Changing epidemiological features of cardiac failure

William B Kannel, Kalon Ho, Thomas Thom

Department of Medicine, Section of Preventive Medicine and Epidemiology, Evans Memorial Research Foundation, Boston University School of Medicine, Boston, USA
W B Kannel

Charles A Dana Research Institute and the Harvard Thorndike Lab of the Department of Medicine, Cardiovascular Division, Beth Israel Hospital and Harvard Medical School, Boston, USA
K Ho

Epidemiology and Biometry Program, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda, Maryland, USA
T Thom

Correspondence to:
Dr William B Kannel, BU/Framingham Heart Study, 5 Thurber Street, Framingham, MA 01701, USA.

Important reductions in cardiovascular mortality that have occurred over the past three decades in most industrialised regions have not been accompanied by a decline in mortality or admissions to hospital for cardiac failure.[1] Congestive heart failure (CHF) continues to be a lethal end stage of cardiovascular disease caused by hypertension, coronary disease, valve deformity, diabetes, and cardiomyopathy. As premature deaths from these conditions are avoided by means of more effective medical and surgical interventions, the prevalence of cardiac failure can be expected to rise because the predisposing conditions are palliated, not cured. Increased size of the elderly population also increases the prevalence of heart failure.

Size of the problem: prevalence and incidence

Based on the National Health and Nutrition Survey, it has been estimated that from one to two million people in the United States under the age of 75, excluding people in nursing homes and other residential institutions, have CHF.[1] When people of $\geqslant 75$ and those in institutions are included, the range is closer to two to three million people of whom about one half are $\geqslant 65$.[1 2] The mild end of the range is based on self reporting and the severe end is based on a clinical score. Prevalence rises with age from 1% of the population aged 25 to 54 to 4·5% at 65–74.[2] It is probably nearer to 10% in those >75. National statistics based on admissions to hospital and visits to clinics also indicate a high incidence of heart failure in the United States.[1 3] There were 722 000 hospital discharges in 1990 with cardiac failure as the primary diagnosis.[3] Taken at more than face value this suggests a fourfold increase of admissions to hospital since 1971 when 165 000 were so listed.[4] This indicates a rapidly expanding problem as the population ages and increases in size (fig 1).[1] If secondary diagnoses are also included, the hospital discharges for heart failure are over two million.[3] Black patients in the United States are twice as likely to get heart failure than white patients, from the discharge diagnosis criterion of prevalence.[3]

Visits to physicians' clinics in the United States for heart failure in 1989 were estimated at 2 340 000, consistent with the data from hospital discharge statistics.[1 3] These discharge estimates, however, understate the extent of the use of health care facilities for heart failure because they do not include outpatient visits or home health care.

Extrapolation of the average annual incidence of heart failure from the Framingham Study to the population of the United States yields an estimate of 465 000 new events each year.[1] In the Framingham Study the incidence of CHF doubles with each decade of age with only slight male predominance (fig 2). National secular trends in measures of incidence for the United States are not available. Incidence of CHF could decline if control of hypertension continues to improve and if primary prevention of coronary heart disease (CHD) improves along with mortality from CHD. Incidence of CHF might well increase if

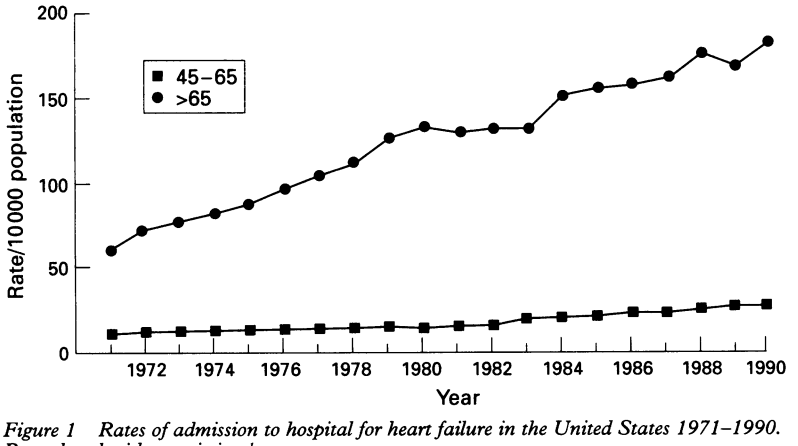

Figure 1 Rates of admission to hospital for heart failure in the United States 1971–1990. Reproduced with permission.[1]

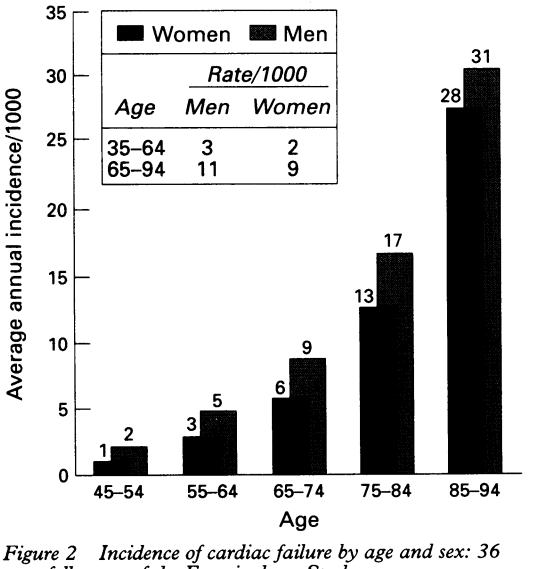

Figure 2 Incidence of cardiac failure by age and sex: 36 year follow up of the Framingham Study.

Table 1 Morbidity after cardiac failure: 30 year follow up of the Framingham Study[5]

	Morbidity at 6 yr (%)		Risk ratio	
	Men	Women	Men	Women
Stroke	26	26	3·6	6·8
Recurrence of cardiac failure	70	63	12·0	21·6

survival after an initial myocardial infarction improves. Preliminary data from the Framingham Study, with uniform criteria and case ascertainment over the decades of follow up, do not suggest a decline in the incidence of CHF.

Morbidity associated with CHF is considerable. Because it is only palliated, 60–70% of patients experience repeated recurrences within six years. It also promotes a fourfold increased risk of stroke rivalling atrial fibrillation as a cause of stroke in elderly people (table 1).

Cardiomyopathy

Reliable estimates of the prevalence and incidence of idiopathic cardiomyopathies are unavailable because of difficulty in diagnosis and their relative rarity in the general population. In 1986 the National Center for Health Statistics reported 21 244 deaths in the United States attributed to cardiomyopathy. About 87% of these were assigned to dilated cardiomyopathy whereas hypertrophic cardiomyopathy accounted for only 2% of cases in men and 6% in women.[6] Alcoholic cardiomyopathy accounted for 8% and was 2·5 times more common in black than white patients. In 1990 there were 49 000 admissions to hospital and 366 000 days of hospital care for cardiomyopathy in the United States.[3] A sharp rise in death rates attributed to cardiomyopathy since 1970 has been noted. It is unclear whether this is a real increase or only an artifact of changes in diagnostic criteria, more intensive and complex diagnostic investigation, or change in death certification practices.

Economic costs

The economic impact of heart failure is substantial. In 1989 the health care cost of heart failure in the United States was estimated by the National Heart, Lung, and Blood Institute to be just under $9 billion with indirect costs of another $1·4 billion. Some $6·4 billion of this was spent on hospital care, $500 million on professional services, $1·7 billion on nursing home care, and $200 million on pharmaceuticals.[1 7]

Table 2 Prevalence of aetiologies for cardiac failure: 32 year follow up

	Congestive heart failure (%)	
Cause	Men	Women
Hypertension*	70	78
Coronary disease†	59	48
Valvar heart†	22	31
Other‡	7	7

*Blood pressure >160/95 mm Hg or on antihypertensive treatment.
†Any clinical manifestation of congestive heart failure.
‡None of the above and cardiomyopathy.

Table 3 Changes in prevalences of pre-existing conditions among patients with congestive heart failure aged 50–89 in the Framingham cohort from 1950–1987[9]

	Age adjusted change (%) calendar decade	
Risk factor	Men	Women
Coronary heart disease	+41*	+25
Diabetes mellitus	+21	+24
Hypertension	−10	−27
ECG-LVH	−23	−33
Valvar heart disease	−45	−32

*$p < 0.05$ (age adjusted odds ratio by logistic regression) ECG-LVH, left ventricular hypertrophy on electrocardiogram.

Aetiology

Accurate specification of the main causes of cardiac failure from clinical data is difficult because of selection bias. Less biased population based data seldom provide accurate estimates of less common aetiologies. Also the various possible aetiologies tend to coexist including coronary disease, hypertension, and diabetes. Coronary disease seems to account for about half of the cases of cardiac failure depending on age and sex (table 2). A substantial proportion, however, have coexistent hypertension.

Coronary disease, hypertension, and diabetes singly or in combination, predominate as causes of heart failure. Some 87% of cases of cardiac failure in the general population are associated with either coronary disease or hypertension.[8] Coronary disease and diabetes seem to be increasingly responsible for heart failure in recent years (table 3). Hypertension and valvar heart disease are diminishing determinants.

Mortality

Overt heart failure is the terminal stage of cardiac disease that ensues when the myocardium has exhausted its reserve capacity and compensatory mechanisms. Once overtly manifest, epidemiological surveillance indicates an ominous outlook for progression and survival, with a cardiac mortality four to eight times that of the general population of the same age. Sudden death, a prominent component of this mortality occurs over six years in 9% of men and 4% of women with symptomatic cardiac failure. The sudden death rate associated with heart failure is five times that of the general population of the same age (table 4).

According to a tabulation of multiple causes of death by the National Center for Health Statistics, in 1988 in the United States heart failure accounted for or contributed to 267 356 deaths. At all ages the death rates from cardiac failure are greater in black than in white patients (fig 3).[1]

Vital statistics in the United States indicate

Table 4 Percentage mortality after congestive heart failure: 36 year follow up of the Framingham Study[5]

	Age of men (yr)			Age of women (yr)		
	35–64*	65–94	All	35–64	65–94	All
All cause mortality:						
<2 yr	40·7	52·6	48·6	25·6	46·0	40·4
<6 yr	63·0	75·4	71·2	43·3	67·9	61·2
Cardiovascular disease mortality:						
<2 yr	35·2	41·2	39·2	18·9	36·7	31·8
<6 yr	51·9	56·9	55·2	33·3	52·7	47·4
Coronary heart disease mortality:						
<2 yr	23·2	28·9	27·0	7·8	19·4	16·2
<6 yr	33·3	39·8	37·6	10·0	27·9	22·9
Sudden death:						
<2 yr	5·6	3·6	4·4	1·1	1·7	1·5
<6 yr	11·1	8·1	9·1	2·2	4·6	4·0

*Age when congestive heart failure developed.

an upward trend in age adjusted death rates attributed to heart failure over the past three decades.[1] Since 1968 CHF as an underlying cause of death has increased fourfold. This upward trend in mortality from CHF is noted in white and black patients of both sexes (fig 4).

Death rates in hospital have tended to improve over the years, but have remained high (7–10%) with no improvement since 1988.[8]

Survival

Based on the Framingham Study data cardiac failure continues to be a highly lethal condition with a median survival of only 1·7 years in men and 3·2 years in women if early mortality is included. If mortality in the first 90 days is excluded, as is the case in most clinical trials, median survival is still only 3·2 years in men and 5·4 years in women. Despite a considerable decline in mortality from CHD, no significant change in the prognostic outlook of CHF over 40 years of follow up has been found in the Framingham Study (fig 5).[8]

In 1971 results from the Framingham Study indicated that the outlook for CHF was not much better than that for cancer,[10] with five year survival rates of 25% in men and 38% in women, and has proved to be even more lethal than many malignancies.[8]

In the Framingham cohort the outlook, although poor in both sexes, was more favourable in women, who had only 64% of the high mortality in men. This female advantage persisted on adjustment for age and the cause of the failure. Other investigations of the outlook by sex have been inconsistent, possibly because of selection bias and small sample sizes.[10–14]

The Framingham Study found that survival is adversely affected by age with a 27% increase in mortality per decade of advancing age in men and a 61% increment in women. This has not been consistently noted in other studies.[12–19] The Framingham Study finding may be closer to the truth because of the longer follow up and complete inclusion of all types of heart failure from the time of onset. This seems to have enhanced the statistical power to show the adverse influence of age.

Framingham Study patients with heart failure from coronary heart disease had a better outlook than has been found in comparable patients in placebo groups of various medical intervention trials and some clinical series.[14–15] This is likely because the Framingham Study survival statistics were calculated from the actual time of diagnosis, in an unselected sample, including people who have been excluded from intervention trials because of advanced age, acute myocardial infarctions, and uncontrolled angina. On restricting the Framingham Study data analysis to patients who survived at least 90 days after the diagnosis of heart failure, the survival results more closely resemble those noted in intervention trials.[8 20]

Women with diabetes and electrocardio-

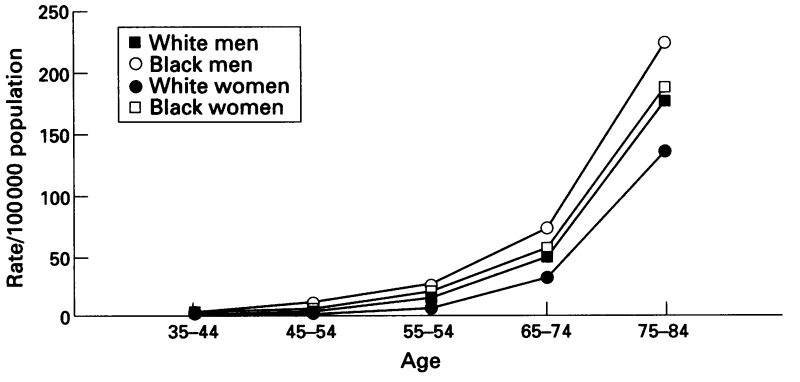

Figure 3 Death rates for heart failure by age, race, and sex in 1988. Reproduced with permission.[1]

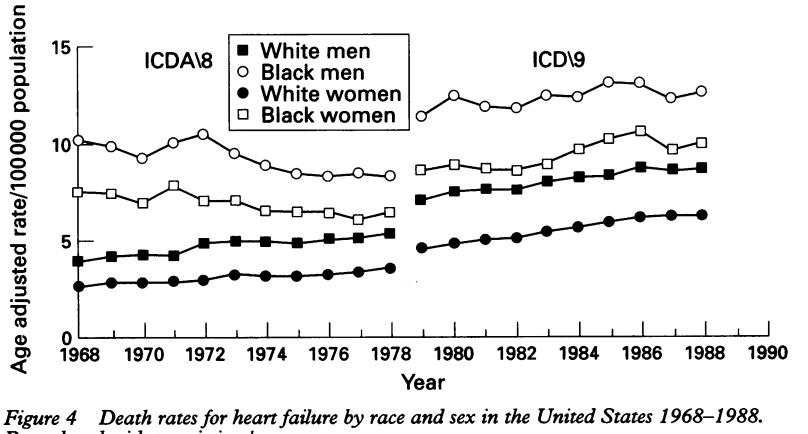

Figure 4 Death rates for heart failure by race and sex in the United States 1968–1988. Reproduced with permission.[1]

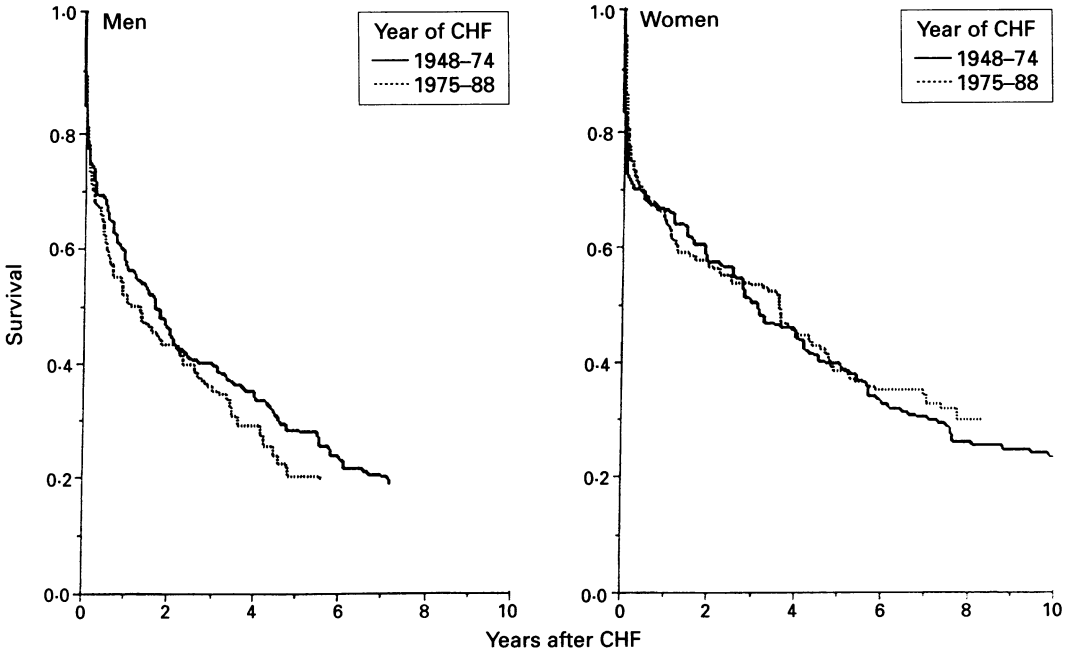

Figure 5 Age adjusted survival rates after CHF by calendar year of first diagnosis of CHF for men and women who developed CHF from 1948–1988. Reproduced with permission.[7]

graphically detected left ventricular hypertrophy who developed CHF had an unfavourable chance of survival, which was decreased by 70% and 63% respectively.[8] These two findings may be interrelated as echocardiographic studies indicate an association of diabetes with increased left ventricular mass in women.[21]

Because of the use of uniform methods of case ascertainment and clinical criteria for CHF during a 40 year period of follow up it has been possible to examine secular trends in incidence of CHF and survival in the Framingham Study. This analysis failed to show any significant temporal change in survival over four decades despite innovations in treatment. No improvement in survival has been noted for any variety of CHF. Most of the follow up period, however, preceded widespread use of vasodilators, angiotensin converting enzyme (ACE) inhibitors, and cardiac transplantation. Even with such treatment the survival, although significantly better than in controls, is still discouragingly low.[22] Despite improvement in treatment options for coronary disease and hypertension, cardiac failure remains highly lethal.

Cardiac failure is a heterogeneous disorder with a variety of inciting pathophysiological processes impairing either systolic function, diastolic function, or both. Further investigation is needed to examine the outlook of the different varieties of cardiac failure and to learn the influence of specific treatments on each variety. There is a need for more individualised strategies for slowing the progression of overt cardiac failure and improving the quality of life and survival after its onset.

Prevention

Despite innovations in treatment of cardiac

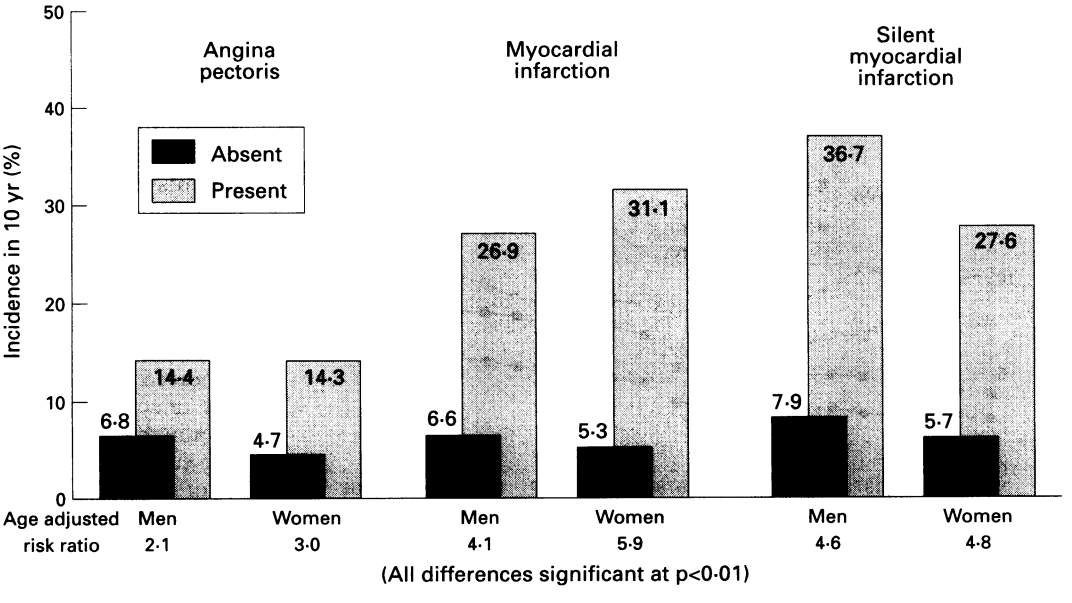

Figure 6 Cardiac failure by clinical manifestations of coronary heart disease: 30 year follow up of the Framingham Study, age range 35–94. Reproduced with permission from: Cupples LA, D'Agostino RB. The Framingham Study, section 35. Survival following initial cardiovascular events. Springfield, VA: DHHS PHS NIH. US Department of Commerce, National Technical Information Service, 1988. (NIH Publ No 88–2969.)

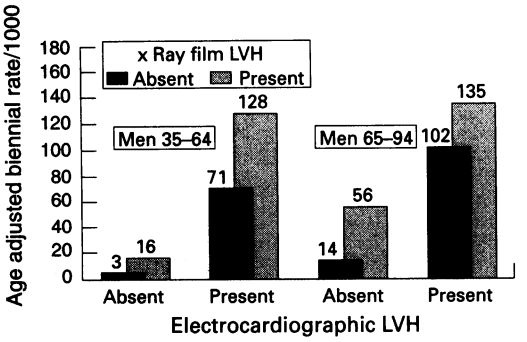

Figure 7 Risk of cardiac failure by evidence from electrocardiography and × ray films of left ventricular hypertrophy (LVH): 32 year follow up to the Framingham Study.

failure and conditions that predispose to it, incidence of heart failure remains high with lethal consequences. From a population perspective prevention of heart failure requires the prevention or correction of hypertension, diabetes, coronary disease, and valvar deformity. Avoidance of alcoholism, viral myocarditis, and Chagas' disease are also important. Because left ventricular hypertrophy is such an important aspect of the evolution of cardiac failure, this must be detected and vigorously treated in patients with hypertension, obesity, diabetes, coronary disease, or valvar heart disease. Effective preventive management of candidates for cardiac failure requires early detection and correction of impaired systolic and diastolic cardiac function.

Predisposing cardiovascular diseases, particularly in the elderly, greatly augment the risk of heart failure. Coronary disease confers a fourfold increase in risk of cardiac failure with rates higher after myocardial infarction, whether silent or overt, than after angina (fig 6). Congenital heart disease and acquired valve disease are also powerful risks for heart failure but carry a lower attributable risk because they are less prevalent. Hypertensive cardiovascular disease with left ventricular hypertrophy is a common and powerful predisposing cardiovascular condition. About 75% of cardiac failure is associated with hypertension with or without other associated cardiac conditions (table 2).

About 18% of cardiac failure is associated with left ventricular hypertrophy previously detected by electrocardiography.[8] Echocardiography provides more reliable and sensitive indications of increase in left ventricular mass that is present in many asymptomatic patients with hypertension, coronary disease, valve disease, diabetes, or obesity. Both anatomical and electrocardiographic indications of left ventricular hypertrophy carry a high risk of cardiac failure (fig 7).

Myocyte hypertrophy, loss of muscle cells, and interstitial fibrosis are common features of all aetiologies of heart failure including myocardial infarction, exposure to toxins, viral myocarditis, Chagas' disease, diabetes, and hypertension. Whatever the cause of myocardial dysfunction, people who have an altered ventricular geometry and function are at greater risk of developing heart failure. It is now possible by non-invasive tests to safely evaluate the structure and function of the heart before the onset of symptoms. Recent investigations have shown that treatment of asymptomatic patients with ventricular dysfunction can delay the onset of cardiac failure and prolong survival.[22]

Seeking out people with predisposing cardiovascular risk factors provides a means for earlier and more efficient prevention of cardiac failure. Hypertension, left ventricular hypertrophy, impaired glucose tolerance, dyslipidaemia, obesity, cigarette smoking (table 5), and excessive alcohol intake are the chief modifiable risk factors now predisposing to cardiac failure. Elderly people are at especially high risk both because of a longer exposure to these risk factors and aging itself.

Hypertension is a main contributor to incidence of heart failure because it increases the risk of CHF threefold and is also highly prevalent in the general population (table 5). Incidence of heart failure increases with the severity of hypertension whether predominantly systolic or diastolic in nature. Risk of CHF is substantial in people with isolated systolic hypertension. Comparing the impact of the various components of blood pressure suggests that in women systolic pressure is most predictive and in men pulse pressure rivals the systolic pressure (table 6).

Diabetes predisposes to cardiac failure at all ages in both sexes (table 5). This is attributed to often associated hypertension and obesity, but diabetes also directly damages the myocardium. Diabetic cardiac failure is not only a product of associated premature coronary disease; structural, functional, and metabolic abnormalities have been found in the diabetic heart that indicate the presence of a diabetic cardiomyopathy.

Although the serum total cholesterol is only weakly related to occurrence of cardiac failure, dyslipidaemia characterised by a high

Table 5 Impact of cardiovascular risk factors on risk of cardiac failure: 36 year follow up of the Framingham Study

	Age 35–64						Age 65–94					
	Biennial rate/1000		Age adjusted risk ratio		Excess risk/1000		Biennial rate/1000		Age adjusted risk ratio		Excess risk/1000	
Risk factors	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Serum cholesterol†	6·9	3·6	1·2*	0·7*	0·9	—	20·6	18·1	0·9*	0·8*	—	—
High blood pressure	13·9	6·3	4·0	3·0	10·4	4·2	33·0	23·5	1·9	1·9	15·8	11·4
Diabetes	22·6	20·7	4·4	7·7	17·5	18·0	40·4	51·4	2·0	3·6	20·2	37·1
ECG-LVH	71·4	35·7	15·0	12·8	16·6	32·9	98·9	83·8	4·9	5·4	78·7	68·4
Smoking	7·1	3·4	1·5	1·1†	2·2	0·2	22·7	22·3	1·0†	1·3	0·3	5·5

*NS; $p < 0.0001$ for all other risk ratios.
†Serum cholesterol > 240 mg/dl. All risk factors adjusted for age only.

Table 6 Risk of cardiac failure by blood pressure components, 34 year follow up of the Framingham Study

	Q_5/Q_1 risk ratio			
	Age 35–64		Age 65–94	
Blood pressure variables	Men	Women	Men	Women
Systolic blood pressure	3·1***	4·4***	1·8***	2·4***
Diastolic blood pressure	1·4*	2·9**	1·6**	1·2*
Mean arterial blood pressure	2·6***	3·9***	2·1***	1·6**
Pulse pressure	3·4***	3·0***	2·3***	2·2***

*p < 0·05; **p < 0·01; ***p < 0·001.
Q_5/Q_1, comparison of rates in 5th *v* 1st quintile of blood pressure variable.

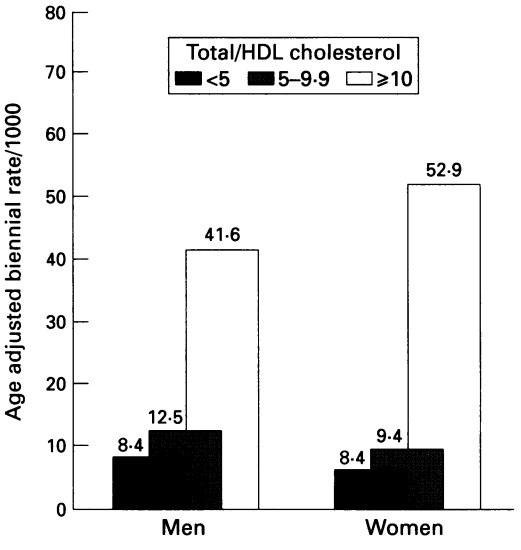

Figure 8 Risk of cardiac failure by the ratio of total/high density lipoprotein (HDL) cholesterol, age range 49–81.

total to high density lipoprotein cholesterol ratio is powerfully associated with the occurrence of CHF (fig 8). It is presumed that the association is mediated by interim promotion of accelerated coronary atherogenesis.

Obesity is an important contributor to cardiac failure, particularly in women, both directly and also by promoting hypertension, left ventricular hypertrophy, insulin resistance, and dyslipidaemia. Cigarette smoking is a weak risk factor for cardiac failure in younger men and older women (table 5).

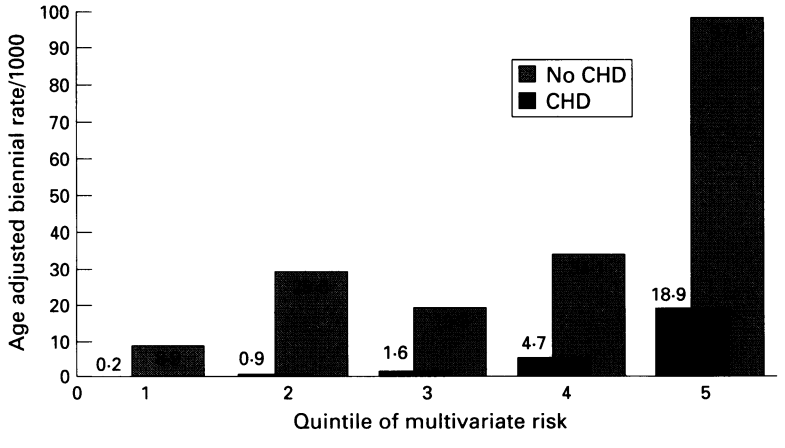

Figure 9 Risk of cardiac failure by quartile of multivariate risk and presence or absence of coronary heart disease (CHD): 32 year follow up to the Framingham Study, age range of men 35–94. Risk variables; age, cardiac enlargement on x ray film, electrocardiographic left ventricular hypertrophy, glucose intolerance, heart rate, systolic blood pressure.

High risk candidates for cardiac failure can be identified from a multivariate cardiovascular risk profile comprising systolic blood pressure, glucose tolerance, left ventricular hypertrophy on electrocardiogram, blood lipids, vital capacity, heart rate, and cardiac enlargement on *x* ray film (fig 9). Evidence of hypertrophy from electrocardiography and *x* ray films each independently predict occurrence of CHF and patients with both are at substantially greater risk than those with either alone (fig 7).

Intervention to correct these risk factors before cardiac disease becomes evident would seem to be more effective than later interventions. Optimal prevention should derive from detection and correction of modifiable predisposing factors before extensive myocardial damage occurs. The causes of idiopathic dilated and hypertrophic cardiomyopathy are too ill defined to be preventive except for those due to alcohol and toxins.

Cardiac failure continues to be a main cause of death and disability despite innovations in treatment and more sophisticated diagnostic methods to detect cardiac malfunction. National and Framingham Study secular trend analysis gives no indication of declining morbidity and mortality from CHF despite improved treatment of coronary disease and hypertension. Coronary disease and cardiomyopathy seem to be assuming increasing importance as causes of cardiac failure. A rising prevalence of diabetes can also be expected to assume greater importance. Improvement in survival seems to require earlier detection and correction of impaired systolic and diastolic function and correction of left ventricular hypertrophy. The greatest impact on incidence of CHF and mortality can be achieved by correction of modifiable risk factors such as hypertension, diabetes, dyslipidaemia, left ventricular hypertrophy and obesity. Multivariate assessment of risk of CHF (fig 9) can be used to detect high risk candidates in whom non-invasive studies of ventricular dysfunction can be carried out to detect highly vulnerable people who require urgent and vigorous preventive measures.

Supported by the Framingham Visiting Scientist Programme and National Institute of Health.

1 National Heart, Lung and Blood Institute. *Morbidity and mortality chartbook on cardiovascular, lung and blood diseases, 1990.* Bethesda: 1992.
2 Schocken DD, Arrieta MI, Leaverton PE. Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol* 1992;**20**:301–6.
3 Graves EJ. Washington DC: US Department of Health and Human Services, *Detailed diagnoses and procedures, national hospital discharge survey.* 1990. National Center for Health Statistics, Vital and Health Statistics, 1991. (Series 13, No 113, DHHS Publ No (PHS) 92–1774.)
4 Ranofsky AL. *Inpatient utilization of short-stay hospitals by diagnosis.* Washington DC: US Department of Health, Education, and Welfare, National Center for Health Statistics, Vital and Health Statistics 1974 (Series 13, No. 16, DHEW Publ No (HRA) 75–1767.)
5 Cupples LA, D'Agostino RB. The Framingham Study, section 35. *Survival following initial cardiovascular events.* Springfield, VA: US DHSS, PHS, NIH. US Department of Commerce. National Technical Information Service, 1988:22161. (MH Public No 88–2969.)
6 Gillum RF. Idiopathic cardiomyopathy in the United States 1970–1982. *Am Heart J* 1986;**111**:752–5.

7 Leavit KR, Lazcerby HC, Conan CA, Letscky SW. National heart expenditures. 1990. *Health Care Financing Review* 1991;**13**:29–54.
8 Ho KKL, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993;**88**:107–15.
9 Kannel WB, Pinsky J. Trends in cardiac failure—incidence and cause over three decades in the Framingham Study [abstract]. *J Am Coll Cardiol* 1991;**17**:87A.
10 McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham Study. *N Engl J Med* 1971;**285**:1441–6.
11 Gillum RF. Heart failure in the United States, 1970–1985. *Am Heart J* 1987;**113**:1043–5.
12 Glover DR, Littler WA. Factors influencing survival and mode of death in severe chronic ischemic cardiac failure. *Br Heart J* 1987;**57**:125–32.
13 Massie B, Ports T, Chattergee K, Parmley W, Ostland J, O'Young J, Haughom F. Long-term vasodilator therapy for heart failure: clinical response and its relationship to hemodynamic measurements. *Circulation* 1981;**68**: 269–78.
14 Wilson JR, Schwartz JS, St John Sutton M, Ferraro N, Horowitz LN, Reidick N, Josephson ME. Prognosis in severe heart failure: relation to hemodynamic measurements and ventricular ectopic activity. *J Am Coll Cardiol* 1983;**2**:403–10.
15 Cleland JGF, Dargie HJ, Ford I. Mortality in heart failure: clinical variables of prognostic value. *Br Heart J* 1987; **58**:572–82.
16 Cohn JN, Archibald DG, Francis GS, Ziesche S, Franciosa JA, Harston WE, *et al.* Veterans Administration Cooperative Study on vasodilator therapy of heart failure: influence of prerandomization variables on the reduction of mortality by treatment with hydralazine and isosorbide dinitrate. *Circulation* 1987; **75**(suppl IV):IV49–54.
17 Kjekshus J, Swedberg K. Enalapril for congstive heart failure. *Am J Cardiol* 1989;**63**(suppl D):26D-32D.
18 Gradman A, Deedwania P, Cody R, Massie B, Packer M, Pitt B, Goldstein S. Predictors of total mortality and sudden death in mild to moderate heart failure. *J Am Coll Cardiol* 1989;**14**:564–70.
19 Fonarow GC, Chelimsky-Fallick C, Stevenson LW, Luu M, Hamilton MA, Moriguchi JD, *et al.* Effect of direct vasodilation with hydralizine versus angiotensin-converting enzyme inhibition with captopril on mortality in advanced heart failure: the Hy-C Trial. *J Am Coll Cardiol* 1992;**19**:845–50.
20 Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, *et al.* A comparison of enalapril with hydralizine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;**325**:303–10.
21 Galderisi M, Anderson KM, Wilson PWF, Levy D. Echocardiographic evidence for the existence of a distinct diabetic cardiomyopathy (the Framingham heart study). *Am J Cardiol* 1991;**68**:85–9.
22 The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;**327**:685–91.