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

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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.

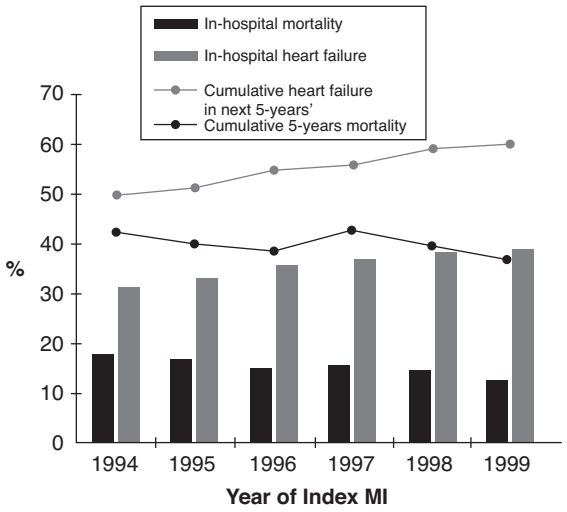

Figure 1.1 Temporal Trends in Mortality Rate and the Development of Heart Failure. **Black bars** indicate in-hospital mortality rate, and **gray bars** indicate in-hospital heart failure rate. **Gray line** indicates cumulative heart failure in the next 5 years for patients who survived index hospitalization,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

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 thi*s "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 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,

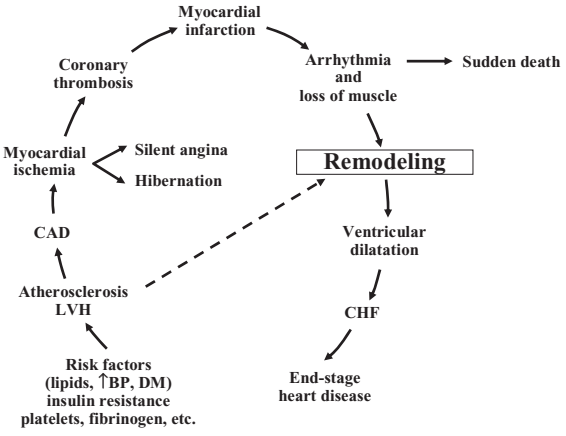

Figure 1.2 Chain of Events Leading to End-stage Heart Failure

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.

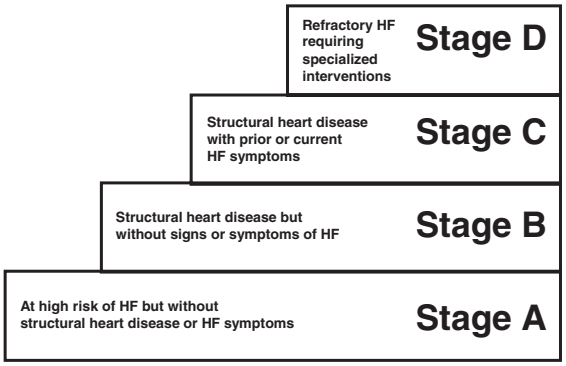

Figure 1.3 Revised ACC/AHA Staging System for Heart Failure

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

- Age, male sex
- Hypertension, LVH
- Myocardial infarction
- Diabetes mellitus
- Valvular heart disease
- Obesity

Minor Clinical Risk Factors

- Smoking
- Dyslipidemia
- Sleep-disordered breathing
- Chronic kidney disease
- Albuminuria
- Homocysteine
- Immune activation, IGF1, TNFα, IL-6, CRP
- Natriuretic peptides
- Anemia
- Dietary risk factors
- Increased HR
- Sedentary lifestyle
- Low socioeconomic status
- Psychological stress

Toxic Risk Precipitants

- Chemotherapy (anthracyclines, cyclophosphamide, 5-FU, trastuzumab)
- Cocaine, NSAIDs
- Thiazolidinediones
- Doxazosin
- Alcohol

Genetic Risk Predictors

SNP (e.g., α2CDel322-325, β1Arg389)

Morphological Risk Predictors

- Increased LVID, mass
- Asymptomatic LV dysfunction
- LV diastolic dysfunction

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.

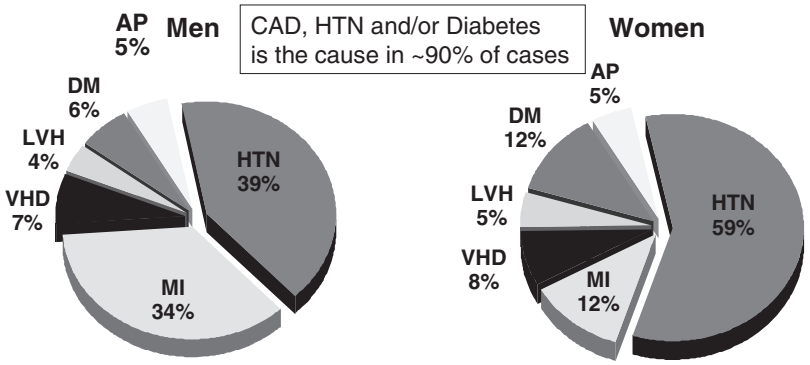

Figure 1.4 Population Attributable Risks for the Development of Heart Failure
Adapted from: Levy et al. JAMA. 1996;275:1557.

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 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).

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 $\leq$ 2 drinks/day, women $\leq$ 1
Smoking	Cessation
Dietary Sodium	Maximum 2–3 g/day

[1] Also see Tables 1.6 and 1.7
[2] Diabetes Care 2006; 29: S4–S42
[3] JAMA 2001; 285:2486–97
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.

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 represented a relative risk reduction (RRR) of 22% with 95% confidence intervals (CI) 14–30%, $p < 0.0001$. Ramipril use was associated with a significant reduction in nonfatal MI with an incidence of 5.6% versus 7.2% in the placebo group; a RRR of 23%, 95% CI 9,34%. Ramipril use was also associated with a trend toward less fatal MI and unexpected death events. Risk reduction in incident MI with ACE inhibition was noted in participants whether or not they were concomitantly receiving ß-blockers, lipid lowering drugs, and/or antiplatelet agents. Ramipril had no impact on hospitalizations for unstable angina, but significantly reduced the risk of either new onset or worsening angina, (RRR 12%, $p < 0.0014$) and of coronary revascularization (RRR 18% $p < 0.0005$). The development of new onset heart failure was not a pre-specified primary or secondary endpoint variable in HOPE, but incident heart failure was reduced from 11.5% to 9% (RRR 23%, 95% CI 13–33%, $p < 0.001$) through the use of an ACE-inhibitor. Though outcome data were not reported separately, 8% of the HOPE population (nearly 5200 patients) who had left ventricular function assessed had an EF <40%, and thus were actually Stage B heart failure.

The PEACE study randomized 8290 patients to receive either 4 mg trandolapril or placebo over a mean follow-up of 4.8 years [34]. Patients had CAD documented by having had prior MI or coronary angiography and preserved LV function (EF >40%) assessed by echocardiography or myocardial perfusion imaging. The combined primary endpoint was different than that of HOPE and included cardiovascular death, MI, or the need for coronary revascularization.

The mean (±SD) age of the patients was 64 ± 8 years, the mean blood pressure was 133 ± 17/78 ± 10 mm Hg, and the mean left ventricular ejection fraction was 58 ± 9 %. The patients received intensive baseline treatment, with 72% having previously undergone coronary revascularization and 70% receiving lipid-lowering drugs. The effect of trandolapril on the primary endpoint was neutral. The ACE inhibitor dose chosen was not titrated for aggressive treatment of HTN, although the mean blood pressure reduction achieved in PEACE (2–3 mm Hg) was similar to that observed in HOPE. The apparent lack of efficacy on the primary endpoint has been postulated as related to the heterogeneity of the HOPE and PEACE populations and the different study endpoints employed. Patients in HOPE were older, had a higher prevalence of diabetes, and a higher incidence of cardiovascular events. In contrast, patients in PEACE were taking more baseline adjunctive therapies for CAD, had superior risk factor modification at baseline, and a lower number of total adverse CV events. Thus, the overall risk for cardiovascular events was lower in PEACE, likely as a result of the baseline therapies employed, reducing the opportunity to demonstrate a positive influence on CV event rates with the addition of an ACE inhibitor. A post-hoc analysis of the PEACE population evaluated whether ACE inhibitor use was associated with a reduction in HF hospitalization or HF related death. Although HF events were infrequent, trandolapril use reduced the incidence of these specific endpoints from 3.7% to 2.8%, RRR 25%, 95% CI 5-41%, p = 0.02.

The EUROPA study was the largest trial conducted in stable, relatively low-risk coronary artery disease patients [35]. EUROPA screened 13,655 patients with coronary artery disease–defined as previous myocardial infarction (64%), angiographic evidence of coronary artery disease (61%), coronary revascularization (55%), or a positive stress echocardiogram (5%). The EUROPA trial did not describe the cardiac function of the patients although it is considered likely that most patients had normal LV systolic function. EUROPA had an open run-in period of 4 weeks during which time patients were treated with 4 mg perindopril, which was increased 8 mg to assess dose tolerability. Nearly 90% of the screened population tolerated the therapy and were subsequently randomized to receive 8 mg perindopril (6110 patients) or placebo (6108 patients). The primary endpoint of the trial was a composite of cardiovascular death, myocardial infarction, or cardiac arrest. This endpoint was observed in 10% of the placebo group and 8% of the perindopril group after a mean follow-up period of 4.2 years. This reflected a 20% RRR (95% CI 9,29, $p = 0.0003$) with the use of an ACE inhibitor. The yearly coronary event rate was only 2.7% in EUROPA vs 3.6% in HOPE, yet the relative risk reduction in the primary endpoint was quite similar. The majority of EUROPA patients were receiving traditional secondary event prevention measures; 92% were on antiplatelet therapy, 62% on beta-blockers, and 58% on lipid-lowering therapy. The development of overt heart failure was not a pre-specified primary or secondary endpoint variable in EUROPA, but incident heart failure was reduced from 1.7% to 1.0% (relative reduction 39%) with perindopril use.

The findings of HOPE, PEACE, and EUROPA were combined in a meta-analysis of the computed cardiovascular outcomes and total mortality rates in the 29,805 patients comprising the three trials [36]. ACE inhibitor use significantly reduced all-cause mortality (7.8 vs 8.9%, p = 0.0004), cardiovascular mortality (4.3 vs 5.2%, p = 0.0002), non-fatal myocardial infarction (5.3 vs 6.4%, p = 0.0001), stroke (2.2 vs 2.8%, p = 0.0004), heart failure (2.1 vs 2.7%, p = 0.0007), coronary-artery bypass surgery (6.0 vs 6.9%, p = 0.0036) but not rates of percutaneous coronary intervention (7.4 vs 7.6%, p = 0.481). The composite outcomes of cardiovascular mortality, non-fatal myocardial infarction, or stroke occurred in 1599 (10.7%) of the patients allocated ACE inhibitor and in 1910 (12.8%) of those allocated placebo (RRR 18%, 95% CI 12,24; p < 0.0001).

A second meta-analysis included three smaller randomized, placebo-controlled trials of similar patient populations with CAD and preserved LV systolic function [37]. This analysis combined the results of the Quinapril Ischemic Event Trial (QUIET), the Prevention of Atherosclerosis with Ramipril Trial (PART-2) and the Effect of Antihypertensive Agents on Cardiovascular events in Patients with Coronary Disease and Normal Blood Pressure Trial (CAMELOT) with the HOPE, PEACE, and EUROPA datasets [38–40]. Similar to PEACE,

both QUIET and CAMELOT had neutral primary endpoints that included the need for coronary revascularization. However, the cumulative meta-analysis of the total of 33,500 patients demonstrated the efficacy of ACE inhibitors in reducing all-cause mortality [RRR 13%, (6,19), p = 0.0003] nonfatal MI [RRR 16%, (6,25) p = 0.003], cardiovascular death [RRR 17%, (4,18), p = 0.01] or the need for coronary revascularization [RRR 7%, (0,13), p = 0.04] in patients with CAD and preserved LV systolic function. Heart failure outcomes were not predetermined in this meta-analysis.

Not surprisingly, the favorable effect of an ACE inhibitor in preventing major adverse cardiovascular events in persons with CAD is lessened when the ACE inhibitor is added to other effective CAD therapies including aspirin, beta-blockers, or statin medications. However, in the Dagenais metanalysis, ACE inhibitor therapy still consistently provided an incremental 15–25% relative risk reduction in adverse cardiovascular events when the other drugs were concurrently utilized (Figure 1.5). Despite use of other CAD therapies and/or revascularization, the number needed to treat with an ACE inhibitor in order to prevent one MACE was 100 patients for 4.4 years [37]. The National Institute for Health and Clinical Excellence in the UK considers medical therapies of "good value" if they cost no more than Ł20 000–Ł30 000 per quality-adjusted life year gained. In a cost-effectiveness analysis of the EUROPA trial, the median incremental cost per quality-adjusted life year gained through ACE inhibitor use was only Ł9700. [41,42]. Given the strength of evidence, RAS inhibition utilizing ACE inhibitors represents a powerful and cost-effective treatment strategy for the prevention of adverse CV outcomes including heart failure in persons with known or suspected CAD but preserved systolic function.

Hypertension

In the year 2000, it was estimated that 26.4% of the worlds' adult population had clinical hypertension, defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg. This represented approximately 1 billion adults worldwide

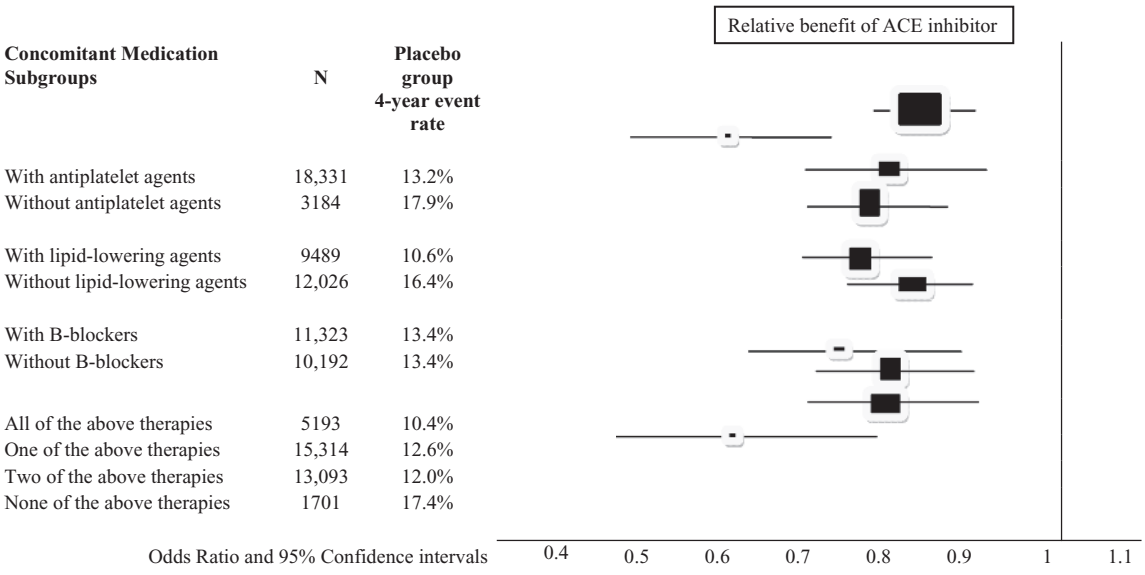

Figure 1.5 Effects of angiotensin converting enzyme (ACE) inhibitor administration in the HOPE and EUROPA trials on adverse cardiovascular outcome events (cardiovascular mortality, non-fatal myocardial infarction, or stroke) when used with other medication subgroups. The metanalysis showed an incremental benefit of ACE inhibitor use in every subgroup. Adapted from [36].

[43]. This prevalence is predicted to increase to a total of 1.56 billion persons by 2025. Hypertension confers at least a 2- to 3-fold increase in the lifetime risk of developing HF [22,44]. Systolic blood pressure and increased pulse pressure (PP) exert a continuous and directly proportional risk for developing HF, while DBP shows a U-shaped risk association curve. In persons over 50 years of age, a SBP of 140 mm Hg or greater is a more potent CVD risk factor than is isolated diastolic HTN. There is an abundance of evidence that treatment of elevated blood pressure represents a major primary risk reduction strategy for the prevention of CAD, MI, stroke, and HF [45–49]. The major classes of agents prescribed as antihypertensive therapy include ACE inhibitors, angiotensin receptor blockers (ARBs), calcium antagonists, beta (β)-blockers, alpha-blockers, and diuretics, particularly thiazide-type diuretics.

Categories of hypertension as defined by the Joint National Commission (JNC-7) are shown in Table 1.5. While optimal BP is unknown, the World Health Organization has suggested 115/75 as the optimal blood pressure for persons with uncomplicated HTN without end-organ disease. The recent TRial Of Preventing Hypertension (TROPHY) demonstrated that pharmacologic treatment of patients in the JNC-7 "prehypertension" category (SBP 120–139 or DBP 80–80) with an ARB effectively prevented the development of HTN [50]. Lifestyle modifications were recommended for all 409 patients. Study patients received candesartan, an ARB, at a dose of 16 mg daily during a two-year placebo-controlled treatment period. The drug was then substituted with placebo, and all patients were followed for a total of 4 years. There was an absolute difference of 27% in the development of hypertension (relative risk reduction 66%) between the 2 groups at year 2. At the 4-year time point (2 years after discontinuation of candesartan) there remained a 10% absolute and 15.6% relative risk reduction in the development of hypertension among previously treated patients. This approach therefore suggests a means of preventing Stage A heart failure. Whether this aggressive early treatment strategy yields the long-term benefit of preventing MACE or progression to more advanced stages of heart failure has yet to be demonstrated, however. A cost-benefit analysis will also be crucial to examine before recommending adoption of this approach.

Numerous national or societal treatment guidelines exist worldwide for both uncomplicated and complicated hypertension, as there is little doubt that even a modest reduction in blood pressure among patients with mostly stage 1 and 2 hypertension has tremendous benefits. However, adequate control rates in treated patients remain disappointingly low worldwide. The United States had the highest rate of controlled hypertension (54%), although the rates in Canada and England were not much lower (47% and 40%, respectively). Germany (30%), Italy (28%), and especially Spain (19%) and Sweden (21%), had much lower rates of achieving a 140/90 mm Hg goal [51]. The population at risk remains substantial, as at the 140/90 mm Hg cut point, two-thirds to three-quarters of hypertensive persons in Canada and Europe remained untreated compared with just under half of such persons in the United States [51]. The U.S. 7th Joint National Commission on Prevention, Detection Evaluation and Treatment of High Blood Pressure (JNC-7) recommendations for treatment initiation for adults with hypertension are shown in Table 1.6.

Non-pharmacologic interventions that prevent or treat hypertension by employing therapeutic lifestyle changes should be recommended. These methods include exercise, weight loss, and dietary interventions such as the Dietary Approaches to Stop Hypertension (DASH) diet and are summarized in Table 1.7 [52,53]. If lifestyle modification is ineffective in

Table 1.5 Categories of Blood Pressure

	BLOOD PRESSURE LEVEL (mm Hg)		
CATEGORY	**SYSTOLIC**		**DIASTOLIC**
Normal	< 120	*AND*	< 80
Pre-hypertension	120–139	*OR*	80–89
Stage 1 hypertension	140–159	*OR*	90–99
Stage 2 hypertension	≥160	*OR*	≥100

Contemporary 7th Joint National Commission (JNC-7) categories of blood pressure in adults of age 18 years and older. When systolic and diastolic blood pressures fall into different categories, the higher category should be used to classify the blood pressure level. For example, 160/80 mm Hg is considered stage 2 hypertension. Adapted from [52].

Table 1.6 Recommended Anti-hypertensive Therapy According to Category of Blood Pressure

	Management of Hypertension by Category		
NBlood Pressure Category	Lifestyle Modifications	Compelling Indications* Absent	Compelling Indications* Present
Normal	Encouraged	No drug therapy	Treat additional risk factors
Pre-hypertension	Advised	No drug therapy	Treat patients with chronic kidney disease or diabetes to a blood pressure goal of 130/80 or lower
Stage 1 hypertension	Advised	Thiazide-type diuretics for most patients. May consider use of ACEI or ARB, BB, CCB, or combination therapy	Treat with drugs recommended for compelling indications, then utilize other antihypertensive drugs (diuretics, ACEI or ARB, BB, CCB as needed)
Stage 2 hypertension	Advised	Two-drug combination for most (typically a thiazide-type diuretic along with ACEI or ARB, or BB or CCB)	Treat with drugs recommended for compelling indications, then utilize other antihypertensive drugs (diuretics, ACEI or ARB, BB, CCB as needed)

Contemporary 7th Joint National Commission (JNC-7) recommendations for the treatment of hypertension in adults of age 18 years and older. *Compelling indications include documented heart failure, prior myocardial infarction, high coronary artery disease risk, diabetes mellitus, chronic kidney disease and prior stroke. ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; CCB = calcium channel blocker. Adapted from [52].

Table 1.7 Non-Pharmacologic Treatment of Hypertension

Therapeutic Lifestyle Change	Recommendation for Risk Modification	Approximate SBP reduction (range)
Weight reduction	Achieve and maintain normal body weight/normal body mass index (BMI 18.5–24.9 kg/m^2)	5–20 mm Hg for each 10 kg excess body weight lost
Adopt DASH diet	Consume a diet rich in vegetables, fruits and low-fat dairy products that provide a reduced content of both saturated fat and total fat	8–14 mm Hg
Dietary sodium restriction	Restrict dietary sodium intake to no more than 100 mmol daily (2.4 grams sodium)	2–8 mm Hg, more in patients with salt-sensitive hypertension
Regular exercise	Aerobic physical activity for at least 30 minutes per day, most days of the week	4–9 mm Hg
Moderation of alcohol consumption	Limit alcohol consumption (if used) to no more than 2 drinks* per day in men; 1 drink* per day in women	2–4 mmHg
Tobacco cessation	Stop smoking or use of nicotine containing products	Variable

Nonpharmacologic measures to prevent or reduce hypertension, along with the anticipated degree of resultant systolic blood pressure (SBP) reduction. Some persons may have greater reduction, as the influence of the intervention can be time and dose dependent. DASH = Dietary Approaches to Stop Hypertension. *For alcohol consumption, one drink is defined as 1 ounce (oz) or 30 mL ethanol; e.g., approximately 24 oz of beer, 10 oz wine, or 3 oz of 80-proof hard alcohol. [52,53]

reducing blood pressure to target range, diuretics have the greatest strength of evidence for treating uncomplicated mild to moderate hypertension in order to prevent MACE in the Stage A HF patient [54]. Thiazides have been shown to reduce the onset of symptomatic heart failure based on the Systolic Hypertension in the Elderly Program (SHEP) and Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial studies [45,48]. Risk reduction (absolute and relative) for adverse cardiovascular events is greatest in severe hypertension, and increases in direct relation with the degree of blood pressure reduction. Thiazides alone are rarely ineffective in treating severe hypertension and initiation of combined therapy with more than a single agent is becoming increasingly common in such patients. Aldosterone antagonists and direct renin inhibitors (DRIs) also may be beneficial in Stage A and/or B HF but lack clinical trial evidence.

Do RAS inhibitors offer an advantage over other drugs in treating hypertension to prevent heart failure?

The Blood Pressure Lowering Treatment Trialists' Collaboration performed a meta-analysis of 29 trials (162,341 participants) comparing the effects of hypertension treatment regimens in hypertensive patients without heart failure [55]. The analysis was designed to facilitate comparisons between hypertension treatment regimens based initially on ACE inhibitors, ARBs, calcium-channel antagonists, diuretics or β-blockers in reducing six prespecified outcomes. The trials included lasted between 2 and 8 years, representing over 700,000 patient-years of follow-up. Although no individual trial studied heart failure as a primary outcome variable, the meta-analysis demonstrated that ARB and ACE inhibitor-based treatment regimens were fairly comparable in terms of the relative risk reduction for heart failure. ACE inhibitor-based regimens reduced the risk of incident heart failure, heart failure hospitalization or death by 18% compared with placebo, (95% CI 2–31%) while ARB-based regimens reduced the risk of HF events by 16% (RRR 3% to 28%). However, the effect of multiple drug regimens using an ACE inhibitor as initial therapy did not differ significantly from those based initially on a diuretic or a β-blocker

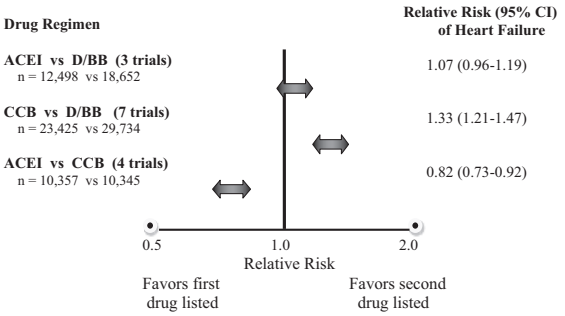

Figure 1.6 Comparison of blood pressure lowering regimens in the Blood Pressure Lowering Trialists' Collaboration meta-analysis.
Drug regimens including angiotensin converting enzyme inhibitors and diuretics with or without beta-blockers were effective in preventing heart failure. In contrast, regimens based upon calcium channel blocker were inferior in reducing the risk of heart failure. ACEI = angiotensin converting enzyme inhibitor; BB = beta-blocker; CCB = calcium channel blocker; D=diuretic.
Adapted from [55].

(7% [−4 to 19]. Calcium-channel antagonist based regimens demonstrated a trend towards an adverse outcome in relationship to heart failure events (21% increased risk [−42, 7]) but this was not statistically significant. Figure 1.6 summarizes these findings. The available evidence suggests that inhibitors of the RAAS (ACE inhibitors and ARBs), diuretics, and β-blockers are equally beneficial for preventing heart failure (as well as preventing other major cardiovascular events and death) in the Stage A patient.

Left ventricular hypertrophy

Hypertension is a major hemodynamic stimulus for the development of left ventricular hypertrophy (LVH) due to the increased systemic afterload imposed on the LV. As shown in Table 1.8, LVH is a marker of underlying physiologic processes that can be modified to reduce the risk of developing symptomatic heart failure. There are many other etiologic and physiologic mechanisms besides HTN that promote increased LV mass and LVH, however. The presence of LVH therefore represents an independent risk

Table 1.8 Hypertension and Myocardial Hypertrophy-Related Effects That Increase the Risk of Heart Failure

1. Increased systemic afterload from hypertension and other stimuli result in myocyte hypertrophy and subsequent myocardial (ventricular) hypertrophy.
2. Myocardial hypertrophy is associated with decreased efficiency of both myofibrilar contractility and relaxation, correlating to systolic and diastolic ventricular dysfunction.
3. Hypertension and ventricular hypertrophy increase myocardial oxygen requirements at rest and with exertion, which can produce myocardial ischemia in the absence of coronary artery disease.
4. Myocyte loss due to ischemia or infarction results in compensatory hypertrophy of previously normal myocardium and subsequent adverse chamber remodeling.
5. Myocyte loss due to apoptosis can also derive from chronically elevated afterload or wall stress.
6. Interstitial fibrosis resulting from myocyte loss is associated with both increased collagen synthesis and decreased collagen degradation.

factor for the development of HF [22]. Documentation of LVH fulfills the structural heart disease criterion for Stage B heart failure and correlates with a higher risk of clinical heart failure events [56,57].

ACE inhibitors and ARBs have well described favorable effects in patients with hypertension and left ventricular hypertrophy (LVH), and there is some evidence to suggest that they reduce LV mass to a greater extent than can be attributed to blood pressure reduction alone. A substudy of the HOPE trial documented a favorable influence of the ACE inhibitor ramipril on LV structure and function in cardiovascular patients with controlled BP and with preserved LVEF [58]. Further, a 941 patient echocardiographic substudy of LIFE (Losartan Intervention For Endpoint reduction) prospectively measured treatment-related change in LV mass in relationship to the primary composite endpoint of CV death, fatal or nonfatal MI, and fatal or nonfatal stroke [59]. Patients with hypertension and electrocardiographic LVH who demonstrated a significant reduction in LV mass or resolution of LVH over time had significantly improved outcomes, regardless of the pharmacologic treatment employed. In the main LIFE trial, losartan was superior to atenolol in achieving both electrocardiographic LVH regression and in reducing the primary endpoint of cardiovascular death, MI or stroke in 9193 patients with hypertension and LVH [60]. However, heart failure hospitalization which was a prespecified additional endpoint in LIFE, occurred in 3% of patients on losartan vs. 4% of patients on atenolol, a difference which was not statistically significant.

Diabetes mellitus

The lifetime risk and prevalence of diabetes mellitus (type 2) is increasing steadily worldwide and CVD, including HF, accounts for up to 80% of the deaths in diabetic persons [61]. The risk of developing heart failure increases incrementally with worsening glycemic control; being higher as hemoglobin A1c levels increase [62]. Therefore, both preventing and controlling diabetes are means by which heart failure can be prevented or reduced. It is difficult to completely dissociate the distinct effect of treating a single risk factor, given co-dependent (additive or multiplicative) associated risks. For instance, hypertension is approximately twice as frequent in patients with diabetes compared to non-diabetics. Diabetes and concomitant hypertension have a synergistic impact on the risk of developing atherosclerosis, MI and ischemic LV dysfunction, particularly when combined with dyslipidemia. Diabetes associated dyslipidemia, microalbuminuria, endothelial dysfunction, platelet hyperaggregability, and coagulation abnormalities add to the risk of MACE [61]. This has led to the recommendation for more aggressive risk factor treatment goals in persons with coexistent diabetes and hypertension [52]. In the LIFE trial, 13% of the population had diabetes, and the (adjusted) proportion of patients experiencing a primary endpoint event was reduced by nearly 25% ($p = 0.031$) in those receiving losartan compared with atenolol [60].

The United Kingdom Prospective Diabetes Group Studies (UKPDS) demonstrated that tight blood pressure control in diabetics is an essential strategy to reduce both macrovascular complications (MACE) and microvascular complications (retinopathy and proteinuria) [62–64]. The UKPDS study also suggested

that the 10-year risk of developing heart failure is reduced by intensive glycemic control [64]. However, the means by which glycemic control is accomplished is important, as the addition of metformin to a sulfonylurea increased the risk of heart failure in this population [65].

An interesting ad hoc finding in the HOPE study was that ramipril treatment was associated with a significant 34% reduction in new onset diabetes [66]. The possibility that ACE inhibitor treatment may retard the development of diabetes in patients at high risk of the disease was then examined prospectively in the Diabetes Reduction Assessment with ramipril and rosiglitazone trial [67]. The study included 5269 patients at 191 sites in 21 countries. Investigators reported that the thiazolidinedione (TZD) rosiglitazone at 8 mg daily for 3 years substantially reduced incident type 2 diabetes and increased the likelihood of regression to normoglycemia in adults with impaired fasting glucose and/or impaired glucose tolerance. The primary outcome was a composite of incident diabetes or death. Cardiovascular event rates were low, but quite similar in both groups, although 14 patients (0.5%) in the rosiglitazone group and two (0.1%) patients in the placebo group developed heart failure ($p = 0.01$). This data, in part, contributed to the recommendation for caution in the prescription of TZDs for patients with or at risk for heart failure [22].

Diabetic cardiomyopathy

A unique metabolic cardiomyopathy associated with diabetes has been described and recognized by the World Health Organization as "diabetic heart muscle disease". Diabetic cardiomyopathy (DCM) is considered Stage A heart failure when structural changes are clinically imperceptible, but may be categorized as Stage B or C HF once detected [22]. Advanced DCM is characterized by prominent interstitial collagen deposition/fibrosis along with ventricular dilation, myocyte hypertrophy along with diastolic and/or systolic dysfunction [68]. The risk of diabetic cardiomyopathy appears independent of either macrovascular and microvascular disease yet contributes significantly to CVD morbidity and mortality in diabetic patients, especially those with coexistent hypertension. Hyperglycemia and insulin resistance induce myocardial injury through a number of mechanisms, including oxidative stress, and activation of both the RAS and sympathetic nervous systems.

Dyslipidemia

Dyslipidemia is a strong and independent risk factor for CAD and MI, and is therefore linked to the development of HF [22,69]. It is not clear whether there is a direct association between dyslipidemia and heart failure that is independent of the risk of atherosclerosis and MI. In 10,813 otherwise healthy male physicians, no relationship was detected between the levels of total or high-density lipoprotein cholesterol and incident heart failure over a 6-year period [70]. In this observational study, high total and low HDL cholesterol levels were associated with an increased risk of CAD in these individuals, as expected. The risk of developing heart failure (if contingent upon CAD and/or MI) may not have had time to manifest in the follow-up period chosen.

Despite ample clinical evidence that treatment of dyslipidemia significantly reduces the risk of MACE, which in turn reduces incident heart failure, effective lipid treatment strategies (both lifestyle interventions and pharmacologic therapies) are highly underutilized. One-third of the U.S. adult population has an LDL of 130 mg/dL or higher, yet fewer than 50% of individuals who would meet the nationally accepted criteria for lipid-lowering therapy are receiving prescribed therapy [1].

Although controversial, treatment of hyperlipidemia in patients with known CAD with 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) has been demonstrated to reduce the development of heart failure [22,44,71]. Beneficial effects of statin medications that are theorized as contributory to a reduction in incident heart failure are summarized in Table 1.9. In a retrospective analysis of the Scandinavian Simvastatin Survival Study (4S), the use of simvastatin effectively decreased incident heart failure by 20% over a 5-year period [28]. Further, in 4S patients who developed heart failure, statin treatment was associated with a 19% reduction in mortality compared with placebo. A similar 20% reduction in heart failure incidence was noted in the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial [72]. A non-statin, randomized, placebo-controlled

Table 1.9 Beneficial Effects of Statins that May Reduce the Risk of Heart Failure

1. Reduce coronary event risk by improving coronary artery plaque stability.
2. Reduce coronary event risk by promoting coronary neoangiogenesis.
3. Improve vascular endothelial cell function.
4. Inhibit production of pro-inflammatory cytokines.
5. Enhance parasympathetic tone and improve autonomic function.
6. Down-regulate angiotensin II receptors.
7. Improve vascular and myocardial calcium influx resulting in improved myocyte contractility.

trial utilizing the fibrate gemfibrozil was conducted in patients with known CAD who had low HDL and mild to moderately elevated low-density lipoprotein (LDL) levels. This study found a statistically significant reduction in the incidence of heart failure requiring hospitalization in the treatment group. The risk of heart failure was 13.3% in the placebo arm and 10.6% in the gemfibrozil arm, a 22% relative risk reduction [73]. In contrast, in 5011 patients 60 years of age or older with established Stage C HF and LV systolic dysfunction, rosuvastatin at 10 mg daily did not reduce the incidence of major adverse events despite lowering LDL levels by 45% compared with placebo ($p < 0.001$) [74]. The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) had a primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcomes included death from any cause, any coronary event, death from cardiovascular causes, and the number of hospitalizations. In a prespecified secondary endpoint analysis, there were fewer hospitalizations for cardiovascular causes including HF in the rosuvastatin group (2193) than in the placebo group (2564) ($p < 0.001$). The CORONA trial suggests that when patients have a preexistent ischemic cardiomyopathy with systolic LV dysfunction and overt HF, aggressive LDL reduction may not reduce mortality substantially.

Avoidable heart failure risk factors

Smoking

Tobacco use represents the single largest preventable cause of disease and premature death from many causes, but particularly cardiovascular diseases. Current smokers have a significantly higher risk for the development of heart failure than do prior smokers or nonsmokers. In the Coronary Artery Surgery Study, smoking was independently associated with a 47% increased risk of developing heart failure [75]. After cessation and 1 year of abstinence, the risk of death due to coronary heart disease is 50% lower than that of people who continue to smoke. In the SOLVD trials (Studies Of Left Ventricular Dysfunction), ex-smokers had a 30% lower mortality than current smokers, a benefit accrued within 2 years after smoking cessation. This survival rate was similar to that of nonsmokers [76]. A recommendation for smoking cessation is included in all guidelines for cardiovascular disease prevention and treatment.

Alcohol

Alcohol consumption has not consistently been implicated as more than a minor risk factor for heart failure. In fact, observational studies have suggested that light to moderate alcohol consumption is associated with a lower risk of heart failure [77,78]. However, heavy alcohol consumption was associated with an increased risk of hypertension in an international, multicenter epidemiological study. Heavy drinking was defined as >=300 ml absolute alcohol per week, corresponding approximately to $\geq$34 g alcohol per day. A unit of alcohol in a standard drink is considered to contain 8–10 g of alcohol in Britain and 12–14 g in the United States. After controlling for other factors associated with hypertension, including body mass index, smoking, and urinary excretion of sodium and potassium, systolic/diastolic blood pressure was on average 2.7/1.6 mm Hg higher for men consuming 300–499 ml alcohol per week than for non-drinkers, and 4.6/3.0 mm Hg higher for men consuming >=500 ml/week. For women consuming >=300 ml/week, blood pressures were 3.9/3.1 mm Hg higher than for non-drinkers [79]. Alcohol also appears to have direct myocardial toxicity that is also dose-related in susceptible

individuals [80]. Chronic consumption of more than 70 g per day is associated with the development of alcoholic cardiomyopathy. The Heart Failure Society of America recommends that if alcohol is consumed, that it be done so in moderation–no more than two drinks per day for men, and one for women [81].

Obesity

Obesity is a problem reaching epidemic proportions in westernized society and is a major cause of preventable death. An increase in the risk of developing heart failure directly correlated with increasing body mass index (BMI) in the Framingham population and other published studies [81,82]. An increased BMI is also an established risk factor for hypertension, diabetes, and dyslipidemia. Obesity, defined as a BMI $\geq$30 kg/m^2 is associated with the metabolic syndrome, a controversial, but generally accepted risk factor for CVD. Obesity predisposes to heart failure not only by contributing to atherogenic risk factors and hypertension, but by increasing cardiac preload through an expanded intravascular volume. Along with augmented afterload and neurohormonal upregulation, the development of LVH is facilitated [82,83]. Obesity is considered by some to be associated with a unique form of cardiomyopathy, but the influence of weight reduction on obesity-related heart failure is not well established [81]. Although obesity can cause abnormalities in both diastolic and systolic function, obese patients with heart failure paradoxically seem to have a more favorable clinical prognosis [84,85].

Treatment of non-classical risk factors

Obstructive sleep apnea A high prevalence of obstructive sleep apnea (OSA) in adults has been well documented by several population-based cohort studies conducted in the United States, Canada, Europe, Australia, and Asia [85]. Approximately 1 in 5 adults in North America has at least mild OSA and 1 in 15 has at least moderate OSA as defined by the apnea/hypopnea index (AHI), or number of apneas and hypopneas per hour of sleep. An obstructive apnea is a >10-second pause in respiration associated with ongoing ventilatory effort. Obstructive hypopneas are decreases in, but not complete cessation of, ventilation, with an associated fall in oxygen saturation or arousal. A diagnosis of OSA syndrome is accepted when a patient has an AHI >5 and symptoms of excessive daytime sleepiness. Even mere hypopneas when accompanied by oxyhemoglobin desaturation of >4% are associated with higher rates of cardiovascular disease independent of confounding covariates. In contrast, no association is observed between cardiovascular disease and hypopneas associated with milder degrees of desaturation or arousals [85]. Incident OSA is higher in persons with CAD, prior MI or nocturnal angina. The mortality rate for cardiovascular disease is higher for those with OSA (35% for AHI <15, 56% for AHI >15).

In the Sleep Heart Health Study, a cross-sectional observational study, the association between documented sleep-disordered breathing and self-reported CVD was determined in 6,424 individuals [86]. A total of 1,023 participants (16%) reported having at least one manifestation of CVD (myocardial infarction, angina, coronary revascularization procedure, heart failure, or stroke). The study reported that patients with OSA were 2.4 times more likely to develop heart failure symptoms than patients without OSA.

Whether OSA can directly cause heart failure has yet to be established, although multiple plausible mechanisms have been hypothesized as shown in Figure 1.7 [85]. The most direct mechanism by which long-standing OSA might induce heart failure is through its known causal relationship with hypertension and association with obesity. Hypertension promotes the development of LVH, nocturnal oxygen desaturation contributes to impaired diastolic ventricular relaxation and marked sympathetic activation. In fact, LVH may be more closely linked to hypertension during sleep than during wakefulness, placing individuals with OSA at greater risk for developing it. Enhanced production of cytokines, catecholamines, endothelin, and other growth factors in OSA patients also may contribute to the development of LVH. Indeed, LVH is more common in patients with obstructive sleep apnea even in the absence of hypertension [85].

It is well documented that patients with preexisting heart failure have an even higher prevalence of OSA and sleep disordered breathing. The prevalence of OSA in heart failure was greater in men (38% versus 31% in women; $p \leq 0.005$) [87]. In men, the main risk factor for OSA was obesity, whereas in women, it was older age. Patients with systolic LV dysfunction

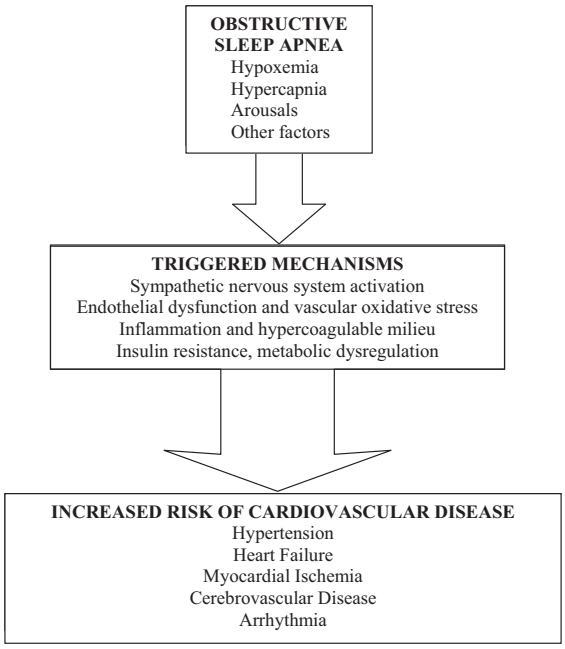

Figure 1.7 Physiologic features of obstructive sleep apnea and the intermediary triggered mechanisms theorized to increase the risk of cardiovascular disease and cardiovascular events. Adapted from [85].

and OSA have a significantly worse prognosis than heart failure patients without OSA [88]. A 40% prevalence of OSA was recently found in a population of patients with heart failure and normal ejection fraction. Whether the same prognostic implications in heart failure and systolic dysfunction apply to this subgroup with preserved ejection fraction is unknown [89].

Treatment of OSA with nocturnal continuous positive airway pressure (CPAP) significantly improved left ventricular systolic function of patients with stable heart failure, systolic LV dysfunction, and coexisting obstructive sleep apnea [90]. One month of therapy was also associated with significant reductions in left ventricular end-systolic dimension, daytime systolic blood pressure, and resting heart rate. There is also evidence suggesting that OSA-associated changes in altered cardiac structure and may be reversible with effective CPAP treatment. However, whether CPAP treatment of patients with OSA can prevent heart failure or improve survival in the setting of heart failure has yet to be proven in a randomized clinical trial [91].

Evidence that treating the stage B patient improves outcomes

Post-MI patients

Over the past 2–3 decades there have been remarkable changes in the treatment of MI patients. Prompt initiation of thrombolytic therapy and, in particular, percutaneous revascularization of severely diseased coronary arteries have greatly improved outcomes in this population. However, even when the full blown consequences of an MI have been aborted, patients still may suffer variable amounts of myocardial damage and irreversible loss of contractile units [7]. While the extent of the acute injury may not be sufficient to cause heart failure, it often leads to progressive remodeling of the heart that involves segments of myocardium that were not involved in the acute event. This later phase of post-MI remodeling results in increases in left ventricular (LV) chamber size and muscle mass (i.e., LV dilatation and eccentric hypertrophy), diffuse perivascular and interstitial fibrosis and transformation of the LV from an ellipsoid to a more spherical chamber [21]. The consequences of remodeling include development of functional mitral valvular regurgitation, increased propensity towards cardiac arrhythmias, and abnormalities in both systolic and diastolic function of the LV.

The factors that cause post-MI remodeling to occur have been identified and are listed in Table 1.10. They include increased wall stress and a variety of neurohormonal agents, most notably Angiotensin II (Ang II) and norepinephrine (NE). These agents promote remodeling by direct effects on the myocardium and also indirectly by causing increases in intravascular volume and arterial pressure, both of which increase LV wall stress.

Drugs that inhibit actions of the renin-angiotensin system (RAS)

Post-MI activation of the RAS has been demonstrated in both animal models and human patients [19,92–97]. Although there is evidence of activation of the circulatory RAS (usually in association with

Table 1.10 Factors Implicated in Promoting Cardiac Remodeling

1. Wall stress
   - increase in LV pressure or volume
2. Neurohormonal Agents
   - catecholamines (epinephrine and norepinephrine)
   - Angiotensin II
   - Aldosterone
   - Endothelin
   - Arginine vasopressin
   - Pro-inflammatory cytokines

the acute hemodyanamic pertubations) early in the course, this system often becomes quiescent once the patient's condition stabilizes. It remains relatively inactive until later in the course when the clinical manifestations of heart failure appear [19]. During this period of relative stability, however, there is good evidence that maladaptive cardiac remodeling is taking place. There is also evidence that this process is driven to a large degree by activation of a local tissue based RAS that is present in the heart [20,98]. Recognition of the role of the tissue based RAS in the remodeling process was the rationale for studies testing the effects of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in the post-MI population. Treatment of both experimental animals and patients with agents that block RAS effects have been shown to significantly inhibit post-MI cardiac remodeling [95,99,100]. There is also compelling evidence that these agents improve the clinical course of patients. In the SAVE study, MI survivors with an EF less than 0.40 but without evidence of heart failure were randomized to receive either the ACE inhibitor captopril or placebo in addition to their standard therapy within the first 21 days post-MI [101]. For the primary endpoint of all cause mortality there was a significant 19% reduction with captopril. Treatment with the ACE inhibitor was also associated with reduction in heart failure related morbidity as well as with recurrent MI. The beneficial effects of captopril in the post-MI population were replicated in several subsequent studies that are summarized in Table 1.4. Based on these findings the use of ACE inhibitors in post-MI patients with LV dysfunction is now strongly recommended in both MI and heart failure guidelines [22].

Once the success of the ACE inhibitors in improving the course of post-MI patients was confirmed, it was impossible for ethical reasons to perform a placebo controlled study evaluating the efficacy of an ARB in this population. Thus, the VALIANT study compared the effects of the ARB, valsartan, to those of captopril in patients with post-MI LV dysfunction [102]. The results demonstrated that for the primary endpoint of all cause mortality, the ARB performed as well as the ACE inhibitor. A third arm of the study, however, failed to demonstrated further benefits when the ACE inhibitor and ARB were combined. Thus, ARBs appear to be equally effective as ACE inhibitors in improving outcomes in post-MI patients. The use of combined ACE inhibitor and ARB in this population, however, does not seem to be warranted.

Beta-blockers in the post-MI population

Although beta-blockers have been shown to improve outcomes in post-MI patients, the initial studies in which these agents were tested avoided including patients with heart failure or LV dysfunction (i.e., the Stage B or C patient) [102]. The CAPRICORN study was designed to fill the void left by the earlier studies which were carried out in an era before the beneficial effects of beta-blockers in heart failure were recognized [104]. It tested the hypothesis that the addition of the beta-blocker carvedilol to the standard treatment of post-MI patients with LV dysfunction would improve outcomes. Patients in the CAPRICORN study were treated in a more contemporary manner than were patients in the previous studies. Most were receiving an ACE inhibitor (or an ARB) and aspirin, thrombolysis and revascularization strategies were utilized as deemed appropriate by the managing physician. The results showed that for the co-primary endpoint of all cause mortality there was a 23% reduction in carvedilol treated patients. The specificity of the beneficial effect was confirmed by a 25% reduction in cardiovascular mortality. The improvement in outcomes was noted

to be of similar magnitude in patients who had undergone revascularization as in those patients who had not been revascularized. The addition of carvedilol to the medical regimen that included an ACE inhibitor was shown to favorably effect remodeling over the 6 months following the event [105]. Thus, use of beta-blockers in the post-MI population is recommended regardless of whether or not a revascularization procedure has been performed.This approach is supported by evidence that even in patients in whom successful revascularization is carried out in a timely fashion, post-MI remodeling still occurs in many cases [7]. Moreover, the occurrence of remodeling in revascularized post-MI patients is associated with a significantly less favorable outcome.

Asymptomatic non-ischemic LVD

Drugs that inhibit the actions of the renin-angiotensin system (RAS)

While there have been no large clinical trials using agents that target the RAS in Stage B patients with non-ischemic LV dysfunction, the Prevention Arm of the Studies of Left Ventricular Dysfunction (SOLVD) program included a large cohort of individuals with a non-ishemic etiology of their heart failure [106]. The patients enrolled into SOLVD Prevention had an EF less than 0.35 and were without signs or symptoms of heart failure and they were not being treated for heart failure. While the results showed that treatment with enalapril was associated with an insignificant mortality reduction, it did significantly reduce new onset heart failure, heart failure hospitalizations, and combined morbidity and mortality. Subgroup analysis did not show evidence of an interaction between etiology (i.e., ischemic vs non-ischemic) and the effects of therapy and the overall impact of enalapril appeared to be similar in both subgroups of patients. As a result, the use of ACE inhibitors is highly recommended in heart failure guidelines.

Beta-blockers in stage B patients with non-ischemic cardiomyopathy

Similar to the situation with ACE inhibitors, the population of patients with asymptomatic LV dysfunction due to non-ischemic etiologies has been less well studied than patients with LV dysfunction post-MI. The Reversal of Ventricular Remodeling with TOPROL-XL (REVERT) study, however, provided insight into the potential benefits of beta blockade in this population [107]. The study enrolled patients with low EF in the absence of coronary artery disease. Patients were optimized on standard therapy which included an ACE inhibitor (or ARB) and then randomized to 3 groups: placebo, metoprolol succinate with a target dose of 50 mg daily, or metoprolol succinate targeted to 200 mg daily. The primary endpoint was the effect of treatment on changes in LV end-systolic volume (ESV) as determined by echocardiogram. The results of REMODEL demonstrated that compared to placebo there was a step greater reduction in LVESV with metoprolol succinate and that the change over time was significant in patients who were randomized to receive the 200 mg dose. Reductions in LV end-diastolic dimension and improvement in LV EF followed a similar pattern. These results showing that early initiation of a beta-blocker in addition to an ACE inhibitor in patients with asymptomatic LV systolic dysfunction leads to reverse remodeling of the LV and improved function suggests that beta-blocker therapy should be initiated in patients with LV dysfunction regardless of the underlying etiology.

Summary

In most patients the development of heart failure is the end result of a long continuum that begins with the presence of a variety of well recognized risk factors. Subsequent damage to the heart effects structural changes that activate neurohormonal systems that lead to maladaptive remodeling and ultimately to the clinical manifestations of heart failure. Once heart failure signs become manifest there is a substantial deterioration in both quality and quantity of life. Heart failure, however, is preventable in the vast majority of cases. Given the personal and societal implications of the heart failure pandemic that has erupted around the world, there is a need to re-emphasize preventive measures that focus on risk factors and the remodeling process. Numerous clinical trials have pointed out the efficacy of this approach and there are clear-cut recommendations in the various heart failure guidelines providing direction for prevention efforts.

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