

Heart Failure: A Serious and Common Comorbidity of Diabetes

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In the 45- to 74-year-old group of the Framingham Study,¹ heart failure (HF) was twice as common in diabetic men and five times more common in diabetic women as it was in nondiabetic subjects and in patients under age 65. HF was fourfold higher in diabetic males and eightfold higher in diabetic females.

In a health maintenance organization of almost 10,000 type 2 diabetic subjects, 12% initially had HF, and HF developed at a rate of 3.3% per year in the remainder. The incidence of heart failure increases with age.² In a 43-month nursing home study, of residents without heart failure,³ 39% of diabetic residents (10.9% per year) and 23% of nondiabetic residents (6.4% per year) developed HF.

Conversely, the prevalence of diabetes in HF patients is between 30 and 40%.⁴ This has been shown in an elderly Italian population, in patients admitted to hospital with HF, and in subjects in HF studies. Furthermore, HF has been shown to be an independent risk factor for the development of diabetes, and, in the U.K. Prospective Diabetes Study,⁵ the prevalence of HF was proportional to the hemoglobin A_{1c} (A1C), with no upper or lower threshold.

The prognosis for diabetic patients with HF is worse than that of nondiabetic HF patients. In the Studies of Left Ventricular Dysfunction (SOLVD) and Randomized Evaluation for Strategies of Left Ventricular Dysfunction trials, the presence of diabetes was an independent risk factor for death. In the Diabetes Insulin Glucose in Acute Myocardial Infarction (DIGAMI) study, HF account-

ed for 66% of the deaths in the first year.⁶

Etiology of HF With Diabetes

Diabetes is clearly associated with an increased prevalence of HF, and the probable reasons for this are the coexistence of hypertension, myocardial ischemia, and a specific diabetic cardiomyopathy (DC), known as the “cardiotoxic triad,” which causes biochemical, physiological, and anatomical alterations in cardiac tissue leading to cardiac dysfunction.⁷

Diabetic Cardiomyopathy

The high incidence and poor prognosis of HF in diabetic patients has been linked to the presence of DC characterized by myocellular hypertrophy and myocardial fibrosis, which leads to diastolic dysfunction. Diastolic dysfunction is present in 50–60% of type 2 diabetic patients and is almost always present in

diabetic patients with microalbuminuria. Diastolic dysfunction is related to A1C levels, and the most likely reason for this is the accumulation of advanced glycosylation end-products in the myocardium. Lipotoxicity due to accumulation of free fatty acids (FFAs) and their oxidative products in the myocardium may also be a factor.⁸

Hypertension can further damage myocardial contractile proteins, increase myocardial fibrosis, and generate a hypertrophic state that results in mild diastolic and later systolic dysfunction. The addition of myocardial ischemia changes a mildly dysfunctional myocardium due to diabetic cardiomyopathy or a moderately dysfunctional myocardium due to the combined effects of diabetic cardiomyopathy and hypertension into a severely dysfunctional myocardium, which can result in terminal heart failure.

The end result of this deadly cardiotoxic triad is a fibrotic noncompliant myocardium initially with diastolic but later with systolic dysfunction. Worsening of the HF can occur if papillary muscle fibrosis causes insufficiency of the mitral valve, which adds a mechanical burden to the already dysfunctional myocardium. In most cases of severe HF, all three components of the cardiotoxic triad are present, but any one of them may predominate.⁹

When a diabetic patient presents with HF, evaluation for coronary artery disease (CAD) is essential, because revascularization can significantly improve myocardial function. It is not unusual for such a patient with severe HF to have unobstructed coronary arter-

IN BRIEF

Because of the cardiotoxic triad (diabetic cardiomyopathy, hypertension, and coronary artery disease), heart failure (HF) has an increased prevalence and worse prognosis in diabetic patients. Treatment of HF is directed to glycemic control and blockade of the renin-angiotensin and sympathetic nervous system, primarily with angiotensin-converting enzyme inhibitors and a combined α -/ β -blocker. The goal is preventing and reversing myocardial remodeling, which will improve ventricular function.

ies. This has led to diabetic microangiopathy being considered in the etiology of diabetic cardiomyopathy and HF.

In general, microvascular ischemia has been excluded by the absence of increased lactate production during atrial pacing in such patients.¹⁰ However, endothelial dysfunction, which is present with both hyperglycemia and insulin resistance, could, with multiple episodes of vasoconstriction and subsequent reperfusion injury, lead to myocardial fibrosis and dysfunction.¹¹ Furthermore, increased permeability of the smaller coronary vessels associated with endothelial dysfunction could lead to interstitial edema, fibrosis, and dysfunction of the myocardium.¹² Finally, defective angiogenesis in response to hypoxia has been reported in diabetic patients, and this could lead to a decrease in capillary density and an ischemic cardiomyopathy.¹³

Activation of the Renin-Angiotensin and Sympathetic Systems

Experimental models of diabetic cardiomyopathy show the same biochemical and molecular abnormalities in the myocardium that occur with hemodynamic overload. In addition, hyperglycemia has been shown to activate the exact same pathways (protein kinase C and mitogen-activated protein kinase) that are activated by hemodynamic overload in mechanical stretch or increased ventricular wall stress.¹⁴ Activation of these pathways leads to decreased myocardial performance, which leads to activation of the renin-angiotensin system (RAS) and the sympathetic nervous system (SNS) to avoid tissue hypoperfusion.

This is initially a protective mechanism, but sustained stimulation of the RAS and SNS and other autocrine and paracrine systems leads to progressive loss of cardiac myocytes. This is because of accelerated myocardial apoptosis and necrosis, which in turn leads to further myocardial dysfunction and the downward spiral of cardiac failure. In addition, activation of the RAS and SNS

leads to cellular hypertrophy and changes in the size and shape of the left ventricle, a process known as remodeling. Although remodeling results in an increase in myocardial mass, the placement of the muscle is such that it decreases rather than improves myocardial performance.

This deterioration in myocardial function further stimulates the RAS and SNS, resulting in acceleration of the remodeling process and further deterioration in myocardial function. Eventually, myocardial function declines to a level that results in HF. Thus, a process that initially is adaptive and protective eventually results in worsening of myocardial function and HF.¹⁵

Early Detection of HF

According to the American College of Cardiology/American Heart Association HF guidelines, diabetes is a risk factor for HF. Older age, longer duration of diabetes, insulin utilization, and obesity are also risk factors for HF. However, the major risk factor for congestive HF in diabetic patients is hypertension, which occurs in 75% of type 2 diabetic patients. Therefore, awareness of the presence of these risk factors should alert prudent physicians to the possibility that HF is present in their diabetic patients and prompt them to look for symptoms and signs of HF.⁷

Unfortunately, many patients with HF do not have symptoms or signs of HF, in many cases because of inactivity. A simple in-office exercise tolerance test, either walking the patient or performing a graded exercise test, can be very revealing.

Screening of patients suspected of having HF with plasma brain natriuretic peptide (BNP) has a sensitivity of 92% and a specificity of 72% for HF.¹⁶ Like atrial natriuretic peptide (ANP), BNP is elevated with increased cardiac filling pressure, but unlike ANP, it is not affected by hyperglycemia. Utilizing BNP as a screen for HF leads to utilization of the definitive two-dimensional and pulsed Doppler echocardiography, which is

needed to visualize the structural and functional changes in HF in diabetic patients before initiating treatment for HF.¹⁷

Treatment of HF

Although diuretics and digoxin improve the symptoms and signs of HF and improve quality of life for diabetic HF patients, their utilization has no effect on mortality.¹⁸ If mortality is to be improved, the remodeling process must be at least halted and preferably reversed. Large clinical trials have shown that remodeling can be halted and reversed, ventricular function improved, and morbidity and mortality reduced through the utilization of drugs that interfere with the RAS and SNS and that, in diabetic patients, glycemic control is likely to be important, as well.

Glycemic Control

The potential for glycemic control in improving the outcome for diabetic patients with HF has never been fully examined. However, based on pathophysiological, epidemiological, and clinical observations, glycemic control should be considered as part of a comprehensive management strategy for HF in diabetic patients.⁷

With hyperglycemia and the inability of glucose to enter the cardiomyocyte due to hypoinsulinemia, the myocardium shifts to utilization of FFAs, which promotes and increases myocardial workload and ischemia. In addition, high FFA levels, which occur with both hyperglycemia and insulin resistance, may, by increasing sympathetic activity and myocardial calcium levels, be cardiotoxic and arrhythmogenic. By stimulating the activity of pyruvate dehydrogenase, dichloroacetate mimics the effect of reducing FFA utilization in nondiabetic patients, with decreased myocardial oxygen consumption and improved ventricular function.¹⁹ In addition, use of the thiazolidinedione (TZD) troglitazone has resulted in decreased myocardial FFA levels and reversed FFA-induced myocardial apoptosis. The cardiotoxicity

of elevated FFAs has been linked to the disruption of the structure and function of plasma membranes and to an increase in intracellular calcium and cardiac workload.²⁰

In the DIGAMI study, diabetic patients who had sustained a myocardial infarction (MI) received intravenous insulin followed by multiple daily injections of subcutaneous insulin based on the belief that shifting substrate utilization of the myocardium away from FFA toward glucose would result in a decreased myocardial workload and less myocardial ischemia. That this strategy worked was seen at 1 and 2 years, with decreased mortality in those patients who had sustained a first MI and had no previous history of HF.²¹

Use of TZDs

TZDs, by reducing insulin resistance, reduce the cardiac risk factors of endothelial dysfunction, inflammation, microalbuminuria, plasminogen activator inhibitor, increased adhesion molecule levels, decreased LDL and HDL particle sizes, and accelerated vascular smooth muscle cell proliferation. In addition, it has been conclusively shown in both animal and human studies that TZDs have no adverse effects on the myocardium. In fact, animal studies have shown that TZDs may have a positive effect on myocardial remodeling.²⁰

However, there is some concern regarding TZD use in patients with or at high risk of HF because of the potential of these drugs to induce edema. Edema with TZDs occurs for three reasons. First, with the return of insulin sensitivity, the ability of insulin to act on the distal tubule of the kidney to retain sodium is increased, an effect that may be relieved with diuretics.²² Second, with the return of insulin sensitivity, the ability of insulin to vasodilate the microcirculation leads to activation of the RAS. This effect may be reversed utilizing angiotensin-converting enzyme (ACE) inhibitors, ARBs, spironolactone, or eperolone.²³ Finally, with all TZDs, there is an increase in

vascular endothelial growth factor, which increases capillary permeability. This causes an edema that is similar in etiology to the edema that occurs with the dihydropyridine calcium channel blockers. The edema does not respond to diuretics, ACE inhibitors, ARBs, or aldosterone receptor blockers.²⁴

Overall, the plasma volume increases by as much as 6% in TZD-utilizing diabetic patients. This increase may cause a dilutional anemia that is potentially advantageous because there is retention of red cell mass and oxygen-carrying capacity and, with the higher plasma volume, a decrease in blood viscosity and improved blood flow.²⁵ However, in diabetic subjects with diastolic dysfunction who are destined to develop HF, this increase in plasma volume can prematurely precipitate the development of HF.⁸ In the situation of an "ill wind," this may be beneficial, because earlier therapy with ACE inhibitors and β -blockers will result in earlier and better remodeling of the ventricle. This is particularly important because undiagnosed left ventricular dysfunction, even in asymptomatic patients, is associated with an increased incidence of sudden death caused by arrhythmias.²⁶

When a patient has been diagnosed with HF, the question of whether TZDs should be used or continued to be used is unanswered. Based on their package inserts, both rosiglitazone and pioglitazone TZDs can be used in both Class 1 and Class 2 New York Heart Association HF (i.e., patients who can walk 200 yards without dyspnea). Until ongoing studies of TZDs in HF are presented or published, TZDs should be used with caution in HF. This is particularly true when TZDs are being utilized with insulin. Starting with a lower-than-recommended dose and slowly increasing the dose is prudent. Patients should be informed that a weight gain of > 7 lb should trigger a call to the physician. Withdrawal of TZDs will, within 3 days, reverse the fluid overload, and restarting the TZDs at half the original dose should then be considered.⁷

ACE Inhibitors and ARBs

Angiotensin II is a potent vasoconstrictor that also causes cardiac myocytic hypertrophy and production of collagen by these cells, leading to myocardial fibrosis.²⁷ Not only are these effects ameliorated by ACE inhibition and blocking of the AT₁ receptor, but also with ACE inhibitors bradykinin and prostacyclin levels are increased, which mediates the release of nitric oxide and improves both the hypertrophy of the myocyte and cardiac fibrosis.²⁸ Previously, based on retrospective subgroup analysis of the Valsartan in Heart Failure Study,²⁹ it was believed that in patients already on ACE inhibitors and β -blockers the addition of an ARB increased mortality. However, the recent Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study showed a benefit of adding candesartan to a HF regimen of β -blockers and ACE inhibitors.³⁰ Conversely, studies of high-risk type 2 diabetic patients with macroalbuminuria utilizing either losartan or iversartan, while showing improvement in progression of renal disease, did not show a benefit in cardiac or overall mortality.³¹

On the other hand, ACE inhibitors have repeatedly shown a reduction in mortality in diabetic HF patients with or without systolic dysfunction. The mechanism for this improvement is through myocardial remodeling. ACE inhibitors prevent rather than reverse remodeling so that their effect depends on how soon after an acute event they are initiated.³²

ACE inhibitors are at least as effective in reducing mortality in diabetic patients as in nondiabetic patients and are clearly of value in the treatment of diabetic patients with HF. Evidence of this is available from the Survival and Ventricular Enlargement Study, in which captopril reduced the mortality rate in both diabetic and nondiabetic subjects following MI, though the mortality rate of treated diabetic patients was higher than that of untreated nondiabetic

patients.³³ Use of enalapril in the SOLVD trials³⁴ was associated with greater efficacy in asymptomatic, compared with symptomatic, diabetic patients, which reemphasizes the prophylactic rather than curative effects of ACE inhibitors on myocardial remodeling. In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) trial,³⁵ use of lisinopril post-MI resulted in a lower 6-week mortality in diabetic subjects. In the Assessment of Treatment with Lisinopril and Survival study³⁶ of class II-IV HF patients, the risk of death was reduced by more than half in diabetic subjects utilizing lisinopril.

β-blockers

In the failing heart, activation of the SNS has harmful effects. Norepinephrine, acting through α-1 receptors, downregulates the β1 and mildly upregulates β2 receptors, is directly toxic to the myocardium, and stimulates fetal gene expression and myocardial remodeling.³⁷ Activation of the SNS is increased in both diabetes and the insulin resistance syndrome, in which hyperinsulinemia is associated with an elevated heart rate.³⁸ In addition, angiotensin II not only is toxic to the cardiocyte, but also increases norepinephrine production.³⁹ Therefore, effectively preventing myocardial remodeling requires blockade not only of the RAS, but also of the SNS. Effective blockade of the latter requires inhibition at both β1 and β2 receptors as well as the α-1 receptor.⁸

There are three generations of β-blockers. First-generation agents, such as propranolol and timolol, are contraindicated in HF because of their depressant effect on the myocardium. The second-generation β-blockers metoprolol, atenolol, and bisoprolol can be used safely in HF but are of limited efficacy at low doses because of their specificity for the β1 receptor. The third-generation β-blockers carvedilol and labetalol were developed to comprehensively inhibit both β1 and β2 receptors as well as the α-1 receptor.

In the normal myocardium, the most predominant activity is through the β1 receptor. However, in the failing myocardium, irrespective of the cause of the HF, there is activity of not only β1 but also β2 and α-1 receptors. In multiple large trials, use of the third-generation β-blocker carvedilol has shown an initial decrease in ejection fraction followed by improvement after 1 month and significant improvement by 3 months, with an increased ejection fraction accompanied by reduced ventricular volumes. Indeed, after 18 months with carvedilol, left ventricular mass is decreased, and the initially spherical ventricle is remodeled to a normal elliptical shape.⁴⁰ Improvement in left ventricular function has also been observed with metoprolol at high doses, in which both β1 and β2 blockade occur, but α-1 blockade does not.⁴¹

As much as 30% of the patients enrolled in β-blocker HF trials had diabetes, and outcomes were equally as good in diabetic and nondiabetic subjects.⁴² However, unlike ACE inhibitors, β-blockers are often withheld from diabetic patients because of fear of hypoglycemia, which is a realistic concern for those with type 1, but not for typical type 2 diabetic patients. Vasoconstriction because of unopposed alpha activity leads to not only worsening of peripheral vascular disease, but also insulin resistance and loss of glycemic control. Many of these problems can be avoided by using a third-generation β-blocker such as carvedilol, a nonselective β-blocker with α-1 blocking properties. Through its vasodilating properties, carvedilol lowers insulin resistance, glucose, and triglyceride levels; increases HDL levels; and improves the peripheral circulation.⁴³

Conclusion

HF has an increased prevalence and carries a worse prognosis in the diabetic population. Diabetic cardiomyopathy in conjunction with hypertension and CAD (the cardiotoxic triad) leads to activation of the RAS and SNS. This, in turn, leads to cardiac remodeling,

induction of the fetal gene program, and a shift in myocardial metabolism toward increased utilization of FFAs, which increases the myocardial workload. Treatment of HF is directed toward glycemic control, which decreases FFA utilization by the myocardium and decreases the cardiac workload, and blockade of the RAS and SNS, primarily with ACE inhibitors and β-blockers, which prevent or (in the case of β-blockers) reverse myocardial remodeling.

REFERENCES

- ¹Kannel WB, McGee DL: Diabetes and cardiovascular disease: the Framingham Study. *JAMA* 241:2305–2308, 1979
- ²Nichols GA, Hillier TA, Erbey JR, Brown JB: Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors. *Diabetes Care* 24:1614–1619, 2001
- ³Aronow WS, Ahn C: Incidence of heart failure in 2737 older persons with and without diabetes mellitus. *Chest* 115:867–868, 1997
- ⁴Reis SE, Holubkov R, Edmundowicz D, McNamara DM, Zell KA, Detre KM, Fieldman AM: Treatment of patients admitted to the hospital with congestive heart failure: specialty-related disparities in practice patterns and outcomes. *J Am Coll Cardiol* 30:733–738, 1997
- ⁵Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000
- ⁶Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, Wedel H, Welin L: Randomized trial of insulin glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 26:57–65, 1995
- ⁷Bell DSH: Heart failure: the frequent, forgotten and often fatal complication of diabetes. *Diabetes Care* 26:2433–2441, 2003
- ⁸Bell DSH: Diabetic cardiomyopathy. *Diabetes Care* 26:2949–2951, 2003
- ⁹Bell DSH: Diabetic cardiomyopathy: a unique entity or a complication of coronary artery disease? *Diabetes Care* 18:708–714, 1995
- ¹⁰Genda A, Mizuno S, Nunoda S, Nakayama A, Takeda R, Bunko H, Hisada K: Clinical studies on diabetic myocardial disease using exercise testing with myocardial scintigraphy and endomyocardial biopsy. *Clin Cardiol* 9:375–382, 1986
- ¹¹Ahmed SS, Jaferi GA, Narang RM, Regan TJ: Preclinical abnormality of left ventricular function in diabetes mellitus. *Am Heart J* 89:153–158, 1975
- ¹²Factor SM van Horeven KH, Cho S, Fein

FS: Microangiopathy and focal myocardial injury: their role in the development of diabetic cardiomyopathy. In *The Diabetic Heart*. Nagano M, Dhalla NS, Eds. New York, Raven Press, 1991, p. 89–101

¹³Yarom R, Zirkin H, Stammner G, Rose AG: Human coronary microvessels in diabetes and ischemia: morphometric study of autopsy material. *J Pathol* 166:265–270, 1992

¹⁴Bristow MR: Why does the myocardium fail? Insights from basic science. *Lancet* 352 (Suppl. 1):S18–S114, 1998

¹⁵Eichhorn EJ, Bristow MR: Medical therapy can improve the biological properties of the chronically failing heart: a new era in the treatment of heart failure. *Circulation* 94:2285–2296, 1996

¹⁶McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE, Tunstall-Pedoe H, McMurray JJ, Dargie HJ: Biochemical detection of left ventricular systolic dysfunction. *Lancet* 351:9–13, 1998

¹⁷Lainchbury JG, Redfield MM: Doppler echocardiographic-guided diagnosis and therapy of heart failure. *Curr Cardiol Rep* 1:55–66, 1999

¹⁸Solang L, Malmberg K, Ryden L: Diabetes mellitus and congestive heart failure: further knowledge needed. *Eur Heart J* 20:789–795, 1999

¹⁹Bersin RM, Wolfe C, Kwasman C, Lau D, Klinski C, Tanaka K, Khorrami P, Henderson GN, deMarco T, Chatterjee K: Improved hemodynamic function and mechanical efficiency in congestive heart failure with sodium dichloroacetate. *J Am Coll Cardiol* 23:1617–1624, 1994

²⁰Zhou YT, Grayburn P, Karim A, Shimabukuro M, Higa M, Baetens D, Orci L, Unger RH: Lipotoxic heart disease in obese rats: implications of human obesity. *Proc Natl Acad Sci U S A* 97:1784–1789, 2000

²¹Malmberg K, Ryden L, Hamsten A, Herlitz J, Waldenstrom A, Wedel H: Effects of insulin treatment on cause-specific one-year mortality and morbidity in diabetic patients with acute myocardial infarction: DIGAMI (Diabetes Insulin-Glucose in Acute Myocardial Infarction) Study Group. *Eur Heart J* 17:1337–1344, 1996

²²DeFronzo RA, Cooke CR, Andres R, Faloona GR, Davis PJ: The effect of insulin on renal handling of sodium, potassium, calcium and phosphate in man. *J Clin Invest* 55:845–855, 1975

²³Baron AD, Brechtel G: Insulin differentially regulates systemic and skeletal muscle vascular resistance. *Am J Physiol* 265:E61–E67, 1993

²⁴Baba T, Shimada K, Neugebauer S, Yamada D, Hashimoto S, Watanabe T: The oral insulin sensitizer, thiazolidinedione, increases plasma vascular endothelial growth factor in type 2 dia-

betic patients. *Diabetes Care* 24:953–954, 2001

²⁵Spivak JL: Erythropoietin use and a base: when physiology and pharmacology collide In Roach RC et al editors *Hypoxia: From Genes to the Bedside*. Roach RC, Wagner PD, Hackett PH, Eds. New York, Kluwer Academic/Plenum Publishers, 2001, p. 207–224

²⁶SOLVD Investigators: Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fraction. *N Engl J Med* 327:685–691, 1992

²⁷Weber KT, Brilla CG: Pathological hypertrophy and cardiac interstitium: fibrosis and renin-angiotensin-aldosterone system. *Circulation* 83:1849–1865, 1991

²⁸Katz AM: The cardiomyopathy of overload: an unnatural growth response in the hypertrophied heart. *Ann Intern Med* 121:363–371, 1994

²⁹Cohn JN, Tognoni G: A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 345:1667–1675, 2001

³⁰McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EC, Olofsson B, Yusuf S, Pfeffer MA, CHARM Investigators and Committees: Effects of candesartan in patients with chronic heart failure and ventricular systolic function taking angiotensin-converting-enzyme inhibitors. *Lancet* 362:767–771, 2003

³¹Brenner BM, Cooper ME, deZeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861–869, 2001

³²Mitchell GF, Lamas GA, Vaughan DE, Pfeiffer MA: Left ventricular remodeling in the year after first anterior myocardial infarction: a quantitative analysis of contractile segment length and ventricular shape. *J Am Coll Cardiol* 19:1136–1144, 1992

³³Moyle LA, Pfeiffer MA, Wun CC, Davis BR, Geltman E, Hayes D, Farnham DJ, Randall OS, Dinh H, Arnold JM: Uniformity of captopril benefit in the SAVE study: subgroup analysis: Survival and Ventricular Enlargement Study. *Eur Heart J* 15(Suppl. B):2–8, 1994

³⁴Shindler DM, Kostis JB, Yusuf S, Quinones MA, Pitt B, Stewart D, Pinkett T, Ghali JK, Wilson AC: 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, 1996

³⁵Zuanetti G, Latini R, Maggioni AP, Franzosi M, Santoro L, Tognoni G: Effect of the ACE inhibitor lisinopril on mortality in diabetic patients with acute myocardial infarction: data from the GISSI-3 study. *Circulation* 96:4239–4245, 1997

³⁶Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Ryden L, Thygesen K, Unetsky BF, ATLAS Study Group: Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *J Am Coll Cardiol* 31:249A, 1998

³⁷Mann DL, Kent RL, Parsons B, Cooper G: Adrenergic effects on the biology of the adult mammalian cardiocyte. *Circulation* 85:790–804, 1997

³⁸Festa A, Dagostino R, Jr., Hales CN, Mykkanen L, Haffner SM: Heart rate in relation to insulin sensitivity and insulin secretion in non-diabetic subjects. *Diabetes Care* 23:624–628, 2000

³⁹Gavras H, Kremer D, Brown JJ, Gray B, Lever AF, MacAdams RF, Medina A, Morton JJ, Robertson II: Angiotensin and norepinephrine-induced myocardial lesions: experimental and clinical studies in rabbits and man. *Am Heart J* 89:321–332, 1975

⁴⁰Bristow MR, Roden RL, Lowes BD, Gilbert EM, Eichhorn EJ: The role of third-generation beta blocking agents in chronic heart failure. *Clin Cardiol* 21 (12 Suppl. 1):I3–I13, 1998

⁴¹Waagstein F, Bristow MR, Swedberg K, Camerini F, Fowler MB, Silver MA, Gilbert FM, Johnson MR, Goss FG, Hjalmarson A: Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet* 342:1441–1446, 1993

⁴²Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH: The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 334:1349–1355, 1996

⁴³Bell DSH: Use of beta blockers in the patient with diabetes. *Endocrinologist* 13:116–123, 2003

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