J. Young, M.D.

DIABETES, OBESITY, AND HEART FAILURE: THE NEW PANDEMIC

James B. Young, M.D.
Cleveland Clinic, Cleveland, Ohio

Introduction

It is important to embrace the fact that diabetes and cardiovascular disease are intimately linked.[1] Indeed, it is not inappropriate to describe diabetes as a "vascular perturbation." Specifically, endothelial dysfunction with vasomotor instability and atherosclerosis is a hallmark of diabetes mellitus. Only recently has the overlap between diabetes and cardiology been emphasized, with epidemiologic studies identifying the increased risk of cardiovascular morbidity with underlying diabetes mellitus. This is unfortunate since there is an epidemic of diabetes and obesity in North America and the rest of the world (thus, a pandemic) that has prompted concern about a sudden rise of cardiovascular deaths in the United States after a decline of about 40% in the last decade.[2] Particularly problematic is the relationship of the metabolic syndrome and diabetes to obesity and myocardial dysfunction leading to heart failure, which is known to have extraordinarily high morbidity itself. Is then diabetes, obesity, and heart failure the new cardiovascular pandemic that should demand more attention with the creation of a new field of "cardiologic diabetology" or "diabetic cardiology"?

The Epidemic of Diabetes and Obesity

In 1990, the estimated prevalence of diabetes mellitus in U.S. adults was 4.9% (Table 1); this rose to 7.9% by the turn of the century. Particularly concerning was the fact that in certain states such as Mississippi, Alabama, and Florida, the prevalence was greater than 10%. Across the United States, this rather dramatic disease prevalence was accompanied by an equally troublesome increase in the number of patients with obesity, defined as a body-mass index greater than 30 kg/m^2. Again, in 1991, the prevalence of obesity in adults was 12% compared to 21% in 2001. Most problematic appear to be Southern states, with Mississippi having a prevalence of obesity in 2001 greater than 25%. Figure 1 demonstrates the problem in more detail with the age-adjusted prevalence data and the U.S. regions in the top two quintiles for both obesity and diabetes.[2] These coun-

Table 1. Interrelationship of Diabetes, Heart Failure, and Obesity – The Epidemic

• **Epidemic proportions – rising dilemma**
Heart failure remains most common reason a patient is hospitalized in USA
Prevalence of obesity in USA >10%
Prevalence of diabetes in USA >8%
• **Cardiovascular Mortality**
Heart failure survival 50% at five years in Framingham cohort
Cardiovascular diseases cause more than 60% of deaths in diabetic males aged >40 years
Obesity doubles the mortality of diabetic heart failure cohorts in same observations

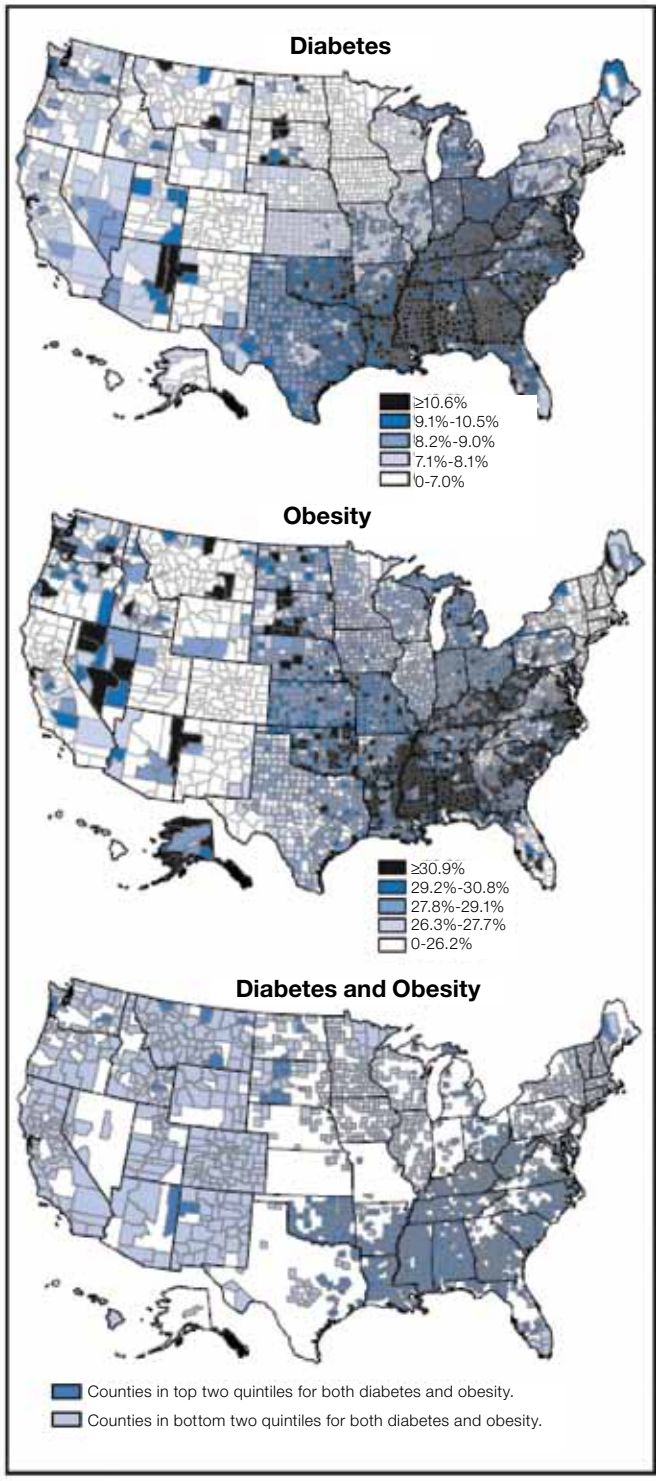

Figure 1. Age-adjusted percentages of persons aged ≥20 years with diabetes and obesity, by county — United States, 2007. Data from the Center for Disease Control. (MMWR Weekly; www.cdc.gov/mmwr/ preview/mmwrhtml/mm5845a2.htm. Accessed 12/10/2090.)

ties were concentrated in the South and Appalachian region, whereas counties having low diabetes and obesity prevalence were mostly in the West, Northern Plains, and New England. Estimated county-level prevalence of diabetes and obesity in the United States in 2007 should be coupled with the fact that the decrease in expected lifespan associated with diabetes at age 40 is 7.1 years in women and 5.5 years in men. Much of the adverse outcome of diabetes is driven by vascular disease resulting from the pathophysiologic effects of this disorder. With the number of diabetic patients predicted to double in the next decade, it is apparent that much work needs to be done to counter the epidemic of "diabesity."

Pathophysiologic Connection between the Cardiovascular System and Diabetes

The epic Framingham Study that documented the impact of a variety of risk factors on cardiovascular disease over the last half-century was one of the initial programs linking cardiovascular disease and diabetes.[3] There can be no disputing the fact that a significant excessive risk of death from cardiovascular disease is apparent in all diabetics. Why is there a connection between heart disease and diabetes? Perhaps most important is because diabetes is a vascular disease that results in early and extensive macrovessel disease manifesting often as atherosclerotic cardiovascular disease and leading to ischemic heart disease, particularly myocardial infarction (Table 2). This does not discount the fact that microvessel disease also occurs with atherosclerotic occlusion in small tertiary vessels and arterial spasm (perhaps most importantly coronary artery spasm). Diabetic cardiomyopathy is one manifestation of this "small vessel" arteriopathy. Interestingly, diabetes has been characterized as a condition that perturbates inflammation.[4]

An up-regulation of proinflammatory and down-regulation of anti-inflammatory cytokines has been described in diabetes with, in particular, an up-regulation of tumor necrosis factor alpha and down-regulation of interleukin 6. This has led to several studies with anti-inflammatory agents, including use of high-dose non-steroidal anti-inflammatory drugs, which has shown that glycated hemoglobin can be decreased with anti-inflammatory modulating agents. The link between inflammation, atherosclerosis, and heart failure has become more apparent over the last decade. Clearly, there is an interrelationship between endothelial pathophysiology, diabetes, and atherosclerotic cardiovascular disease.

Table 2. Interrelationship of Diabetes, Heart Failure and Obesity – Pathophysiology

• **Is there a common pathophysiology?**
"large vessel" atherosclerosis
"small vessel" atherosclerosis
Inflammation
Hypertension
Pulmonary hypertension (sleep apnea)
• **Are co-morbidities and outcomes linked?**
myocardial infarctions
stroke
increased hospitalizations and death
• **What is the role of adverse effects of drugs?**
TZD controversy
Feufluramine/phentermine (Fen-Phen) cardiotoxicity observations
• **Management issues affect pathophysiology?**
What HgbA1 level is best
Bariatric surgery rational?

Another key factor is that diabetes is a neurologic perturbation with evidence of a "diabetic neuropathy" of the heart occurring. Both parasympathetic and sympathetic intervention, neurologic tracking, and impulse transmission occur with, in particular, reduction of parasympathetic control of the heart and cardiovascular system in general. Heart rate and blood pressure tend to be higher in diabetics, with loss of parasympathetic-driven heart rate variability. The combination of endothelial vascular disease and neuropathic processes undoubtedly creates the underpinnings for cardiovascular dysfunction and heart failure.

Heart Failure and Diabetes

The OPTIMIZE-HF (Organized Program To Initiate Life Saving Treatment in Hospitalized Patients With Heart Failure) registry demonstrated that patients hospitalized for decompensated congestive heart failure (CHF) with the diagnosis of diabetes had a significantly elevated rehospitalization rate at 90 days compared to non-diabetic patients (33.7% versus 27.2%, P <0.0003).[5] This emphasizes the challenge and economic burden that diabetes presents and is particularly concerning because patients in this study revealed a substantially higher prevalence of diabetes mellitus than that seen in patients generally enrolled in heart failure clinical trials. Indeed, 42% of patients hospitalized with decompensated CHF in that effort were diabetic. Of the approximately 20,000 diabetics, more than 8,000 were treated with insulin. Patients with diabetes also were younger, more likely to have heart failure with preserved left ventricular systolic function, and had a higher incidence of hyperlipidemia and hypertension with worse renal function.

In the Candesartan and Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) clinical trials, diabetes was seen in about 30% of the patients, still one of the largest representations of patients in a chronic outpatient clinical heart failure trial.[6] Outcomes in diabetics with respect to all-cause mortality, cardiovascular death, or hospitalization due to CHF were all increased in patients with diabetes. Overall, the use of the angiotensin receptor antagonist candesartan decreased the rate of new-onset diabetes during follow-up in this heart failure study.

Emphasizing the problematic link between diabetes, obesity, and heart failure is a recent analysis of 4,205 consecutive patients undergoing cardiac catheterization at the Cleveland Clinic who had a body mass index (BMI) greater than 30 kg/m^2 and a diagnosis of heart failure. Rajmanikan and Butler noted that 46% of these patients had an ejection fraction greater than 50% and 21% less than 30%. When diabetes was present and the BMI was between 30-35 kg/m^2, the 36-month mortality was about 25% for both heart failure patients having ejection fractions less than 30% and those with "diastolic heart failure" or an ejection fraction greater than 50%. This should be compared to those patients with a BMI greater than 35, where the mortality rate was well over 50% at 36 months for the ejection fraction <30% group.

What Can Be Done about the Heart Failure, Obesity, and Diabetes Link?

It has been noted that insulin resistance, impaired fasting glucose, and hyperinsulinemia are common in patients with CHF even when diabetes mellitus has not been explicitly diagnosed. These three situations are also risk factors for the development of CHF independent of the presence of diabetes and other established atherosclerotic and CHF risk factors. Focusing attention on the underlying problem driving these three scenarios seems important to prevent the development of diabetes and heart failure. Clearly the two problems are intimately linked to obesity as well.

Why insulin resistance is so frequent in patients with heart failure is not well understood for many reasons. Particularly intriguing is the possibility that sympathetic overactivity (the change from a more normal

parasympathetic-driven cardiovascular system to a sympathetic-driven one in heart failure) may be responsible. Also important could be the sedentary lifestyle mandated by severe heart failure and the cachexia that appears, particularly when pro-inflammatory cytokines such as tumor necrosis factor alpha are elevated. Leptin is a small hormone that has received great attention because of its adipose-derived nature.[7] Leptin appears responsible for maintaining energy balance and perhaps drives the development of obesity in a variety of situations. Leptin has been found to affect peripheral insulin sensitivity and is linked to the development of heart failure, particularly in obese populations. Perhaps pharmaceutical approaches that interdict these molecular relationships will decrease development of CHF. Nonetheless, it is extraordinarily important to note that preventing obesity seems key to modulating hyperinsulinemia, impaired glucose tolerance, and insulin resistance in patients who have not overtly developed diabetes.

It is interesting to speculate on whether or not pharmaceutical modulation of endothelial dysfunction can prevent the development of heart failure in diabetics. One must remember that endothelial dysfunction is a prominent feature of both diabetes and heart failure. Hyperglycemia reduces nitrous oxide production in vascular preparations and can lead to extracellular matrix production, and thickening of the basement membrane, in cultured human endothelial cells with resultant impaired vasodilation, particularly when the nitrous oxide pathways are disrupted. Perhaps this is related to the microvascular disease that can develop in diabetics. Clearly, this can create perfusion abnormalities that set the stage for CHF, particularly for diabetic cardiomyopathy (loosely defined as systolic left ventricular dysfunction in patients with diabetes but without large coronary vessel obstruction). When these pathophysiologic situations are coupled to the autonomic neuropathy that develops in diabetes, normal coronary vasodilatory response to sympathetic stimulation is not noted. Again, whether or not pharmaceutical manipulation with "vasodilators" such as long-acting nitrates will be particularly beneficial in this patient population is unclear. Surely, however, controlling blood glucose and blood pressure is essential. Furthermore, the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) can be extraordinarily beneficial.[8]

The MICRO-HOPE (Microscopic Proteinuria in the Heart Outcomes Prevention Trial) was a sub-study of the HOPE trial where 3,577 patients diagnosed with diabetes were evaluated with respect to the development of CHF.[8] HOPE was a large clinical trial that gave either ramipril or placebo to patients at risk of developing heart failure and atherosclerotic events. Presentation of CHF was reduced by 20%. In a sub-study of 1,502 diabetic patients without CHF enrolled in EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease),[9] there was a 46% reduction (although not statistically significant) in first hospitalization for heart failure with an angiotensin converting enzyme (ACE) inhibitor.

In the LIFE (Losartan Intervention For Endpoint Reduction in Hypertension) study diabetes sub-group, losartan reduced the risk of first hospitalization for CHF compared to the beta blocker Atenolol that was used to treat hypertension.[10] The RENAAL study (Reduction in End Points in NIDDM with the Angiotensin II Antagonist Losartan) compared losartan to placebo in 1,513 patients with diabetes and nephropathy, and observed a 32% reduction in the rate of first hospitalization of heart failure with losartan therapy.[11] Similarly, in the Irbesartan Diabetic Nephropathy Trial (IDNT), 1,715 patients with diabetes and nephropathy were randomized to irbesartan, amlodipine, or placebo; irbesartan reduced the incidence of heart failure compared to placebo in significant fashion.[12]

Still, the most important issue is preventing obesity and hyperglycemia while instituting evidence-based therapies when indicated for hypertension (stage A heart failure) and early heart failure (stage B) that include ACE inhibitors or ARBs.

Controversial Issues

When diabetes and hyperglycemia are present, what should treatment targets be with respect to glycated hemoglobin? The ACCORD trial (the Action to Control Cardiovascular Risk in Diabetes Study Group) evaluated the effects of intensive glucose lowering in Type II diabetics.[13] The goal was to test the hypothesis that a combination of non-fatal myocardial infarction, stroke, or death from cardiovascular causes would be reduced in patients whose glycated hemoglobin levels were driven below 6% with aggressive Type II diabetes management. More than 10,000 patients were randomized into this study, with a mean age of 62 years and a median glycated hemoglobin level of 8.1%. Patients were assigned to receive "intensive" therapy to decrease glycated hemoglobin to the goal or "standard" therapy that targeted a level of 7 to 7.9%. The study was terminated early because of a higher mortality in the intensive therapy group after a mean follow-up of 3.5 years. At one year follow-up, the median glycated hemoglobin level was 6.4% in the intensive therapy group

and 7.5% in the standard therapy group. There were 257 deaths in the intensive therapy group compared to 203 in the standard therapy group, with a hazard ratio of 1.22 and a 95% confidence interval of 1.01 to 1.06 (P = 0.04). Important was the observation that hypoglycemia requiring therapy and weight gain of more than 10 kg were more frequent in the intensive therapy group, probably related to the medications used to drive the glycated hemoglobin to target (frequently a thiazolidinedione [TZD]). The ACCORD group concluded that the use of intensive therapy to target normal glycated hemoglobin levels increased mortality and did not significantly reduce major cardiovascular events. This has led to a reconsideration of what the target for glycated hemoglobin should be. Conventional wisdom was challenged. Rather than driving glycated hemoglobin levels to the lowest level possible, consensus is beginning to emerge that higher levels are, arguably, safer (target of 7% or less). Certainly the risk of hypoglycemia could have been related to the adverse morbid outcomes. Reflex activation of the autonomic nervous system associated with hypoglycemia could have been detrimental.

The ACCORD study group demonstrated results that were different from other clinical trials. The ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation Collaborative Group) and the VADT trial (Veterans Affairs Diabetes Trial) did not have similar outcome morbidity observations, raising the question of whether the specific types of therapy used might be the important issue.[14, 15] Also, long-term follow-up of other trials did suggest cardiovascular risk reduction for individuals with both Type I and Type II diabetes having intensive glycemic control. Addressing the different observations in large-scale clinical trials, the American College of Cardiology, the American Diabetes Association, and the American Heart Association issued a joint statement suggesting that there was no need to change treatment goals for most people with diabetes, and clinicians should continue to strive for good glycemic control by maintaining glycosylated hemoglobin levels at or below 7%.[16]

Related to "tight glycemic control" is the challenging issue of the use of thiazolidinediones (glitazones). These are a relatively new group of oral anti-diabetic agents that are peroxisome proliferator-activated (PPAR-GAMMA) receptor agonists. They are effective drugs that efficiently lower blood glucose levels. Two agents have generated the most experience — rosiglitazone and pioglitazone. Both agents cause significant weight gain, with an increase in subcutaneous but decrease in visceral fat. Fluid retention has been noted with these agents and appears associated with hemodilution, causing a reduction in hemoglobin. Peripheral edema also appears. This prompted great concern about these agents with respect to causing CHF. Particularly bothersome was the increase in peripheral edema noted when the glitazones were used with insulin. Because of this observation, and the fact that morbidity and mortality trials have not been done with these drugs, physicians concerned about the development of CHF in diabetic patients have frequently turned elsewhere for managing glycated hemoglobin levels. One cohort study of 23,440 patients with diabetes but no CHF at the initiation of a single new drug for diabetes suggested that pioglitazone, compared to sulphonylureas, did not significantly increase the incidence of CHF hospitalization, though there was a higher incidence of CHF noted throughout the time of observation.[17]

The fluid retention noted might create more egregious problems when advanced CHF patients are treated. A retrospective case review of CHF patients treated with glitazones noted that almost 20% of NYHA functional class III patients developed substantive fluid retention following initiation of these drugs, though the problem was usually quickly reversed by discontinuing glitazone and intensifying diuretic therapy.[18] A consensus statement published jointly by the American Diabetes Association and the American Heart Association suggested that glitazones can be used cautiously in patients with NYHA class I and II CHF but not in patients with class III or IV heart failure.[16]

Perhaps the most concerning observation regarding a TZD is the meta-analysis suggesting that rosiglitazone increases the risk of myocardial infarction and death from cardiovascular causes.[19] Nissen and Wolsky analyzed morbidity outcomes data in 42 trials and suggested that the odds ratio from myocardial infarction was 1.43 (95% confidence interval 1.03 to 1.98; P = 0.03) and the odds ratio for death from cardiovascular causes 1.64 (95% confidence interval 0.98 to 2.74; P = 0.06). This disturbing observation was, however, flawed by all of the problems of meta-analysis, and subsequent data has not clarified the situation. Indeed, the joint ACC, ADA, and AHA statement regarding diabetes treatment did not specifically address how the lower glycolated hemoglobin levels should be achieved and when to use the TZDs, yet did not specifically sanction their prescription. It is important to consider clinical trial design as we move forward with new oral agents to manage diabetes and clarify the role of TZDs.

Another controversy is the role of bariatric surgery in patients with diabetes, heart failure, and obesity. Bariatric surgery has evolved from a rather primitive,

extensive, and draconian "massive intestinal bypass" procedure — producing substantive metabolic perturbation with respect to malabsorption and dumping syndromes — to a laparoscopic procedure with multiple operative choices including "lap band," "gastric sleeve," and more limited "reux-en-y" gastric bypass methods. Each approach interdicts the problem differently with subtle nuances that relate to the manner in which satiety is achieved, nutrient absorption occurs, and proteins such as leptin fluctuate. Morbidity and mortality after these operations has dramatically decreased. Long-term studies show that bariatric surgery causes significant weight loss, recovery from diabetes, and a decrease in cardiovascular risk factors as well as a reduction in mortality that ranged from 23-40%.[20] Presently, the National Institutes of Health recommends bariatric surgery for obese people with a BMI of 40 or greater and for patients with a BMI of 35 who have co-morbidities such as diabetes mellitus. It is not entirely clear why a reduction in mortality and morbidity is seen after bariatric surgery, but the fact that this procedure results in highly significant blood pressure reduction, improvement (and indeed elimination) of diabetes, and optimization and normalization of serum lipid levels that place patients at risk for cardiovascular events is likely related. Since today laparoscopic bariatric surgery requires only a short hospital stay with quite acceptable perioperative morbidity rates and proven beneficial outcomes means we should be considering this approach much more often than we presently do.

Conclusion

It is clear that diabetes and obesity are major health dilemmas that need to be addressed aggressively by preventive maneuvers as well as sometimes radical interventions including bariatric surgery. Linking the cardiologist, endocrinologist, and bariatric surgeon is wise and a focus that will emerge in the future. Making sure that we aggressively treat heart failure conditions in these patients will be helpful as well. It behooves clinicians to work as a team focusing on these three critical maladies. A new specialty of cardiologic diabetology is on the horizon.[1]

References

1. Fisher M, McMurray JJ (eds). Diabetic Cardiology. West Sussex, UK: John Wiley
2. MMWR: Estimated County-Level Prevalence of Diabetes and Obesity — United States, 2007 [Internet]. Atlanta, GA: Centers for Disease Control and Prevention; c2009. Age-adjusted percentages of persons aged ≥20 years with diabetes and obesity, by county — United States, 2007; 2009 Nov 20 [cited 2009 20 Dec]; [figure at bottom of screen]. Available from: www.cdc.gov/mmwr/preview/mmwrhtml/mm5845a2.htm
3. Fox CS, Coady S, Sorlie PD, D'Agostino RB Sr, Pencina MJ, Vasan RS, Meigs JB, Levy D, Savage PJ. Increasing cardiovascular disease burden due to diabetes mellitus: The Framingham Heart Study. Circulation. 2007 Mar 27;115(12):1544-50.c
4. Fleischman A, Shoelson SE, Bernier R, Goldfine AB. Salsalate improves glycemia and inflammatory parameters in obese young adults. Diabetes Care. 2008 Feb;31(2):289-94
5. Greenberg BH, Abraham WT, Albert NM, Chiswell K, Clare R, Stough WG, Gheorghiade M, O'Connor CM, Sun JL, Yancy CW, Young JB, Fonarow GC. 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. 2007 Aug;154(2):277-88.
6. Yusuf S, Östergren JB, Gerstein HC, Pfeffer MA, Swedberg K, Granger CB, Olofsson B, Probstfield J, McMurray JV; Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity Program Investigators. Effects of candesartan on the development of a new diagnosis of diabetes mellitus in patients with heart failure. Circulation. 2005 Jul 5;112(1):48-53.
7. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature. 1998 Oct 22;395(6704):763–70.
8. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000 Jan 20;342(3):145-53.
9. Fox KM; EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003 Sep 6;362(9386):782-8.
10. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H; LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002 Mar 23;359(9311):995-1003.
11. Brenner BM, Cooper ME, De Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z,

Shahinfar S. Effects of losartan on renal and cardiovascular outcomes of patients with type 2 diabetes and nephropathy. N Engl J Med. 2001 Sep 20;345(12):861-9.

12. Deferrari G, Ravera M, Deferrari L, Vettoretti S, Ratto E, Parodi D. Renal and cardiovascular protection in type 2 diabetes mellitus: angiotensin II receptor blockers. J Am Soc Nephrol. 2002 Nov;13 Suppl 3:S224-9.
13. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2545-59.
14. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2560-72.
15. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009 Jan 8;360(2):129-39.
16. ADA: Press Room [Internet]. Alexandria, VA: American Diabetes Association; c1995-2009. Joint statement from ACC, ADA, AHA revises recommendations for glycemic targets for some patients; 2008 Dec 17 [cited 2009 Dec 10]. Available from: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=citmed&part=A59231#A59530.
17. Karter AJ, Ahmed AT, Liu J, Moffet HH, Parker MM. Pioglitazone initiation and subsequent hospitalization for congestive heart failure. Diabet Med. 2005 Aug;22(8):986-93.
18. Tang WH, Francis GS, Hoogwerf BJ, Young JB. Fluid retention after initiation of thiazolidinedione therapy in diabetic patients with established chronic heart failure. J Am Coll Cardiol. 2003 Apr 16;41(8):1394-8.
19. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007 Jun 14;356(24):2457-71.
20. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, Lamonte MJ, Stroup AM, Hunt SC. Long-term mortality after gastric bypass surgery. N Engl J Med. 2007 Aug 23;357(8):753-61.