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Peripheral artery disease patients may benefit more from aggressive secondary prevention than aneurysm patients to improve survival

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ABSTRACT

Background and aims: Although it has become clear that aneurysmal and occlusive arterial disease represent two distinct etiologic entities, it is still unknown whether the two vascular pathologies are prognostically different. We aim to assess the long-term vital prognosis of patients with abdominal aortic aneurysmal disease (AAA) or peripheral artery disease (PAD), focusing on possible differences in survival, prognostic risk profiles and causes of death.

Methods: Patients undergoing elective surgery for isolated AAA or PAD between 2003 and 2011 were retrospectively included. Differences in postoperative survival were determined using Kaplan-Meier and Cox regression analysis. Prognostic risk profiles were also established with Cox regression analysis.

Results: 429 and 338 patients were included in the AAA and PAD groups, respectively. AAA patients were older (71.7 *vs.* 63.3 years, $p < 0.001$), yet overall survival following surgery did not differ (HR: 1.16, 95% CI: 0.87–1.54). Neither was type of vascular disease associated with postoperative cardiovascular nor cancer-related death. However, in comparison with age- and gender-matched general populations, cardiovascular mortality was higher in PAD than AAA patients (48.3% *vs.* 17.3%). Survival of AAA and PAD patients was negatively affected by age, history of cancer and renal insufficiency. Additional determinants in the PAD group were diabetes and ischemic heart disease.

Conclusions: Long-term survival after surgery for PAD and AAA is similar. However, overall life expectancy is significantly worse among PAD patients. The contribution of cardiovascular disease towards mortality in PAD patients warrants more aggressive secondary prevention to reduce cardiovascular mortality and improve longevity.

1. Introduction

Traditionally, dilatation and occlusion were considered to represent two extremes on the same spectrum of arterial disease. As such, it was presumed that both entities were the result of extensive atherosclerosis [1]. This assumption was largely based on the fact that the two vascular diseases share a number of risk factors, such as smoking, hypertension, and older age [2–6].

However, over the years, disparities in etiologic cardiovascular risk profiles were demonstrated [7–11], as well as differences in the severity of atherosclerotic burden between patients suffering from aneurysmal and occlusive disease [7,12–16]. In addition, differences in cytokine levels, inflammation, and enzyme activity were found in the arterial walls affected by aneurysmal or occlusive disease [9,17,18]. Also, recent studies show that genetic susceptibility, rather than environmental risk factors, plays a particularly important role in the pathogenesis of aneurysmal disease [19–21]. Although it is becoming clear that aneurysm formation and atherosclerosis are two separate clinical entities, it remains unclear whether this also translates into long-term prognostic differences between the two patient categories. Differences in long-term outcome, particularly of cardiovascular nature, would warrant more aggressive secondary prevention regimens for those at the highest risk.

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With surgical treatment as a uniform indicator of severe disease, we aim to determine the long-term vital prognosis for abdominal aneurysmal and peripheral occlusive disease patients, focusing on possible differences in survival, risk profiles, and causes of death.

2. Patients and methods

Patients undergoing elective surgery for AAA or PAD at the Erasmus University Medical Centre in Rotterdam between January 2003 and December 2011 were retrospectively identified using operation codes and surgical reports. Long-term survival was assessed from the day of surgery onward. In order to improve homogeneity in terms of operative stress and severity of disease, all percutaneous endovascular procedures, i.e. percutaneous endovascular aneurysm repair (EVAR) and percutaneous lower limb PTA or stenting procedures, were excluded. AAA patients who underwent prior endovascular or open surgical revascularization for lower limb ischemia were excluded from this study. PAD patients who underwent prior treatment of an abdominal or thoracic aortic aneurysm were also excluded. Treatment indications for AAA and PAD were both in accordance with the European Society for Vascular Surgery guidelines [22,23]. Similarly, all vascular surgery patients were treated in accordance with these guidelines regarding secondary cardiovascular prevention. As a result, all patients followed a lifelong regimen of anti-platelets and statins, as well as anti-hypertensive and anti-diabetes medication on indication. Baseline characteristics were obtained from hospital charts and included age, gender, comorbidity, prior vascular interventions, smoking status (current/former or non-smoker), and body mass index (BMI). Institutional approval for this study was obtained, and no informed consent was required according to local directives for retrospective studies. The study complies with the Helsinki declaration on research ethics.

2.1. Definitions

Diabetes mellitus was recorded if diabetes was mentioned in the medical history or if patients used insulin or oral anti-diabetics. Hypertension was defined as blood pressure >140/90 mmHg or use of anti-hypertensive medication. A history of cancer was defined as past or current malignant neoplastic disease, except for basal cell carcinoma. Renal insufficiency was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min as calculated from preoperative serum creatinine levels using the MDRD formula. Smoking status and BMI were derived from the medical records. Cerebrovascular disease was defined as mentioning of symptomatic carotid artery disease (i.e., transient ischemic attack or stroke) and/or a carotid endarterectomy or stenting procedure in the medical history. Ischemic heart disease was considered if one of the following was present: reference to previous cardiac ischemic events in cardiology notes, prior coronary intervention or evidence of myocardial ischemia in provocative pre-operative tests (dobutamine stress echocardiography or myocardial scintigraphy). Prior vascular interventions were defined as either surgical or percutaneous vascular treatment prior to the index operation, not including coronary revascularization.

2.2. Endpoints

The primary endpoint was overall mortality. Secondary endpoints were cardiovascular and cancer-related death.

2.3. Cause of death

Causes of death were obtained from the Dutch Central Bureau of Statistics (CBS). A database consisting of medical data on the study participants was anonymized by authorized data managers employed by CBS. This data set was subsequently imported and linked to the Dutch death registry, which is maintained by the CBS. According to Dutch privacy legislation, data analysis was only allowed to authorized researchers (KU, FBG) from designated institutions inside a secure environment after approval from the institutional ethical committee. Furthermore, output was checked by the CBS for privacy violations before it was allowed for publication purposes. Autopsy was not routinely performed. The cause of death was defined as the initial cause of health deterioration, consequently resulting in death. This approach is similar to the strategy used for the overall Dutch population. The causes of death were grouped according to the *International Classification of Diseases, 10th Revision* (ICD-10). For cardiovascular death, the following codes were used: I10-I79; for cancer-related death: C00-C43, C45-C97, D00-D03, and D05–09; for death due to obstructive pulmonary disease: J40-J47; and for digestive system-related causes: K00-K93.

For survival estimation in the general population, a comparative age and gender matched control group was derived from civil registries of the Dutch population –also maintained by the CBS– for both the AAA and PAD group separately. To assess differences in causes of death compared to the general population, deaths in the respective study groups were individually matched on demographic properties to cause of death distributions in the general population. For example, if deaths in the AAA group consisted for 5% of males between the aged between 80 and 85 at the time of death, the AAA matched cohort corresponds proportionally to the death distribution for males with the same age and gender characteristics from the general population.

2.4. Statistical methods

Baseline characteristics were described as counts and percentages (dichotomous variables), or means and standard deviations (continuous variables). Differences at baseline were determined using Pearson's chi-square analysis and student t-test, where appropriate. Survival for the aneurysmal and occlusive disease cohorts was initially assessed using Kaplan-Meier and log-rank analyses. Differences in the vital prognosis were subsequently investigated using adjusted Cox proportional hazards regression. Multivariable analyses adjusted for demographics, comorbidities, and other risk factors (age, gender, diabetes mellitus, ischemic heart disease [IHD], history of cancer, renal insufficiency, BMI, and current smoking). The AAA group was designated as the reference category in these analyses. Prognostic risk profiles for the two study groups were established by determining hazard ratios for potential risk factors separately for the AAA and PAD group using Cox proportional hazards model. Univariately significant covariates were included in the multivariable model. All tests were two-sided and significance was considered when p-value < 0.05. Statistical analysis was performed using the SPSS Statistics 20 (IBM Inc., Chicago, IL).

3. Results

A total of 470 patients undergoing elective surgery for AAA and 353 patients for PAD were identified. In the AAA group, 40 patients were excluded because of prior treatment for PAD, while 14 patients were excluded in the PAD group for prior aneurysm treatment. Two patients, one in each treatment group, were excluded due to unavailable follow-up data as a result of emigration. The remaining 429 AAA and 338 PAD patients were considered suited for analysis.