow responses to cold pressor test normalized [18].

Changes in vascular function may also contribute to the poorer outcomes in diabetes mellitus. Increased levels of endothelin-1 stimulate vasoconstriction, induce vascular smooth muscle hypertrophy, and activate the renin-angiotensin system. At the same time, reduced prostacyclin and nitric oxide activity enhances platelet aggregation and adhesiveness, which leads to endothelial dysfunction [19,20]. In addition to the atherosclerotic and vascular effects, the hematologic system is also adversely affected. Diabetes mellitus promotes platelet activation by increasing platelet-surface expression of glycoprotein Ib, which mediates binding to the glycoprotein IIb/IIIa receptor and to the von Willebrand factor [21]. It also increases coagulation activity by stimulating production of pro coagulants such as tissue factor and by reducing levels of anticoagulants such as protein C and anti thrombin III [22]. Also, patients with diabetes have increased levels of plasminogen activator inhibitor type 1 in plasma and in atheromas [23]. Elevated tissue plasminogen activator inhibitor type 1 could decrease fibrinolysis, increase thrombus formation, and accelerate plaque formation [24]. Therefore, agents directing at inhibiting platelet aggregation, such as aspirin, clopidogrel, and glycoprotein IIb/IIIa blockers, are indispensable in reducing the incidence of thrombotic events [25].

Clinical Outcomes

Myocardial infarction

Myocardial infarction rates are increased among diabetics of all ages. In a study by DeLuca et al, [26] the prevalence of unrecognized myocardial infarction and silent myocardial ischemia detected by a treadmill exercise sestamibi stress test was increased in patients with diabetes mellitus. In patients without a history of myocardial infarction, myocardial infarction was diagnosed by a treadmill exercise sestamibi stress test in 40 of 217 patients (18%) with diabetes mellitus and in 16 of 224 patients (7%) without diabetes mellitus. In patients without a history of angina pectoris, silent myocardial ischemia was diagnosed in 62 of 189 patients (33%) with diabetes mellitus and in 35 of 191 patients (15%) without diabetes mellitus [26].

A Finnish population-based study by Haffner et al. [27] showed that, among 1,373 non diabetic subjects and 1,059 diabetic subjects, 7-year incidence rates of myocardial infarction in non diabetic subjects with and without prior myocardial infarction at baseline were 18.8% and 3.5%, respectively, whereas for diabetic subjects were 45% and 20.2%, respectively [27]. This study showed that diabetics who have not had a myocardial infarction have as high a risk of myocardial infarction as non diabetics with previous myocardial infarction.

In a study of 274 elderly diabetics and 386 elderly non dabetics with peripheral arterial disease and hypercholesterolemia treated with and without statins, diabetics with no coronary artery disease had a higher incidence of new coronary events than did non diabetics with prior myocardial infarction [28]. On the basis of these data, diabetics without coronary artery disease should be treated as aggressively for cardiovascular risk factors as patients who have had prior myocardial infarction.

Following an acute myocardial infarction, diabetics carry worse short- and long-term outcomes. In a study based on the FINMONICA myocardial infarction registry, a part of the Finnish contribution to the WHO MONICA Project (World Health Organization Multinational Monitoring of Trends and Determinants of Cardiovascular Disease), diabetic and non diabetic patients with their first myocardial infarction were followed to determine their overall 1-year mortality, and out-of-hospital mortality during the years 1988-1992. This study showed that the 1-year mortality rate was 44.2% in diabetic men and 32.6% in non diabetic men (a significant 38% increase in diabetic men) and 36.9% in diabetic women and 20.2% in non diabetic women (a significant 86% increase in diabetic women). The out-of-hospital mortality rate was 28.3% in diabetic men and 22.4% in non diabetic men (a 25% significant increase in diabetic men) and 10.4% in diabetic women and 11.0% in non diabetic women (an insignificant difference). The high mortality rate of diabetic patients after their first myocardial infarction and the high proportion of out-of-hospital deaths in this group indicate that vigorous primary and secondary preventive measures should become an integral part of their medical care [29].

Coronary revascularization

Patients with diabetes mellitus have increased morbidity and mortality after coronary revascularization. A study by Elezi et al. [30] analyzed a consecutive series of 715 patients with diabetes and 2,839 patients without diabetes after successful stent placement. At 1-year follow-up, event-free survival was significantly lower in diabetic than in non diabetic patients (73.1% versus 78.5%). Survival free of myocardial infarction was also significantly reduced in the diabetic group (89.9 % versus 94.4% in nondiabetics). The incidence of both restenosis (37.5 % versus 28.3%) and stent vessel occlusion (5.3 % versus 3.4%) was significantly higher in diabetic patients. Diabetes mellitus was identified as an independent risk factor for adverse clinical events and restenosis and lower rates of event-free survival than nondiabetic patients. Diabetes mellitus confers a higher incidence of death, recurrent myocardial infarction, restenosis, and repeat revascularization rates [30].

Multiple subgroup analyses of major trials, such as the SIRolim US-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions (SIRIUS) trial [31], the German Multicenter Investigation on the Effectiveness of Sirolimus-Eluting Stents in Diabetic Patients (SCORPIUS) trial [32], the DIABETes and sirolimus Eluting Stent (DIABETES) trial [33], and the Paclitaxel-Eluting Stent (TAXUS) trials [34] have shown better outcomes in diabetic patients with drug-eluting stents compared to bare-metal stents. Significantly lower rates of target lesion revascularization were noted with sirolimus-eluting stents in the SIRIUS trial (7% versus 22% at 9 months), in the SCORPIUS trial (5.3% versus 21.1% at 1 year), in the DIABETES trial (7.7% versus 35.0% at 2 years), and with paclitaxel-eluting stents in the TAXUS trials (12.4% versus 24.7% at 4 years).

Similarly, death and adverse nonfatal outcomes after coronary artery bypass graft surgery are higher in patients with diabetes mellitus. In multiple large observational studies, diabetic patients had higher mortality rates at 30 days (5% versus 2.5%) and at 5 to 10 years (22% versus 12% and 50% versus 29%, respectively) [35,36]. However despite a worse long-term prognosis after coronary artery bypass grafting in patients with diabetes mellitus, the outcomes are still better than with medical therapy or percutaneous coronary intervention in selected subgroups [37].

For patients with diabetes mellitus or multi vessel coronary artery disease, several trials have demonstrated long-term benefits of coronary artery bypass grafting over percutaneous coronary intervention. In the Bypass Angioplasty Revascularization Investigation (BARI) trial, 1,829 symptomatic patients with multi vessel coronary artery disease were randomly assigned to initial treatment with percutaeous coronary intervention or coronary artery bypass grafting and followed up for an average of 10.4 years. At 10.4 years, the percutaneous coronary intervention group had significantly higher subsequent revascularization rates than the coronary artery bypass grafting group (76.8% vs. 20.3%), and in the subgroup with treated diabetes, the coronary artery bypass grafting group had a significantly higher survival than the percutaneous coronary intervention assigned group (57.8% vs. 45.5%). The study concluded that among patients with treated diabetes mellitus, coronary artery bypass grafting conferred long-term survival benefit which persisted at 10-years [38].

Similarly, the synergy between PCI with Taxus drug-eluting stent and cardiac surgery (SYNTAX) trial, which randomized 1,800 patients with severe coronary artery disease to either bypass surgery or drug-eluting stents, showed that the use of coronary artery bypass grafting, as compared with percutaneous coronary intervention, resulted in lower rates of the combined end points of the major adverse cardiac or cerebrovascular events at 1 year [39]. In addition, in a meta-analysis of 10 studies involving 7,812 patients who had undergone either percutaneous coronary intervention or coronary artery bypass grafting, there was a significant 30% reduction in total mortality among patients with diabetes mellitus who had undergone coronary artery bypass grafting [40].

Recently, the results of the BARI 2D trial replicated the principal findings of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial that an initial strategy of percutaneous coronary intervention provided no incremental clinical benefit over intensive medical therapy in patients with diabetes mellitus and coronary artery disease. In this study 2,368 patients with type 2 diabetes mellitus and stable ischemic heart disease (≥50% stenosis of at least 1 major epicardial coronary artery associated with a positive stress test or ≥70% stenosis and classic angina pectoris) were randomly assigned to either initial revascularization (either coronary artery bypass grafting or percutaneous coronary intervention based on the cardiologist's selection) within 4 weeks versus intensive medical therapy. The mode of revascularization was left to the investigator's discretion. At 5 years, the primary end points of the rates of survival or freedom from major cardiovascular event (death, myocardial infarction, or stroke) did not differ significantly between the revascularization group and the medical-therapy group (88.3% versus 87.8% and 72.2 versus 77.7%, respectively) [41].

However, in a sub-group analysis, the rate of major cardiovascular events was significantly lower in the coronary artery bypass grafting group (22.4% versus 30.5%), predominantly attributable to a reduction in non-fatal myocardial infarction. The trial reinforced prior scientific evidence supporting the benefits of coronary artery bypass grafting, with the goal to reduce long-term events such as myocardial infarction, over percutaneous coronary intervention in patients with diabetes mellitus or multi vessel coronary artery disease.

Congestive heart failure

Diabetes mellitus is also a strong and independent risk factor for congestive heart failure [42]. Risk factors for development of heart failure include age (5% increase per 1 year increase in age), male gender (40% increase), diabetes mellitus (60% increase), hypertension (2.5 times increase), and coronary artery disease 4.0 times increase) [43]. Older persons with diabetes mellitus, mean age 81 years, had a 1.3 times higher chance of developing congestive heart failure than those without diabetes mellitus [44].

In a substudy of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, patients with new-onset diabetes mellitus had a significantly 49% higher event rate of new-onset atrial fibrillation compared with patients without diabetes mellitus. Diabetics also had more persistent atrial fibrillation (87% significant increase). Patients with new-onset diabetes mellitus and atrial fibrillation had a 3.56 times significant increased in heart failure compared with patients with new-onset diabetes without atrial fibrillation [45].

Not only are diabetic patients at higher risk for congestive heart failure, but those who develop congestive heart failure having a worse prognosis than non diabetics with congestive heart failure. Poor glycemic control increases the risk of developing heart failure in patients with diabetes mellitus. The importance of glycemic control was illustrated in a report from Kaiser Permanente that evaluated 48,858 diabetic patients ≥19 years of age and no heart failure who were followed for a mean of 2.2 years. Each 1% increase in hemoglobin A1c was associated with a significant 8% increase in heart failure, and a hemoglobin A1c ≥10 increased the risk of heart failure by 1.56 times compared to a hemoglobin A1c <7 [46]. In addition, Barzilay et al. [47] showed in a study of 5,201 patients that the higher the fasting blood glucose, the higher the incidence of heart failure at 5-8 year follow-up (41% increase in heart failure for each increase in fasting blood glucose of 61 mg/dl) [47].

In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPIMIZE-HF) trial looking at 48,612 patients from 259 hospitals, of which 42% of patients had diabetes mellitus, there was no difference in in-hospital mortality observed between diabetics and nondibetics, but heart failure patients with diabetes mellitus experienced a significantly longer length of stay (5.9 days versus 5.5 days for nondiabetic patients). In the 5,791 patients in the follow-up cohort, 2,464 patients with diabetes mellitus had a similar post-discharge mortality but significantly increased all-cause re-hospitalization (31.5% versus 28.2% for nondiabetic patients). This study revealed a high prevalence of diabetes mellitus in patients hospitalized with heart failure. Heart failure patients with diabetes mellitus had a similar short-term mortality compared with patients without diabetes but had a higher risk of re-hospitalization [48].

A study by Halon et al. [49] looked at the development of heart failure and its prognostic implications in 363 diabetic patients, of which 193 underwent percutaneous transluminal coronary angioplasties and 170 coronary artery bypass operations, over 13-year follow-up. The cumulative incidence of hospitalization for heart failure was significantly higher in the diabetic cohort (25% versus 11%), with a rapidly increasing incidence after 5 years. Survival after first hospitalization for heart failure was significantly reduced in diabetics (11 of 20 (55%) versus 25 of 31 (81%) in non diabetics at 3 years), as was survival free of further hospitalization for heart failure (5 of 20 (25%) for diabetics versus 20 of 30 (63%) for nondiabetics) [49].

Long-term 13-year survival (43% versus 78%) and survival free of heart failure (33% versus 71%) were significantly decreased in diabetics, especially in those with reduced left ventricular function at baseline (17% versus 42%). Multivariate analysis showed diabetes mellitus to be the strongest independent predictor of decreased survival

(3.6 times significant increase) and survival free of heart failure (4.0 times significant increase) in patients undergoing revascularization. This study concluded that late-onset heart failure was frequent in diabetic patients after percutaneous transluminal coronary angioplasty or coronary artery bypass grafting and once present heralded an unrelenting progressive downhill clinical course [49].

Diabetes mellitus and ischemic heart disease interact to accelerate the progression of myocardial dysfunction. According to the Studies of Left Ventricular Dysfunction (SOLVD) Prevention and Treatment trials, which enrolled 6,791 patients, including 1,310 with diabetes, patients with diabetes were 1.6 times significantly more likely to be admitted for heart failure and had higher rates at one year of all-cause mortality (32% versus 22%), cardiovascular mortality (28% versus 19%) and mortality related to pump failure (11% versus 6%) (50). A study by Gustafsson et al. [51] showed that, among 5,491 patients hospitalized with heart failure, diabetes mellitus significantly increased mortality in men by 40% and in women by 70% [51]. For those with left ventricular dysfunction, diabetes mellitus significantly increased mortality in patients with ischemic cardiomyopathy by 37% [52].

Echo cardiographic evaluation of cardiac performance in diabetic patients with heart failure has demonstrated a prolonged pre-ejection period and a shortened ejection time, both of which correlate with reduced resting left ventricular ejection fraction and diminished systolic function. A study by Zarich et al. [53] showed the ratio of peak early to peak late atrial filling velocity was significantly decreased in diabetic compared with control subjects (1.24 versus 1.66). Atrial filling velocity was significantly increased in diabetic patients (74.3 versus 60.3 cm/s), whereas early filling velocity was reduced by a borderline significant degree (88.8 versus 98.5 cm/s). The atrial contribution to stroke volume as assessed by area under the late diastolic filling envelope compared to total diastolic area was also significantly increased in diabetic compared with control subjects (35% versus 27%) [53].

Diabetic patients also have a lower left ventricular ejection fraction in response to exercise, suggestive of a reduction in cardiac reserve. In a study by Mildenberger et al. [54] both groups of patients (with and without diabetes) had a similar rest and exercise heart rate and blood pressure, and both achieved similar workloads. The control group without diabetes mellitus had an ejection fraction at rest of 65.4% and a peak exercise ejection fraction of 77.1%. The diabetic group had a mean ejection fraction at rest of 63.7%, similar to that of the control group, but a peak exercise ejection fraction of 67.7%, significantly lower than that of the control group [54]. The diabetic patients varied widely in ejection fraction response to exercise, ranging from an increase of 25% to a decrease of 21% [53]. This subclinical left ventricular dysfunction may be explained by a defective blunted recruitment of myocardial contractility or an impairment of cardiac sympathetic innervation [55].

Even in the absence of left ventricular dysfunction, abnormal diastolic function has been noted in 27-69% of asymptomatic diabetic patients [56]. Impaired diastolic compliance and maintenance of the systolic function is usually the initial cardiac manifestation in the progression of diabetic cardiomyopathy [57]. Failure of diastolic relaxation of the left ventricle leads to impaired filling and reduced cardiac reserve on exercise. In a sex-specific linear regression analysis of 1,986 men, mean age 48 years, and 2,529 women, mean age 50 years, from the original Framingham Study cohort and the Framingham Offspring Study, diabetics had significantly higher heart rates than non diabetics (67.9 versus 64.0 beats/minute in men, and 73.1 versus 68.3 beats/minute in women). Diabetic women had significantly increased left ventricular wall thickness, relative wall thickness, left ventricular end-diastolic dimension, and left ventricular mass corrected for height [58]. Diabetes mellitus, especially with worse glycemic control, is independently associated with abnormal left ventricular relaxation. The severity of abnormal left ventricular relaxation is similar to the well-known impaired relaxation associated with hypertension. The combination of diabetes and hypertension has more severe abnormal left ventricular relaxation than groups with either condition alone [59].

A variety of factors may contribute to left ventricular dysfunction in diabetic patients, one of which may be autonomic neuropathy [60]. Under normal circumstances, sympathetic stimulation improves left ventricular contraction and increases left ventricular relaxation rates by facilitating calcium uptake into the sarcoplasmic reticulum. Autopsy studies of diabetic patients have shown that myocardial catecholamine stores are depleted which could impair both systolic and diastolic function [61].

In addition, cardiac autonomic neuropathy is portrayed by a significant reduction in heart rate variability and an alteration in the parasympathetic/sympathetic balance leading to parasympathetic reduction and sympathetic overactivity. Resting tachycardia reduces the time of ventricular filling, and over time, may predispose to arrhythmias and left ventricular dysfunction [62]. In a study by Rathmann et al. [63] patients with diabetes and mild cardiac autonomic neuropathy have been shown to have distal left ventricular sympathetic denervation, whereas those with severe cardiac autonomic neuropathy have a pattern of distal sympathetic denervation associated with proximal ventricular islands of hyperinnervation. These areas of denervation and hyper innervation may cause unstable regions of electrical, vascular, or autonomic heterogeneity conducive to diabetic cardiomyopathy [63].

Decreased insulin availability or responsiveness in diabetes can impair the transport of glucose across the cell membrane. In perfused hearts from diabetic mice, the rate of glycolysis and glucose oxidation was impaired due to reduced content of insulin-sensitive glucose (GLUT4) transporters, whereas palmitate oxidation was increased. These changes were associated with increases of ceramide content, a mediator of apoptosis, and inducible nitric oxide synthase expression. Nitric oxide was found to inhibit creatine kinase and impair contractile reserve in rat hearts [64].

Since ischemic myocardium depends upon anaerobic metabolism of glucose, increased glucose uptake and metabolism are necessary for maintenance of myocardial function [65]. Diminished insulin activity in diabetic hearts limit glucose availability, which results in a shift toward fatty acid metabolism. These changes increase myocardial oxygen utilization, generate reactive oxygen species, accumulate toxic products of fatty acid metabolism, impair calcium handling, and upregulate the renin-angiotensin system [66].

Treatment

Besides glycemic control, the goals of treatment of left ventricular dysfunction and heart failure in diabetic patients are the same as those in nondiabetics. Patients need to stop smoking, lose weight if obese, have hypertension treated with the blood pressure reduced to less than 130/80 mm Hg, have dys lipidemia treated with the serum low-density lipoprotein (LDL) cholesterol level reduced to less than 70 mg/dL, and to perform physical activity if the heart failure is mild to moderate [67-70].

In an observational prospective study of 529 older patients, mean age 79 years, with prior myocardial infarction, diabetes mellitus, and a serum LDL cholesterol of 125 mg/dL or higher, 53% of patients were

treated with statins [71]. At 29-month follow-up, compared with no treatment with statins, use of statins significantly decreased coronary artery death or nonfatal myocardial infarction by 37% and stroke by 47%. The lower the serum LDL cholesterol in persons treated with statins, the greater was the reduction in new coronary events [72] and stroke [73].

Beta-adrenergic blocking agents and angiotensin-converting enzyme (ACE) inhibitors are commonly used for their sympatholytic activity and influence on the renin-angiotensin system. In the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial, at 10.4-months follow-up of 2,289 pts with a mean left ventricular ejection fraction of 20% and Class IV heart failure treated with diuretics and ACE inhibitors with or without digoxin, carvedilol significantly decreased mortality by 35% (7.1% absolute reduction). This trial supports and reassures the safety and benefit of beta blockers in a subset of patients with more advanced heart failure [74].

Similarly, the Metoprolol CR/XL Randomised Intervention (MERIT-HF) trial showed that, metoprolol controlled release/extended release (CR/XL) once daily in addition to standard therapy significantly lowered mortality in patients with decreased ejection fraction and symptoms of heart failure. A group of 3,991 patients with chronic heart failure in New York Heart Association (NYHA) functional class II-IV and with an ejection fraction of 40% or less, stabilized with optimum standard therapy, was randomly assigned metoprolol CR/XL 12.5 mg (NYHA III-IV) or 25.0 mg once daily (NYHA II) and 2,001 were assigned placebo. The target dose was 200 mg once daily, and doses were up-titrated over 8 weeks. At 1 year follow-up, all-cause mortality was lower in the metoprolol CR/XL group than in the placebo group (7.2%, per patient-year of follow-up versus 11.0% in the placebo group), with a 34% significant reduction in all-cause mortality in patients treated with metoprolol CR/XL [75].

There were 41% significantly fewer sudden deaths and 49% significantly fewer deaths from worsening heart failure in the metoprolol CR/XL group than in the placebo group. All-cause mortality or hospitalization due to worsening heart failure was significantly reduced 30% in diabetics treated with metoprolol CR/XL (76). In 532 pts, mean age 78 years, with prior myocardial infarction and diabetes mellitus and no contraindications to beta blockers, use of beta blockers caused a 27% significant independent reduction in the incidence of new coronary events [77].

ACE inhibitors or angiotensin receptor blockers are the drugs of choice in treating diabetics with hypertension and chronic renal disease [78]. They facilitate reverse remodeling and slow the progression of left ventricular dysfunction. An overview of 32 randomized trials of ACE inhibitors in 7,105 pts with congestive heart failure showed that ACE inhibitors significantly reduced all-cause mortality by 23% and significantly reduced all-cause mortality or hospitalization for congestive heart failure by 35%. Patients with the lowest ejection fraction appeared to have the greatest benefit.

In the Heart Outcomes Prevention Evaluation (HOPE) study, 3,577 people with diabetes mellitus aged 55 years or older who had a previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or a low ejection fraction, and who were not taking ACE inhibitors, were randomly assigned ramipril 10 mg daily or placebo. The combined primary outcome was myocardial infarction, stroke, or cardiovascular death. Overt nephropathy was a main outcome in a substudy. At 4.5 year-follow-up, ramipril significantly lowered the risk of the combined primary outcome by 25%, myocardial infarction by 22%, stroke by 33%, cardiovascular death by 37%, and total mortality by 24%, revascularization by 17%, and overt nephropathy by 24%. After adjustment for the changes in systolic (2.4 mm Hg) and diastolic (1.0 mm Hg) blood pressures, ramipril still lowered the risk of the combined primary outcome by 25% [79].

The Reduction in Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study assessed the role of the angiotensin-II-receptor antagonist losartan in patients with type 2 diabetes and nephropathy. A total of 1,513 patients were enrolled in this randomized, double-blind study comparing losartan (50 to 100 mg once daily) with placebo, both taken in addition to conventional antihypertensive treatment, for a mean of 3.4 years. At the end of the study, losartan reduced the incidence of a doubling of the serum creatinine concentration (significant risk reduction of 25%) and end-stage renal disease (significant risk reduction of 28%) but had no effect on the rate of death. The benefit exceeded that attributable to changes in blood pressure. The composite of morbidity and mortality from cardiovascular causes was similar in the two groups, although the rate of first hospitalization for heart failure was significantly lower with losartan (risk reduction of 32%). The level of proteinuria significantly declined by 35% with losartan [80].

In terms of diuretics use, mild congestive heart failure may be treated with a thiazide diuretic. However, thiazide diuretics are ineffective when the estimated glomerular filtration rate is <30 ml/min. For moderate or severe heart failure, patients should be treated with a loop diuretic. Metolazone may be needed in addition to loop diuretic for those with severe congestive heart failure or renal insufficiency.

When severe heart failure persists with diuretics, ACE inhibitors or angiotensin receptor blockers, and beta blockers, one can add an aldosterone antagonist [70]. Digoxin may be used in the presence of an abnormal left ventricular to reduce hospitalization for heart failure if symptoms persist despite optimal medical therapy with a class IIa indication, but the serum digoxin level must be maintained between 0.5-0.8 ng/ml [70]. Isosorbide dinitrate plus hydralazine may be used if symptoms persist despite optimal medical management in blacks with a class I indication and in other races with a class IIa indication [70]. Calcium channel blockers must be avoided if the left ventricular ejection fraction is abnormal.

In addition to optimal pharmacologic therapy, a study by Ghali et al. [81] showed that diabetics with advanced heart failure had substantial benefits from device therapy. Over 600 patients treated with cardiac resynchronization therapy had a 33% significant reduction in mortality and a 48% significant reduction in mortality or hospitalization for heart failure [81].

In addition to modifying cardiovascular risk factors such as obesity, dys lipidemia, hypertension, glycemic control, smoking, and sedentary lifestyle, the current standard of care for type-2 diabetes includes pharmacologic therapies that aim to restore normoglycemia. Sulfonylureas were among the first widely used oral hypoglycemic agents. Initially, it was thought that sulfonylureas confer an increase risk of cardiovascular mortality and coronary artery disease in patients taking this agent [82]. Sulfonylureas are insulin secretagogues, triggering insulin release by direct action on the K^+-ATP channel of the pancreatic β cells. K^+-ATP channels also exist in the myocardium and blocking them with sulfonylureas contributed to ischemic injury in diabetic patients [83]. Because there are data showing an increased incidence of coronary events and of mortality in diabetics with coronary artery disease treated with sulfonylureas [84-86], these drugs should be avoided if possible in diabetic patients with coronary artery disease.

Thiazolidinediones are widely used oral hypoglycemic agents which decrease glucose levels in type-2 diabetic patients by increasing the insulin sensitivity of target tissues and also by inducing a wide variety of nonglycemic effects mediated through activation of the peroxisome proliferator-activated receptor (PPAR)-γ nuclear receptor that may benefit the cardiovascular system [87,88]. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study, 5,238 patients with diabetes mellitus who had evidence of macrovascular disease were randomized to oral pioglitazone titrated from 15 mg to 45 mg daily or to placebo to be taken in addition to their glucose-lowering drugs and other medications [89].

The primary endpoint was the composite of all-cause mortality, nonfatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. At 34.5 month follow-up, pioglitazone insignificantly reduced the primary endpoint by 10% [89].

In the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, 5,269 adults aged 30 years or older with impaired fasting glucose or impaired glucose tolerance or both and no previous cardiovascular disease were randomized to rosiglitazone 8 mg daily or placebo and followed for a median of 3 years. The primary outcome was a composite of incident diabetes mellitus or death. At follow-up, 11.6% of persons given rosiglitazone and 26.0% of persons given placebo developed the composite primary outcome (a significant 60% reduction by rosaglitazone). Normoglycemia was significantly increased 71% by rosaglitazone (50.5% versus 30.3% by placebo). Cardiovascular event rates were similar in both groups, except for rosaglitazone significantly increasing heart failure (0.5% versus 0.1% in the placebo group) [90].

In both PROactive and DREAM, nonfatal congestive heart failure was significantly more common in patients treated with thiazolidinediones presumably because of reversible fluid retention rather than loss of myocardial function. Glitazones may precipitate heart failure in patients with poor left ventricular function and can worsen heart failure [91]. None of the thiazolidinediones are recommended for use in patients with NYHA Class III or IV heart failure.

Among the oral hypoglycemic agents, metformin is the most popular to use due to its favorable profile. Metformin lowers blood glucose both by increasing insulin sensitivity and by decreasing hepatic gluconeogenesis. While it improves glycemic control, this drug does not induce hypoglycemia. Metformin causes weight loss and a modest reduction in serum LDL cholesterol and triglyceride levels (92). Lactic acidosis is a rare but potentially life-threatening complication of metformin use and is seen more commonly in patients with renal insufficiency or with tissue hypoperfusion and hypoxemia [93]. Because patients with heart failure are at higher risk for hypoperfusion or hypoxemia, the use of metformin is contraindicated in those patients who require pharmacologic treatment of heart failure.

Three trials showed that intensive therapy improves the outcome of micro vascular disease [94-96]. Hyperglycemia is an important risk factor for the development of micro vascular disease in patients with diabetes mellitus. Improving glycemic control improves micro vascular outcomes.

The United Kingdom Prospective Diabetes Study (UKPDS) compared the efficacy of different treatment regimens (diet, sulfonylurea, metformin, and insulin) on glycemic control and the complications of diabetes mellitus. The target fasting blood glucose concentration was ≤108 mg/dL. Patients in the intensive-therapy group received a sulfonylurea or insulin. Metformin was added to the sulfonylurea if the fasting blood glucose concentration was >270 mg/dL, whereas insulin was initiated if the combination of oral agents remained ineffective. The conventional therapy group was treated with diet alone. Drugs were added if there were hyperglycemic symptoms or if the fasting blood glucose concentration was >270 mg/dL. Over 10 years, the average hemoglobin A1c value was 7% in the intensive-therapy group compared with 7.9% in the conventional therapy group (an 11% reduction). Most of the risk reduction in the intensive therapy group was due to a 25% significant risk reduction in micro vascular disease [94].

The Kumamoto study was a randomized controlled trial of 110 patients with type 2 diabetes mellitus randomized to a multiple insulin injection therapy group or a conventional insulin injection therapy group and followed for 10 years. The goal of therapy in the multiple insulin injection therapy groups was to reduce the hemoglobin A1c value below 7%. Compared to the conventional insulin injection therapy group, the multiple insulin injection therapy groups had a significant reduction in the progression of retinopathy by 67%, progression of nephropathy by 66%, albuminuria by 100% and clinical neuropathy by 64%. The multiple injection insulin therapy groups also had a significant prolongation of the period in which the patients were free of complications, including 2.0 years for progression of retinopathy, 1.5 years for progression of nephropathy, and 2.2 years for clinical neuropathy. The multiple insulin injection groups achieved a mean hemoglobin A1c level of 7.1% compared with 9.4% in the control group [95].

Diabetics with micro albuminuria have more severe angiographic coronary artery diseaser than diabetics without micro albuminuria [96]. The Action in Diabetes and Vascular disease: Preterax and Diamicron-Modified Release Controlled Evaluation (ADVANCE) trial assessed the potential benefits of blood pressure lowering using a fixed low-dose combination of perindopril and indapamide versus placebo and of tighter glucose control, using an intensive gliclazide-MR-based glucose control regimen versus a standard guidelines-based regimen separately and together in 11,140 patients with long-standing diabetes mellitus. At 4.3-year follow-up, combination treatment significantly reduced the risk of new or worsening nephropathy by 33%, new onset macro albuminuria by 54% and new onset micro albuminuria by 26%. Combination treatment was associated with an 18% significant reduction in the risk of all-cause death. This study concluded that the effects of routine blood pressure lowering and intensive glucose control were independent of one another and when combined produced additional reductions in clinically relevant outcomes [97].

Target hemoglobin A1c levels in patients with type 2 diabetes mellitus should be tailored to the individual, balancing the improvement in micro vascular complications with the risk of hypoglycemia. Diabetics also have a significant increasing trend of hemoglobin A1c levels over the increasing number of vessels with coronary artery disease [98]. In addition, the higher the hemoglobin A1c levels in diabetics with peripheral arterial disease, the higher the prevalence of severe peripheral arterial disease [99].

A reasonable goal of therapy might be a hemoglobin A1c value of ≤7% for most patients. In order to achieve this hemoglobin A1c goal, a fasting glucose of 70 to 130 mg/dL and a postprandial glucose of <180 mg/dL are usually necessary.

Conclusion

Cardiovascular disease, particularly coronary artery disease, is a

major cause of morbidity and mortality among patients with diabetes mellitus. Compared to non diabetic patients, diabetic patients are more likely to have coronary artery disease, which is often multi vessel, and to have episodes of silent myocardial ischemia. As a result of this and other factors, diabetic patients with coronary artery disease have a lower long-term survival rate then non diabetic patients with coronary artery disease. The medical and revascularization management of coronary artery disease are generally similar in patients with and without diabetes mellitus. However, the short-term and long-term results of revascularization with percutaneous coronary intervention or coronary artery bypass graft surgery are often worse in diabetic patients. It is therefore of paramount importance that our healthcare system deliver quality primary and secondary prevention of diabetes mellitus with the goal to reducing its prevalence as well as lessening the progression of its micro vascular and macro vascular complications.

References

1. National Diabetes Statistics. The National Diabetes Clearinghouse.
2. Wild S, Roglic G, Green A, DR MED SCI, Richard Sicree, et al. (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27: 1047-1053.
3. Gu K, Cowie CC, Harris MI (1999) Diabetes and decline in heart disease mortality in US adults. JAMA 281: 1291-1297.
4. Expert panel on detection, evaluation and treatment, of high blood cholesterol in adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood pressure in adults. (Adult treatment panel III) (2001) JAMA 285: 2486-2497.
5. Fox CS, Coady S, Sorlie PD, Levy D, Meigs JB, et al. (2004) Trends in cardiovascular complications of diabetes. JAMA 292: 2495-2499.
6. Preis SR, Hwang SJ, Coady S, Michael J Pencina, Ralph B D'Agostino, et al. (2009) Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes in the Framingham Heart Study, 1950 to 2005. Circulation 119: 1728-1735.
7. Leibson C (1999) Loss of the female advantage with cardiovascular disease for women with diabetes. Lupus 8: 351-355.
8. Lundberg V, Stegmayr B, Asplund K, Eliasson M, Huhtasaari F (1997) Diabetes as a risk factor for myocardial infarction: population and gender perspectives. J Intern Med 241: 485-492.
9. Kautzky-Willer A, Handisurya A (2009) Metabolic diseases and associated complications: sex and gender matter! Eur J Clin Invest 39: 631-648.
10. National Diabetes Information Clearinghouse (NDIC).
11. McWilliams JM, Meara E, Zaslavsky AM, Ayanian JZ (2009) Differences in control of cardiovascular disease by race, ethnicity, and education: U.S. trends from 1999 to 2006 and effects of Medicare coverage. Ann Intern Med 150: 505-515.
12. American Diabetes Association (2008) Economic costs of diabetes in the U.S. in 2007. Diabetes Care 31: 596-615.
13. Nathan DM (1993) Long-term complications of diabetes mellitus. N Engl J Med 328: 1676-1685.
14. Nesto RW. Diabetes and heart disease. In: Braunwald E, Libby P, Bonow RO, Zipes DP, Mann DL (eds), (2008) Braunwald's Heart Disease: a Textbook of Cardiovascular Medicine. (8th edn), Saunders Elsevier, Philadelphia, pp 1547-1560.
15. Moreno PR, Murcia AM, Palacios IF, Leon MN, Bernardi VH, et al. (2000) Coronary composition and macrophage infiltration in atherectomy specimens from patients with diabetes mellitus. Circulation 102: 2180-2184.
16. Beckman JA, Creager MA, Libby P (2002) Diabetes and atherosclerosis-epidemiology, pathophysiology and management. JAMA 287: 2570-2581.
17. Cipollone F, Iezzi A, Fazia M, Mirco Zucchelli, Barbara Pini, et al. (2003) The receptor RAGE as a progression factor amplifying arachidonate-dependent inflammatory and proteolytic response in human atherosclerotic plaques: role of glycemic control. Circulation 108: 1070-1177.
18. Quinones MJ, Hernandez-Pampaloni M, Schelbert H, Isabel Bulnes-Enriquez, Xochi jimenez, et al. (2004) Coronary vasomotor abnormalities in insulin-resistant individuals. Ann Intern Med 140: 700-708.
19. Cosentino F, Eto M, De Paolis P, van der Loo B, Bachschmid M, et al. (2003) High glucose causes upregulation of cyclooxygenase-2 and alters prostanoid profile in human endothelial cells: role of protein kinase C and reactive oxygen species. Circulation 107: 1017-1023.
20. Cardillo C, Campia U, Bryant MB, Panza JA (2002) Increased activity of endogenous endothelin in patients with type 2 diabetes mellitus. Circulation 106: 1783-1787.
21. Vinik AI, Erbas T, Park TS, Roger Nolan, Gary L Pittenger (2001) Platelet dysfunction in type II diabetes. Diabetes Care 24: 1476-1485.
22. Ceriello A, Giugliano D, Quatraro A, Marchi E, Barbanti M, et al. (1990)Evidence for a hyperglycemia-dependent decrease of antithrombin III-thrombin complex formation in humans. Diabetologia 33: 163-167.
23. Pandolfi A, Cetrullo D, Polishuck R, Alberta MM, Calafiore A, et al. (2001) Plasminogen activator inhibitor type 1 is increased in the arterial wall of type 2 diabetic subjects. Arterioscler Thromb Vasc Biol 21: 1378-1382.
24. Sobel BE, Woodcock-Mitchell J, Schneider DJ, Robert E Holt BA, Kousuke Marutsuka MD, et al. (1998) Increased plasminogen activator inhibitor type 1 in coronary artery atherectomy specimens from type 2 diabetic compared with nondiabetic patients: a potential factor predisposing to thrombosis and its persistence. Circulation 97: 2213-2221.
25. Colwell JA, Nesto RW (2003) The platelet in diabetes: focus on prevention of ischemic events. Diabetes Care 26: 2181-2188.
26. DeLuca AJ, Kaplan S, Aronow WS, Rasham Sandhu MD, Abid Butt MD, et al. (2006) Comparison of prevalence of unrecognized myocardial infarction and of silent myocardial ischemia detected by a treadmill exercise sestamibi stress test in patients with versus without diabetes mellitus. Am J Cardiol 98: 1045-1046.
27. Haffner SM, Lehto S, Ronnemaa T, Kalevi Pyörälä MD, Markku Laakso MD (1998) Mortality from coronary heart disease in subjects with type II diabetes and in non-diabetic subjects with and without prior myocardial infarction. N Engl J Med 339: 229-334.
28. Aronow W, Ahn C (2003) Elderly diabetics with peripheral arterial disease and no coronary artery disease have a higher incidence of new coronary events than elderly non diabetics with peripheral arterial disease and prior myocardial infarction treated with statins and with no lipid-lowering drug. J Gerontol Med Sci 58: 573-575.
29. Miettinen H, Lehto S, Salomaa V, M Mahonen, M Miemela, et al. (1998) Impact of diabetes on mortality after the first myocardial infarction. Diabetes Care 21: 69-75.
30. Elezi S, Kastrati A, Pache J, Anne Wehinger MD, Martin Hadamitzky MD, et al. (1998) Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. J Am Coll Cardiol 32: 1866-1873.
31. Moussa I, Leon MB, Baim DS, O'Neill WW, Popma JJ, et al. (2004)Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. Circulation 109: 2273-2278.
32. Baumgart D, Klauss V, Baer F, Franz Hartmann MD, Helmut Drexler MD, et al. (2007) One-year results of the SCORPIUS study: a German multicenter investigation on the effectiveness of sirolimus-eluting stents in diabetic patients. J Am Coll Cardiol 50: 1627-1634.
33. Jimenez-Quevedo P, Sabate M, Angiolillo DJ, Alfonso F, Hernández-Antolín R, et al. (2007) Long-term clinical benefit of sirolimus-eluting stent implantation in diabetic patients with de novo coronary stenoses: long-term results of the DIABETES trial. Eur Heart J 28: 1946-1952.
34. Kirtane AJ, Ellis SG, Dawkins KD, Antonio Colombo MD, Eberhard Grube MD, et al. (2008) Paclitaxel-eluting coronary stents in patients with diabetes mellitus: pooled analysis from 5 randomized trials. J Am Coll Cardiol 51: 708-715.
35. Cohen Y, Raz I, Merin G, Mozes B (1998) Comparison of factors associated with 30-day mortality after coronary artery bypass grafting in patients with versus without diabetes mellitus. Israeli Coronary Artery Bypass (ISCAB) Study Consortium. Am J Cardiol 81: 7-11.
36. Thourani VH, Weintraub WS, Stein B, Gebhart SS, Craver JM (1999) et al. Influence of diabetes mellitus on early and late outcome after coronary artery bypass grafting. Ann Thorac Surg 67: 1045-1052.

37. Barzilay JI, Kronmal RA, Bittner V, Eaker E, Evans C, et al. (1994) Coronary artery disease and coronary artery bypass grafting in diabetic patients aged > or = 65 years (report from the Coronary Artery Surgery Study [CASS] Registry). Am J Cardiol 74: 334-339.

38. BARI Investigators et al. (2007) The final 10-year follow-up results from the BARI randomized trial. J Am Coll Cardiol 49: 1600-1606.

39. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, et al. (2009) Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 360: 961-972.

40. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, et al. (2009) Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomized trials. Lancet 373: 1190-1197.

41. The BARI 2D Study Group, Frye RL, August P, et al. (2009) A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 360: 2570-2572.

42. Ingelsson E, Arnlov J, Sundstrom J, Zethelius B, Vessby B, et al. (2005) Novel metabolic risk factors for heart failure. J Am Coll Cardiol 46: 2054-2060.

43. Aronow WS, Ahn C, Kronzon I (1999) Comparisons of incidences of congestive heart failure in older African-Americans, Hispanics, and whites. Am J Cardiol 84: 611-612.

44. Aronow WS, Ahn C (1999) Incidence of heart failure in 2,737 older persons with and without diabetes mellitus. Chest 115: 867-868.

45. Aksnes TA, Schmieder RE, Kjeldsen SE, Ghani S, Hua TA, et al. (2008) Impact of new-onset diabetes mellitus on development of atrial fibrillation and heart failure in high-risk hypertension (from the VALUE trial). Am J Cardiol 101; 634-638.

46. Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, et al. (2001) Glycemic control and heart failure among adult patients with diabetes. Circulation 103: 2668-2673.

47. Barzilay JI, Kronmal RA, Gottdiener JS, Nicholas L Smith, Gregory L Burke, et al. (2004) The association of fasting glucose levels with congestive heart failure in diabetic adults > or =65 years: the Cardiovascular Health Study. J Am Coll Cardiol 43: 2236-2341.

48. Greenberg BH, Abraham WT, Albert NM, Chiswell K, Clare R, et al. (2007) Influence of diabetes on characteristics and outcomes in patients hospitalized with heart failure: a report from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). Am Heart J 154: 277-278.

49. Halon DA, Merdler A, Flugelman MY, Rennert HS, Weisz G et al. (2000) Late-onset heart failure as a mechanism for adverse long-term outcome in diabetic patients undergoing revascularization (a 13-year report from the Lady Davis Carmel Medical Center registry). Am J Cardiol 85: 1420-1426.

50. Shindler DM, Kostis JB, Yusuf S, Quinones MA, Pitt B, et al. (1996) Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. Am J Cardiol 77: 1017-1020.

51. Gustafsson I, Brendorp B, Seibaek M, Hans Burchardt MD, Per Hildebrandt MD, et al. (2004) Influence of diabetes and diabetes-gender interaction on the risk of death in patients hospitalized with congestive heart failure. J Am Coll Cardiol 43: 771-777.

52. Dries DL, Sweitzer NK, Drazner MH, Lynne W Stevenson, Bernard J Gersh, et al. (2001) Prognostic impact of diabetes mellitus in patients with heart failure according to the etiology of left ventricular systolic dysfunction. J Am Coll Cardiol 38: 421-428.

53. Zarich SW, Arbuckle BE, Cohen LR, Roberts M, Nesto RW, et al. (1998) Diastolic abnormalities in young asymptomatic diabetic patients assessed by pulsed Doppler echocardiography. J Am Coll Cardiol 12: 114-120.

54. Mildenberger RR, Bar-Schlomo B, Druck MN, Jablonsky G, Morch JE, et al. (1984) Clinically unrecognized dysfunction in young diabetic patients. J Am Coll Cardiol 4: 234-238.

55. Scognamiglio R, Avogaro A, Casara D, Crepaldi C, Marin M, et al. (1998) Myocardial dysfunction and adrenergic cardiac innervation in patients with insulin-dependent diabetes mellitus. J Am Coll Cardiol 31: 404-412.

56. Raey DC Which left ventricular dysfunction is impaired earlier in the evolution of diabetic cardiomyopathy? An echocardiographic study of young type 1 diabetic patients. (1994) Diabetes Care 17: 633-639.

57. Margonato A, Gerundini P, Vicedomini G, Gilardi MC, Pozza G, et al. (1986) 90 Abnormal cardiovascular response to exercise in young asymptomatic diabetic patients with retinopathy. Am Heart J 112: 554-560.

58. Galderisi M, Anderson KM, Wilson PW, Levy D (1991) Echocardiographic evidence for the existence of a distinct diabetic cardiomyopathy (the Framingham Heart Study). Am J Cardiol 68: 85-89.

59. Liu JE, Palmieri V, Roman MJ, Bella JN, Fabsitz R, et al. (2001) The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: the Strong Heart Study. J Am Coll Cardiol 37: 1943-1949.

60. Debono M, Cachia E (2007) The impact of cardiovascular autonomic neuropathy in diabetes: is it associated with left ventricular dysfunction? Auton Neurosci 132: 1-7.

61. Neubauer B, Christensen NJ (1976) Norepinephrine, epinephrine, and dopamine contents of the cardiovascular system in long-term diabetes. Diabetes 25: 6-10.

62. Ewing DJ, Boland O, Neilson JM, Cho CG, Clarke BF, et al. (1991) Autonomic neuropathy, QT interval lengthening, and unexpected deaths in male diabetic patients. Diabetologia 34: 182-185.

63. Rathmann W, Ziegler D, Jahnke M, Haastert B, Gries FA (1993) Mortality in diabetic patients with cardiovascular autonomic neuropathy. Diabet Med 10: 820-824.

64. Belke DD, Larsen TS, Gibbs EM, Severson DL (2000) Altered metabolism causes cardiac dysfunction in perfused hearts from diabetic (db/db) mice. Am J Physiol Endocrinol Metab 279: E1104-E1113.

65. Sun D, Nguyen N, DeGrado TR, Schwaiger M, Brosius FC 3rd (1994) Ischemia induces translocation of the insulin-responsive glucose transporter GLUT4 to the plasma membrane of cardiac myocytes. Circulation 89: 793-798.

66. Lazar HL (2006) Alterations in myocardial metabolism in the diabetic myocardium. Semin Thorac Cardiovasc Surg 18: 289-292.

67. American Diabetes Association (2003) Standards of medical care for patients with diabetes mellitus. Diabetes Care 26: 533-550.

68. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, et al. (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report. JAMA 289: 2560-2572.

69. Grundy SM, Cleeman JI, Merz CNB, H Bryan Brewer Jr, Luther T Clark, et al. (2004) Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 110: 227-239.

70. Jessup M, Abraham WT, Casey DE, Arthur M. Feldman, Gary S. Francis, et al. (2009) 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 53: 1343-1382.

71. Aronow WS, Ahn C, Gutstein H (2002) Reduction of new coronary events and of new atherothrombotic brain infarction in older persons with diabetes mellitus, prior myocardial infarction, and serum low-density lipoprotein cholesterol ≥125 mg/dL treated with statins. J Gerontol: Med Sci 57: M747-M750.

72. Aronow WS, Ahn C (2002) Incidence of new coronary events in older persons with prior myocardial infarction and serum low-density lipoprotein cholesterol ≥125 mg/dL treated with statins versus no lipid-lowering drug. Am J Cardiol 89: 67-69.

73. Aronow WS, Ahn C, Gutstein H (2002) Incidence of new atherothrombotic brain infarction in older persons with prior myocardial infarction and serum low-density lipoprotein cholesterol ≥125 mg/dL treated with statins versus no lipid-lowering drug. J Gerontol: Med Sci 57: M333-M335.

74. Packer M, Coats AJ, Fowler MB, Michael B Fowler, Hugo A Katus, et al. (2001) Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 344: 1651-1658.

75. MERIT-HF Study Group (2001) Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 353: 2001-2007.

76. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, et al. (2000) 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). MERIT-HF Study Group. JAMA 283: 1295-1302.

77. Aronow WS, Ahn C (2001) Effect of beta blockers on incidence of new coronary events in older persons with prior myocardial infarction and diabetes mellitus. Am J Cardiol 87: 780-781.

78. Garg R, Yusuf S (1995) Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA 273: 1450-1456.

79. Heart Outcomes Prevention Evaluation Study Investigators (2000) Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 355: 253-259.

80. Brenner BM, Cooper ME, de Zeeuw D, William F Keane, William E Mitch, et al. (2001) Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 345: 861-869.

81. Ghali JK, Boehmer J, Feldman AM, Saxlon Leslie A, Demarco Teresa, et al. (2007) Influence of diabetes on cardiac resynchronization therapy with or without defibrillator in patients with advanced heart failure. J Card Fail 13: 769-773.

82. Brady PA, Terzic A (1998) The sulfonylurea controversy: more questions from the heart. J Am Coll Cardiol 31: 950-956.

83. Quast U, Stephan D, Bleger S, Russ U (2004) The impact of ATP-sensitive K+ channel subtype selectivity of insulin secretagogues for the coronary vasculature and myocardium. Diabetes 53: 156-164.

84. Garratt KN, Brady PA, Hassinger NL, Diane E Grill, Andre Terzic, et al. (1999) Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. J Am Coll Cardiol 33: 119-124.

85. O'Keefe JH, Blackstone EH, Sergeant P, McCallister BD (1989) The optimal mode of coronary revascularization for diabetics. Eur Heart J 19: 1696-1703.

86. Aronow WS, Ahn C (2001) Incidence of new coronary events in older persons with diabetes mellitus and prior myocardial infarction treated with sulfonylureas, insulin, metformin, and diet alone. Am J Cardiol 88: 556-557.

87. Lehmann JM, Moore LB, Smith-Oliver TA, et al. (1995) An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). J Biol Chem 270: 12953-12956.

88. Zinn A, Felson S, Fisher E, Schwartzbard A (2008) Reassessing the cardiovascular risks and benefits of thiazolidinediones. Clin Cardiol 31: 397-403.

89. Dormandy JA, Charbonnel B, Eckland DJ, E Erdmann, M Massi Benedetti, et al. (2005) Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (Prospective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. Lancet 366: 1279-89.

90. DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, Pogue J, et al. (2006) Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized contolled trial. Lancet 368: 1096-1105.

91. Wang CH, Weisel RD, Liu PP, Paul WM Fedak, Verma S (2003) Glitazones and heart failure: critical appraisal for the clinician. Circulation 107: 1350-1354.

92. DeFronzo RA, Goodman AM, Multicenter Metformin Study Group (1995) Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 333: 541-549.

93. Bailey CJ, Turner RC (1996) Metformin. N Engl J Med 334: 574-579.

94. UK Prospective Diabetes Study (UKPDS) Group (1998) Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352: 837-853.

95. Wake N, Hisashige A, Katayama T, Hideki Kishikawa, Yasuo Ohkubo, et al. (2000) Cost-effectiveness of intensive insulin therapy for type 2 diabetes: a 10-year follow-up of the Kumanoto study. Diabetes Res Clin Pract 48: 201-210.

96. Sukhija R, Aronow WS, Kakar P, Luis Garza, Rajesh Sachdeva, et al. (2006) Relation of microalbuminuria and coronary artery disease in patients with and without diabetes mellitus. Am J Cardiol 98: 279-281.

97. Zoungas S, de Galan BE, Ninomiva T, Diederick Grobbee, Pavel Hamet, et al. (2009) The combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes; new results from ADVANCE. Diabetes Care Aug 3.

98. Ravipati G, Aronow WS, Ahn C, Sujata K, Saulle LN, et al. (2006) Association of hemoglobin A1C level with the severity of coronary artery disease in patients with diabetes mellitus. Am J Cardiol 97: 968-969.

99. Aronow WS, Ahn C, Weiss MB, Babu S (2007) Relation of increased hemoglobin A1c levels to severity of peripheral arterial disease in patients with diabetes mellitus. Am J Cardiol 99: 1468-1469.