Vascular disease as a predictor of long-term mortality in patients hospitalized for new-onset heart failure

La maladie vasculaire périphérique est un facteur prédictif de mortalité à long terme après hospitalisation pour une première poussée d’insuffisance cardiaque

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**KEYWORDS**
Heart failure; Vascular disease; Prognosis

**Summary**

**Background.** — Comorbidities have an adverse influence on the outcome of patients with heart failure (HF).

**Aim.** — We investigated the impact of peripheral vascular disease (PVD) on long-term mortality in hospitalized patients with HF.

**Methods.** — We included prospectively consecutive patients (N = 799) hospitalized for a first episode of HF in all healthcare establishments within a single French department during 2000. Patients with peripheral arterial disease and/or history of stroke were considered to have PVD. Baseline characteristics and 5-year mortality were compared according to PVD status.

**Results.** — PVD was diagnosed in 172 patients (22%) and clinical coronary artery disease in 302 patients (38%). Patients with PVD were older, predominantly men, smokers, and more often had diabetes and coronary artery disease. PVD was associated with an increased risk of crude 5-year overall mortality (hazard ratio [HR] 1.65, 95% confidence interval [CI] 1.35—2.03; P < 0.001). After adjustment for covariates, the relationship remained significant (HR 1.33, 95% CI 1.08—1.65; P = 0.008). Compared with the expected survival, the 5-year survival of the PVD...
The aim of this study was to determine the impact of PVD on the long-term prognosis (5-year overall and cardiovascular mortality) of patients hospitalized for a first episode of HF.

Methods

Study population and inclusion criteria

Épidémiologie et traitement de l’insuffisance cardiaque dans la Somme (ETICS) [12,13] was a prospective observational study conducted in the Somme department of France. The study was designed to establish the epidemiological characteristics and treatment of patients hospitalized for a first episode of HF during 2000. Patients were followed for 5 years. In 1999, the Somme population was 555,551. Physicians—mainly cardiologists, but also internal physicians and general practitioners representing primary care and referral centres in all private and public hospitals providing healthcare to the Somme community—agreed to participate in the study. There were 11 participating healthcare establishments: one university hospital, seven general hospitals, two private clinics and one medium and long-stay unit.

Consecutive patients 20 years old or above, hospitalized for a first episode of HF in all these establishments during 2000, were enrolled prospectively. Patients living outside the Somme department, patients hospitalized...
for subsequent episodes of HF and patients with severe valvular heart disease requiring surgery were excluded. The diagnosis of HF was made by the attending physician, based on history, symptoms, physical signs and chest X-ray on admission [2]. Initially, 811 patients were enrolled. During the index hospitalization, all medical files were reviewed by two senior cardiologists to validate the diagnosis of HF according to Framingham criteria [14] amended by the Task Force on Heart Failure of the European Society of Cardiology [2]. The diagnosis was not validated in 12 patients. A total of 799 patients (410 men and 389 women) were finally included.

Data collection

Clinical data, including medical history, cardiovascular risk factors, comorbidities (chronic obstructive pulmonary disease, PAD, stroke, TIA and cancer), as well as results of complementary investigations (laboratory tests, electrocardiogram, chest X-ray on admission, echocardiography and coronary angiography) were recorded on individual case report forms.

Patients with PAD and/or history of stroke/TIA were considered to have PVD. Clinical coronary artery disease was assumed in patients with a history of ischaemic heart disease, recent documented history of myocardial infarction or angina pectoris, or significant coronary atherosclerosis confirmed by coronary angiography before the index hospitalization for HF [1]. A patient was considered to have hypertension in the presence of one of the following criteria: high blood pressure during hospitalization (>160/95 mmHg), previous diagnosis of hypertension or normal blood pressure with ongoing antihypertensive therapy [15]. Dyslipidaemia and diabetes mellitus were defined by the presence of the disease in the patient’s history or during hospitalization, or by the use of specific medication (lipid-lowering therapy and insulin or oral hypoglycaemic drugs, respectively). An estimate of the glomerular filtration rate on admission was calculated with the simplified Modification of Diet in Renal Disease (sMDRD) formula, including age, race, sex and serum creatinine [16]. An estimated glomerular filtration rate of less than 60 mL/min for 1.73 m² was used to define renal failure according to the National Kidney Disease Foundation Guidelines [17]. Left ventricular ejection fraction — available for 662 patients (83%) — was measured by echocardiography (N = 648) and/or left ventriculography (N = 103) during hospitalization. When ejection fraction was assessed by both methods (N = 89), a mean value was recorded.

The endpoints were overall mortality and cardiovascular mortality. One-year, 3-year and 5-year overall and cardiovascular mortality rates after admission were determined. Sudden death was classified as cardiovascular death. The vital status was obtained either at a consultation by the general practitioner or the referring cardiologist or by consulting the civil registry. The cause of death was ascertained by hospital records, death certificates and autopsy records or by contacting the patient’s physician or the referring cardiologist. No patients were lost to follow-up at 1 year and 3 years. Five patients (0.6%) were lost to follow-up at 5 years.

Statistical analysis

Continuous variables were expressed as mean ± S.D. and were compared with Student’s t-tests. Categorical variables were reported as absolute numbers and frequency percentages and analysed with Chi-square tests. Analyses of mortality were performed using Cox proportional hazards models. For multivariable analyses of mortality, we used a predefined Cox proportional hazard model that included covariates of potential prognostic impact (age, sex, history of hypertension, diabetes mellitus, dyslipidaemia, smoking, chronic obstructive pulmonary disease, renal failure, cancer, coronary artery disease and PVD). To avoid spurious relationship, covariates were entered in the model regardless of the P-value on univariate analysis. The assumption of proportional hazards was checked using log-minus-log survival plots.

Overall survival curves were generated using Kaplan—Meier survival estimates. Survival of patients in the PVD and no-PVD groups was compared with the expected survival of persons of the same age and sex in the Somme department. Control data were obtained from Somme life tables for 1999 provided by the French Institute of Statistics. The relative survival was computed as the ratio of the observed to expected survival (observed number of deaths/expected number of deaths in the general population).

Cardiovascular death was analysed in a Cox proportional hazards multivariable model, while patients who died of non-cardiovascular causes were censored (as non-events) at the time of death [18,19]. Hazard ratios (HRs) and 95% CIs for the two groups (PVD and no PVD) were estimated for cardiovascular death. Plots of cumulative hazard functions were used for cardiovascular mortality. For all tests, a P-value less than 0.05 was considered to be significant. All P-values are results of two-tailed tests. Statistical analysis was performed with SPSS 13.0 statistical software (SPSS Inc., Chicago, IL, USA). The study conforms to the principles outlined in the Declaration of Helsinki and was approved by local institutional review boards. Written informed consent was obtained from all patients. The database was approved by the French Computers and Privacy Commission.

Results

Baseline characteristics

PVD was diagnosed in 22% of the study population (N = 172). The frequency of stroke/TIA was 10% (N = 80). Fourteen percent of patients (N = 112) had PAD. Only 20 patients had bipolar PVD. Table 1 shows the baseline characteristics of patients according to PVD status. Patients in the PVD group were older, mostly men and had significantly more cardiovascular risk factors (diabetes mellitus, smoking and hypertension). Clinical coronary artery disease was more frequent in the PVD group. Medication at discharge in patients surviving the index hospitalization was similar for the PVD and no-PVD groups, except for an underuse of digoxin and a higher rate of prescription of platelet aggregation inhibitors in PVD patients.
Table 1  Baseline characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall population (n = 799)</th>
<th>PVD (n = 172)</th>
<th>No PVD (n = 627)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± S.D.)</td>
<td>75 ± 12</td>
<td>78 ± 9</td>
<td>75 ± 12</td>
<td>0.002</td>
</tr>
<tr>
<td>Women</td>
<td>49 (389)</td>
<td>41 (71)</td>
<td>51 (318)</td>
<td>0.03</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>62 (498)</td>
<td>69 (118)</td>
<td>61 (380)</td>
<td>0.06</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>27 (215)</td>
<td>30 (51)</td>
<td>26 (164)</td>
<td>0.36</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25 (196)</td>
<td>32 (55)</td>
<td>23 (141)</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>35 (283)</td>
<td>47 (81)</td>
<td>32 (202)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of cardiovascular disease</td>
<td>9 (68)</td>
<td>7 (12)</td>
<td>9 (56)</td>
<td>0.42</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>20 (156)</td>
<td>22 (37)</td>
<td>19 (119)</td>
<td>0.46</td>
</tr>
<tr>
<td>Renal failure</td>
<td>55 (441)</td>
<td>61 (105)</td>
<td>54 (336)</td>
<td>0.10</td>
</tr>
<tr>
<td>Cancer</td>
<td>11 (85)</td>
<td>12 (20)</td>
<td>11 (65)</td>
<td>0.66</td>
</tr>
<tr>
<td>Clinical coronary artery disease</td>
<td>38 (302)</td>
<td>52 (90)</td>
<td>34 (212)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction ≥ 50%</td>
<td>44 (294)</td>
<td>50 (70)</td>
<td>43 (224)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Treatment at discharge

Angiotensin-converting enzyme inhibitors            | 55 (401)                    | 56 (88)     | 54 (313)        | 0.67  |
Beta-blockers                                       | 23 (168)                    | 24 (37)     | 23 (131)        | 0.82  |
Diuretics                                           | 89 (656)                    | 90 (142)    | 89 (514)        | 0.59  |
Spironolactone                                      | 25 (183)                    | 21 (33)     | 26 (148)        | 0.24  |
Calcium channel blockers                            | 19 (141)                    | 22 (35)     | 18 (106)        | 0.27  |
Digoxin                                             | 25 (186)                    | 18 (28)     | 27 (158)        | 0.02  |
Platelet aggregation inhibitors                      | 37 (268)                    | 44 (69)     | 34 (199)        | 0.03  |
Oral anticoagulants                                  | 26 (214)                    | 26 (40)     | 30 (174)        | 0.26  |
Amiodarone                                          | 33 (243)                    | 27 (43)     | 35 (200)        | 0.09  |
Statins                                             | 14 (105)                    | 16 (25)     | 14 (80)         | 0.49  |

PVD: peripheral vascular disease; S.D.: standard deviation. Data are percentages (N) unless denoted otherwise.

* Patients assessed for left ventricular ejection fraction (N = 662).
* Patients alive at discharge (N = 735).

Figure 1. Survival curves for patients with heart failure according to peripheral vascular disease status compared with the expected survival of the age- and sex-matched general population.
Prognostic impact of PVD

PVD was associated with an increased risk of crude overall 5-year mortality (HR 1.65, 95% CI 1.35—2.03; p < 0.001) (Fig. 1). The relationship remained significant after adjustment for age and sex (HR 1.42, 95% CI 1.18—1.79; p < 0.001) (Table 2) and after adjustment for covariates of potential prognostic importance (HR 1.33, 95% CI 1.08—1.65; p = 0.008) (Table 2). Further adjustment for ejection fraction did not modify this association (HR 1.48, 95% CI 1.16—1.90; p = 0.002). The 5-year overall survival of the PVD group was dramatically lower than the expected survival of the age- and sex-matched general population (Fig. 1). One-year, 3-year and 5-year relative survival rates (i.e. observed/expected survival) in the PVD group were lower compared with those in the no-PVD group (65% versus 79%, 49% versus 68% and 37% versus 61%, respectively) (Fig. 2).

On multivariable analysis, PVD, age equal to 75 years or above, coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease, cancer and renal failure were independent predictors of 5-year overall mortality (Table 2). After adjustment for age, female sex was associated with better outcome. After adjustment for covariates of prognostic importance (including age), female sex was no longer associated with 5-year mortality. Dyslipidaemia was associated with better outcome (Table 2).

Cardiovascular causes were responsible for 63% of deaths in patients with PVD. On multivariable Cox analysis, the risk of cardiovascular death in patients with PVD was significantly higher than that in the no-PVD group (HR 1.39, 95% CI 1.07—1.80; p = 0.014) (Fig. 3).

We further analysed the prognostic impact of covariates in the two groups (PVD and no PVD). Coronary artery disease, diabetes mellitus, renal failure and cancer were associated

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 75 years</td>
<td>2.56 (2.08—3.14)</td>
<td>&lt;0.001</td>
<td>2.20 (1.77—2.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.81 (0.67—0.97)</td>
<td>0.02</td>
<td>0.88 (0.71—1.10)</td>
<td>0.25</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1.12 (0.92—1.35)</td>
<td>0.26</td>
<td>1.11 (0.91—1.35)</td>
<td>0.30</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>0.80 (0.64—0.99)</td>
<td>0.04</td>
<td>0.71 (0.57—0.90)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.45 (1.18—1.79)</td>
<td>&lt;0.001</td>
<td>1.28 (1.03—1.58)</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.18 (0.94—1.48)</td>
<td>0.15</td>
<td>0.93 (0.73—1.17)</td>
<td>0.52</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1.22 (0.98—1.53)</td>
<td>0.07</td>
<td>1.49 (1.18—1.88)</td>
<td>0.001</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.41 (1.16—1.70)</td>
<td>&lt;0.001</td>
<td>1.57 (1.30—1.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.93 (1.50—2.48)</td>
<td>&lt;0.001</td>
<td>2.17 (1.68—2.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical coronary artery disease</td>
<td>1.23 (1.02—1.47)</td>
<td>0.03</td>
<td>1.27 (1.05—1.54)</td>
<td>0.01</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.42 (1.18—1.79)</td>
<td>&lt;0.001</td>
<td>1.33 (1.08—1.65)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

* Covariates in the model: age, sex, history of hypertension, diabetes mellitus, dyslipidaemia, smoking, chronic obstructive pulmonary disease, renal failure, cancer, clinical coronary artery disease and peripheral vascular disease.
with mortality in patients without PVD but not in patients with PVD (Fig. 4). Dyslipidaemia appeared to be a protective factor only in patients without PVD. The presence of chronic obstructive pulmonary disease was predictive of mortality in both groups. Finally, age equal to 75 years or above predicted mortality in both groups, but the association was stronger in the no-PVD group.

**Discussion**

This prospective analysis shows that the presence of PVD in patients hospitalized for the first time for HF has a strong influence on the course of the disease, especially in terms of cardiovascular mortality. Moreover, PVD probably modulates the prognostic impact of other covariates such as age, dyslipidaemia, diabetes mellitus, chronic obstructive pulmonary disease, renal failure, cancer and coronary artery disease. Our results confirm that, compared with the survival of the age- and sex-matched general population, the long-term outcome of patients hospitalized for a first episode of HF remains poor. PVD and other comorbidities should, therefore, be monitored carefully and managed appropriately in HF patients.

In this study, we used a clinical definition for PVD: the presence of PAD and/or stroke/TIA as markers of vascular disease. The prevalence of PAD is acknowledged to be underestimated in the general population as well as in high-risk populations [20]. Moreover, previous studies suggest that PAD or stroke/TIA are strong predictors of adverse outcomes in different categories of patients with cardiovascular diseases [8,21—28]. PVD can be considered to be a global marker of an increased degradation of the cardiovascular system. Secondary prevention strategies are crucial, as patients with previous vascular events have a high risk of recurrence [21].

In our study, PAD or stroke/TIA can be interpreted as the first symptoms of a generalized vascular disease. HF appears as a subsequent event in this elderly population with significant vascular history [22,29,30]. One explanation for this hypothesis is that inflammation, oxidative stress and neurohormonal activation are phenomena involved in both arteriosclerosis and progression of HF [31—34]. Moreover, PVD is associated with an unbalanced cardiovascular coupling and can be held responsible for a more severe and rapid cardiac impairment. Arterial stiffening and increased wave reflection to the heart — two main features of arteriosclerosis — are factors that contribute to an increased cardiac load. Increased pulsed pressure is one of the consequences of this degenerative vascular process. It has been demonstrated clearly that increased pulsed pressure is related to adverse outcomes in patients with left ventricular dysfunction [35]. Furthermore, in patients with PAD, pulsed pressure is correlated with increased levels of natriuretic peptides [30]. Natriuretic peptides are markers of adverse outcomes in HF [36]. Finally, PAD and stroke/TIA are associated with disability, impaired exercise capacity and cognitive decline in elderly patients with HF, with potential adverse consequences on survival [25,37].

<table>
<thead>
<tr>
<th>Variable</th>
<th>p value</th>
<th>HR (Confidence interval 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 75 years</td>
<td>0.003</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.17</td>
<td>0.71</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.21</td>
<td>0.72</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>0.34</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.79</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.53</td>
<td>0.78</td>
</tr>
<tr>
<td>COPD</td>
<td>0.04</td>
<td>0.004</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0.77</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**Figure 4.** Prognostic impact of age, sex and comorbidities on 5-year overall mortality in heart failure patients with and without peripheral vascular disease (adjusted for age, sex, history of hypertension, diabetes mellitus, dyslipidaemia, smoking, chronic obstructive pulmonary disease, renal failure, cancer and coronary artery disease).
In our study, the presence of PVD seemed to modulate the effect of age, dyslipidaemia, diabetes mellitus, chronic obstructive pulmonary disease, renal failure, cancer and coronary artery disease on mortality. Older age, diabetes mellitus and renal failure had prominent adverse effects in patients without PVD. Therefore, these variables might be involved in the incidence and progression of vascular disease \[20,38,39\]. Once the vascular disease is clinically detectable, the prognostic impact of these covariates is no longer observed. Similar underlying causes are responsible for both central vascular disease and PVD, although the magnitude is probably different. The first location of the vascular disease drives the nature and incidence of fatal outcomes. However, a cumulative effect – several locations of the vascular disease – may represent a marker of generalized disease. Dyslipidaemia was related to better outcome in patients without PVD. The protective effect of dyslipidaemia might be interpreted as a drug effect (lipid-lowering therapy was used to define the presence of the disease). However, some data suggest a favourable effect of normal or high total cholesterol levels on outcome in elderly and patients with HF \[40,41\]. Chronic obstructive pulmonary disease has been reported to be a marker of reduced survival in HF patients \[8\]. In this study, the prognostic importance of chronic obstructive pulmonary disease was confirmed in both groups. Finally, cancer was associated with mortality in the no-PVD group exclusively.

**Limitations**

The ETICS study was a prospective study that included hospitalized patients exclusively. The characteristics of hospitalized patients and those of patients managed on an outpatient basis are certainly different in terms of severity of symptoms and management. Ejection fraction was determined during the initial hospitalization in 83% of patients; a higher rate compared with other epidemiological studies \[8\]. We aimed to establish the prognostic impact of a history of PVD at the time of first hospitalization for acute HF on long-term mortality. As PVD was not assessed systematically, the true frequency of PAD and stroke were probably underestimated and the diagnosis undoubtedly focused on symptomatic patients with more severe disease. As a coronary angiography was not performed systematically in this elderly population with new-onset HF, the diagnosis of coronary artery was based on clinical data. We acknowledge that multivariable analyses in subgroups of patients with HF may be underpowered due to the small size of the samples.

**Conclusions**

Patients hospitalized for a first episode of HF have a poor long-term prognosis. In patients with HF, comorbidities are potent determinants of outcome and important variables for risk stratification. We have demonstrated that PVD is a marker of increased 5-year overall and cardiovascular mortality in patients with new-onset HF. PVD is likely to modulate the effect of other variables on outcome. Therefore, tracking and management of vascular diseases and reduction of the occurrence of cardiovascular events related to these diseases appear to be of paramount importance, together with adequate guideline-orientated HF treatment.

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**Conflicts of interests**

None.

**References**


