AHA Scientific Statement

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

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Abstract—The increase in heart failure (HF) rates throughout the developed and developing regions of the world poses enormous challenges for caregivers, researchers, and policymakers. Therefore, prevention of this global scourge deserves high priority. Identifying and preventing the well-recognized illnesses that lead to HF, including hypertension and coronary heart disease, should be paramount among the approaches to prevent HF. Aggressive implementation of evidence-based management of risk factors for coronary heart disease should be at the core of HF prevention strategies. Questions currently in need of attention include how to identify and treat patients with asymptomatic left ventricular systolic dysfunction (Stage B HF) and how to prevent its development. The relationship of chronic kidney disease to HF and control of chronic kidney disease in prevention of HF need further investigation. Currently, we have limited understanding of the pathophysiological basis of HF in patients with preserved left ventricular systolic function and management techniques to prevent it. New developments in the field of biomarker identification have opened possibilities for the early detection of individuals at risk for developing HF (Stage A HF). Patient groups meriting special interest include the elderly, women, and ethnic/racial minorities.

Future research ought to focus on obtaining a much better knowledge of genetics and HF, especially both genetic risk factors for development of HF and genetic markers as tools to guide prevention. Lastly, a national awareness campaign should be created and implemented to increase public awareness of HF and the importance of its prevention. Heightened public awareness will provide a platform for advocacy to create national research programs and healthcare policies dedicated to the prevention of HF. (***Circulation*. 2008;117:2544-2565.**)

Key Words: AHA Scientific Statements ■ heart failure ■ prevention ■ left ventricular dysfunction ■ genetics ■ awareness

The prevention of heart failure (HF) is an urgent public health need with national and global implications. According to the American Heart Association, an estimated 550 000 new cases occur each year.[1] More than 5 million Americans have HF. Among Medicare beneficiaries, HF is the leading cause of hospitalization. In 2007, the American Heart Association estimates that >$33 billion was spent on HF.[1] The syndrome of HF poses many challenges. Because of the complexity of its many causes and pathophysiological origins, HF may escape a unifying definition. From many

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This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on January 14, 2008. A single reprint is available by calling 800-242-8721 (US only) or by writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0440. A copy of the statement is also available at http://www.americanheart.org/presenter.jhtml?identifier=3003999 by selecting either the "topic list" link or the "chronological list" link. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.107.188965**

roots, HF leads to common pathways of significant morbidity and mortality. Because HF is commonly the result of acute and chronic cardiac injury that can be prevented with aggressive risk factor management, there is a critical need to examine our current approach to this enormous health threat. Converging developments in demography and patient care have combined to foster a growing epidemic of HF. These trends include improved care of acute myocardial infarction (MI) and improved care of those patients already diagnosed with HF. Moreover, the aging of the population and the emerging pandemic of cardiovascular disease (CVD) in the developing nations of the world presage a rise in the incidence and prevalence of HF globally and magnify the importance of its prevention.[2]

This scientific statement is intended for several audiences. First, it is a knowledge base aimed at general practitioners, preventive medicine specialists, and cardiologists. Second, it is a primer for epidemiologists and clinical researchers. Lastly, this statement is meant to serve as a document for health planners and policymakers, 2 groups who need increased awareness of the magnitude and gravity of the problem of HF.

The lifetime risk of HF places this epidemic in perspective as a public health issue. Framingham investigators have estimated that the lifetime risk for developing HF[3] at age 40 years was 21% for men and 20% for women.[3] They showed that a substantial proportion of the risk was independent of MI. In the absence of a documented MI, the risk of developing HF for a 40-year-old was 11% in men and 15% in women. Lifetime risk was strongly associated with blood pressure level.[3]

Community-based studies in the United States also provide evidence of declining mortality with HF, thereby increasing its prevalence. The incidence of HF and survival after diagnosis were investigated in a population-based cohort study of the population of Olmsted County, Minnesota, in the United States.[4] The age-adjusted incidence rate of HF there (1996–2000) was 38 per 10 000 for men and 29 for women. HF mortality, however, had declined over time, with a 5-year mortality rate of 57% in 1979 to 1984 and 48% in 1996 to 2000.[4] Men experienced a greater mortality decline than women. Similarly, Framingham investigators recently evaluated long-term trends in the survival of patients with HF.[5] Age-adjusted survival rates between 1950 and 1999 improved for men and women. Over these time periods, risk of death declined 12% per decade. Canadian investigators have also found an improvement in 1-year deaths among those individuals ≥65 years of age who were hospitalized with HF.[6]

Perhaps the biggest factor boosting HF prevalence and incidence will be the burgeoning growth in the elderly population. In the United States, the number of elderly (≥65 years of age) is expected to grow from 35 million in the year 2000 to 70.3 million in 2030.[7] The risk of HF incidence increases with older age.[1,3,8,9] Even if incidence remains constant, the total number of people with HF is expected to double over this period.

A study using the California hospital discharge database from the years 1991 through 1998 examined trends in hospitalization rates for HF for individuals 21 to 64 years of age.[10] From 1991 to 1998, the HF hospitalization rate per 10 000 people increased among men from 15.2 to 29.7 in blacks, from 2.9 to 4.2 in Asians, from 4.3 to 5.8 in whites, and from 2.9 to 4.2 in Hispanics.[10] These findings highlight the higher risk of HF morbidity in blacks and the increasing trend for all groups. Because these racial and ethnic minorities tend to be underrepresented in clinical studies, the implications of these data are especially important.

From the European perspective, the Rotterdam Study, a prospective, population-based cohort study, was examined to determine the prevalence, incidence rate, and lifetime risk of HF.[11] In 1997, the lifetime risk of HF for a person 55 years of age was estimated at 33.0% in men and 28.5% in women.[11] Other investigators from the Netherlands have also predicted the future burden of HF given estimates about the incidence, recurrence, and outcomes of heart disease.[12] On the basis of several scenarios, they find that heart disease is in the midst of a transition from predominantly an acute disease to a more chronic disease. The authors suggest that the number of years spent with heart disease morbidity will increase across the population. Similarly, in Scotland, there are estimates of markedly increased numbers of patients with HF over the next 20 years.[13]

As discussed in the following section, the HF epidemic is not a problem unique to developed countries. Omran[14] describes epidemiological transitions that involve the shift from pandemics of infection to degenerative and man-made diseases. This type of transition places developing countries at risk for new health problems. Cardiovascular risk factors and CVDs are on the rise in developing countries.[15,16] HF will therefore likely become a major public health burden for these countries.

The importance of the present task is underscored by the recent update from the venerable New York Heart Association function-based classification system for HF (class I through class IV) to the new American Heart Association clinical/pathophysiology-based classification by stages (A through D). Two developments have made the consideration of HF stage highly relevant. Scientific evidence indicates that HF prognosis can be greatly modified by appropriate medical therapy. Second, growing evidence has shown that primary prevention of HF by intervention in stages A and B is a realistic, attainable, and measurable goal.

All this having been said, most management strategies have focused on HF with left ventricular (LV) systolic dysfunction. The presence of HF with preserved LV systolic function is increasingly recognized as a clinically important problem.[17] Despite documented evidence of progress in the treatment of HF due to LV systolic dysfunction in clinical trials and in the community, the successful management of HF with preserved systolic function remains elusive.[18] Moreover, by extension, the prevention of this type of HF is a formidable task indeed.

The Global Burden of HF

Most of the knowledge about the epidemiology, risk factors, prognosis, treatment, and prevention of HF is based on North American and European studies. For instance, in the United

States, we appreciate that the lifetime risk of HF is 20% (in whites),[3] and the prevalence of symptomatic HF in the United States is >5 million.[1] The prevalence and burden of HF will likely continue to increase in developed countries,[5,8] where better care has improved survival with cardiovascular conditions such as MI and HF.[4] Although survival in clinical trials is improving, HF remains a lethal condition in the community, with an estimated annual mortality of approximately 21% in men and 17% in women.[4] The epidemiology of HF has also been well characterized in Europe.[11] Unfortunately, similar epidemiological data are essentially unavailable from the remaining developing and developed world.

The World Health Organization (WHO) has begun to focus on noninfectious, chronic diseases in the developing world. Interest in chronic diseases stems from a growing awareness of the global epidemiological transition from infectious to chronic degenerative diseases.[15,16] According to the WHO, in 2003, 16.7 million individuals died of CVD (29.2% of deaths globally).[19,20] In contrast to popular misconceptions, 80% of CVD deaths worldwide took place in developing countries.[19] As early as 2010, it is projected that CVD will be the leading cause of death in developing and developed countries. CVD is also an important cause of morbidity; at least 20 million people survive their heart attacks and strokes annually.[19] The same globalization forces that lead to industrialization, urbanization, unhealthy diet, sedentary lifestyles, obesity, and smoking, which have resulted in epidemic CVD in developing countries, are also likely contributing to a global rise in HF.[21]

The WHO has also started to evaluate coronary heart disease and stroke data more systematically. HF data have not yet been examined in this fashion.[19] Mendez and Cowie[22] in a 2001 review noted an inability to find published population-based studies of HF. Instead, they relied on inherently biased, referral-based case series and hospital studies from developing countries. Extrapolating from the published literature, McMurray and colleagues[23] estimated that 23 million individuals worldwide have HF. Because incidence and prevalence data for HF in the majority of countries are scanty, it is not surprising that epidemiological data from developing countries are woefully inadequate. Data from Singapore[24] and Hong Kong[25] suggest that hospitalization for HF is increasing in that region. The magnitude of the HF burden in the developing world is essentially unknown, but the potential for its enormous growth is unquestioned.

The causes of HF in developing countries may vary widely. Consistent with the process of epidemiological transition, infectious causes, particularly rheumatic heart disease, are a more common finding in Africa, as well as Central and South America.[22,26,27] The high prevalence of hypertension in Africa[22,26–28] and Asia[29] has contributed to its important role in the pathogenesis of HF in these regions. As introduced above, coronary artery disease (CAD) is emerging as a cause of HF as countries undergo an epidemiological transition.[19,22]

The design of a prevention program for HF in the developing world must consider that access to expensive diagnostic equipment and drugs is severely constrained by economic resources. Nonetheless, the WHO estimates that simple measures could advance life expectancy by 5 to 10 years[30] and would dramatically reduce global disparities in life expectancy. Three of the 10 items on the WHO's list of simple measures would directly and indirectly prevent HF, including control programs aimed at blood pressure, cholesterol, and tobacco.

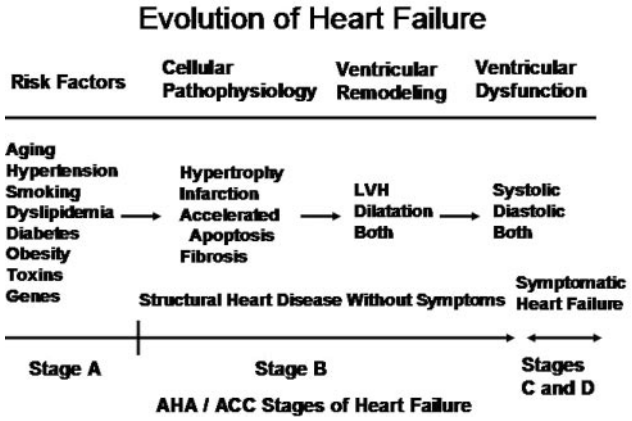

Figure. The evolution of HF along American Heart Association/American College of Cardiology (AHA/ACC) guidelines for the diagnosis and management of HF clinical stages.[188] These guidelines are extraordinarily important and unique because they include a "pre-HF" category (stage A) and a long latent period (stage B) during which structural heart disease is present without symptoms of HF. Stage A and stage B present ideal opportunities to intervene to prevent HF. LVH indicates LV hypertrophy.

In summary, the next decades will offer tremendous opportunities for advancing the prevention of HF. Genetic research will provide insights into the pathophysiology of HF, risk stratification to detect those at highest risk of HF, and pharmacogenetic insights to target interventions to maximize efficacy and minimize toxicity. We must continue to advocate for the implementation of simple, cost-effective preventive measures that will directly improve world health. These measures should be at the forefront of public health directives at the local, national, and international levels. WHO, the World Bank, and other nongovernmental organizations have a major role to play in this regard.[31] The challenge of the emerging pandemic of HF demands preventive intervention on a scale not previously imagined. If unmet, this challenge will be an ominous legacy for our children.

The presence of well-recognized, traditional risk factors for CVD (stage A) is sufficient to trigger a management response with the long-term goal of avoiding the development of HF. Patients in stage B are likewise ideal targets for HF prevention.[32] These individuals with prevalent CVD but without overt symptomatic HF include the vast majority of patients whose hearts are undergoing progressive maladaptive cardiac remodeling, which leads to HF (Figure). The concept of "functional myocyte reserve" is fundamental here. For practical purposes, cardiac myocytes cease dividing early in life; therefore, an overarching goal of CVD management should be the preservation of normal myocytes, thereby preventing myocardial hypertrophy, MI, accelerated apoptosis, and myocardial fibrosis. These events are well-established antecedents of clinical HF (stages C and D). The following paragraphs review the concepts and scientific evidence providing a compelling argument for the prevention of HF.

Screening for Patients at High Risk of HF

With the increasing focus on addressing stage A HF as the best means of preventing the final common pathway of HF (stages C and D), attention needs to be directed toward screening for well-recognized conditions such as those noted above, including hypertension, diabetes mellitus, and dyslipidemia. Furthermore, evidence continues to mount that indicates that other conditions, such as chronic kidney disease and sleep-disordered breathing, place patients at risk of subsequent development of HF. Subjective and objective measures should be analyzed for their contributions to risk and HF in individual patients. Behavioral and lifestyle issues confound and modify the more traditional risk factors and may contribute independently to the origin of HF.

Prospective epidemiological studies have identified risk factors and risk markers for development of HF (stage A). The identification of individuals who are at risk for HF is useful for the implementation of strategies to prevent HF (Figure). It is not yet clear whether all stage A patients or only those at high risk of developing HF should be subjected to serial noninvasive assessment for the advent of ventricular dysfunction (stage B). Such a strategy would require screening of an enormous number of individuals with the likelihood of detecting a relatively small number of patients who would develop systolic dysfunction. If we follow guidelines for the management of causative diseases in stage A patients, it is not currently established that we would recommend any different management strategy, even if we detected the patients who might develop morphological evidence of ventricular dysfunction. It will, however, be necessary to develop accurate natural histories to predict the evolution of remodeling. We also need to create algorithms that combine accurate histories (as yet to be defined) and peripheral biomarkers to better predict the specific population at higher risk among stage A subjects. It is imperative that we serially monitor those with a strong family history of cardiomyopathy and those receiving potentially cardiotoxic pharmacological interventions. For now, routine periodic assessment of LV function in all stage A patients or in the general population cannot be recommended. Studies asserting the cost-effectiveness of B-type natriuretic peptide as a screening tool need further replication and extension to a variety of populations.[33] The future creation of an objective scoring system for risk of developing HF, perhaps along the lines of the Framingham risk assessment for HF,[34] will help identify those individuals in stage A with especially high risk for early events and development of stage B, C, or D disease. These individuals represent the most appropriate targets for particularly aggressive intervention and surveillance.

Major Clinical Risk Factors

The prevalence of HF increases proportionally with advancing age.[2,5,8,9,34–45] Increased incidence of HF in men[8,9,35–37,39–44] is explained in part by greater prevalence of CAD.[3,36,41]

Hypertension is one of the most common risk factors for CAD, and in turn HF, with a 2- to 3-fold categorical increased risk for the occurrence of HF.[8,39–41,44–48] (Each of these subjects is treated in greater detail later.)

MI is an important risk factor for HF, increasing risk 2- to 3-fold.[34,36,40–44,48] MI stimulates cardiac remodeling.[49,50] Angiotensin-converting enzyme (ACE) inhibitors,[51–53] β-blockers,[54] aldosterone antagonists,[55] and angiotensin II receptor antagonists[56] reduce mortality and the need for hospitalization for HF in patients with MI and LV systolic dysfunction but without overt HF.[51,57]

Diabetes mellitus is consistently associated with a 2- to 5-fold increase in the risk of HF,[2,8,39–41,42–45,58] more so in women.[48] Diabetes is an important predictor of HF in patients with asymptomatic LV dysfunction.[59] With every 1% increase in hemoglobin A1c, there is an 8% to 16% increase in the risk of hospitalization for worsening of HF and death.[60,61] Diabetes may predispose to HF by promoting atherogenic risk traits, obesity, LV hypertrophy, disease of the coronary microvasculature, endothelial dysfunction, autonomic dysfunction, and metabolic abnormalities.[62]

Valvular heart disease is associated with an increased risk of HF.[2,8,34,35,44,63] Hemodynamic overload on the ventricles imposed by any valve disease eventually leads to myocardial dysfunction.[46] Surgical management of stenotic and regurgitant mitral and aortic valves has been associated with marked improvement in LV function and survival.[64,65]

Obesity has recently been demonstrated to be a major cardiovascular risk factor[2,40,44,45,66] and predisposes to HF by contributing to atherogenic risk factors and increasing preload and afterload, as well as through neurohormonal upregulation (but natriuretic peptide inadequacy) and an association with sleep-disordered breathing or chronic kidney disease.[67] The specific influence of weight reduction on obesity-related HF is not well established and needs further investigation.

Table 1 presents an overview of the established and hypothetical risk factors for HF.

Minor Clinical Risk Factors

Multiple other risk factors are less consistently associated with HF. Excessive alcohol intake may increase the risk of HF by up to 45%[45] by increasing blood pressure[68–71] or by direct myocardial toxicity.[72] However, light to moderate alcohol consumption is inversely associated with the risk of HF, especially in men, both in the general population and in those with asymptomatic LV dysfunction (stage B).[43,44,73] Cigarette smoking may promote insulin resistance,[74] dyslipidemia,[74] diabetes mellitus,[75,76] endothelial dysfunction,[77] coronary vasospasm, and oxidative stress[78] and may induce direct toxic effects on myocytes.[79,80]

Dyslipidemia is associated with an increased risk of HF, although it is not clear whether this association is independent of a predisposition to atherosclerosis and MI.[2] Lipid lowering with simvastatin resulted in a 21% reduction in the risk of developing HF in patients with established coronary disease.[81] An increased ratio of total cholesterol to high-density lipoprotein cholesterol is strongly associated with an increased risk of HF.[82] Elevated triglycerides increase the risk of HF at an advanced age.[47] High cholesterol levels, low levels of high-density lipoprotein cholesterol, and high triglyceride levels are all correlated with greater LV mass and

Table 1. 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 (eg, α2CDel322-325, β1Arg389)

Morphological Risk Predictors
- Increased LVID, mass
- Asymptomatic LV dysfunction
- LV diastolic dysfunction

5-FU indicates 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; and HR, heart rate.

impaired diastolic function, particularly in hypertensive subjects.[83–85]

Renal insufficiency predicts the occurrence of new cases of HF,[41,86,87] showing a graded increase in risk with increasing levels of serum creatinine.[87] Even mild insufficiency is associated with a progression of asymptomatic LV systolic dysfunction to overt HF.[88] Complications of chronic renal insufficiency, including anemia (erythropoietin deficiency), worsening of hypertension, arterial stiffening,[89] and hypervolemia (sodium and water retention), neuroendocrine activation,[90] hypercoagulability,[91] endothelial dysfunction,[34,40,44,45] and an increase in proinflammatory cytokines[91–94] and homocysteine,[95,96] may contribute to HF. Anemia itself is a marker of more advanced HF, indicates a worse prognosis, and may be a target for future therapies.[97]

Sleep-disordered breathing may be associated with HF.[98–100] An apnea-hypopnea index >11 was reported to increase the odds of self-reported HF by 2.4-fold.[100] The impact of sleep-disordered breathing on the subsequent risk of HF is not known, and continuous positive airway pressure has not been demonstrated to prevent incident HF. Low physical activity,[44] low socioeconomic status,[44] coffee consumption,[45] and increased dietary salt intake[101] have been suggested to increase the risk of HF, but their independent risk attributions remain to be confirmed. An increased heart rate has been shown to be associated with a 10% to 15% increased odds of HF for every increase of 10 beats per minute.[34] This observation may indicate a compensatory response to lower stroke volume[102] or underlying asymptomatic LV systolic dysfunction and neurohumoral activation. Mental stress and depression also precipitate worsening of established HF.[42,103,104]

Systemic biomarkers may indicate the risk of development of HF. Microalbuminuria, defined as an albumin/creatinine ratio of 2 mg/mmol, is associated with a 3-fold increase in the risk of hospitalization for HF, and every 0.4-mg/mmol increase in the albumin/creatinine ratio is associated with a >10% increase in worsening of HF.[105] Albuminuria, a marker of exaggerated renal endothelial permeability and microvascular or macrovascular disease,[106] is associated with multiple other precipitants of HF.[107–113] Homocysteine,[96] insulinlike growth factor,[114] proinflammatory cytokines, and C-reactive protein[41,94] are associated with a significantly increased risk of HF. Increased levels of plasma B-type natriuretic peptide have shown a strong association with an increased risk of HF.[115]

Toxic Risk Precipitants

Chemotherapeutic agents such as doxorubicin, cyclophosphamide, and 5-fluorouracil are associated with myocardial damage that results in LV dysfunction,[116–118] HF, and death. The incidence of doxorubicin-induced cardiotoxicity is higher when the cumulative dose exceeds 550 mg/m^2,[119,120] and it may range from 2.2% to 26%.[119,121,122] Reports have also described HF after the use of trastuzumab (Herceptin).[123] Evidence indicates nonsteroidal antiinflammatory drugs may precipitate HF and increase the risk of hospitalization for HF in patients receiving diuretics.[124,125] The recent recognition that some (and perhaps all) members of the class of cyclooxygenase-2 inhibitors may predispose some individuals to an increased risk of MI should also, therefore, be seen as increasing the risk of HF.[126–129] Although insulin sensitizers hold great promise in the management (and prevention) of type 2 diabetes mellitus, at least 1 (troglitazone) has been

withdrawn from the market because of safety issues regarding precipitation of HF. Other thiazolinedione agents may increase the incidence of HF by nearly 50% over that encountered by nonuser diabetic patients (absolute incidence of 8.2% over 40 months).[130] The US Food and Drug Administration has mandated specific warnings in this regard for both pioglitazone and rosiglitazone. Among illicit drugs, cocaine abuse may precipitate acute MI and subsequent HF.[131]

Morphological and Physiological Risk Predictors

Multiple morphological and physiological measures obtained by echocardiographic and magnetic resonance imaging identify individuals at higher risk for developing HF. Ventricular dilatation, represented by an increase in end-diastolic or end-systolic dimensions,[132] increased LV mass,[133] and evidence of LV diastolic filling impairment, and asymptomatic systolic dysfunction[133–135] are associated with an increased likelihood of overt HF. Increased LV mass and systolic dysfunction act synergistically to predict HF,[133] and attenuation of ventricular dilatation by neurohumoral antagonists is associated with a reduction in the risk of manifest HF.[136,137]

Genetic Risk Predictors

The percentage of cardiomyopathies and HF attributable to mendelian mutation is difficult to estimate accurately owing to incomplete penetrance and variable expression.[138] Single mendelian mutations leading to HF are rare, representing perhaps 1% of HF cases. With regard to idiopathic dilated cardiomyopathy, it is estimated that up to one half of referred patients have familial disease,[139] but the prevalence in the population is lower.[140] Several different functional pathways may lead to the clinical syndrome of HF, including energy production and regulation (eg, matrilineal inheritance of mitochondrial mutations), calcium cycling abnormalities (eg, *RyR2* mutations), and mutations in transcriptional regulators (eg, Nkx2.5, which leads to ventricular hypertrophy).[141] Similarly, multiple genetic polymorphisms in sympathetic neuroreceptors, such as those of the gene coding for α_{2C}-adrenergic receptors (α_{2C}Del322-325) and another for β_1-adrenergic receptors (β_1Arg389), have been evaluated as candidates for the risk of HF.[142] Blacks who are homozygous for α_{2C}Del322-325 alone demonstrate 5-fold higher odds of HF.[142] If this polymorphism is also associated with homozygosity for β_1Arg389, the risk of HF increases by 10-fold.[142] Numerous other genetic polymorphisms have been linked with known HF risk factors such as hypertension.[143] ACE and *AT1R* gene polymorphisms have been associated with vascular stiffness, which could also affect LV remodeling.[144] At this time, only a detailed family history can be recommended as a means of detecting individuals with a potential genetic risk of developing HF.

Advances in the Prevention of CAD Events and HF

CAD is a major contributing cause of HF.[35,41,44] The prevention of CAD events is key to maintaining functional myocyte reserve and preventing LV systolic dysfunction. Essential strategies for prevention of HF focus on modification of risk factors for HF development. Objectives include comprehensive prevention, detection, and treatment of hypertension, atherosclerosis, and diabetes (stage A) and detection and treatment of asymptomatic LV dysfunction (stage B). In patients with established CAD, other atherosclerotic vascular disease, dyslipidemia, hypertension, or diabetes mellitus, a number of cardiovascular-protective medications, including ACE inhibitors, β-blockers, antiplatelet agents, and statin therapy, can prevent progression to symptomatic HF. These medications should be employed aggressively. Therapeutic lifestyle change may also have considerable impact on these risk factors. The role of diet in the management of hypertension and diet plus exercise in the prevention of diabetes should receive greater emphasis in clinical practice. Substantial opportunities remain to improve implementation of therapies proven to prevent HF in the large number of patients at risk.

Ischemic heart disease is the leading cause of HF in Western countries. In the 24 multicenter HF-treatment trials reported in the *New England Journal of Medicine* over the past 20 years, CAD was the underlying cause of HF in 62% of 43 568 patients enrolled.[145] Clinical trials, however, may not properly reflect the natural history or broader range of causes of HF found in the community, especially for HF related to hypertension. It is estimated that >15 million people in the United States have a history of MI, symptomatic CAD, or both.[1] The 5-year risk of developing HF after a first acute MI at 40 to 69 years of age is 12% for women and 7% for men, and the corresponding risk at age 70 and older is 25% and 22%, respectively.[1] A recently published multinational study documents the steep decline for in-hospital new congestive HF after acute MI over the period 1999 to 2006.[146] Patients with peripheral vascular disease, cerebral vascular disease, or diabetes mellitus may be at similarly high risk for HF and cardiovascular events.[147] If established, these diseases should be managed with due vigor to reduce HF incidence.[147]

The contribution of CAD to HF is not limited to the initial ischemic insult alone. The progressive nature of CAD also contributes to recurrent cardiovascular events, sudden death, and the progression to HF.[148] An acute MI depletes functional myocyte reserve, with ensuing myocardial fibrosis and development of LV remodeling. The resulting chamber dilation and neurohormonal activation lead to progressive deterioration of the remaining viable myocardium.[149] This process can be attenuated by early myocardial reperfusion[150] and the use of ACE inhibitors,[151] β-blockers,[152] and aldosterone antagonists.[153]

Long-standing (chronic) ischemia superimposed on damaged myocardium may result in "hibernation," which produces a further progressive decline of ventricular function. Restoration of blood flow by mechanical or pharmacological revascularization with β-blockers or statins may improve contractility in hibernating areas.[148] Endothelial dysfunction, an inherent component of the pathophysiology of atherosclerosis, may have a direct effect on ventricular function.[154,155] Many drugs known to reduce mortality, reinfarction, and HF, including lipid-lowering agents, ACE inhibitors, β-blockers, nitrates, and aspirin, can also potentially improve endothelial function. In addition, acute and chronic myocardial ischemia

can induce diastolic dysfunction through mechanisms that involve impaired calcium ion sequestration into the sarcoplasmic reticulum during the energy-dependent process of relaxation, scarring, fibrosis, and compensatory hypertrophy of noninfarcted myocardium.[156]

MI survivors are also at substantial risk for reinfarction. The recognition that progression of CAD may contribute to the progression of HF has prompted reconsideration of secondary prevention strategies. The standards of care that formerly emphasized neurohormonal antagonism and symptomatic relief after MI have evolved to embrace and emphasize aggressive secondary prevention of atherosclerosis. This approach focuses on aggressive risk factor reduction, plaque stabilization, enhancement of endothelial function, and prevention or reversal of LV remodeling.

The combination of cardiovascular protective medications along with therapeutic lifestyle changes as recommended in the American Heart Association/American College of Cardiology secondary prevention guidelines, last updated in 2006,[157] should be applied aggressively in all appropriate patients to reduce the risk of HF. Multiple clinical trials support these recommendations. The Heart Outcomes Prevention Evaluation (HOPE) study demonstrated ACE inhibitor therapy (with ramipril) to be an effective means of curbing progression from established atherosclerotic vascular disease to HF.[158] The benefits of ACE inhibitor therapy were additive to preexisting therapies such as aspirin, β-blockers, and lipid-lowering therapy and included additional decreases in subsequent MI and all-cause mortality. The HOPE trial expands the indication for ACE inhibitor therapy to all patients with documented CAD, presumed CAD based on presence of other atherosclerotic vascular disease, or diabetes. The EUROPA trial (EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease) has added similar data with perindopril.[159]

Antiplatelet therapy with aspirin in patients with established vascular disease or similar risk has been demonstrated to reduce the risk of cardiovascular events and HF.[160] The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial demonstrated that clopidogrel in combination with aspirin reduces the risk of major cardiovascular events in patients with acute coronary syndromes,[160,161] but that study did not include an HF end point.

The integral role of β-blockers in the prevention of HF in the postinfarction population has been reinforced by the recent Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial, which found a significant reduction in all-cause mortality when the nonselective β-blocker and α1-blocker carvedilol was added to the treatment regimen of post-MI patients with LV dysfunction already treated with ACE inhibitors.[54] Revascularization in patients with low LV ejection fraction and significant CAD may be associated with improved survival.[162] The ongoing STICH Trial (Surgical Treatment for Ischemic Heart Failure) will provide much-needed information in this regard.[163]

Because of the magnitude and importance of hypertension both as a risk factor for CAD and as an independent risk factor for the development of HF, an entire section of this scientific statement has been devoted to this area.

Diabetes Mellitus

Diabetes, which affects 20 million Americans, is highly associated with risk factors for HF such as CAD and hypertension.[164] From 1990 to 2001, the prevalence of diabetes increased by 61%, with ≈1.3 million Americans developing diabetes annually.[165,166] Diabetes is an independent risk factor for development of HF. The Framingham Study revealed a 2.4-fold increase in symptomatic HF in diabetic men and a 5.0-fold increase in diabetic women, independent of coexisting hypertension or ischemic heart disease.[58] Diabetes also may act synergistically to increase the risk of HF by accelerating the development of atherosclerosis, MI, and ischemic HF. Incrementally increased risk for HF is seen at higher hemoglobin A1c levels.[61] (See also paragraphs to follow for impact of diabetes on other risk factors, including dyslipidemia and hypertension.)

Because patients with diabetes are at substantially increased risk for developing HF, strategies aimed at preventing or delaying the onset of type 2 diabetes mellitus would be an effective means to reduce the incidence of HF.[167,168] Multiple randomized, controlled trials have demonstrated that the progression from prediabetes to diabetes could be delayed or prevented by intensive lifestyle modification (nutritional and exercise interventions).[168,169] In addition, the use of glucose-lowering drugs such as metformin[169] or acarbose[170] to prevent or delay the onset of type 2 diabetes mellitus has also been demonstrated.[171] ACE inhibitors have not been consistently shown to lower the incidence of new-onset diabetes.[172] Regardless, more investigation will be required to analyze the varying contributions of nonglycemic and glycemic effects of diabetes to the risk of developing HF.

An aggressive approach to the prevention of diabetes is integral in the prevention of stage A HF.[167–171] Evidence from the United Kingdom Prospective Diabetes Study Group (UKPDS) is of critical importance in forming HF preventive strategies for patients with established diabetes. UKPDS demonstrated blood pressure control with ACE inhibitors and/or β-blockers as an integral part of cardioprotective, preventative therapy in patients with diabetes.[173] The UKPDS clinical trial comparing tight blood pressure control (<150/85 mm Hg) to lesser control of blood pressure (<180/105 mm Hg) in 1148 diabetic hypertensive patients demonstrated that a 10-mm Hg decrease in systolic blood pressure was associated with a 56% decreased risk of incident HF.[174] ACE inhibitor therapy and β-blocker therapy were equally efficacious in reducing the risk of HF and other diabetes-related complications.[171,175]

In contrast to the benefits of ACE inhibitors and β-blockers, a UKPDS trial evaluating glycemic control reported that tight blood glucose control (blood glucose <108 mg/dL) with insulin or oral sulfonylureas compared with conventional treatment (blood glucose <270 mg/dL) did not affect HF incidence.[175] Despite the limited data with regard to HF risk, strict glycemic control in patients with diabetes should be reinforced, with a goal of glycosylated hemoglobin of <7%, in accordance with published guidelines.[176]

Dyslipidemia

Elevated cholesterol levels have long been recognized as an important independent risk factor for CAD. Dyslipidemia,

therefore, is linked to the development of HF. Elevated total cholesterol is not a strong predictor of new-onset HF,[177] but an increased ratio of total cholesterol to high-density lipoprotein cholesterol is associated with elevated HF risk.[82] Dyslipidemia treatment has been demonstrated to be effective in preventing HF. Statin treatment in CAD patients was demonstrated to reduce HF incidence and to decrease all-cause mortality in the subset of patients who developed HF in an analysis of the Scandinavian Simvastatin Survival Study (4S).[81] The Heart Protection Study (HPS) demonstrated a significant reduction in all-cause mortality and cardiovascular events with statin treatment in patients with established atherosclerotic vascular disease and/or diabetes, irrespective of baseline low-density lipoprotein cholesterol levels.[178] Recent experimental evidence suggests that statins may also play a cardioprotective role independent of their lipid-lowering capacity.[179] If confirmed in clinical trials, statins may soon be used as a treatment to prevent HF in patients with asymptomatic LV dysfunction (stage B), regardless of cause and regardless of baseline low-density lipoprotein levels.

Although dietary approaches and highly effective lipid-lowering medications are available, 32.5% of the US adult population have a low-density lipoprotein cholesterol level of 130 mg/dL or higher.[1] Of individuals who would meet the criteria for lipid-modifying treatment set out by the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III), fewer than 50% are actually receiving treatment.[1] This finding is true even for those who are at highest risk: those who have symptomatic coronary heart disease. Adherence poses an additional major problem. Half of all individuals who are prescribed lipid-lowering drugs stop taking them within 6 months.[180] Recent modification of the ATP III guidelines advocating even lower optional low-density lipoprotein goals places further emphasis both on intensity of therapy and on an even greater need for adherence.[181] Although as yet untested in terms of impact on incident HF, it is reasonable to hypothesize that these more aggressive lipid-lowering strategies will prevent HF.

Overweight, Obesity, and the Metabolic Syndrome

Obesity is a common condition associated with increased risk for CAD and cardiovascular mortality.[182] Excess body weight is also an independent risk factor for the development of HF and contributes to other HF risk factors, such as hypertension, dyslipidemia, and type 2 diabetes mellitus.[66] The percentage of Americans who are overweight or obese has increased rapidly over the past 25 years. Nearly two thirds (64%) of adults in the United States 20 years of age or older met the criteria for overweight or obesity in 1999 to 2000, and 30.5% qualified as obese.[183] Data from the Framingham Heart Study showed that each unit increase in body mass index was associated with a 5% increase in the risk of HF in men and 7% in women.[182] Modest weight loss and increases in physical activity have been demonstrated to reduce cardiovascular risk factors such as hypertension, dyslipidemia, and type 2 diabetes mellitus. Weight reduction, often achieved by the combination of reduced caloric intake and increased physical activity, has been shown to impact cardiovascular risk factors, decrease insulin resistance, and prevent or delay the onset of diabetes. Given the available data, it is clear that obesity is a risk factor for HF and multiple other HF-related risk factors. Therefore, measures should be taken to achieve and maintain normal body weight (body mass index <25 kg/m^2).

Metabolic syndrome is a constellation of clinical conditions that includes dyslipidemia, impaired glucose tolerance, insulin resistance, obesity, and hypertension.[184] These risk factors may place individuals at even greater risk of cardiovascular events. Therefore, prevention programs targeting this growing vulnerable population will likely also reduce HF risk. It has not been established whether insulin sensitizers such as metformin and other agents might reduce later development of HF, although at least 1 such agent has been withdrawn from the market because of the potential for directly increasing the risk of HF.

Smoking

Tobacco use is the single largest preventable cause of disease and premature death in the United States. Approximately 440 000 Americans die each year of illnesses related to active smoking.[185] Current smokers have significantly higher risk for the development of HF than prior smokers and nonsmokers. In the Coronary Artery Surgery Study (CASS), smoking was independently associated with a 47% increased risk of developing HF. Among people who quit smoking, after 1 year of abstinence, the risk of death due to coronary heart disease is 50% lower than that of people who continue to smoke.[186] 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.[187]

All individuals should be asked about tobacco use, and smokers should be counseled to quit. Patients should be referred to formal cessation programs, and pharmacological therapy should be offered to increase the success rate.[188] The broad public health policy of the United States should reflect vigorous advocacy to create and sustain effective tobacco-control programs.

Sedentary Lifestyle

Physical inactivity has been recognized as an important risk factor for CVD and HF. Prospective epidemiological studies of occupational and leisure-time physical activity have documented a reduced incidence of CAD, HF, and stroke in the more physically active and fit individuals. Increased physical activity, even by the modest amount of 30 minutes at least 5 days per week, has been documented to reduce risk for cardiovascular events.[189] Increased physical activity has also been demonstrated to reduce the incidence of diabetes.[169] However, the integration of physical activity into the daily lives of the population has proved challenging, and improvements will require concerted, ongoing efforts.

Table 2. Medical Therapies to Reduce Risk of HF

	Clinical Trial	No. of Patients*	Patient Inclusion Criteria	HF Incidence	Relative Risk Reduction, %
Randomized, placebo-controlled trials					
ACEI	HOPE[137] (ramipril, 2.5 or 10 mg)	9297	Vascular disease (CAD, PVD, or stroke) or diabetes plus cardiac risk factor; creatinine <2.4 mg/dL	Ramipril vs placebo, 9% vs 11%	23
ACEI	EUROPA[138] (perindopril, 8 mg)	12 218	Documented stable CAD	Perindopril vs placebo, 1.0% vs 1.7%	39
ACEI	SAVE[34] (captopril, target 50 mg, TID)	2231	After acute MI; LVEF ≤40%; without HF symptoms	Captopril vs placebo, 11% vs 16%	37
Antiplatelet (ADP inhibitor)	CURE[141] (clopidogrel 300-mg load, then 75 mg)	12 562	Acute coronary syndrome: non–ST-segment elevation ECG changes or elevated cardiac enzymes	Clopidogrel vs placebo, 3.7% vs 4.4%	18
ARB	RENAAL (losartan, 50–100 mg)	1513	Type 2 diabetes mellitus, nephropathy	Losartan vs placebo, 11.9% vs 16.7%	32
ARB	IDNT (irbesartan, 300 mg)	1715	Hypertension, type 2 diabetes, nephropathy	Irbesartan vs placebo, N/A	23
Statin	4S[63] (simvastatin 20–40 mg)	4444	History of MI or angina, cholesterol 213–309 mg/dL, triglycerides <221 mg/dL	Simvastatin vs placebo, 8.3% vs 10.3%	19
Randomized, active-controlled trials					
β-Blocker or ACEI, with tight BP control	UKPDS[153] (captopril or atenolol, goal BP <150/85 mm Hg)	1148	Type 2 diabetes mellitus, hypertension	Captopril or atenolol (BP <150/85 mm Hg) vs other drugs (BP <180/105 mm Hg), 3.6% vs 8.1%	56
Retrospective studies					
β-Blocker	SOLVD[270] (subanalysis of prevention trial)	2107	Asymptomatic LV dysfunction, ejection fraction <35%	Enalapril plus β-blocker vs enalapril plus no β-blocker, N/A	36
β-Blocker	SAVE[271] (subanalysis)	2231	Ejection fraction <40%, no overt HF, post-MI patients	β-Blocker vs no β-blocker, 16.5% vs 22.6%	32

ACEI indicates ACE inhibitor; PVD, peripheral vascular disease; SAVE, Survival And Ventricular Enlargement Trial; TID, 3 times per day; LVEF, LV ejection fraction; ADP, adenosine diphosphate; ARB, angiotensin receptor blocker; ECG, electrocardiogram; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; IDNT, Irbesartan in Diabetic Nephropathy; N/A, not applicable; and BP, blood pressure.

*Including whites, blacks, and Hispanics.

Summary of Efforts to Prevent HF Due to Atherosclerotic CVD

HF incidence will only be lowered if evidence-based treatments for CAD and its risk factors are initiated effectively (Table 2). Hospital-based treatment programs that aim to increase treatment rates and long-term patient compliance have been successful, demonstrating improved long-term cardiovascular outcomes and a marked reduction of mortality. The American Heart Association's Get With The Guidelines program encourages in-hospital initiation of lipid-lowering medications and other secondary prevention measures.[190]

Recently published clinical studies have identified highly effective therapies for prevention of HF. Therapy with ACE inhibitors and β-blockers is strongly indicated in all patients with asymptomatic LV dysfunction, hypertension, CAD, peripheral vascular disease, cerebral vascular disease, and diabetes. Antiplatelet therapy and statins are indicated in all patients with atherosclerosis or diabetes in the absence of contraindications. Preferred antihypertensive medications in patients with stage B disease include ACE inhibitors, β-blockers, and thiazide diuretics. Blood pressure control is especially important in the diabetic population. Renal insufficiency is an indication for ACE inhibitor therapy and perhaps β-blocker therapy, which offers both cardioprotection and renal protection. Aldosterone receptor blockade has a documented role in prevention of HF in the postinfarction patient; its HF-prevention role in stage A patients is not yet established. Therapeutic lifestyle changes including smoking cessation, regular physical activity, and maintenance of ideal body weight are also essential components of HF prevention. In light of the rising incidence of and mortality from HF, more research is clearly necessary to determine the best and most cost-effective methods for screening and detect-

ing asymptomatic LV dysfunction and wider application of evidence-based preventive strategies.

Advances in Prevention of Hypertensive Heart Disease

Increased systolic blood pressure and pulse pressure are associated with HF risk in a continuous and graded manner,[39,191,192] whereas diastolic blood pressure demonstrates a U-shaped association with risk.[39] The increased risk of HF associated with wide pulse pressure is not explained by isolated systolic hypertension or excessive diastolic blood pressure lowering alone.[192] Hypertension promotes myocyte hypertrophy (secondary to increased afterload), myocardial fibrosis (increased collagen synthesis and decreased degradation), and loss of myocardial contractile tissue (through increased incidence of MI). All of these processes reduce functional myocyte reserve. Treatment of hypertension confers a reduced risk of HF.[193–196] Use of diuretics, β-blockers, and ACE inhibitors in hypertensive patients is associated with prevention of development of HF.[193–197] Blood pressure lowering also leads to regression of LV hypertrophy,[198] itself an independent risk factor for HF.[48,199]

Data from the Framingham Heart Study showed that hypertension increases the risk for developing HF by 2-fold in men and 3-fold in women.[48] CAD preceded the development of HF in 60% of these cases. A meta-analysis of 17 randomized trials in 47 000 patients confirmed the beneficial effect of hypertension treatment on HF risk reduction.[193]

Hypertension confers an increased risk of developing structural heart disease and HF.[200] The prevention and adequate control of hypertension provides the earliest opportunity to prevent HF.[200] There is abundant evidence that therapeutic lifestyle change can prevent the development of hypertension. Hypertension can be prevented both by exercise[201] and by diet modification, such as the DASH (Dietary Approaches to Stop Hypertension) diet.[202,203] In addition, recent data from the TRial Of Preventing HYpertension (TROPHY) indicate that drug treatment of "prehypertension" can effectively prevent the development of hypertension.[204] Emphasis should be placed both on identifying individuals and populations at risk of developing hypertension and on supporting clinicians to provide evidence-based, age-appropriate, and culturally competent care that includes the patient as a healthcare partner.

Hypertension trends in the United States are concerning. In a recent analysis of the NHANES (National Health and Nutrition Examination Survey) 2000 data, it was reported that in 1999 to 2000, almost 29% of the adult US population ($\approx$58.4 million individuals) had hypertension, which indicates an increase in prevalence from 1988 to 1991.[205] Women, non-Hispanic blacks, and older participants had the highest rates of hypertension. Almost 30% of all hypertensive individuals were unaware of their condition, and >50% were not being treated. In addition, 69% of adults with high blood pressure did not have their hypertension controlled. Women, older participants, and Mexican Americans tended to have the lowest rates of control.[205,206]

Poor blood pressure control (60% uncontrolled at follow-up) was also observed in the Framingham Heart Study.[207] In addition, nearly 75% of all patients with diabetes and hypertension did not have their hypertension controlled to the target of <130/85 mm Hg recommended in the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7).[205,208]

Increasing body mass index has been associated with increased hypertension prevalence in all 3 NHANES surveys (1988 to 1991, 1991 to 1994, and 1999 to 2000),[183] and weight reduction must serve as a cornerstone of blood pressure reduction recommendations.[209] The role of obesity prevalence and management in the prevention of HF is more fully discussed in the section on risk factors. Hypertension is a common comorbid condition in diabetes, affecting 20% to 60% of individuals with diabetes.[210] Diabetes increases the risk of cardiovascular morbidity and mortality, including HF.[211] Aggressive treatment of hypertension is associated with reduction in cardiovascular risk and has been well-documented in large clinical trials.[158,159,173,174,212,213] The role of diabetes in the prevention of HF is discussed more fully above.

Hypertension, as defined by JNC-7,[208] includes a categorized range of values (Table 3). As with other risk factors for HF, the achievement of adequate blood pressure control is directly related to early detection, identification of an optimal treatment goal/plan for each individual, combination of therapeutic lifestyle modifications with targeted pharmacological intervention, and persistent follow-up until the target blood pressure goal is achieved. The key messages of JNC-7[208] are outlined in Table 4.

The benefit of treating hypertension to the specified goal is clear, and achievement of adequate blood pressure control is a major goal of Healthy People 2010.[214] In the past few years, in response to established guidelines,[215–220] clinicians have been more likely to prescribe therapeutic lifestyle changes, assess the patient's hypertension in relation to the individual's global cardiovascular risk, and set a blood pressure goal that is based on individual risk. Given the current rates of prevalence, treatment, and control, it is clear that achievement of adequate blood pressure control at the population level will involve addressing many issues, including individual biological, psychosocial, and environmental factors, as well as provider variables.

Several studies have attempted to define the characteristics of patients with uncontrolled hypertension and factors associated with increased control. The data suggest that an age of at least 65 years, isolated systolic hypertension, and obesity accounted for the greatest proportion of patients whose blood pressure was not controlled.[205,206,208,221] Given the aging demographics of the United States, the propensity of older adults to have isolated systolic hypertension, and the developing obesity epidemic, these data have special relevance. In addition, race/ethnicity, gender, and not having visited a physician within the preceding 12 months predicted poor control and low rates of awareness.[205,221,222]

Table 3. Classification and Management of Blood Pressure for Adults*

BP Classification	SBP* mm Hg	DBP* mm Hg	Lifestyle Modification	Initial drug therapy: Without Compelling Indication	Initial drug therapy: With Compelling Indications (See Table 8†)
Normal	<120	and <80	Encourage		
Prehypertension	120–139	or 80–89	Yes	No antihypertensive drug indicated.	Drug(s) for compelling indications.‡
Stage 1 Hypertension	140–159	or 90–99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.	Drug(s) for the compelling indications.‡ Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
Stage 2 Hypertension	≥160	or ≥100	Yes	Two-drug combination for most§ (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).	

BP indicates blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; and CCB, calcium channel blocker.

*Treatment determined by highest BP category.

†In the original publication.

‡Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mm Hg.

§Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

Reprinted from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute. NIH publication No. 03–5233, December 2003.

Special Considerations in Hypertension

The Elderly

The prevalence of hypertension increases with age and is especially great in individuals 60 years of age or older. This group also has lower rates of control despite being equally likely to be treated.[205] Isolated systolic hypertension, which confers increased risk for hypertension-related morbidity and mortality, including HF, occurs more commonly in older individuals and is considerably more difficult to control.[208,221,223] Its successful treatment, however, reduces development of incident HF[194] even among the oldest old (≥80 years).[224,225]

Table 4. Key Messages of JNC-7

1. In persons older than 50 years, systolic BP >140 mm Hg is a much more important CVD risk factor than diastolic BP.
2. The risk of CVD, beginning at a BP of 115/75 mm Hg, doubles with each increment of 20/10 mm Hg; individuals who are normotensive at 55 years of age have a 90% lifetime risk for developing hypertension.
3. Individuals with a systolic BP of 120 to 139 mm Hg or a diastolic BP of 80 to 89 mm Hg should be considered prehypertensive and require health-promoting lifestyle modifications to prevent CVD.
4. Thiazide-type diuretics should be used in drug treatment for most patients with uncomplicated hypertension, either alone or in combination with drugs from other classes. Certain high-risk conditions are compelling indications for the initial use of other antihypertensive drug classes (ACE inhibitors, angiotensin-receptor blockers, β-blockers, calcium channel blockers).
5. Most patients with hypertension will require ≥2 antihypertensive medications to achieve goal BP (<140/90 mm Hg, or <130/80 mm Hg for patients with diabetes or chronic kidney disease).
6. If BP is >20/10 mm Hg above goal BP, consideration should be given to initiating therapy with 2 agents, 1 of which usually should be a thiazide-type diuretic.
7. The most effective therapy prescribed by the most careful clinician will control hypertension only if patients are motivated. Motivation improves when patients have positive experiences with and trust in the clinician. Empathy builds trust and is a potent motivator.

BP indicates blood pressure.

The PREMIER trial (PREvention of Myocardial Infarction Early Remodeling) demonstrated that elderly patients can participate in self-care and achieve blood pressure reductions with an effective multidisciplinary behavioral intervention. This intervention lowered blood pressure in individuals older and younger than 50 years of age, but significantly more so in older individuals.[226] The elderly are often socially isolated, socioeconomically disadvantaged, and depressed. Older persons may suffer from vascular-related cognitive impairment and are often not referred to cardiac rehabilitation for risk reduction.[227]

Women

Women are at increased risk of developing hypertension. Although some NHANES phases (1988 to 1991, 1991 to 1994, and 1999 to 2002) documented better blood pressure control in women than in men,[205,206] 1 analysis of NHANES data that examined a smaller sample size for a shorter period of follow-up (1999–2000) demonstrated higher control rates in men than in women.[205] Overall blood pressure control, however, appears to have been better in women than in men.[206] Women also are more likely than men to have HF with preserved LV systolic function,[228] often a consequence of longstanding and poorly controlled hypertension. In addition, women over the age of 60 years and minority women had the highest prevalence of hypertension, which reflects the triple jeopardy conferred by being older, a minority, and a woman.[205,206] The fact that women are at increased risk of obesity, are more likely to be socioeconomically disadvantaged, and are more likely to suffer depression suggests that intervention strategies should focus on persistent follow-up

Table 5. Guidelines With URLs

Guideline	URL
The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (the JNC-7 report)	http://www.nhlbi.nih.gov/guidelines/hypertension/
Management of High Blood Pressure in African Americans: Consensus Statement of the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks	http://archinte.ama-assn.org/cgi/content/extract/163/5/525
Guidelines Subcommittee of the World Health Organization–International Society of Hypertension (WHO-ISH) Mild Hypertension Liaison Committee	http://www.who.int/cardiovascular_diseases/guidelines/hypertension_guidelines.pdf
Guidelines for Management of Hypertension: Report of the Fourth Working Party of the British Hypertension Society, 2004–BHS VI	http://www.bhsoc.org/pdfs/BHS_IV_Guidelines.pdf
2003 European Society of Hypertension–European Society of Cardiology Guidelines for the Management of Arterial Hypertension	http://www.guideline.gov/summary/summary.aspx?doc_id=4765&nbr=3445
2004 Canadian Recommendations for the Management of Hypertension, Part I: Blood Pressure Measurement, Diagnosis, and Assessment of Risk; and Part II: Therapy	http://hypertension.ca/chep/recommendations2004va.html
AHA Scientific Statement: Clinical Implications of Obesity With Specific Focus on Cardiovascular Disease	http://circ.ahajournals.org/cgi/content/full/110/18/2952
AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update	http://circ.ahajournals.org/cgi/content/full/106/3/388
AHA/ACC Guidelines for Preventing Heart Attack and Death in Patients With Atherosclerotic Cardiovascular Disease: 2001 Update	http://circ.ahajournals.org/cgi/content/full/104/13/1577
AHA Scientific Statement: Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women	http://circ.ahajournals.org/cgi/content/full/109/5/672

and risk factor reduction through varied therapeutic lifestyle interventions.[229–231] JNC-7 recommendations should guide the identification and treatment of high blood pressure in women.[208]

Racial and Ethnic Minorities

Non-Hispanic blacks have a high prevalence of hypertension[205,206] and high rates of hypertension-related heart disease, including HF.[1] Non-Hispanic black women have a particularly high hypertension prevalence and represent a unique group at risk. Mexican Americans who participated in NHANES had the lowest prevalence of hypertension, as well as the lowest rates of awareness and control, and thereby pose unique challenges. Urban minorities, particularly blacks, American Indians, and Hispanics, present additional care challenges owing to their higher prevalence of adverse health behaviors, including smoking, sedentary lifestyle, and dietary intake high in saturated fat.[209,221,222,226,232–234]

Racial/ethnic minority and low-income populations are also subject to differences in access and utilization of healthcare services. These populations are often affected by racism, low education, low income, underemployment and unemployment, lack of insurance, and lack of health-enhancing resources in the community. Lack of culturally relevant care limits access to primary, secondary, and tertiary services.[235–238] Even when income and insurance are controlled for, racial disparities persist.[237]

The consensus statement published by the working group of the International Society on Hypertension in Blacks argues that the barriers to achieving blood pressure control in blacks have been attributed largely to biological and social factors, with inadequate focus on the role of medical management. This working group asserts that failure of medical providers to treat high blood pressure early and to goal is one key obstacle.[220] When treated in compliance with established guidelines, blacks are able to achieve the same level of blood pressure control as their non-Hispanic white counterparts.[206] These data urge that emphasis should be placed on best-practice strategies that are evidence-based, culturally and linguistically competent, and target early detection and aggressive pursuit of individual blood pressure goals.[206] Table 5 provides specific URLs for the guidelines discussed in this section.

Other Risk Factors and the Prevention of HF

Sleep-Disordered Breathing

Sleep-disordered breathing may be an important risk factor for HF. In the Sleep Heart Health Study, the presence of obstructive sleep apnea was associated with a 2.4 relative risk of HF independent of other known risk factors.[100] This risk of HF exceeded that for all other CVD syndromes evaluated, including hypertension, stroke, and CAD. Although there is no direct evidence that treating obstructive sleep apnea prevents incident HF, treatment of established LV dysfunction with continuous positive airway pressure has been shown to improve LV structure and function in patients with either obstructive or central sleep apnea syndrome.[239]

Chronic Kidney Disease

Activation of the renin-angiotensin-aldosterone system and sympathetic nervous system plays an important pathophysiological role in the initiation and progression of both renal disease and HF. It is not surprising, therefore, that renal insufficiency and microalbuminuria have become recognized

as independent risk factors for new-onset HF.[86,87] Prevention of chronic kidney disease represents another important strategy to reduce HF. ACE inhibitor therapy has been demonstrated to reduce HF risk, in addition to delaying progression to renal failure, in patients with renal insufficiency. In the HOPE trial, ACE inhibitor therapy afforded enhanced HF protection to a subset of patients with renal insufficiency (creatinine 1.4 to 2.3 mg/dL) compared with those without renal insufficiency.[240] Two recently published randomized, placebo-controlled trials studying patients with diabetes and nephropathy have established a role for angiotensin-receptor blockers in reducing the risk of developing HF in this population.[213,214] However, no reduction in cardiovascular or all-cause mortality was noted with the use of angiotensin-receptor blocker therapy in diabetic subjects with proteinuria.[213,214] Carvedilol (a nonselective β-blocker with α1-adrenergic–receptor blocking characteristics) has been demonstrated to significantly reduce proteinuria in patients with hypertension or diabetes to a greater extent than short-acting β1-selective β-blockers.[241]

Future Directions

Two areas present opportunities for growth in our understanding of HF prevention: advances in genetic research and improving awareness of HF and its treatment and prevention.

The Future Role of Genetics in HF

Prevention implications of a family history of dilated or hypertrophic cardiomyopathy are presently uncertain. Current guidelines recommend routinely inquiring about family history of CVD and cardiomyopathy.[200] These guidelines also suggest that individuals with a strong family history of cardiomyopathy should receive noninvasive evaluation of LV function (class IIa indication); however, the level of supporting evidence is only class C.[200] In the future, we will be better able to risk-stratify those with a family history of such disorders by use of a combination of genetic and noninvasive testing.

Most individuals with HF do not have rare mendelian mutations underlying their HF. Those with HF due to idiopathic dilated cardiomyopathy likely have a complex disorder, the product of genomics, proteomics, genetic epidemiology, and environmental exposures. All of these areas are ripe for exploration to expand our understanding of the heritability or genetic linkage of HF. For example, there has been a paucity of descriptions of the twin[242–244] or familial correlation of HF, whereas most prior studies have emphasized mendelian disorders.[141,245]

The next steps in understanding the role of common genetic variants will include a mixture of genome-wide association, genetic-linkage, and candidate-gene approaches.[141,245] Sources of candidate genes for future study include the expression of genes in animal models and in human HF. The frequent problems with both false-positive and false-negative findings with candidate genotype-phenotype studies have been well documented.[246,247] Early efforts to describe the contribution of common single-nucleotide polymorphisms often have been negative[248] or have not been replicated. Interpretation of single-nucleotide polymorphism screening has been further complicated by effects of modifier genes and incomplete penetrance.[245]

The complexity of the HF phenotype also has contributed to difficulties in discovering the role of common genetic variation. Although HF is a well-defined clinical syndrome, it is the end result of interactions among dozens of pathogenetic pathways, such as hypertension, obesity, coronary ischemia, and dysfunctional LV remodeling. Moreover, genetic underpinnings for HF that arises from systolic dysfunction may vary from those predisposing to HF due to diastolic dysfunction. Large, high-quality data sets and complex analyses will be required for successful pursuit of the underlying common genetic variation of HF.

Increasingly, researchers have examined "endophenotypes,"[249,250] also referred to as intermediate pathways,[143] to uncover genetic mechanisms of disease. The study of intermediate pathways (eg, subclinical disease), such as LV wall thickening, diameter, mass, volume, and contractility,[251,252] has several advantages. Endophenotypes are more likely to be quantifiable and may be more genetically homogenous. The heritability of LV phenotypes has been established.[252–256] In the future, primordial prevention will motivate more aggressive implementation of lifestyle interventions in those at highest genetic risk for disease, thereby facilitating the focus of preventive therapy[257] toward those identified by modification of existing HF risk-prediction algorithms.[34]

Understanding the genetic components of HF will also provide targets for drug therapy. Genetic knowledge might direct drug development to focus on prevention and treatment of HF risk factors (stage A) and/or blocking and regressing LV remodeling (stage B). In addition, understanding pharmacogenetic variation will aid in selecting the optimal drugs and doses of preventive medications to maximize efficacy and minimize drug toxicity.[258] These single-nucleotide polymorphisms may enhance susceptibility to HF or delineate response to therapy for HF. Various phenotypes for ACEs and the β-adrenergic receptor have been described that characterize individuals who are more susceptible to HF.[259,260]

Genetic testing also raises great ethical and legal concerns.[261,262] Subjects participating in genetic research must be assured of protected confidentiality.[263] The public is wary that genetic testing may lead to genetic discrimination in workplace hiring, as well as in access to life and health insurance. National legislation prohibiting genetic discrimination has been adopted recently and is a major step forward in this area.

Concept of Awareness of HF

Our current knowledge regarding prevention of HF should recognize the importance of awareness in the prevention process. Awareness of CVDs in general and the relationship of now well-established risk factors to the development of heart disease has emerged only since the mid-20th century. The increased awareness of this relationship is particularly true for hypertension and its sequelae. In 1950, for example, the role of hypertension in the demise of Franklin D. Roosevelt, the 32nd president of the United States, was largely unknown.[264,265] Indeed, the unknown relationship of "risk" factors for atherosclerotic CVD, cerebral vascular

accident, and HF led to the clinical inattention to Roosevelt's clinical picture, which included malignant hypertension, angina pectoris, and congestive HF. This story underscores the ignorance of clinicians, scientists, and the public at that time with regard to heart disease and its risk factors. We now must consider the importance of awareness and perception of HF in today's world.

Public awareness of heart disease risk has increased markedly. Contemporary media attention to diet and fitness is but one example. Despite this seeming improvement in awareness of risk factors for CVD, we are still in the midst of an extraordinary epidemic of obesity, diabetes, metabolic syndrome, hypertension, and atherosclerosis. In fact, we have made little progress in improving patient awareness of hypertension and translating that awareness into treatment and control.[205] The emergence of HF as a global scourge with high prevalence, high morbidity, and extraordinary cost amply underscores the urgency of efforts to increase public and professional awareness. Despite the importance of public and professional education with respect to diagnosing and preventing HF, this area remains largely unexplored.

European investigators are currently studying HF awareness.[266] The Study on Heart failure Awareness and Perception in Europe (SHAPE) aims to improve HF care by increasing awareness and perception of the disease in Europe in a 2-phase process. This approach will first assess HF awareness in 9 European countries and then use that data to design, deliver, and evaluate a program to increase awareness of HF and improve HF care. The premise of the SHAPE effort is that public and professional education is mandatory to translate recent clinical research advances into reductions in morbidity and mortality due to HF at the public health level.

It appears that understanding of HF is low among professionals and the public. Patients having risk factors for the development of HF (stage A), the presence of structural heart disease without symptoms (stage B), or the symptomatic clinical syndrome itself (stages C and D) may not be detected quickly or treated appropriately.[267–269] Increasing awareness of the problem of HF will facilitate appropriate diagnosis and referral of patients, should improve compliance with guidelines, and more importantly, should direct attention to treatment of risk factors that lead to HF. An effort similar to the SHAPE study ought to be undertaken in North America.

Conclusions

In summary, this scientific statement serves manifold purposes. First, the writing group wishes to emphasize that HF represents the final common pathway of many risk factors and cardiovascular illnesses. Second, many of these illnesses can be prevented by implementation of aggressive lifestyle and pharmacological interventions. Third, it is apparent that progress in the prevention of HF must begin with a renewed commitment to enhance public awareness of HF and its antecedent illnesses as remediable processes. This awareness should include a national and international effort to approach all of the known risk factors for CVD aggressively and to support research to identify further such factors, especially to identify the role of genetics in predisposing individuals to the development of HF and to characterize their responses to therapeutic interventions.

Recommendations

I. Research

1. Improve the collection of epidemiological data about the incidence, prevalence, hospitalization, mortality, risk factors, and prevention of HF in the United States and worldwide.
2. Investigate levels of professional and public awareness of HF and the association between awareness and treatment/prevention of HF.
3. Encourage research that investigates disparities in cardiovascular outcomes for special populations, including racial and ethnic minorities, women, and the elderly.
4. Develop appropriate studies to identify and eventually treat asymptomatic individuals with LV dysfunction (stage B) and to prevent its development.
5. Investigate and define the underlying pathophysiology in HF patients with preserved LV systolic function to focus on prevention.
6. Develop a multidisciplinary approach to understanding the cardiorenal connection in HF with emphasis on prevention.
7. Encourage research into the contribution of genetic and environmental factors to CAD, other HF risk factors, and the risk markers of progression to HF.
8. Pursue pharmacogenetic research to maximize the efficacy and minimize the toxicity of medications for HF prevention.
9. Investigate more effective systems to ensure use of evidence-based, guideline-recommended therapies for prevention of CAD and HF.
10. Promote behavioral research on improving compliance and adherence to proven therapies for managing risk factors.

II. Education

1. Improve professional awareness of the increasing burden of CAD and HF in the United States and worldwide. Improve public awareness of CAD and HF risk factors and evidence-based strategies to reduce risk.
2. Improve awareness of the increasing burden of hypertension-related HF in the United States and worldwide and the benefits of hypertension control in the prevention of HF by following established guidelines.
3. Develop programs to address deficiencies in awareness by the public, professionals, and policy makers, and develop and implement means of monitoring the effectiveness of programs to increase awareness.
4. Increase public awareness of the issues involving genetic testing applied to HF.

III. Policy/Advocacy

1. Advocate for increases in federal funding for research and implementation of efforts to prevent CAD and HF in the United States and worldwide.
2. Advocate for national legislation that provides reimbursement for prevention services for hypertension and CVD.
3. Create local, national, and international programs to increase awareness of HF among policymakers, underscoring the vital role of multidisciplinary prevention.
4. Create alliances among state and federal governmental and nongovernmental organizations to identify HF awareness, treatment, and prevention as national mission-specific goals.
5. Advocate for national research programs on outcomes and pay-for-performance with HF-prevention end points.

Acknowledgments

The authors thank Karen Modesitt for excellent assistance preparing the manuscript.

Disclosures

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of writing group are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit.

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Circulation. 2008;117:2544-2565; originally published online April 7, 2008;
doi: 10.1161/CIRCULATIONAHA.107.188965
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539