Management of Heart Failure

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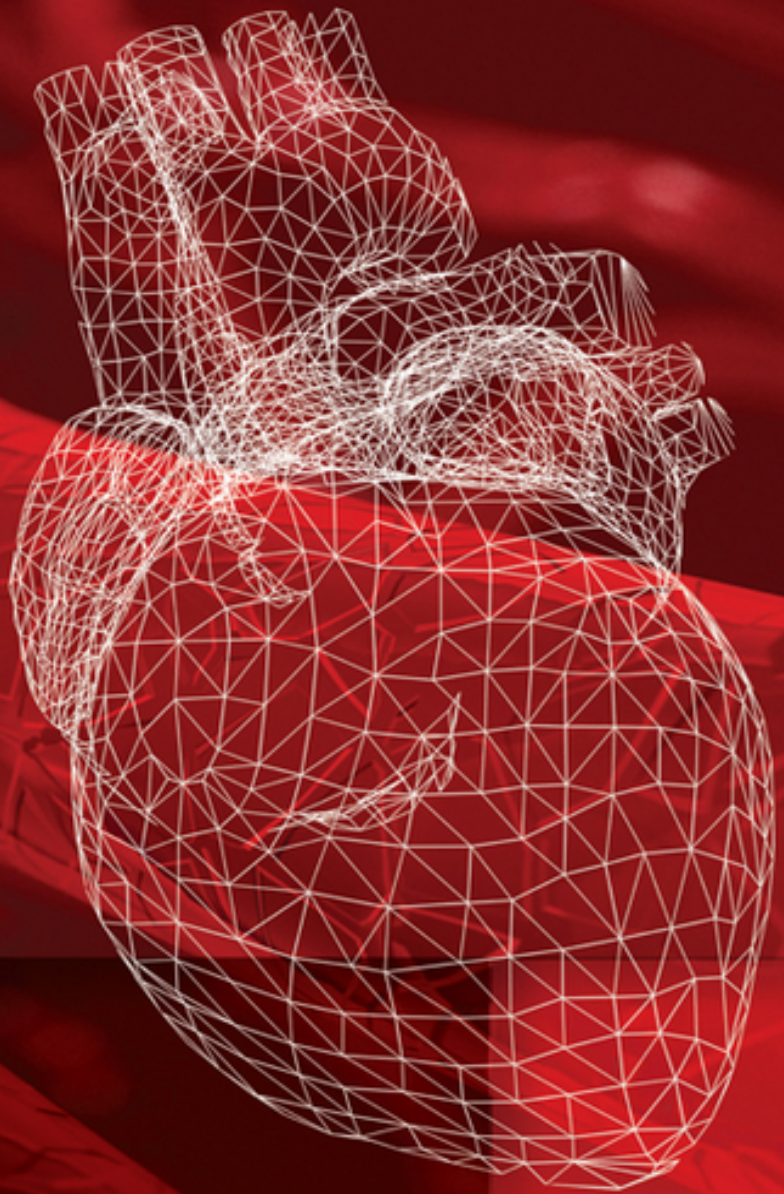

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Contents

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Section 1 Prevention and evaluation of heart failure

1 Preventing heart failure

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Introduction

Epidemiology

Heart failure is pandemic amongst industrialized nations. In the United States alone it is estimated that there are over 5 million individuals suffering from heart failure, and each year an estimated 555,000 new cases are diagnosed [1]. The impact of heart failure on the health care system, and on society in general, is staggering. It is the leading cause of hospitalization in Medicare beneficiaries and, overall, it results in over 1 million hospitalizations each year. The cost to the United States healthcare system was estimated in 2007 to be more than $33 billion annually [1]. Although therapeutic advances have improved survival in heart failure patients, estimated 5-year mortality is still in the range of 50% [2].

On top of this disturbing picture is the certainty that heart failure prevalence will increase substantially over the next several decades. The major reasons for this are outlined in Table 1.1. The most important of these is the aging of the population. Heart failure is predominantly a disease of older people [3] and the population of industrialized nations is increasing in age. In the U.S., the number of individuals

greater than 65 years will nearly double from 35 million in the year 2000 to over 70 million in 2030 [4]. Data from the Framingham study indicates that the lifetime risk of developing heart failure for individuals who are age 40 is 21% for men and 20% for women [5]. Similarly alarming figures have been reported from European studies. The Rotterdam study reported a lifetime risk of heart failure in individuals of 55 years to be 33% in men and 28.5% in women [6]. Thus, growth in the segment of the population that is at the highest risk for developing heart failure will substantially increase future incidence and prevalence.

Along with the aging of the population, patients with a variety of cardiovascular diseases, including coronary artery disease (CAD), valvular lesions, or congenital abnormalities, now experience much better outcomes and longer survival than in the past. In particular, aggressive revascularization strategies have resulted in improved survival of patients following a myocardial infarction (MI). Many of these patients, however, have experienced some degree of myocardial injury and are at risk of further structural changes (i.e., cardiac remodeling) that can lead to progressive deterioration in cardiac function and increased mortality over time [7]. A recent publication points out the reciprocal relationship between increased survival of older patients who suffer a MI and higher risk for developing heart failure in the future (Figure 1.1). In this work, Ezekowitz and colleagues noted that in a cohort of 4291 MI survivors >65 years who were without heart failure during their index hospitalization, 71% developed heart failure within 5 years with nearly two-thirds of the cases presenting with the first year post-MI [8].

Another factor that has resulted in the growth of the heart failure population is, paradoxically, the improved survival of patients with chronic heart

Table 1.1 Reasons for the Increasing Prevalence of Heart Failure

1. Aging of the population.
2. Improved survival in patients with other cardiovascular conditions (e.g., myocardial infarction, valvular heart disease, congenital lesions).
3. Impact of current therapy (e.g., ACEIs, ARBs, aldosterone blockers, BBs, ICDs) in prolonging survival of patients with existing heart failure.
4. Increased incidence and prevalence of obesity, type 2 diabetes and the metabolic syndrome in the population.
5. Better and earlier recognition of the presence of heart failure.
6. Reduction in premature mortality due to infectious disease in developing countries.

ACEIs = angiotensin converting enzyme inhibitors;
ARBs = angiotensin receptor blockers;BBs = beta-blockers;
ICDs = intracardiac defibrillators.

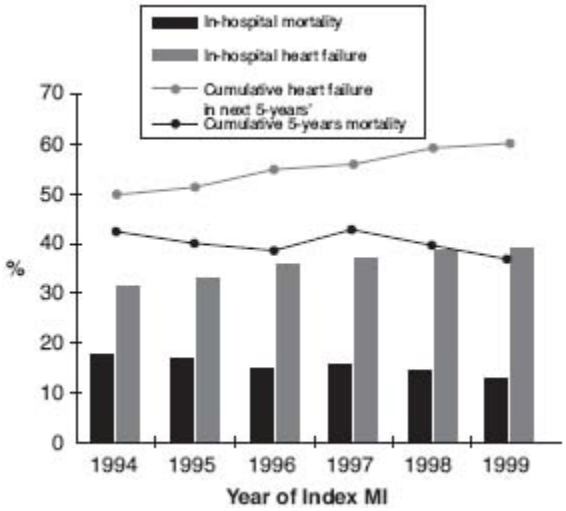
failure. As the use of lifesaving therapies such as beta-blockers, angiotensin converting enzyme (ACE) inhibitors, intracardiac defibrillators (ICDs) and cardiac resynchronization therapy (CRT) becomes more widespread, a greater number of patients will survive a longer period of time with heart failure. While this is unarguably a positive development, improved therapy is in most cases only palliative. Moreover, the increasing number of patients who are well treated with these therapies has resulted in the emergence of a cohort of patients with 'advanced chronic HF' who have severely limiting symptoms, marked hemodynamic impairment, and increased hospitalizations and mortality [9]. The implications of this development is that this "*emerging cohort of patients with advanced chronic heart failure (ACHF) represents a population for which additional treatments are required".*

Over the past several years there has been an alarming increase in the incidence and prevalence of obesity [10], diabetes (mostly Type II) [11], and the metabolic syndrome [12], all of which have been shown to be associated with increased risk of developing heart failure. These conditions

are strongly related [11] to each other and while genetic factors

Figure 1.1 Temporal Trends in Mortality Rate and the Development of Heart Failure. **Black bars** indicate in-hospital mortality rate, and **gray bars** indicate in-hospital heart failure rate. **Gray line** indicates cumulative heart failure in the next 5 years for patients who survived index hospitalization, and **black line** indicates the cumulative 5-year mortality. X-axis indicates year of hospitalization for index myocardial infarction (MI).

From: Ezekowitz JA, Kaul P, Bakal JA, Armstrong PW, Welsh RC, McAlister FA. Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. J Am Coll Cardiol. 2009;53(1):13–20. Reproduced by permission of Elsevier.



are involved, they are caused to a large degree by profoundly unhealthy dietary and exercise patterns [13]. As will be discussed later in the chapter, while both diet and exercise are lifestyle choices that are amenable to preventive strategies, there is little evidence that such strategies will reduce the risk of heart failure in the future.

Finally, there has been increased emphasis on early recognition and improved accuracy of diagnosing heart failure. A variety of imaging and blood chemistry tests are being used for that purpose. Probably the most promising of

these is the use of biomarkers in the diagnosis of patients with heart failure [14–16]. As these tests are more widely applied as screening tools, the prevalence of heart failure is likely to increase substantially. The reason for this is that they will provide a mechanism for the earlier recognition of heart failure in patients with either minimal or ambiguous symptoms.

While most of the current epidemiologic information about heart failure originates from industrialized countries, there has been a sizeable shift in disease patterns in the developing world. As infectious diseases decline in prevalence due to more effective prevention and treatment, there has been a transition in patterns of morbidity and mortality to chronic degenerative diseases. This trend will only accelerate in the future as these countries experience changes in lifestyle, including modifications in diet, exercise patterns, smoking, and obesity that will put large segments of the population at risk for CV disease. The prevalence and incidence data about heart failure in developing countries is scanty and probably misleading since it is based on referral or hospital based data [17]. Nonetheless, there is evidence that in Asia hospitalization rates from heart failure are increasing [18].

Heart failure as a continuum

In seeking ways to most effectively deal with the increasing worldwide burden of heart failure it is worthwhile considering the sequence of events that led to its development. Heart failure is a clinical syndrome that is the consequence of a variety of diseases, most of which directly affect the heart. Although there are numerous causes of heart failure, the common denominator of these diverse etiologies is that they either directly damage the myocardium (e.g., MI or exposure to myocardial toxins) or they expose it to increased levels of wall stress (e.g.,

hypertension or valvular lesions). The initial insult to the myocardium then activates a complex process in which the heart attempts to compensate for a loss in contractile performance and/or an increase in wall stress through alterations in structure. Many of the compensatory changes are mediated by activation of neurohoromonal systems such as the sympathetic nervous system (SNS) and renin angiotensin system (RAS) [19]. Neurohormonal activation is widespread occuring systemically [19] and locally within the heart itself [20]. The direct consequences on the heart include cardiac remodeling characterized by hypertrophy, dilatation, deposition of fibrous tissue in the cardiac interstitium, and reversion of the left ventricle (LV) to a spherical shape [21]. Neurohormonal activation also promotes salt and water retention and vasoconstriction, both of which further increase the load on the heart. While the immediate goal of these compensatory mechanisms is the maintenance of perfusion of vital organs, the long-term effects are highly deleterious. Recognition of the central role of neurohormonal systems in the pathogenesis of heart failure provides a rationale for selecting therapies that are effective in its prevention and treatment.

The continuum of heart failure which begins with the presence of risk factors that injure or increase stress on myocardium and initiate remodeling is outlined in Figure 1.2. Recognition of this evolution was instrumental in the formulation of the ACC/AHA staging criteria for heart failure [22] that is shown in Figure 1.3. The importance of this staging system is that it identifies patients who are at risk of developing heart failure due to the presence of well defined risk factors and also those patients who are at risk of undergoing maladaptive remodeling. Once identified,

Figure 1.2 Chain of Events Leading to End-stage Heart Failure

Adapted from: Dzau and Braunwald. Resolved and unresolved issues in the prevention and treatment of coronary artery disease: a workshop consensus statement. Am Heart J. 1991;121(4 part 1):1244–63.

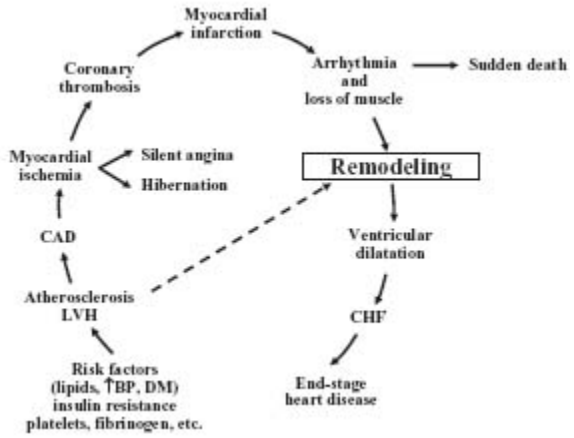
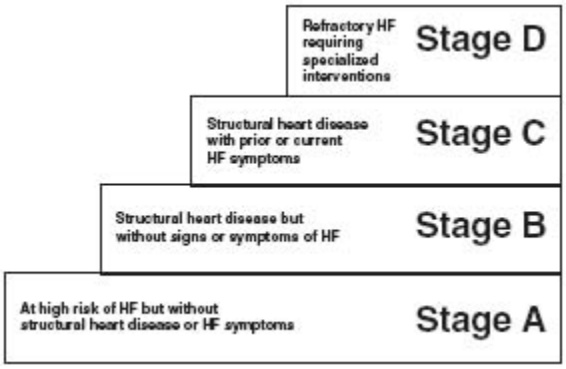


Figure 1.3 Revised ACC/AHA Staging System for Heart Failure

Adapted from: Hunt SA et al. ACC/AHA 2005 CHF Guideline Update. Circulation 2005;112: e154–235.



high risk Stage A and B patients can be treated with the goal of preventing the development of heart failure in the future.

Risk factors for heart failure

The major and minor risk factors for heart failure are summarized in Table 1.2. Of the major risk factors, other than age and male sex, virtually all of them can be prevented or treated. As shown in Figure 1.4, heart failure could be attributed to MI, hypertension and/or diabetes in

approximately 90% of the cases [23]. Thus, attention to these conditions is of paramount importance in developing strategies for preventing heart failure. An aspect of this profile of risk factors that deserves particular attention is the fact that many of them, including obesity, smoking, diet, sedentary life style and exposure to toxins such as alcohol, can be influenced or prevented by lifestyle choices. The presence of one or more of these 'lifestyle risk factors' in patients who have other more traditional risk factors increases their importance and makes them particularly inviting targets for therapeutic interventions.

Ischemic heart disease has been recognized as the leading cause of heart failure in the developed world [24–26]. In the U.S. it is estimated that greater than 15 million individuals have had an MI [1]. For patients between 40–69 years of age, the risk of developing heart failure in the 5-year period after a first MI is 7% and 12% for men and women, respectively. Moreover, this incidence goes up strikingly with age so that it is 22% and 25% in men and women over 70 in the 5 years post-MI [1]. Recent findings from Canada summarized in Figure 1.1, however, indicate that the risk of heart failure following an MI in older patients may be considerably higher [8]. Treatment of risk factors for CAD, particularly hypertension, hyperlipidemia, and smoking can reduce the future likelihood of heart failure by preventing coronary events. The well defined target goals of risk modification proposed by various specialty and subspecialty societies are summarized in Table 1.3. Patients with recognized CAD will also benefit from vigorous attention to these issues as well as the use of anti-platelet agents [27] and judicious use of revascularization strategies. The presence of risk factors such as hypertension and hyperlidemia in the post-MI population deserves particular attention since there is compelling evidence that treating

with anti-hypertensive agents or statins will significantly lower the future risk of heart failure [28,29].

One of the most alarming trends in public health in the United States is the exuberant growth of the percent of the population that is defined as being obese. The prevalence of obesity in adults in the U.S. increased by ~50% for each decade from 1980–2000 [30] and at present two-thirds of adults are obese or overweight. While obesity is now recognized as an independent risk factor for heart failure, it is also strongly associated with diabetes, insulin resistance, and the metabolic syndrome [31,32]. These latter conditions, in turn, all have been associated with increased heart failure risk. While the mechanisms through which obesity, diabetes, and the metabolic syndrome cause heart failure have not yet been fully defined there is increasing evidence that changes in myocardial metabolism, neurohormonal effects, and activation of pro-inflammatory mediators are all involved.

Evidence that treating risk factors prevents heart failure

Risk factors for the development of heart failure show substantial overlap with those for the development of coronary artery disease (CAD). As shown in Figure 1.4, ischemic heart disease is the major contemporary

Table 1.2 Established and Hypothesized Risk Factors for HF

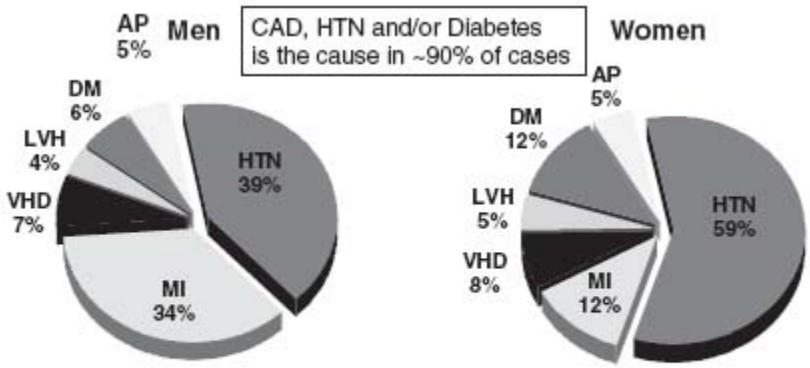
Major Clinical Risk Factors	Toxic Risk Precipitants
• Age, male sex	• Chemotherapy (anthracyclines, cyclophosphamide, 5-FU, trastuzumab)
• Hypertension, LVH	
• Myocardial infarction	• Cocaine, NSAIDs
• Diabetes mellitus	• Thiazolidinediones
• Valvular heart disease	• Doxazosin
• Obesity	• Alcohol

Minor Clinical Risk Factors	Genetic Risk Predictors
• Smoking	SNP (e.g., α2CDel322–325, β1Arg389)
• Dyslipidemia	**Morphological Risk Predictors**
• Sleep-disordered breathing	• Increased LVID, mass
• Chronic kidney disease	• Asymptomatic LV dysfunction
• Albuminuria	• LV diastolic dysfunction
• Homocysteine	
• Immune activation, IGF1, TNFα, IL-6, CRP	
• Natriuretic peptides	
• Anemia	
• Dietary risk factors	
• Increased HR	
• Sedentary lifestyle	
• Low socioeconomic status	
• Psychological stress	

5–FU = 5-fluorouracil;SNP = single-nucleotide polymorphism;LVID = left ventricular internal dimension;LVH = left ventricular hypertrophy;NSAIDs = nonsteroidal antiinflammatory drugs;IGF = insulinlike growth factor;TNF = tumor necrosis factor;IL = interleukin;CRP = C-reactive protein;HR = heart rate.
From: Schocken DD, Benjamin EJ, Fonarow GC, Krumholz HM, Levy D, Mensah GA, Narula J, Shor ES, Young JB, Hong Y;American Heart Association Council on Epidemiology and Prevention;American Heart Association Council on Clinical Cardiology;American Heart Association Council on Cardiovascular Nursing;American Heart Association Council on High Blood Pressure Research;Quality of Care and Outcomes Research Interdisciplinary Working Group;Functional Genomics and Translational Biology Interdisciplinary Working Group. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research;Quality of Care and Outcomes Research Interdisciplinary Working Group;and Functional Genomics and Translational Biology Interdisciplinary Working Group. *Circulation.* 2008;117(19):2544–65. Reproduced by permission of the American Heart Association.

Figure 1.4 Population Attributable Risks for the Development of Heart Failure

Adapted from: Levy et al. JAMA. 1996;275:1557.



Population-attributable risk defined as:
(100 x prevalence x [hazard ratio – 1])/(prevalence x [hazard ratio – 1] + 1)

CHF = chronic heart failure; AP = angina pectoris; DM = diabetes mellitus; LVH = left ventricular hypertrophy; VHD = valvular heart disease; HTN = hypertension; MI = myocardial infarction

etiologic determinant of heart failure with systolic ventricular dysfunction in modernized countries. Hypertension, diabetes, and dyslipidemia represent additional important and modifiable risk factors for heart failure independent of their disease-attributable risk for CAD. Each disease therefore represents a target

Table 1.3 Heart Failure Society Of America Guideline Recommendation for Treating Risk Factors for Heart Failure

Risk Factor	Goal
Hypertension	Generally < 130/80[1]
Diabetes	See ADA guidelines[2]
Hyperlipidemia	See NCEP guidelines[3]
Inactivity	20–30 min. aerobic 3–5 x wk.
Obesity	Weight reduction < 30 BMI
Alcohol	Men ≤ 2 drinks/day, women ≤ 1
Smoking	Cessation
Dietary Sodium	Maximum 2–3 g/day

From: Heart Failure Society Of America. Prevention of ventricular remodeling, cardiac dysfunction, and heart failure. J Card Fail. 2006 Feb;12(1):e12–5. Reproduced by permission of Elsevier.

[1] Also see Tables 1.6 and 1.7

[2] Diabetes Care 2006; 29: S4–S42

[3] JAMA 2001; 285:2486–97
for primary prevention (preventing Stage A or Stage B heart failure) as well as secondary prevention (preventing disease progression to Stage B, C, or D). The studies summarized in this section represent pivotal risk factor intervention trials that prevent the development of heart failure for patients at risk (Stage A) or with asymptomatic structural heart disease (Stage B).

Treating high risk patients with drugs that inhibit the renin-angiotensin system

Coronary artery disease

The efficacy of renin-angiotensin system (RAS) blockade in reducing all major adverse cardiovascular events (MACE), including MI in high risk patients, has been well studied. Three large and several smaller trials have assessed the influence of angiotensin converting enzyme (ACE) inhibitor therapy in stable patients with atherosclerotic CAD who had preserved ventricular systolic function and no symptoms of heart failure (Stage A). The three largest trials were the Heart Outcomes Prevention Evaluation (HOPE), the Prevention of Events with ACE inhibition (PEACE) study, and the EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA)

Table 1.4 Summary of the Results of the Major Clinical Trials Evaluating the Influence of ACE Inhibitor Therapy on the Development of overt Heart Failure in Stage A Populations With CAD

TRIAL/Year	n	ACE inhibitor	Duration	Heart Failure Outcome	RRR (95% CI)	p value
HOPE 1993	9297	Ramipril Placebo	4.5 years	Incident HF ramipril 9%/placebo 11%	23% (13–33%)	p < 0.001
PEACE 1996	8290	Trandolapril Placebo	4.8 years	HF hospitalization/death trandolapril 2.5%/ placebo 3.7%	25% (5–41%)	p = 0.02
EUROPA 1997	12,218	Perindopril Placebo	4.2 years	Incident HF hospitalization perindopril 1.0%/placebo 1.7%	39% (17–56%)	p = 0.002
META-Analysis	29,805	Any ACE-i Placebo	4+ years	Incident HF ACE-inhibitor 2.1%/placebo 2.7%		p = 0.0007

ACE = angiotensin converting enzyme;n = number of patients;HF = heart failure;RRR = relative risk reduction;CI = confidence intervals. Trial acronyms are expanded in text. Adapted from [33–35,36].

[33–35]. These trials and heart failure outcome data are summarized in Table 1.4. Heart failure was not a pre-specified primary outcome variable in any of these studies, but secondary or post-hoc heart failure outcome data were reported. Overall, the results confirm that the RAS has an important role in reducing the development and progression of atherosclerosis, and that treatment with ACE inhibitors favorably influences cardiovascular morbidity and mortality beyond that achieved by blood pressure reduction alone.

HOPE was designed to evaluate the effects of the ACE inhibitor ramipril (along with vitamin E) in patients at high risk for cardiovascular events [33]. The trial prospectively randomized 9297 patients over 55 years of age without overt heart failure, hypertension or systolic ventricular dysfunction, but who had previously documented CAD, or diabetes and one additional risk factor. Patients were randomized to receive either ramipril 10 mg or placebo and either vitamin E or placebo in a 2 × 2 factorial design, with a 4.5-year follow-up. Results of the original study showed a highly significant 22% relative reduction in the primary composite endpoint of MI, stroke or cardiovascular death with ramipril use. There was no beneficial effect related to treatment with vitamin E.

During the mean follow-up period of 4.5 years, there were 651 (14%) primary endpoint events in the ramipril group compared with 826 (17.8%) in the placebo group. This