

## Review

## Demographics and concomitant disorders in heart failure

Henry Krum, Richard E Gilbert

**Chronic heart failure is an increasingly common cause of premature death and poor quality of life. Community-based epidemiological studies have provided much-needed information on the demography of chronic heart failure, providing insight into its influence on public health. In most patients, chronic heart failure is accompanied by a range of concomitant disorders that both contribute to the cause of the disease and have a key role in its progression and response to treatment. Information on the most common comorbidities in chronic heart failure—*ischaemic heart disease, hypertension, and diabetes mellitus*—is presented for prespecified subgroups in the reports of many large-scale, multicentre trials; despite their limitations, these subanalyses provide guidance in therapeutic decision-making. Similarly, because chronic heart failure is commonly an endpoint in intervention trials of both hypertension and diabetes, such studies afford important information on the prevention of chronic heart failure in these common diseases.**

Chronic heart failure is a common disorder of increasing frequency, associated with high mortality and poor quality of life, including the need for frequent admissions.<sup>1</sup> Knowledge of its demography and comorbidities may provide insight not only into the pathophysiology of chronic heart failure, but also into its effect on public health and the potential for both therapeutic intervention and disease prevention.

### Demography

The demographic characteristics of patients with chronic heart failure have mostly been obtained from community-based epidemiological studies and large, multicentre intervention trials.<sup>2</sup> However, compared with participants of intervention trials, populations in community-based studies are generally older, less predominantly male, more likely to have comorbidities, and presentation with diastolic failure is common<sup>3</sup> (tables 1 and 2).<sup>4–55</sup>

### Ethnic origin

Hypertension is a major aetiological factor for subsequent chronic heart failure in African-American patients. These patients are generally thought to respond less well than white patients to inhibitors of angiotensin-converting enzyme (ACE) for treatment of hypertension,<sup>56</sup> perhaps owing to their overall low renin status. Such observations have, however, been challenged by the findings of the recent AASK trial<sup>57</sup> (see panel for explanation of trial acronyms). In the setting of established chronic heart failure, the responsiveness to ACE inhibitors (and  $\beta$  blockers) has also been assessed

in major trials. The beneficial effects of enalapril in mild to moderate chronic heart failure observed overall in the SOLVD study were not seen among black patients.<sup>58</sup> Similarly, the Ve-HeFT II trial showed an overall survival benefit from enalapril compared with the vasodilator combination of hydralazine and isosorbide dinitrate,<sup>59</sup> but this benefit was not apparent among African-American patients.<sup>60</sup> The response to  $\beta$ -blocker therapy is also diminished in African-Americans.<sup>56</sup> Indeed, the absence of a reduction in overall mortality with bucindolol in BEST<sup>4</sup> has partly been attributed to an apparent lack of benefit of this agent among African-American patients. By contrast, however, the US Carvedilol<sup>19</sup> trial of mild to moderate heart failure and the COPERNICUS<sup>7</sup> study of carvedilol in patients with severe heart failure found a similar risk reduction among African-American patients and the overall cohort.

### Sex

Women have a greater risk of symptoms associated with heart failure than men after myocardial infarction. Nevertheless, survival is better in women than men among patients with established heart failure. There may also be sex-based differences in comorbidities in patients with chronic heart failure: women tend to be older, to have associated diabetes mellitus and hypertension, and to have more preserved ventricular function.

Sex-based differences in mortality have generally not been observed for conventional treatments such as ACE inhibitors and  $\beta$  blockers. By contrast, the DIG trial<sup>61</sup> suggested that women had a higher risk of death than men. This difference may relate to a pharmacokinetic interaction of digoxin with hormone-replacement therapy that increases plasma concentrations of digoxin.

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**NHMRC Centre of Clinical Research Excellence in Therapeutics Departments of Epidemiology and Preventive Medicine and Medicine, Monash University, Alfred Hospital, Melbourne, Australia** (Prof H Krum FRACP); **and University of Melbourne Department of Medicine, St Vincent's Hospital, Melbourne** (R E Gilbert FRACP)

**Correspondence to:** Prof Henry Krum, Clinical Pharmacology Unit, Monash University Medical School, Alfred Hospital, Commercial Road, Prahran Victoria 3181, Australia (e-mail: henry.krum@med.monash.edu.au)

### Search strategy and selection criteria

The search strategy for this review was based on published epidemiological studies and trials in heart failure involving more than 1000 patients during the past 10 years, from which baseline data on demography and comorbidity could be derived. These sources were supplemented by relevant further papers that provided epidemiological, mechanistic, or therapeutic information within comorbid disorders judged of greatest importance to patients with heart failure.

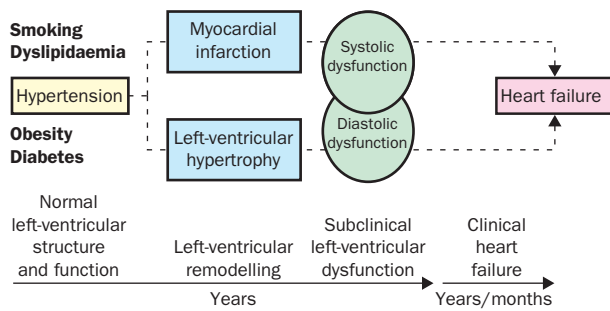


Figure 1: **Simplified schematic of the relation between hypertension and progression to overt heart failure via increased incidence of myocardial infarction as well as left ventricular hypertrophy**

Adapted from Levy et al.<sup>66</sup>

### Age

Although age does not seem to influence the beneficial effects of ACE inhibitors or  $\beta$  blockers in chronic systolic heart failure, tolerability of treatment can decrease with advancing age. However, most major intervention trials have generally excluded the extreme elderly, either through the entry criteria or the choice of patients

recruited. However, current trials such as SENIORS<sup>62</sup> (nebivolol) and PEP-CHF<sup>63</sup> (perindopril) are currently addressing therapeutic interventions in elderly patients with heart failure.

### Concomitant disorders

Many patients with chronic heart failure have a range of comorbidities that both contribute to the cause of the disease and have a key role in its progression and response to therapy.

### Hypertension

Hypertension is not only an important coexisting disorder but also contributes pathogenetically to the development of systolic and diastolic heart failure (figure 1). As well as being a major risk factor for ischaemic heart disease, hypertension can also lead directly to the development of chronic heart failure by afterload-induced cardiac hypertrophy<sup>64</sup> and impairment of diastolic function.<sup>65</sup> Early investigations of the characteristics of patients with chronic heart failure, such as the Framingham study,<sup>66</sup> cited hypertension as the most frequent comorbidity. However, in recent intervention trials, hypertension is cited less frequently as a comorbidity and underlying aetiology of chronic heart

Trial ref	Treatment groups	n	% male	Mean (SD) age, years	Proportion (%) with			
					Hypertension	IHD	Diabetes	AF
4	Bucindolol	1354	79	60	59	59 (IHF)	37	11
	Placebo	1354	77	60	59	58 (IHF)	34	12
5	Candesartan/placebo in patients given ACE-I*	2546	79	64	48	55 (MI)	30	26
	Candesartan/placebo in ACE-I-intolerant patients*	2028	68	67	49	61 (MI)	27	25
6	Bisoprolol	1327	81	61	..	50	..	..
	Placebo	1320	80	61	..	50	..	..
7	Carvedilol	1156	79	63.2 (11.4)	..	67 (IHF)	..	..
	Placebo	1133	80	63.4 (11.5)	..	67 (IHF)	..	..
8	Dofetilide	762	72	70	15	67	20	25
	Placebo	756	75	70	15	67	19	27
9	Digoxin	3397	78	63.4 (11.0)	45	71 (IHF), 65 (MI), 27 (angina)	28	..
	Placebo	3403	78	63.5 (10.8)	46	70 (IHF), 65 (MI), 26 (angina)	29	..
10	Losartan	1578	70	71.4 (6.7)†	48	79	24	31
	Captopril	1574	69	71.5 (6.9)†	50	79	24	29
11	Mibefradil	1295	79	62.6 (11.0)	30	68 (IHF), 63 (MI), 62 (angina)	31	13
	Placebo	1295	80	63.0 (10.9)	28	68 (IHF), 63 (MI), 60 (angina)	30	14
12	Metoprolol CR/XL	1990	77	Subdivided by age	44	65 (IHF), 48 (MI)	25	16
	Placebo	2001	78	Subdivided by age	44	66 (IHF), 49 (MI)	24	17
13	Enalapril 2.5 mg twice daily	506	63	70	10‡	70 (IHF)	11	25
	Enalapril 5 mg twice daily	510	62	70	11‡	70 (IHF)	10	25
	Enalapril 10 mg twice daily	516	66	70	8‡	74 (IHF)	12	23
14	Amlodipine	571	74	64.7 (0.5)	55	63 (IHD), 53 (angina)	..	..
	Placebo	582	78	64.7 (0.5)	57	64 (IHD), 54 (angina)	..	..
15	Ibopamine	953	82	64.6 (9.6)	3.7‡	59 (IHF)	21	24
	Placebo	953	79	64.8 (9.5)	4.6‡	59 (IHF)	21	23
16	Spironolactone	822	73	65 (12)	..	55 (IHF)	..	..
	Placebo	841	73	65 (12)	..	54 (IHF)	..	..
17	Enalapril	2111	89	59	37	84	15	4
	Placebo	2117	89	59	37	83	15	4
18	Enalapril	1285	81	61	43	70	25	12
	Placebo	1284	80	61	42	72	27	8
19	Carvedilol	696	77	57.9 (12.2)	..	48 (CAD)	..	..
	Placebo	398	76	58.1 (12.3)	..	48 (CAD)	..	..
20	Valsartan	2511	80	62.4 (11.1)	6.1‡	58 (IHF)	26	12
	Placebo	2499	80	63.0 (11.0)	7.3‡	57 (IHF)	25	12
5§	Candesartan/placebo	3025	60	67	64	44 (MI)	28	29

IHD=ischaemic heart disease; AF=atrial fibrillation; IHF=ischaemic heart failure; MI=myocardial infarction; ACE-I=angiotensin-converting enzyme inhibitors;

CAD=coronary-artery disease. \*Left-ventricular ejection fraction <40% in all. †Patients had to be 65 years or older on entry. ‡Hypertension-induced heart failure. §Trial of diastolic heart failure; in patients with preserved left-ventricular function (left-ventricular ejection fraction >40%).

Table 1: **Baseline demographic and comorbidity data from published trials on heart failure during the past 10 years involving a total of more than 1000 patients**

failure (table 1). About 15% of participants in SOLVD<sup>67</sup> had diastolic blood pressure above 90 mm Hg on entry, but other studies have not reported on this issue. Recent trials have probably underestimated the contribution of hypertension to development and progression of chronic heart failure. Blood pressure falls as systolic chronic heart failure develops such that the contribution of hypertension to the failure syndrome may be underappreciated. Hypertension is also a major risk factor for ischaemic heart disease, but with the ischaemic contribution to heart failure listed as the primary cause, the underlying hypertension may be relegated to a secondary role and not acknowledged as a comorbidity.

The effect of antihypertensive therapies in limiting the development of chronic heart failure in patients with essential hypertension supports a major contribution of this comorbidity to onset and progression of chronic heart failure.<sup>68-71</sup>

### Intervention studies

Placebo-controlled studies have examined the effect of antihypertensive therapy in the prevention of chronic heart failure among patients with raised diastolic blood

pressure<sup>69,70</sup> and those with isolated systolic hypertension.<sup>68,71</sup> These studies have consistently shown impressive reductions in the subsequent development of chronic heart failure among such patients.

Although the cause of diastolic heart failure is incompletely understood, hypertension is probably a major contributor. Therefore, an important aim of therapy in hypertensive patients with diastolic heart failure should be the reduction of blood pressure. Other important aims include avoidance of fluid overload (with care, however, to avoid iatrogenic underperfusion), recognition and treatment of ischaemia and arrhythmia, and correction of underlying contributory valvular disease. Several studies, mainly in patients with chronic heart failure and predominant diastolic dysfunction are in progress—the I-PRESERVE study with irbesartan, the CHARM<sup>72</sup> study with candesartan cilexetil, SENIORS<sup>62</sup> with nebivolol, and the PEP-CHF<sup>63</sup> study with perindopril. These studies are expected to enrol patients with hypertension as a major comorbidity; for example, in the CHARM study 64% of the study population had pre-existing or concomitant hypertension at baseline.

### Ischaemic heart disease

Coronary-artery disease features prominently as a cause of chronic heart failure<sup>73</sup> (table 1). As with hypertension, the contribution of ischaemia to chronic heart failure is also probably under-reported.<sup>74</sup> Many patients enrolled in trials of chronic heart failure have ischaemia but do not have a high degree of documentation of it. Furthermore, many trials exclude patients with active ischaemia from entry.

Coronary-artery disease can lead to heart failure through various mechanisms. Extensive myocardial necrosis will result in pump failure. Infarction of smaller areas can lead to regional contractile dysfunction and adverse remodelling with myocyte hypertrophy, apoptosis, and deposition of extracellular matrix. In addition, transient reversible ischaemia can occur with episodic dysfunction even in the presence of normal resting ventricular dysfunction.<sup>75</sup>

Thus, patients with myocardial ischaemia may have hibernating<sup>76,77</sup> (but potentially viable) myocardium. Ventricular function may therefore be potentially improved by myocardial revascularisation<sup>78,79</sup> in this setting. In the CHRISTMAS Study<sup>80</sup> over 50% of patients with ischaemia and chronic heart failure had evidence of hibernation affecting two or more segments on echocardiography. However, this notion has not yet been rigorously tested. Revascularisation in such patients may result in not only improved ventricular function but also long-term symptomatic and prognostic benefits.<sup>81,82</sup>

Many of the pathogenetic factors that contribute to endothelial dysfunction and atherosclerosis<sup>83</sup> (and thus ischaemia) are also involved in the progression of chronic heart failure. These factors include activation of the renin-angiotensin-aldosterone, sympathetic, and endothelin systems.<sup>84</sup> Therefore, part of the beneficial effect of neurohormonal antagonists in chronic heart failure may result from improvements in underlying ischaemia. For example, ACE inhibitors improve coronary endothelial function<sup>85</sup> and reduce development of chronic heart failure in patients at high risk of cardiovascular disease.<sup>86</sup> Similarly, the SOLVD<sup>18</sup> and SAVE<sup>87</sup> studies (in patients with systolic ventricular dysfunction) showed reductions in both ischaemic events and hospital admissions for heart failure. In CAPRICORN,<sup>88</sup> patients with ventricular systolic dysfunction after myocardial infarction derived benefit from the  $\beta$  blocker, carvedilol, in terms of both

### Acronyms of trials used in this review

AASK=African American Study of Kidney Disease and Hypertension  
 BEST=Bucindolol Evaluation of Survival Trial  
 CAPRICORN=Carvedilol Post-Infarct Survival Control in LV Dysfunction  
 CARE=Cholesterol and Recurrent Events  
 CHARM=Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity  
 CHF-STAT=Survival Trial of Antiarrhythmic Therapy  
 CHRISTMAS=Carvedilol Hibernation Reversible Ischemia Trial Marker of Success  
 CIBIS=Cardiac Insufficiency Bisoprolol Study  
 COPERNICUS=Carvedilol Prospective Randomized Cumulative Survival Study  
 DIG=Digitalis Intervention Group  
 ELITE=Evaluation of Losartan in the Elderly Study  
 HOPE=Heart Outcomes Prevention Evaluation Study  
 IDNT=Irbesartan Diabetic Nephropathy  
 I-PRESERVE=Irbesartan in Heart Failure with Preserved Systolic Function  
 MADIT=Multicenter Automatic Defibrillator Implantation Trial  
 MERIT-HF=Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure  
 MICRO-HOPE=Microvascular Outcomes—HOPE  
 PEP-CHF=Perindopril for Elderly People with Chronic Heart Failure  
 PRAISE=Prospective Randomized Amlodipine Survival Evaluation  
 RALES=Randomized Aldactone Evaluation Study  
 RENAAL=Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan  
 SAVE=Survival and Ventricular Enlargement  
 SCOPE=Study on Cognition and Prognosis in the Elderly  
 SENIORS=Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure  
 SOLVD=Studies of Left Ventricular Dysfunction  
 SYST-EUR=Systolic hypertension in Europe  
 TRACE=Trandolapril Cardiac Evaluation Study  
 TREND=Trial of Reversing Endothelial Dysfunction  
 UKPDS=UK Prospective Diabetes Study  
 Val-HeFT II=Valsartan Heart Failure Trial  
 4S=Scandinavian Simvastatin Survival Study

Study ref	Design	Patients (% with or developing CHF)	Male
<b>Community samples</b>			
2	Self-report, prescribed drug	8783 (100%)	..
21	Observational, retrospective design using national population and mortality data		..
22	Prospective	208 discharges, 13 deaths (14% of cohort)	NR (34%)
23	Prospective	173 (10% of cohort)	49.1%
24	Surveillance	51 incident cases (of 45–74-year-olds) during follow-up (0.46% of age group)	38 (75%)
25	Prospective	551 (9%)	..
26–28	Prospective	652 (7%)	331 (51%)
29	Retrospective examination of national mortality data on patients with CHF	..	..
30	Retrospective review	1980: 13 202 (100%); 1990: 20 929 (100%)	1980: 6306 (48%) 1990: 9937 (48%)
31	Self-report and use of digoxin or vasodilator and diuretic or diagnosis of CHF by hospital or physician	..	Prevalence according to sex and age, and classification as definite or possible CHF
32	Hospital discharge data codes of hypertensive heart disease and myocardial degeneration	1980: 14 441 (100%) 1999: 24 868 (100%)	..
33	Retrospective review	1980: 27 415 deaths 1995: 46 484 deaths	Mortality according to age, sex, and ethnic origin
34	Retrospective analysis of all death certificates in which HF was coded	137 891 (16%)	61 320 (44.5%)
35	Prospective	1382 (10%)	741 (54%)
Nijmegen Study*	Surveillance	701 prevalent cases, 197 incident cases	..
37	Retrospective	1981: 46 incident cases 1982: 113 prevalent cases	27 (59%) incident 57 (50%) prevalent
38	Observational	..	40.6 (whole cohort)
39	Observational	181 (3%)	72 (40%)
40	Retrospective	216 (100%)	125 (58%)
41	Retrospective	1981: 107 (100%); 1991: 141 (100%)	1981: 57 1991: 59
Transition Project*	Surveillance	459 prevalent cases, 245 incident cases (2%)	125 (47%)
<b>Hospital-based studies</b>			
42	Referral of all CHF cases; clinical history and physical examination	1164 (100%)	713 (61%)
43	Observational, retrospective on admission and medical admission records	27 477 (3%)	NR (49%)
44	Retrospective audit of medical admission records	4606 (100%)	2381 (52%)
45	Retrospective review of all admissions for HF in USA for patients aged ≥65 years	1986: 631 306 (100%); 1993: 803 506 (100%)	1986—black: 40 white: 42 1993—black: 40 white: 42
46	Review of randomly selected medical records of Medicare-eligible CHF patients, aged >65 years, admitted to Louisiana acute care hospitals	1133 (100%)	NR (36%)
1	Retrospective review of all admissions for HF in USA for patients aged ≥35 years	..	..
47	Prospective with 1-year follow-up	579 (0.75%), with follow-up of 409 (0.53%)	196 (48%)
48	Observational, retrospective on admission data	66 547 (100%)	31 040 (47%)
49	Observational	29 686 (100%)	47%
50	Observational	823 917 admissions, 441 378 deaths	50% admissions, 40% deaths
51	Observational survey of patients with proven or suspected HF	3921 (100%)	60%
<b>General-practice studies</b>			
52	Assessment of patients aged ≥60 years; cause and diagnostic assessments documented for patients with CHF	2905 (13%)	NR (45%)
53	Observational based on PACT	281 (56%)	..
54	Retrospective	266 (2%)	40%
55	Observational	117 (0.39%)	46 (39%)
36	Observational	4166 prevalent cases, 1076 incident cases	

CHF=chronic heart failure; NR=not reported; HF=heart failure; IHD=ischemic heart disease; AF=atrial fibrillation; MI=myocardial infarction; CAD=coronary-artery disease; HIIHF=hypertension-induced heart failure; PACT=Prescribing Analysis and Cost. \*Cited in Cowie et al, 1997.<sup>38</sup> †See community-sample section.

Table 2: **Epidemiological studies published during the past 10 years involving more than 1000 patients, in which demographic and comorbidity data on chronic heart failure are presented**

Age distribution (years)	Proportion (%) with: Hypertension	IHD	Diabetes	AF
20-64: 6529 (74%); >65: 2254 (26%)	..	..	..	..
30-85 years	..	..	..	..
Mean 77.9 (SD 5.0)	55%	10% (CHD)	19%	3%
65-74: 50%; 75-84: 38%; ≥85: 12%	..	28% (MI)	21%	..
NR	..	..	..	..
>25: 100%	..	..	..	..
Mean 70.0 (SD 10.8)	74%	..	19%	..
..	..	..	..	..
..	..	..	..	..
..	..	..	..	..
1980: Mean men, 71.2; Mean women, 75.0 years	..	..	..	..
1999: Mean men, 72.9; Mean women 77.7 years	..	..	..	..
..	..	..	..	..
Men <65: 11 372 (8%); Men ≥65: 49 948 (36%)	..	..	..	..
Women <65: 6362 (5%); Women ≥65: 70 209 (51%)	..	..	..	..
Mean in men: 52.2 (SD 15.2)	Men 30%; Women 27%	Men: 7% Women: 3% (CHD)	Men: 4%; Women: 4%	..
..	..	..	..	..
Prevalence 0-44: 3, 45-54: 6, 55-64: 31, 65-74: 73	..	..	..	..
Mean (overall): 68.9 (SD 8.7)	30%	11% (MI); 7% (angina)	10%	..
Mean 77.3 (SD 8.0)	34%	49% (MI); 37% (angina)	18%	21%
Mean 77.3 (SD 12.1); Age >65: 88%; Age >80: 49%	52%	40% (CAD); 24% (CAD)	..	24%
1981: mean 75.0 (SD 14.7);	1981: 48%;	1981: 58% (CAD)	1981: 14%	..
1991: mean 77.4 (SD 11.7)	1991: 54%	1991: 52% (CAD)	1991: 12%	..
..	..	..	..	..
13-24: 2%; 13-2: 2%; 35-44: 10%	24.9	52% (IHF)	..	12.6
45-54: 17% 55-64: 37%; ≥65: 30.3%	..	..	..	..
Mean: Men, 71.5 years (SD 10.8); Women, 76.6 years (10.5)	5%	13% (MI) 7% (angina/chest pain)	10%	15.41
Mean <70, 1453 (32%); SD ≥70, 3153 (69%)	..	51% (IHF)	..	..
Provided only for discharges to another care facility	1986: 47%;	1986: 66%;	1987: 37%;	..
Mean 77.6 (SD 7.9)	1993: 60%	1993: 60%	1994: 45%	..
..	56%	61% (MI/IHD)	35%	18%
Men: 35-64, 22%, 65-74, 30%, 75-84 32%, ≥85, 16.0%;	..	..	..	..
Women: 35-64 years 15%, 65-74 22%, 75-84, 36%; ≥85, 27.5%	..	..	..	..
Mean 77 years (range 60-95)	32%	66% (IHF)	18%	18%
Median men 72 years, women 78 years	1.1%	15% (AMI)	3%	3%
Mean white women, 73.7 (SD 13.3), men 69.2 (13.6);	..	..	..	..
Black women 68.1 (15.1) men 65.6 years (15.0);	..	..	..	..
Other races women 73.7 (13.3) women 70.7 (14.0)	..	..	..	..
45-64: 60.2% men; ≥65: 49.7% men; 65: 43.5% men	..	..	..	..
<65: 39.6%; 65-75: 35.7%; ≥75: 24.7%	15%	33% (IHF)	..	28% (tachy- arrhythmia)
60-69: 39%;	69% (in newly diagnosed HF), 64% (in pre-existing HF)	Angina, 44.2 (in newly diagnosed HF), 53.4 (in pre-existing HF); MI, 28.1 (in newly diagnosed HF), 39.3% (in pre-existing HF)	..	..
70-79: 43%;	..	..	..	..
≥80 years: 19%	..	..	..	..
30-39, 1.9%; 40-49, 3.3%; 50-59, 7.8%; 60-69, 21.1%;	..	..	..	..
70-79, 39.6%; 80-89, 22.2%; ≥90, 4.1%	..	..	..	..
35-44, 0.4%; 45-54, 4.1%; 55-64, 12.4%; 65-74, 31.6%;	..	..	..	..
>75, 51.5%; <65, 16 (13.7%); ≥65 101 (86.3%)	18%	45% (IHF)	..	..
..	6%	32% (IHF)	..	..
..	..	..	..	..

subsequent ischaemic endpoints and events related to chronic heart failure.

Several analyses have examined differences in responses to pharmacological therapies between ischaemic and non-ischaemic causes of heart failure. In some studies, such as CHF-STAT (amiodarone),<sup>89</sup> PRAISE I (amlodipine),<sup>14</sup> and an early  $\beta$ -blocker study,<sup>90</sup> the magnitude of the benefit was greater among patients with a non-ischaemic cause. By contrast, however, other trials have not reported substantial differences in clinical response between these causes (CIBIS-II,<sup>6</sup> COPERNICUS,<sup>7</sup> RALES,<sup>16</sup> ELITE II,<sup>10</sup> and Val-HeFT<sup>20</sup>).

### Diabetes mellitus

Diabetes is a common but overlooked comorbidity in chronic heart failure. Patients with diabetes not only are at higher risk of developing chronic heart failure but also have worse symptoms for their degree of systolic function and higher mortality than non-diabetic individuals.<sup>91–93</sup>

The Framingham study<sup>27</sup> first reported an over-representation of diabetic patients in chronic heart failure; 14% of men and 26% of women with chronic heart failure were noted to have concomitant diabetes. In a further report<sup>94</sup> from that study, in which 5209 middle-aged people in the community were followed up prospectively for 10 years, diabetes was associated with a two-fold increase in risk of chronic heart failure in men and a five-fold increase in risk in women. Moreover, the increased risk persisted after adjustment for other potential contributors such as known coronary-artery disease, age, blood pressure, and cholesterol.

Community-based studies<sup>35,95,96</sup> in elderly people have also found that diabetes is an independent risk factor for the development of chronic heart failure with relative risks of 1.7–2.9. In the UKPDS,<sup>97,98</sup> the development of chronic heart failure was examined over 10 years in almost 4000 community-based, middle-aged people with type 2 diabetes. In these patients, the absolute risk of admission for chronic heart failure was 3.0–8.1 per 1000 patient-years, depending on the assigned treatment group. This risk can be compared with those of non-fatal myocardial infarction, non-fatal stroke, and renal failure (7.5–9.5, 4.0–8.9, and 0.6–2.3 per 1000 patient-years, respectively) in the same study.

Three major factors contribute to the high prevalence of chronic heart failure in diabetes—hypertension, coronary-artery disease, and diabetic cardiomyopathy. Patients with diabetes characteristically develop premature atherosclerotic coronary-artery disease, which is commonly widespread and asymptomatic and presents late.<sup>99</sup> Indeed, patients with diabetes are two to three times more likely than non-diabetic people to develop chronic heart failure after myocardial infarction, and diabetic women are at particularly high risk.<sup>100</sup> Hypertension, another risk factor for the development of chronic heart failure, is present in 71–93% of patients with type 2 diabetes.<sup>100</sup> Both experimental and clinical studies have provided evidence for the existence of diabetic cardiomyopathy, independent of large-vessel disease.<sup>93,101,102</sup> The clinical manifestations of this cardiomyopathy are poorly understood, with asymptomatic diastolic dysfunction a common finding on echocardiographic investigation in diabetic patients.<sup>101</sup> The roles of autonomic dysfunction, endothelial dysfunction, and abnormal energy metabolism in the development of chronic heart failure in diabetic patients are less well understood.<sup>103</sup>

The presence of chronic heart failure as a comorbid disorder should be taken into account in the choice of drugs for treatment of diabetes. In particular, metformin

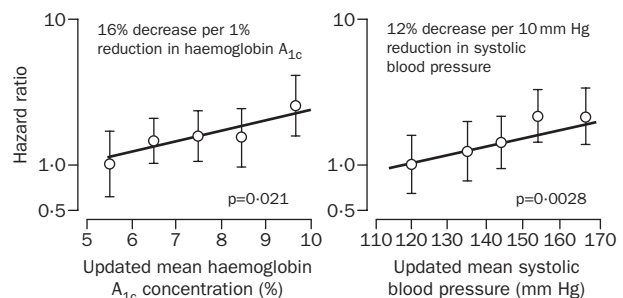
is contraindicated in chronic heart failure. Similarly, the thiazolidenediones should be avoided in heart failure of New York Heart Association class III or IV and used with caution in less severe chronic heart failure.

### Intervention studies

In the UKPDS,<sup>98</sup> intensive blood-glucose control did not significantly reduce the probability of macrovascular disease. However, that study also examined the risk of complications at different blood glucose concentrations. In this prospective, observational component of UKPDS, a continuous relation between glycaemic exposure and the development of chronic heart failure was noted, with no threshold of risk, such that for each 1% (absolute) reduction in haemoglobin A<sub>1c</sub> there was an associated 16% decrease in admissions for heart failure (figure 2).<sup>104</sup> Similar findings have been reported from a large cohort study in the USA.<sup>105</sup>

The UKPDS also examined the effect of blood-pressure control on the development of chronic heart failure in diabetic patients. Tight control was associated with a 56% reduction in the risk of chronic heart failure.<sup>98</sup> As with glycaemia, the frequency of chronic heart failure was significantly associated with systolic blood pressure, such that a decrease of 10 mm Hg in systolic blood pressure was accompanied by a 12% decrease in chronic heart failure, also with no apparent threshold of risk (figure 2).<sup>106</sup> Several other intervention trials with angiotensin-receptor blockers have also shown a reduction in the development of chronic heart failure in high-risk patients, apparently independent of blood pressure. Such studies, which included patients with diabetes, hypertension, and left-ventricular hypertrophy (LIFE)<sup>107</sup> and with diabetic nephropathy (IDNT and RENAAL),<sup>108,109</sup> highlight the importance of blocking the renin-angiotensin system in the prevention as well as in the treatment of heart failure in diabetes.

Diabetes is a noted comorbidity in between 10% and 30% of participants in clinical trials in chronic heart failure.<sup>110</sup> Despite limitations, analysis of the diabetic subgroup within these trials has provided both some



**Figure 2: Hazard ratios (95% CI as floating absolute risks) for chronic heart failure in UKPDS, as estimate of association between category of updated mean haemoglobin A<sub>1c</sub> concentration (left) or systolic blood pressure (right) and heart failure**

Log linear scales. Reference category (hazard ratio 1.0) for relation between glycaemic control and chronic heart failure is haemoglobin A<sub>1c</sub> <6% with log linear scales. p value reflects contribution of glycaemia to multivariate model. Data are adjusted for age at diagnosis of diabetes, sex, ethnic group, smoking, presence of albuminuria, systolic blood pressure, HDL and LDL cholesterol, and triglycerides. Reference category (hazard ratio 1.0) for relation between blood pressure and chronic heart failure is systolic blood pressure <130 mm Hg. p value reflects contribution of systolic blood pressure to multivariate model. Data adjusted for age at diagnosis of diabetes, ethnic group, smoking status, presence of albuminuria, haemoglobin A<sub>1c</sub>, HDL and LDL cholesterol, and triglycerides. Adapted with permission from UKPDS.<sup>97,98</sup>

insight into the relation between chronic heart failure and diabetes and information on a range of pharmacological interventions including ACE inhibitors, angiotensin-receptor blockers, and  $\beta$  blockers. For instance, in SOLVD,<sup>111</sup> diabetes was associated with increased mortality, but only in patients with ischaemic cardiomyopathy (relative risk 1.37 [95% CI 1.21–1.55],  $p < 0.0001$ ) and not in those with a non-ischaemic cardiac dysfunction (relative risk 0.98). Fortunately, patients with diabetes and ischaemic cardiomyopathy do respond to therapeutic intervention, particularly after acute myocardial infarction.<sup>112</sup>

Diabetes, particularly in the presence of chronic heart failure, has traditionally been viewed as a contraindication to the use of  $\beta$ -blocking agents. Nevertheless,  $\beta$  blockers consistently improve prognosis and reduce rates of admission for systolic chronic heart failure when added to background therapy with ACE inhibitors and diuretics. Furthermore, the major trials of  $\beta$  blockers in chronic heart failure have shown similar benefit in the diabetic subgroup to the overall benefit, such that this class of drug should be strongly considered for treatment of diabetic patients with chronic heart failure.<sup>7,113</sup>

In Val-HeFT, the addition of the angiotensin-receptor blocker valsartan significantly reduced morbidity and mortality in patients with chronic heart failure of New York Heart Association class II–IV, reporting a consistent beneficial effect among predefined subgroups of patients, including those with diabetes.<sup>20</sup>

Although patients with diabetes were not excluded from RALES, no subgroup analysis is mentioned in the report.<sup>16</sup> However, patients with diabetes, in whom hyporeninaemic hypoaldosteronism is common, may be at particularly high risk of developing hyperkalaemia when an aldosterone antagonist is added to baseline ACE-inhibitor therapy, and vigilant monitoring of serum potassium concentration is recommended.

### Cardiac arrhythmias

Many factors contribute to the frequent development of arrhythmias in chronic heart failure, including ischaemia and infarction, electrophysiological abnormalities, myocardial hypertrophy, and the activation of various neurohormonal systems.<sup>114</sup> Furthermore, alterations in electrolyte status as well as the proarrhythmic effect of many antiarrhythmic drugs used in heart failure may also contribute.

### Ventricular arrhythmias

Ventricular arrhythmias in patients with chronic heart failure range from benign (asymptomatic premature ventricular contractions) to fatal (ventricular fibrillation),<sup>115</sup> with “sudden” death estimated to account for about half of all deaths in chronic heart failure. In patients with advanced chronic heart failure, 11% had previously had a cardiac arrest plus ventricular tachycardia and a further 3.4% had a history of ventricular fibrillation.<sup>116</sup>

The management of ventricular arrhythmias in patients with established chronic heart failure is controversial.<sup>117</sup> Amiodarone is the preferred antiarrhythmic drug for severe, symptomatic, and sustained ventricular tachycardia,<sup>114</sup> but large-scale trials do not support its prophylactic use in non-sustained asymptomatic arrhythmias.<sup>89</sup> The antiarrhythmic properties of  $\beta$  blockers, together with the lower risk of sudden death with these agents,<sup>6,7,19</sup> suggest benefit in reducing lethal arrhythmias.

Implantable cardioverter defibrillators have proved beneficial in patients with a high risk of sudden death

(eg, those with impaired ventricular function, life-threatening ventricular arrhythmias,<sup>118,119</sup> or those resuscitated from near sudden death<sup>120</sup>). Because some of the studies contributing to the database on implantable cardioverter defibrillators used electrophysiological entry criteria (eg, MADIT<sup>118</sup>), this approach may also be indicated in selection of patients with chronic heart failure for implantation of a device. The MADIT II trial has lately been terminated because of benefit of implantable cardioverter defibrillators (compared with standard medical therapy) in patients more than 1 month after myocardial infarction, with left-ventricular ejection fractions of 30% or less, and ten or more ventricular extrasystoles per hour on Holter monitoring.<sup>121</sup> Because many patients with ischaemic chronic heart failure would fit into this category, there are major potential cost implications, despite the small absolute risk reduction observed.

### Atrial fibrillation

Atrial fibrillation is a common comorbidity with chronic heart failure, present in up to a third of all patients enrolled in major intervention trials (table 1). Although atrial fibrillation is in many cases a consequence of the aetiological factors contributing to chronic heart failure, it can (in very rare cases) lead to development of heart failure, particularly if the ventricular response is not adequately controlled.  $\beta$  blockers are commonly used (in conjunction with digoxin) to control ventricular response. Nonetheless, there is some controversy about their effect on outcome in patients with atrial fibrillation in the setting of chronic heart failure. In particular, in a subgroup analysis of the CIBIS II trial of bisoprolol,<sup>122</sup> there was no apparent benefit of active therapy among patients with atrial fibrillation, contrasting with the findings for the whole study cohort. However, this heterogeneity in response was not observed in other trials of  $\beta$  blockers in chronic heart failure.<sup>123</sup>

Although there is no evidence that restoration of sinus rhythm is better than control of the ventricular response in patients with chronic heart failure and atrial fibrillation,<sup>114</sup> both electrical cardioversion and amiodarone, alone or together, are commonly used. The use of other antiarrhythmics is limited by their negative inotropic and proarrhythmic effects, although dofetilide improved atrial fibrillation reversion rates, without increasing mortality, in patients with chronic heart failure.<sup>8</sup>

Anticoagulation with warfarin should be standard therapy<sup>114</sup> for patients with heart failure and concomitant atrial fibrillation, unless contraindicated. Far more controversial is the use of thromboprophylaxis in patients with ventricular dysfunction and normal sinus rhythm.

### Other important comorbid disorders

#### Respiratory disorders

The interaction between chronic heart failure and concomitant respiratory disease is important. Many patients with heart failure are misdiagnosed as having airflow obstruction on the basis of overlapping symptoms (and vice versa). Optimum assessment and management of these patients needs careful consideration of the possibility that cardiac and respiratory disease may coexist in the individual patient.

$\beta$  blockers are deemed to be contraindicated in patients with chronic heart failure and airflow obstruction. In practice, because of the overwhelming benefits of these agents in systolic heart failure, many patients with fixed or limited airways reversibility are given them and tolerate them surprisingly well.<sup>124</sup> Whether  $\beta$ -1-selective agents

offer advantages over non-selective agents such as carvedilol is not clear.<sup>125</sup>

Sleep apnoea may be both a cause and consequence of chronic heart failure. Central sleep apnoea with Cheyne-Stokes respirations during sleep affects about 40% of patients with chronic heart failure.<sup>126</sup> Obstructive sleep apnoea also commonly coexists and may also contribute to disease progression.<sup>127</sup> Trials of continuous positive airways pressure in such patients have improved autonomic dysfunction in the short term<sup>128</sup> and increased left-ventricular ejection fraction.<sup>129</sup>

### Cognitive dysfunction

There is clear evidence that cognitive dysfunction coexists with heart failure.<sup>130,131</sup> Chronic heart failure is associated with low cardiac output, which may further compromise cerebral blood flow in a patient with borderline perfusion of the cerebrum. In addition, chronic heart failure is largely driven by vascular disease (at least in the more developed countries) and cerebrovascular disease is an important contributor to multi-infarct dementia.

Measures of cognitive function have rarely been used in heart-failure trials, unlike recent hypertension trials such as SYST-EUR<sup>72</sup> and SCOPE.<sup>132</sup> Given the consistent reporting of impaired cognitive function in cross-sectional studies of patients with heart failure, perhaps this should be considered as an endpoint for future trials of heart-failure pharmacotherapy.

### Hyperlipidaemia

Despite the classic perception of the patient with chronic heart failure as being cachectic with low plasma cholesterol concentrations, hyperlipidaemia coexists with chronic heart failure in a significant proportion of patients. In intervention trials on chronic heart failure, up to 26% of patients were classified as hyperlipidaemic on entry.<sup>133</sup> Of particular interest is whether inhibitors of hydroxymethylglutaryl-coenzyme-A reductase (statins) are beneficial in patients with established chronic heart failure. This issue has never been formally tested in prospective trials, because trials of lipid-lowering therapy have generally excluded patients with significant systolic left-ventricular dysfunction.<sup>134,135</sup> In addition, there is concern that these agents may lower concentrations of ubiquinone (coenzyme Q10),<sup>136</sup> which may be important in maintenance of myocardial function in chronic heart failure.<sup>137</sup> Furthermore, maintenance of circulating lipoproteins may be necessary to lower high circulating concentrations of proinflammatory cytokines,<sup>138</sup> which may adversely affect disease progression.<sup>139,140</sup>

Nevertheless, because statins beneficially affect progression of coronary-artery disease, there should be long-term benefits in patients with chronic heart failure of an ischaemic aetiology. Indeed, post-hoc, retrospective analyses of major lipid-lowering trials support statin therapy as being of benefit for chronic heart failure. In the 4S trial, simvastatin decreased the rate of development of chronic heart failure after myocardial infarction as well as mortality among patients who developed heart failure during the study.<sup>141</sup>

The effect of statin therapy in patients with established chronic heart failure has been retrospectively assessed in non-randomised, subset analyses within major intervention trials. In the ELITE II study, mortality was significantly lower in patients receiving statins than in those who were not (10.6% *vs* 17.6%).<sup>142</sup>

Statins have antiapoptotic effects<sup>143</sup> and stimulate endothelial progenitor cells<sup>144</sup> and vascular endothelial growth factor;<sup>145</sup> these effects and antagonism of

proinflammatory cytokines<sup>146</sup> may contribute to improvement in myocardial function directly and independently of effects on coronary-artery disease. This hypothesis has been supported by animal studies in which a statin improved measures of ventricular function and decreased pathological fibrosis in the absence of changes in plasma cholesterol.<sup>147</sup>

### Chronic anaemia

Anaemia is common in chronic heart failure, with a mean haemoglobin of 12 g/dL.<sup>148,149</sup> The probability of anaemia in patients with chronic heart failure is related to disease severity.<sup>150</sup> In small-scale studies, administration of subcutaneous erythropoietin and intravenous iron to patients with chronic heart failure and mild anaemia produced improvement in overall clinical status and ventricular function.<sup>150,151</sup> Nevertheless, the importance of identifying and correcting mild anaemia is generally under-recognised in this setting.

### Renal failure

The close relation between cardiovascular and renal function in normal physiology is also apparent in disease; renal dysfunction may develop secondary to cardiac disease or vice versa. As a consequence of accelerated atherosclerotic coronary-artery disease, concomitant hypertension, and fluid retention, patients with primary renal disease are at high risk of heart failure.<sup>152</sup> Conversely, many patients with heart failure have evidence of kidney dysfunction in the absence of intrinsic renal disease.<sup>153</sup> The observed low glomerular filtration rate in chronic heart failure is a consequence of diminished cardiac output, with decreased renal perfusion and intrarenal vasoconstriction accompanied by sodium and water retention.<sup>152</sup> Indeed, given the relation between renal function and cardiac output, renal dysfunction is not surprisingly an adverse prognostic marker<sup>154</sup> but also a stronger predictor of poor outcome in heart failure than functional class.<sup>153</sup>

Blockade of the renin-angiotensin system is central to both therapy of chronic heart failure and renoprotective treatment in patients with diabetic or non-diabetic kidney disease.<sup>109,155</sup> However, since the renal vasoconstriction that develops in the setting of reduced cardiac output depends on angiotensin II, treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker commonly leads to a (generally clinically unimportant) increase in the serum creatinine concentration.

### Arthritis

Many patients with chronic heart failure are old and therefore have other non-cardiovascular disorders of this age-group. Arthritis is one such disorder, and its treatment influences heart-failure status. Both non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 selective inhibitors, widely prescribed to patients with arthritis, are associated with potentially significant cardiovascular adverse effects in chronic heart failure.<sup>156,157</sup> Sodium and water retention with these agents may adversely affect volume status<sup>158</sup> partly because of activation of vasodilator prostanoids such as E<sub>2</sub><sup>159</sup> and I<sub>2</sub>.

The role of the prostaglandin inhibitor aspirin in attenuating the beneficial effects of renin-angiotensin blockade in chronic heart failure is highly controversial.<sup>160,161</sup> Concern has also been expressed that certain cyclo-oxygenase-2 inhibitors may be prothrombotic, clearly an unfavourable effect in chronic heart failure, particularly with an ischaemic aetiology.<sup>162</sup>

Blockade of tumour necrosis factor (TNF), now an established therapy for rheumatoid arthritis and other autoimmune disorders,<sup>163</sup> has been studied in patients with established chronic heart failure. Blockade of this cytokine in chronic heart failure is based on its multifaceted contribution to progression of this disease.<sup>164</sup> However, neither the TNF-receptor fusion protein etanercept<sup>165</sup> nor the monoclonal antibody infliximab resulted in beneficial outcomes in this setting.

## Conclusions

Chronic heart failure is a complex disease with progression and response to therapy influenced by various important demographic factors and comorbid disorders. These factors also have substantial influence on therapeutic decision-making for this disorder.

### Conflict of interest statement

H Krum and R Gilbert have received funding and served on advisory boards for various pharmaceutical companies that manufacture drugs used in the treatment of disorders summarised in this review. Neither investigator owns stock in any of these companies.

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