Impact of polyvascular disease on baseline characteristics, management and mortality in acute myocardial infarction. The Alliance project

Impact de l’atteinte vasculaire extracoronarienne sur les caractéristiques, la prise en charge et la mortalité des patients admis pour infarctus du myocarde à partir des données du registre Alliance

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A substantial number of patients with acute myocardial infarction (AMI) have polyvascular disease (PolyVD), defined as cerebrovascular disease (CVD), peripheral arterial disease (PAD) or both.

Aim. — To investigate the impact of PolyVD on baseline characteristics, management and outcomes.

Methods. — The Alliance project is a multicentre, cross-sectional database of patients with myocardial infarction throughout France from 2000 to 2005. A pooled analysis of individual patient data was performed by aggregating data from five registries, representing 9783 patients hospitalized for acute coronary syndromes. Data were collected on history of PAD and CVD and correlated to baseline characteristics, management and hospital outcomes.

Results. — Eight thousand nine hundred and four patients had full datasets for this analysis (13% with a history of CVD or PAD, 87% without). Patients with PolyVD were older (72 vs 65 years, \( p < 0.0001 \)), had a more frequent history of AMI (26% vs 15%, \( p < 0.0001 \)), percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), renal insufficiency (12% vs 3%, \( p < 0.0001 \)) and consistently more risk factors for atherosclerosis (hypertension, dyslipidemia, smoking, diabetes), but less frequently a body mass index > 30 kg/m² (14.0% vs 20.1%, \( p < 0.0001 \)) compared to patients with coronary artery disease (CAD) alone. Killip class, left-ventricular ejection fraction and GUSTO risk score were all worse among patients with PolyVD.

Management of patients with PolyVD was less aggressive (with later admission and less frequent use of in-hospital angiography or evidence-based therapies at discharge). Mortality of patients with PolyVD was consistently higher than in those with CAD alone, regardless of age. Multivariable analysis, adjusting for age, showed that both PAD (odds ratio 1.36 95% confidence interval 1.03—1.79) and history of CVD (odds ratio 1.74, 95% confidence interval 1.27—2.40) were independent predictors of hospital mortality relative to patients with CAD only.

Conclusion. — Patients with PolyVD represented a substantial group among AMI patients, at particularly high risk of death, yet were managed less aggressively than patients with CAD alone. This was associated with markedly higher in-hospital mortality. Further research is warranted to design and test strategies to decrease mortality in this high-risk subset.
Impact of polyvascular disease in acute myocardial infarction

Background

Cardiovascular disease, due to cerebrovascular disease (CVD), peripheral arterial disease (PAD) or coronary artery disease (CAD), is the leading cause of mortality and morbidity in industrialized countries [1]. Atherothrombosis is a common (but not exclusive) underlying cause of these three diseases. Therefore, CVD, PAD and CAD are often different locations of a similar underlying disease, share similar risk factors (albeit with a different relative weight for each of the locations) and frequently coexist [2]. In the REduction of Atherothrombosis for Continued Health (REACH) Registry, there was major overlap between the various locations of the symptomatic location of the disease [3], and mortality and morbidity increased with the extent of atherosclerotic burden (i.e., number of arterial beds affected) [4].

Major advances have been made in the prevention, diagnosis and treatment of CAD. Randomized trials provide robust evidence that pharmacological and interventional therapies improve the outcome of patients with acute coronary syndromes (ACS) and have led to changes in clinical practice and guidelines [5–8]. Observational data from the Global Registry of Acute Coronary Events (GRACE) [9] have shown that in routine practice, improvement in the management of patients with ACS is associated with a significant rate reduction in heart failure, acute myocardial infarction (AMI) and death. In contrast, patients with non-coronary atheroclerotic vascular disease, and especially PAD, are regarded as particularly high-risk, yet are often underdiagnosed and undertreated [10–12]. For example, patients with PAD, compared to those with CAD, were less likely to be treated with aspirin or lipid-lowering therapy if they were hypercholesterolaemic [13].

Acute myocardial infarction is the most frequent and potentially fatal event in patients with cardiovascular disease, and the impact of the association of PAD or CVD on the management and outcome of patients hospitalized for AMI has not been fully evaluated. We hypothesized that a history of PAD or CVD may affect clinical presentation, management and outcome. We therefore used data from the Alliance consortium of AMI to compare baseline characteristics, management and in-hospital outcomes of patients with AMI alone with those of patients with associated CVD or/and PAD.

Methods

Study design

The Alliance project is a multicentre, cross-sectional database of 9783 patients admitted for AMI throughout France from 2000 to 2005. The purpose of the project is to provide aggregate data and test hypotheses regarding AMI in France. It is a pooled analysis of data from five registries: FACT (2003 nationwide survey with 2517 patients) [14], USIC (2000 nationwide survey with 2315 patients) [15,16], RICO (2000–2005 continuous registry department of Burgundy with 4057 patients) [17], Paris (2000–2005 continuous registry of University Hospital Pitié-Salpêtrière Paris with 652 patients) [18] and eParis (2000–2005 continuous registry with 242 patients). All patients gave informed consent for participation in the survey and follow-up.

Definitions

Acute myocardial infarction was defined as an increase in one cardiac biochemical marker of necrosis (troponin I or T or creatine phosphokinase [CPK] MB) at least twice the upper normal limit [19] and at least one of the following criteria: chest pain lasting for at least 20 minutes not relieved by nitrates, electrocardiographic changes on at least two contiguous leads with persisting ST elevation or depression ≥ 0.1 mV and/or pathological Q waves. Patients were classified into three categories: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) [20] or undetermined electrocardiographic pattern (left bundle-branch block or paced rhythm).

Vascular disease

Diagnosis of PAD was made on the basis of the presence of one of the following: history of claudication, peripheral vascular surgery, vascular angioplasty or amputation or documented abdominal aortic aneurysm. The diagnosis of CVD was based on a history of transient ischaemic attack (TIA), stroke, carotid endarterectomy or carotid stent implantation. TIA was defined as a history of loss of neurological function caused by ischaemia that was abrupt in onset but with complete return of function within 24 hours. Stroke was defined as a loss of neurological function caused by an ischaemic event, with residual symptoms.

Data collection

Data regarding patient demographics, risk factors, medical history, clinical presentation, prehospital delay, in-hospital management and in-hospital mortality were collected. Polyvascular disease (PolyVD) was defined as patients with CVD, PAD or both. Items used for the pooled analysis were defined in a similar manner across registries, using simple clinical definitions.

Statistical analysis

Data are presented as number of patients (per cent) or mean ± standard deviation (SD). Differences in baseline characteristics, hospital management and mortality
Table 1
Clinical characteristics of the overall population and according to the presence or absence of polyvascular disease (PolyVD).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n = 8904)</th>
<th>No PolyVD (n = 7743)</th>
<th>PolyVD (n = 1161)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 ± 14</td>
<td>65 ± 14</td>
<td>72 ± 12</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Men</td>
<td>6409 (72)</td>
<td>5550 (72)</td>
<td>859 (74)</td>
<td>0.10</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4455 (50)</td>
<td>3691 (48)</td>
<td>764 (66)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1830 (21)</td>
<td>1435 (19)</td>
<td>395 (34)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>3867 (43)</td>
<td>3317 (43)</td>
<td>550 (47)</td>
<td>0.004</td>
</tr>
<tr>
<td>History of smoking (current or former)</td>
<td>5277 (59)</td>
<td>4543 (59)</td>
<td>734 (63)</td>
<td>0.003</td>
</tr>
<tr>
<td>Obesity (body mass index ≥ 30 kg/m²)</td>
<td>1606 (19)</td>
<td>1457 (20)</td>
<td>149 (14)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Renal insufficiency (glomerular filtration rate ≤ 30 mL/min)</td>
<td>239 (4)</td>
<td>140 (3)</td>
<td>99 (12)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1441 (16)</td>
<td>1138 (15)</td>
<td>303 (26)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>943 (11)</td>
<td>765 (10)</td>
<td>178 (15)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Coronary artery bypass graft</td>
<td>384 (4)</td>
<td>303 (4)</td>
<td>81 (7)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Values are number (%) or mean ± standard deviation.

between patients with and without PolyVD were assessed by use of the t test or the χ²-test as appropriate. Final regression models were adjusted for age divided into three categories (< 60; 60—75; > 75 years) or as a continuous variable. A p value < 0.05 was considered significant.

**Results**

**Baseline characteristics**

Among the 9783 patients with AMI enrolled in the five registries between 2000 and 2005, 91% (n = 8904) had complete datasets and constituted our study population. Clinical characteristics are summarized in Table 1. Briefly, the mean age was 66 ± 14 years, 72% were men and the prevalence of cardiovascular risk factors was high.

Among the 8904 patients, 4% (n = 356) patients had a history of stroke or TIA (CVD), 8% (n = 712) had a history of PAD and 1% (n = 89) had a history of both CVD and PAD. Therefore, 13% (n = 1161) of patients had a history of PolyVD (Fig. 1). Patients with a history of PolyVD were older (p < 0.0001), had consistently more cardiovascular risk factors (all p < 0.005), but were less frequently obese (body mass index ≥ 30 kg/m²) (p < 0.0001) (Table 1). They were also more likely to have a history of CAD (p < 0.0001) or renal insufficiency (p < 0.0001).

**Clinical presentation**

Among the 8904 patients analyzed, 70% (n = 6224) presented with STEMI, 25% (n = 2244) with NSTEMI, and 5% (n = 436) with an undetermined electrocardiographic pattern.

Patients with prior PolyVD were less likely to present with STEMI (p < 0.0001) and more likely to have NSTEMI (p < 0.0001) or an undetermined electrocardiographic pattern (p < 0.0001) than patients without PolyVD. They also presented with a higher Killip class and a lower ejection fraction (both p < 0.0001) and the delay from symptom onset to admission was longer (p < 0.0001) than that of patients without PolyVD (Table 2).

**In-hospital mortality**

The overall in-hospital mortality was 6.5% (n = 577), 7.2% (n = 506) in patients with STEMI, 4.3% (n = 96) in NSTEMI and 12.5% (n = 57) in patients with an undetermined electrocardiographic pattern. A two-fold increase in hospital mortality was observed in patients with PolyVD (p < 0.001) compared to patients without PolyVD (Fig. 2A). Mortality was highest in AMI patients with prior CVD or both prior CVD and PAD (14% [n = 365]) and 13% (n = 77), respectively, vs. 9.8% (n = 703) in patients with AMI and PAD and 5.7% (n = 7739) in patients without PolyVD, (p < 0.001) (Fig. 2B).
Impact of polyvascular disease in acute myocardial infarction

Mortality increased sharply with age, from 1.7% in patients aged < 60 years to 4.6% between 60 and 75 years, and 11.8% after 75 years. Even though patients with PolyVD were on average older than patients with CAD alone, mortality remained higher across all age categories (Fig. 2C) and remained higher after adjustment for age (odds ratio [OR] 1.52, 95% confidence interval [CI] 1.23—1.88, \( p < 0.001 \)) (Table 3). Similar results were observed after additional adjustment for the five registries (OR 1.50, 95% CI 1.23—1.82, \( p < 0.001 \)).

In-hospital management

Procedures

During the index hospitalization, 84% (\( n = 7398 \)) of patients underwent coronary angiography, 59% (\( n = 5244 \)) percutaneous coronary intervention (PCI), 23% (\( n = 2048 \)) primary PCI and 72% (\( n = 836 \)) coronary artery bypass graft (CABG) surgery. Compared to patients without PolyVD, patients with prior PolyVD less frequently underwent coronary angiography (72% [\( n = 839 \)] vs 85% [\( n = 6582 \)], \( p < 0.0001 \)) or PCI (48% [\( n = 560 \)] vs 62% [\( n = 4470 \)], \( p < 0.0001 \)), whereas the rate of CABG was similar (7% [\( n = 85 \)] vs 7% [\( n = 542 \)], \( p = 0.75 \)), espe-
was a strong and independent predictor of in-hospital mortality. Thus, our data show that in patients admitted for AMI, the extent of the atherosclerotic burden is associated with worse in-hospital mortality. An important clinical implication of the present study is that a history of symptomatic PAD or CVD, which can be simply assessed by physicians in a few minutes, is a strong prognostic factor.

**Less-aggressive management**

Despite the high prevalence of PolyVD and its strong association with cardiovascular morbidity and mortality, PolyVD has received relatively little attention in the context of AMI. Cardiovascular risk factors are less-often controlled in patients with PAD and guideline-recommended medications (antiplatelet therapy, beta-blockers, statins and ACE/ARBs [5–8,10,22]) are less often used despite the obvious benefits of these guideline-recommended medications on outcomes [12,23].

The present study documents less-aggressive management of patients with prior PolyVD admitted for AMI, with delayed times to admission, a lower procedural rate (angiography), and less frequent use of guideline-recommended medications at discharge. The rates of primary PCI were similar regardless of the presence or absence of PolyVD, suggesting that the more conservative management of polyVD patients was related mostly to patients with NSTEMI. It is not clear why higher risk patients with PolyVD underwent fewer coronary procedures. Some physicians may decide to withhold coronary angiography in this older population, who have more frequent comorbidities including renal insufficiency.

The underuse of guideline-recommended medications is a missed opportunity in patients eligible for these drugs, since if they are not introduced during the index hospitalization, they are rarely initiated afterwards. Only 41% of patients with PolyVD received the four guideline-recommended medications. However, in the present study, we could not investigate whether the differences in medication use between patients with and without PolyVD were or were not appropriate. It is possible that beta-blockers were prescribed less frequently because patients with PolyVD had more severe heart failure or because of a fear of potential adverse effects in patients with PAD or in patients with more frequent history of smoking. The lower use of statins in patients with PolyVD is less easy to understand, as multiple studies have demonstrated the consistent effectiveness

### Table 2

Clinical presentation and management of the overall population and according to the presence or absence of polyvascular disease (PolyVD).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n = 8904)</th>
<th>No PolyVD (n = 7743)</th>
<th>PolyVD (n = 1161)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of acute coronary syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-elevation myocardial infarction</td>
<td>6224 (70)</td>
<td>5523 (71)</td>
<td>701 (60)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Non-ST-elevation myocardial infarction</td>
<td>2244 (25)</td>
<td>1871 (24)</td>
<td>373 (32)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Undetermined</td>
<td>436 (5)</td>
<td>349 (4)</td>
<td>87 (8)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Killip class ≥2</td>
<td>2419 (27)</td>
<td>1959 (25)</td>
<td>460 (40)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>GUSTO score mean (standard deviation)</td>
<td>23 (55)</td>
<td>24 (44)</td>
<td>23 (42)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Ejection fraction &lt; 40%</td>
<td>739 (14)</td>
<td>609 (14)</td>
<td>130 (20)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Delay from symptom to admission (h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3</td>
<td>2761 (35)</td>
<td>2450 (35)</td>
<td>311 (31)</td>
<td>0.012</td>
</tr>
<tr>
<td>&lt; 6</td>
<td>4732 (60)</td>
<td>4197 (61)</td>
<td>535 (54)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>&lt; 12</td>
<td>6001 (76)</td>
<td>5274 (88)</td>
<td>727 (73)</td>
<td>0.039</td>
</tr>
<tr>
<td>Procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>7398 (84)</td>
<td>6582 (85)</td>
<td>836 (72)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>5244 (59)</td>
<td>4470 (62)</td>
<td>560 (48)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Primary percutaneous coronary intervention</td>
<td>2048 (23)</td>
<td>1858 (24)</td>
<td>219 (19)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Coronary artery bypass graft</td>
<td>623 (7)</td>
<td>542 (7)</td>
<td>85 (7)</td>
<td>0.75</td>
</tr>
<tr>
<td>Medical therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>7012 (84)</td>
<td>6166 (85)</td>
<td>846 (82)</td>
<td>0.09</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>5891 (71)</td>
<td>5232 (72)</td>
<td>659 (64)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Statin</td>
<td>5373 (65)</td>
<td>4753 (65)</td>
<td>620 (60)</td>
<td>0.003</td>
</tr>
<tr>
<td>ACE or ARB</td>
<td>4696 (56)</td>
<td>4071 (56)</td>
<td>625 (61)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Values are number (%). ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

### Table 3

Age-adjusted case-fatality rates (referent: coronary vascular disease alone).

<table>
<thead>
<tr>
<th>Prior disease</th>
<th>Odds ratio (95% confidence interval)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAD</td>
<td>1.36 (1.03–1.79)</td>
<td>0.027</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>1.74 (1.27–2.40)</td>
<td>0.001</td>
</tr>
<tr>
<td>Both PAD and stroke/TIA</td>
<td>1.73 (0.87–3.44)</td>
<td>0.115</td>
</tr>
<tr>
<td>PolyVD</td>
<td>1.52 (1.23–1.88)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

PAD: peripheral arterial disease; PolyVD: polyvascular disease; TIA: transient ischaemic attack.
of statin therapy in patients presenting with AMI regardless of their clinical profile.

Thus, despite a higher risk profile and a greater incidence of comorbidities, patients with a history of PAD or CVD were less likely to receive effective cardiac medications and interventional procedures. Even if it would appear intuitive, whether these treatment disparities contributed to the observed difference in hospital mortality is not entirely clear and cannot be inferred from the present data. Nevertheless, guideline-recommended medications should be strongly recommended in this high-risk subgroup [24]. In the GRACE registry, improvement in the clinical outcome resulting from changes in pharmacological and procedural care of patients with AMI was independent of the risk status of the study population [9], and use of guideline-recommended medications was associated with improved outcome in all subgroups [25]. In addition, use of a combination of guideline-recommendmedicationswas associated with lower 6-month mortality, with an incremental and synergistic effect [24]. These findings suggest a need for further evaluation of treatment decisions in patients with PolyVD presenting with an AMI and demonstrate considerable opportunity to improve the outcomes of these high-risk patients. Future clinical trials will evaluate the impact of an aggressive atherosclerosis risk-factor management and strategy on outcomes in patients with PolyVD admitted for AMI.

**Limitations**

The Alliance project is an observational study gathering data from five different registries and is therefore subject to inherent limitations particularly related to the potential heterogeneity between studies [26]. However, definitions were homogeneous and endpoints (medications, coronary intervention or total death) were unambiguous and easy to ascertain. Almost all (91%) of the patients in these five studies contributed data to the pooled analysis, therefore it is unlikely that patient selection created bias. Furthermore, an excess mortality in patients with PolyVD was observed in each registry (ORs ranging from 1.21 to 1.85) and the excess mortality in PolyVD patients was also observed after adjustment for the type of registry. Another concern relates to the fact that the use of additional key therapies such as clopidogrel or glycoprotein IIb/IIIa inhibitors was not recorded in each registry and therefore could not be analysed, yet their underuse may have contributed to the higher mortality of PolyVD patients. Third, PolyVD was self-reported. This may lead to under-diagnosis of PAD or CVD, and whether our findings can be extrapolated to patients with asymptomatic PAD or CVD deserves further investigation. Finally, the present study did not evaluate long-term morbidity and mortality.

**Conclusion**

Polyvascular disease is frequent among patients admitted for AMI and is an easy and simple predictor of outcome. Despite a more severe clinical presentation and a worst outcome, patients with PolyVD received fewer guideline-recommended medications and had fewer coronary procedures performed, which may explain, at least partially, their higher in-hospital mortality. These results demonstrate considerable opportunity to improve the outcome of these high-risk patients. Flagging patients with known PolyVD early after admission and early recognition of their intrinsic poor prognosis may help clinicians to ensure that they receive appropriate care while in hospital and are prescribed evidence-based medications at discharge.

**Conflict of interest statement**

None.

**Acknowledgements**

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