Incidence, Clinical and Etiologic Features, and Outcomes of Advanced Chronic Heart Failure: The EPICAL Study

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OBJECTIVES

Characterize the incidence, clinical and etiologic features and outcomes of advanced congestive heart failure.

BACKGROUND

This condition is frequent, severe and costly, yet no population-based epidemiological data are available that take into account modern advances in diagnosis and therapy.

METHODS

The EPICAL (Épidémiologie de l’Insuffisance Cardiaque Avancée en Lorraine) study was based on a comprehensive registration of patients with ACHF (defined as hospital admission for presence of NYHA class III or IV symptoms, radiological and/or clinical signs of pulmonary congestion and/or signs of peripheral edema, left ventricular ejection fraction <30% or a cardiothoracic ratio >60%) in patients aged 20–80 years during year 1994, in the community of the Lorraine region in France (n = 1,592,263). Average follow-up for readmission to hospital and mortality was 18 months (12–24 months).

RESULTS

From 2,576 registered patients, 499 were enrolled into the study among which, 358 were new presentations. This represents a crude incidence rate of 225 per million. 46.3% had a coronary heart disease. One-year mortality rate was 35.4% and the rate of mortality and/or readmission to hospital was 81%. Patients were admitted to hospital 2.05 times per year (64% of these for worsening heart failure), spending 27.6 days per year in hospital. Twenty received a heart transplant (4%). On discharge, 74.8% were using ACE inhibitors and 49.6% digitalis.

CONCLUSIONS

Mortality and hospitalization rate of advanced CHF remain very high despite recent therapeutic progress. Major therapeutic and managed-care research is required. (J Am Coll Cardiol 1999;33:734–42) © 1999 by the American College of Cardiology

With the increasing mean age of the population and the longer survival of patients with chronic heart disease (CHD), the growing prevalence of congestive heart failure (CHF) has been interpreted as an "ironic failure of success" (1). Indeed, as medical and surgical advances have lengthened survival rates in CHD patients, the number who live long enough to develop CHF has increased. Consequently, as a common sequel of many forms of cardiovascular disease, CHF is becoming a major health problem.

Once overtly manifest, CHF is an extremely lethal condition associated with a very poor quality of life and prognosis. Advanced CHF is associated with a shorter life expectancy than many common malignancies (2), and its present prognosis has remained unchanged since the Framingham survey (1948–1988) (3). Recent improvements in the medical and surgical management of patients with advanced CHF include the use of vasodilators, angiotensin-converting enzyme (ACE) inhibitors, viable myocardium revascularization, heart transplantation and cardiac assist device systems. These management strategies are, however, not used sufficiently or properly by the medical community (4,5).

Earlier epidemiological descriptions of CHF (6,7) were based on small surveys, limited data, hospital records or death certificates. No recent, nationally representative epidemiological survey has been published taking these recent improvements in the medical and surgical management of patients with CHF into account, and to date, only single-center, hospital-based studies of patients referred for (8), awaiting cardiac transplantation for (9) or presenting to the emergency room for decompensated CHF (10) are available for reference.
The EPICAL study (EPidémiologie de l’Insuffisance Cardiaque Avancée en Lorraine), a prospective observational, community-based, epidemiological evaluation of advanced CHF, was therefore undertaken to investigate the incidence, quality of life, prognosis and use of healthcare resources related to CHF in a local large French community. The aim of the study was to focus on patients hospitalized with advanced CHF, defined by the presence of signs and symptoms and poor systolic function.

METHODS

Study population. Lorraine is an urban and rural area situated in the Northeast of France. Following an intensive briefing concerning the rationale of the study, physicians (mainly cardiologists and also internists, pneumologists, emergency and intensive care and rehabilitation specialists) representing all primary care and referral centers into all the private and public hospitals providing healthcare to the Lorraine community agreed to participate in the study. There are 35 participating hospitals (list at Appendix 2) among which three were university hospitals including one transplant center, 26 were community hospitals and six were private hospitals.

Inclusion criteria and enrollment. On admittance to hospital, patients presenting with a history and/or symptoms compatible with the diagnosis of advanced CHF were screened and registered prospectively by the attending investigator-physician and subsequently investigated by trained research nurses using a structured questionnaire. Registration was also active and randomly and independently audited by trained research nurses. All cases were validated via a thorough review of the medical records by a steering committee composed of five senior cardiologists: one cardiac surgeon, one clinical pharmacologist, one physiologist and two epidemiologists.

Inclusion criteria for enrollment into the study included: established residence in the Lorraine region, age between 20 and 80 years (inclusive), admission to hospital during 1994, diagnosis of advanced CHF (defined as at least one hospital admission during a one-year period with NYHA class III or IV symptoms of CHF, radiological and clinical signs of pulmonary congestion, and/or signs of peripheral edema, left ventricular ejection fraction [LVEF] <30% [determined by the technique routinely available in the hospital concerned, mainly echocardiography] or a cardiothoracic ratio [CTR] >60%).

Data collection and follow-up. After enrollment, a case record form for every patient was collected by the research nurse using the medical records of each patient, as well as interviews with the attending physician, the patient and/or the patient’s relatives. Data on risk factors, comorbidities, history of cardiac disease and of CHF, as well as data regarding hospitalizations for CHF during the previous 18 months, were recorded. During the hospitalization immediately preceding enrollment, the results of clinical and laboratory tests (Table 1 and 2) with potential prognostic value were also collected. After obtaining informed consent, every surviving enrolled patient was visited at home by a trained research nurse one month after discharge and subsequently every four months. Data concerning survival status, heart transplantation, subsequent hospital readmissions, length of hospital stay and drug prescriptions were collected using structured questionnaires.

Etiology of CHF. Ischemic heart disease was defined by the presence of at least one of the following: history of acute myocardial infarction (MI); with at least two of the following signs: typical chest pain lasting more than 20 min, Q-wave MI on EKG, significant cardiac enzyme elevation), typical angina with ischemic signs on resting EKG and/or exercise EKG and/or thallium scan, significant coronary artery narrowing on coronary angiogram, history of coronary angioplasty or coronary artery bypass graft (CABG). Valvular and congenital heart disease were defined by the presence or a history of hemodynamically significant valvular or congenital disease, respectively. Patients with dilated cardiomyopathy with no criteria for ischaemic, valvular or congenital heart disease were separated into two subgroups according to the presence or the absence of one or several of the following contributing factors: history of hypertension, present alcohol abuse and presence of other rare causes of specific cardiomyopathy (11).

Data analysis. Incidence rates were calculated from the observed number of new cases of CHF divided by the age and sex-specific person-years of observation. An estimation of the number of people in the Lorraine region aged between 20 and 80 years was derived from 1990 census data (95% confidence intervals [CI] were constructed around the point estimates of incidence by assuming a Poisson distribution). Subgroup comparisons were made with the Pearson Chi-square test for each variable, expressed as a percentage of all patients. Nonnormally distributed variables were analyzed using the nonparametric Mann-Whitney U test.

Survival and hospitalization function estimates as well as event rates at one year were derived using the method of Kaplan and Meier (12). The date of entry was the first day
of admission to hospital immediately preceding enrollment into the study; the endpoint date was 31 December 1995. The relative risk conferred by advanced CHF was calculated according to gender and age as the ratio between the rate of death within the EPICAL cohort and the rate of death from all causes within the general population of Lorraine during 1994. The analyses used to estimate survival were also used to estimate hospital readmission-free survival. After the examination of hospital records by an appropriate events committee, hospital readmissions were classified as being related to worsening CHF, other cardiac causes or noncardiac causes.

Computations were performed using BMDP software (13). A two-sided probability value of 0.05 or less was required for statistical significance. Numerical values are expressed as mean ± 95% CI.

RESULTS

Registration of prospective patients began in September 1993 and ended in mid-June 1995. After an initial phase required for stabilization of the weekly average rates of registrations and of enrollments, the registration rate reached a plateau between January 1994 and early 1995 and was further ascertained by “capture-recapture analysis.” On this basis, it was decided to enroll all eligible patients registered between 1 January 1994 and 31 December 1994. A total number of 2,576 registrations were made during this period, corresponding to 2,033 patients (543 registrations were duplicates). Of the 2,033 registered patients 1,534 were excluded (54 not from the Lorraine Region, 552 not

Table 1. Demographic and Clinical Characteristics and History of Cardiac Disease of the Patients

<table>
<thead>
<tr>
<th></th>
<th>All Cases (n = 499)</th>
<th>CHD (n = 231)</th>
<th>Non-CHD (n = 268)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio (M/F)</td>
<td>3.2</td>
<td>4.5</td>
<td>2.5</td>
<td>0.0058</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.6 [63.7–65.5]</td>
<td>66.1 [64.9–67.4]</td>
<td>63.3 [62.0–64.7]</td>
<td>0.0025</td>
</tr>
<tr>
<td>Cigarette use (%)</td>
<td>57.3</td>
<td>64.5</td>
<td>51.1</td>
<td>0.0026</td>
</tr>
<tr>
<td>History of diabetes (I+II) (%)</td>
<td>25.6</td>
<td>32.5</td>
<td>19.8</td>
<td>0.0012</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>43.7</td>
<td>44.6</td>
<td>42.9</td>
<td>0.7063</td>
</tr>
<tr>
<td>Alcohol abuse (%)</td>
<td>18.8</td>
<td>10.8</td>
<td>25.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>History of hyperlipidaemia (%)</td>
<td>27.0</td>
<td>36.8</td>
<td>18.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>First diagnosis of cardiac disease (%)</td>
<td>0.0541</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 months</td>
<td>19.1</td>
<td>14.3</td>
<td>23.4</td>
<td></td>
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<tr>
<td>3–12 months</td>
<td>6.6</td>
<td>8.3</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td>1–5 years</td>
<td>28.1</td>
<td>27.0</td>
<td>28.7</td>
<td></td>
</tr>
<tr>
<td>5–10 years</td>
<td>19.5</td>
<td>22.2</td>
<td>17.4</td>
<td></td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>26.7</td>
<td>28.3</td>
<td>25.7</td>
<td></td>
</tr>
<tr>
<td>History of CABG (%)</td>
<td>9.2</td>
<td>19.9</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>History of coronary angioplasty (%)</td>
<td>6.0</td>
<td>13.0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>History of valve surgery (%)</td>
<td>6.0</td>
<td>2.6</td>
<td>9.0</td>
<td>0.0029</td>
</tr>
<tr>
<td>Pacemaker (%)</td>
<td>9.6</td>
<td>10.0</td>
<td>9.3</td>
<td>0.8124</td>
</tr>
<tr>
<td>Implantable defibrillator (%)</td>
<td>0.6</td>
<td>0.9</td>
<td>0.4</td>
<td>0.5985</td>
</tr>
<tr>
<td>Quetelet index (kg/m²)</td>
<td>25.5 [25.1–25.9]</td>
<td>25.4 [24.8–25.9]</td>
<td>25.6 [25.0–26.3]</td>
<td>0.5492</td>
</tr>
<tr>
<td>CTR(†)</td>
<td>59.1 [58.3–59.4]</td>
<td>57.5 [56.4–58.6]</td>
<td>60.4 [59.3–61.4]</td>
<td>0.0003</td>
</tr>
<tr>
<td>Non-sinus rhythm (%)</td>
<td>25.6</td>
<td>14.3</td>
<td>35.5</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>86.5 [85.0–88.0]</td>
<td>83.7 [81.7–85.7]</td>
<td>88.9 [86.7–91.1]</td>
<td>0.0007</td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>138.3 [137.8–138.6]</td>
<td>137.8 [137.2–138.4]</td>
<td>138.6 [138.1–139.2]</td>
<td>0.0450</td>
</tr>
<tr>
<td>Serum creatinine (mmol/L)</td>
<td>129.8 [123.6–136.0]</td>
<td>137.1 [127.7–146.7]</td>
<td>123.4 [115.4–131.4]</td>
<td>0.0274</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>4.2 [4.1–4.3]</td>
<td>4.2 [4.1–4.3]</td>
<td>4.2 [4.1–4.3]</td>
<td>0.2044</td>
</tr>
</tbody>
</table>

*Comparison of coronary heart disease (CHD) vs. non-CHD (Non-CHD); †Left ventricular ejection fraction (LVEF) and cardiothoracic ratio (CTR) data were available in 459 (216 CHD, 243 Non-CHD) and 309 (139 CHD, 170 Non-CHD) patients, respectively.

Table 2. Drug Therapy at Discharge From Hospital Following Enrollment (n = 417)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total diuretics</td>
<td>404</td>
<td>96.9</td>
</tr>
<tr>
<td>Potassium-sparing diuretics</td>
<td>47</td>
<td>11.3</td>
</tr>
<tr>
<td>Potassium supplements</td>
<td>275</td>
<td>66.0</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>312</td>
<td>74.8</td>
</tr>
<tr>
<td>Digitalis</td>
<td>207</td>
<td>49.6</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>140</td>
<td>33.5</td>
</tr>
<tr>
<td>Class I antiarrhythmic drugs</td>
<td>13</td>
<td>3.1</td>
</tr>
<tr>
<td>Nitrates</td>
<td>170</td>
<td>40.7</td>
</tr>
<tr>
<td>Other vasodilators</td>
<td>62</td>
<td>14.8</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>133</td>
<td>31.9</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>118</td>
<td>28.3</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>22</td>
<td>5.3</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>53</td>
<td>12.7</td>
</tr>
</tbody>
</table>

*Of 499 patients, 69 died during the hospitalization following enrollment and 13 had incomplete treatment records.
aged between 20 and 80 years, 289 not admitted within study period, 552 had a LVEF >30% and/or a CTR <60%, 106 no evidence of class III or IV dyspnea and edema or hypotension and 11 incomplete data). Thus, 499 patients had all the inclusion criteria and were enrolled into the study. Among these, LVEF data were available for 466 patients (93.4%); for the other 33 patients (6.6%), the only criterion of left ventricular dysfunction was a CTR greater than 60%.

Incidence and patient characteristics. Of the 499 patients enrolled into the study, 358 had not been hospitalized for CHF during the preceding 18 months and were considered to be incident cases of advanced CHF. Using an estimate of 1,592,263 people in the Lorraine region aged between 20 and 80 years, this corresponds to an incidence rate for advanced CHF of 225 per million (95% CI 202–249). Incidence rate varied from 6 per million (CI 0–32 per million) in women aged less than 30 years to 1,480 per million (1,164–1,855 per million) in men aged 70–80 years (Fig. 1).

Patient characteristics are summarized in Table 1. The socioeconomic characteristics of the patients from the entire cohort were comparable to those of the age- and gender-adjusted population of Lorraine. Overall, 9.2% were professionally active, 63.9% were retired, 50.7% were civil servants and blue-collar workers, 22.4% had a nonmanual occupation and 26.1% had no hobbies; 85.8% received only primary level education.

Attributable causes of CHF included CHD (n = 231; 46.3%) (history of MI in 202 patients [87.4%]) and non-CHD causes (n = 268; 53.6%) (congenital heart disease [n = 3], valvular heart disease [n = 4], dilated cardiomyopathy [n = 214], unknown causes [n = 47]). Of the dilated cardiomyopathy group, 157 (31.5% of the total cohort) had at least one concomitant predisposing or contributing risk factor: alcohol abuse (37.6%), arterial hypertension (61.8%) and/or other rare conditions (20.4%). Other rare conditions included: thyroid disease (n = 14; 9.0%), immune system dysfunction, history of cancer chemotherapy, postpartum heart disease, thalassemia, toxic syndrome, sick sinus syndrome, myocarditis and obstructive cardiomyopathy. No contributing risk factors were seen in the 57 patients (11.4% of the total cohort) who were considered to have idiopathic cardiomyopathy.

Eighty-seven patients had undergone a coronary angiogram. Within the cardiomyopathy subgroup, these patients differed from those who had not undergone a coronary angiogram only in the fact that they were younger (58 ± 10 years vs. 66 ± 10 years, respectively; p < 0.0001).

The non-CHD group differed significantly from the CHD group in terms of older age, higher ratio of males to females, more frequent cigarette use, less frequent alcohol abuse, greater history of diabetes and hyperlipidemia, and higher rate of nonsinus rhythm (Table 1). Table 2 summarizes the drugs patients were using at discharge from the hospitalization immediately preceding enrollment into the study. Only three percent of the patients were not receiving diuretic therapy at discharge. This therapy had been discontinued in four patients after heart transplantation, and eight others had been temporarily withdrawn from diuretics.

Figure 1. Incidence of advanced congestive heart failure according to age and gender.
for various reasons (acute renal failure, hypotension, dehydration, initiation of ACE inhibitor therapy). Drug prescription patterns during follow-up did not change significantly, except for the prescription of statins, which increased steadily from use in 3.6% of patients on discharge to use in 24% of patients surviving at 18 months.

**Patient outcomes.** Survival status was obtained for all patients as of 31 December 1995. Average follow-up was 18 months (range 12–24 months). One-year mortality was 35.4% for the whole cohort (Fig. 2) and was not affected by gender when adjusted for age. Mortality during the initial enrollment was 13.8%. The relative risk of death conferred by advanced CHF, adjusting for age and gender was 12.7 (95% CI 10.9–14.4).

During the follow-up period, 20 patients received a heart transplant, two of whom had previously used the cardiac assist Novacor™ system. One other patient died while on a cardiac assist device. Survival analysis was censored for heart transplantation. Of the transplanted patients, 15 were still alive at the end of follow up.

The one-year rate for all-cause hospitalization was 2.01 (95% CI 2.00–2.03). It was 2.18 (95% CI 2.16–2.21) in CHD and 1.99 (95% CI 1.96–2.02) in dilated cardiomyopathy subgroup. The cumulative length of hospital stay was 26.4 days per year (95% CI 26.1–26.7), corresponding to an average yearly rate of hospitalization of 2.05 (95% CI 2.04–2.07). It varied from 28.3 (95% CI 27.9–28.6) to 24.8 (95% CI 24.3–25.3) in the CHD and dilated cardiomyopathy subgroups respectively (p < 0.0001). The hospital readmission-free survival curve is depicted in Figure 3. Within the follow-up period, the cause of hospitalization was known for 684 of the 1,074 hospitalizations for the whole cohort. Hospitalization was related to worsening of CHF in 50.3% of patients, to other cardiac causes in 29.7% and to noncardiac causes in 20.0% of patients. Survival, but not hospital readmission-free survival, varied significantly according to the attributable cause of CHF, and was greater in the dilated cardiomyopathy subgroup (Fig. 2). In this subgroup of patients, age-adjusted one-year survival did not differ according to whether the patient had or had not undergone normal coronary angiography (77% vs. 64%; not significant).

**DISCUSSION**

To date, the EPICAL study is the only descriptive, observational, community-based cohort study with a prospective one-year survival period that provides epidemiological descriptors of advanced CHF in a Western country within the ACE inhibitor and heart transplantation era. Among the epidemiological studies of CHF published after 1989 (8–10,14–21), only three specifically addressed patients with advanced CHF (8,10). All three were, however, restricted to single centers where patients were referred for emergency admission (10,14) or for transplant programs (8,9).

**Diagnostic criteria and definition of advanced CHF.** The lack of agreement of a definition of CHF, as well as the lack of gold-standard diagnostic criteria, may result in a considerable heterogeneity in the diagnosis of CHF in clinical trials and in epidemiological studies (7). The definition of CHF should combine clinical features with an
objective measure of cardiac performance (22). It is to be emphasized that the aim of the present study was to select only patients with advanced heart failure. Thus, a combination of clinical symptoms (class III and IV dyspnea) and signs of fluid retention and of severe left ventricular dysfunction were used to diagnose CHF. An LVEF of less than 30% was arbitrarily chosen as a cut-off point for severe left ventricular dysfunction, a percentage that has been used previously in published studies of advanced CHF (8,9,23,24).

The definition of advanced CHF used in the EPICAL study excluded patients with preserved or normal systolic function, even if severe symptoms of fluid retention were present. In advanced CHF, however, diastolic failure with no evidence of systolic failure is usually rare (25,26).

Incidence of advanced CHF. The incidence of CHF found in the EPICAL study is consistent with all previously published data, and the results show that the incidence of advanced CHF increases dramatically with increasing age. In EPICAL, patient entry was restricted to those less than 80 years of age because of the high numbers of institutionalized men and women aged over 80 years who would escape the case finding procedures used. Consequently, the results of EPICAL cannot be extrapolated to all patients with advanced CHF. The gender ratio reported in EPICAL was comparable to that reported in the Study Of Left Ventricular Dysfunction (SOLVD), which included asymptomatic patients and those with less severe symptoms than the patients included in EPICAL (27).

Etiology. When all possible etiological or risk factors, such as hypertension and alcohol abuse, were excluded, the rate of "idiopathic" dilated cardiomyopathy in EPICAL was 11%. A similar approach was used in the SOLVD studies, where the resulting rate of dilated cardiomyopathy was 18% (28). In the Framingham Heart Study (3), 11.2% of the men and 16.8% of the women had CHF that was not attributable to hypertension, CHD or rheumatic fever. Conversely, as in other series (23,29), a large majority of patients with CHD in EPICAL had a history of MI, because this was the most readily available hard evidence of CHD. Thus, patients diagnosed as having a nonischemic heart disease may actually have undiagnosed ischemic heart disease, but, because they did not experience an MI or severe angina or undergo a coronary angiogram, this was not identified. In postmortem studies up to 34 to 50% of patients diagnosed with nonischemic dilated cardiomyopathy have been shown to have significant coronary artery narrowing (30,31).

In EPICAL, 44% of the CHD subgroup had hypertension or a history of hypertension, a similar percentage to those patients whose CHF was attributable to CHD. The high incidence of a history of hypertension in the EPICAL cohort is consistent with that reported for CHF in the Framingham study (32), and SOLVD (28) and the Flolan International Randomized Survival Trial (FIRST) (23). Hypertension was the sole cause of CHF in 13.8% of the EPICAL patients, a relatively high percentage when compared to that reported in white patients in SOLVD (7%) (27).

Alcoholic cardiomyopathy is a well-known entity and alcohol abuse is a strong risk factor for idiopathic dilated...
cardiomyopathy (33–35). A number of studies (36,37) have shown that disease progression is different in alcoholic cardiomyopathy compared with idiopathic dilated cardiomyopathy. In EPICAL, 19% of patients presented with alcohol abuse, and the level of alcohol abuse appeared higher in the non-CHD subgroup than in the CHD subgroup (26% vs. 11%, respectively).

Outcome, survival and hospital re-admission. Although multiple clinical trials with pharmacological agents have been conducted that describe survival in CHF patients, patients enrolled in these trials do not depict an accurate picture of CHF in usual care. Very few observational studies have reported survival data in CHF patients who have received optimal, up-to-date, management, including ACE inhibition. Single-center series tend to reflect the patient population of the specialists’ referral hospital(s), and thus often include younger patients, who are more usually eligible for cardiac transplantation or for aggressive therapy (8,9). Data on the prognosis of advanced CHF from clinical trials may be also biased as a result of highly selective entry criteria (23,24). Published information concerning the rate of hospital admission of patients with advanced CHF is even scarcer. The EPICAL study is the first to report detailed information on readmission-free survival, hospital readmission rates, primary causes of hospitalization and length of hospital stay. This information is required (particularly for the calculation of sample sizes) when designing an outcome trial in patients with advanced CHF. Readmission-free survival is extremely poor in advanced CHF: less than 20% of EPICAL patients were readmitted to hospital and survived at one-year follow-up.

The effect of aging on the prognosis of CHF remains a controversial issue, and it has not been reported to be an independent predictor of death in recent studies with severe CHF (8–10,38,39). In the EPICAL cohort, mortality was independently affected by age: patients aged 70 to 80 years had a 50% higher risk of death than those aged less than 70 years. This may explain the higher mortality among women since, when adjusted for age, survival was not related to gender.

There is also conflicting evidence as to whether CHF patients with underlying CHD have a better or worse prognosis than those with CHF due to other causes. Patients with ischemic CHF have been reported to have a worse (27,29,40,41), comparable (42) or better (21) prognosis than patients with CHF of nonischemic etiology. These discrepancies may be partly explained by selection biases in hospital series of patients and partly by possible etiological misclassification. In the present study, patients with ischemic CHF carried a significantly increased (30%) risk of death compared to patients whose CHF was due to nonischemic causes.

Study limitations. The methodology of patient enrollment used in EPICAL allowed the identification of incident cases of advanced CHF. According to the definition of CHF used, which required at least one hospital admission for signs and symptoms of severe CHF, incident cases were comprehensively recorded. The organization of the French healthcare system permits easy and immediate access to the hospital. Moreover, patient registration was not only passive, but also active and randomly audited via the review of medical records by trained clinical research nurses. Nevertheless, despite considerable efforts to ascertain complete and comprehensive patient notification, we may have missed few cases, especially among patients admitted with other initial diagnoses. Thus, our incidence figures may be slightly underestimated. Moreover, because of the relatively short follow-up period, it was not possible to provide a relevant estimation of the prevalence of advanced CHF.

In extrapolating these data to other Western countries, it should be borne in mind that the incidence of morbidity and mortality from cardiovascular disease, and especially from CHD, is significantly lower in France when compared to other European countries and to the U.S.A. (although the Lorraine region has one of the highest incidences of cardiovascular morbidity and mortality in France) (43) (standardized mortality ratio: 1.3).

Conclusions. Despite the above limitations, the EPICAL study is the only observational epidemiological study available to date that provides estimates of the incidence of advanced CHF, together with information regarding outcome and use of medication, for a large Western community population in the post-ACE inhibitor and heart transplantation era. The findings of this study may aid estimating and decision making concerning the utilization of healthcare resources, especially costly interventional surgical procedures. Further analyses of our database would estimate the use of healthcare resources and the utilization of medication and may help in the design of managed-care strategies.

Acknowledgments
We wish to thank V. Midenet and B. Risse (clinical research nurses), S. Ronchetti, C. Van Dorsselaere, M. Sellier (secretary), P. Doveze, M. Echemann, L. Feldman, N. Ficher, D. Jeannelle, S. Lebihan, P. Melchior, E. Penetrate, M. O. Stein and various PhD students (statistics and data management).

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APPENDIX 1

Steering Committee:
Pr. E. Aliot (Nancy), Dr. Ch. Breton (St Max), Pr. S. Briançon (Nancy), Pr. Y. Juilliére (Vandœuvre), Dr. K. Khalife (Metz), Dr. P. M. Merts (Vandœuvre), Dr. J. L. Neumann (Metz), Pr. J. P. Villenot (Vandœuvre), Dr. F. Zannad (Nancy)

Investigators Committee:
Dr. S. Allam (Verdun), Dr. Ph. Admant (Epinal), Dr. N. Baille (Metz), Dr. Ph. Bellanger (Chaumont), Dr. R. D’Hôtel (Remiremont), Dr. P. Dambrine (Freyming
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