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REVIEW

The Risk of Disease Progression in Peripheral Arterial Disease is Higher than Expected: A Meta-Analysis of Mortality and Disease Progression in Peripheral Arterial Disease

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WHAT THIS PAPER ADDS

This review of available data of risk to limb and life among subjects with peripheral arterial disease indicates a higher risk of disease progression than expected. These findings should be considered when evaluating patients for treatment and interventions.

Objective: Peripheral arterial disease (PAD) afflicts up to 20% of older people and is associated with a high risk of cardiovascular (CV) morbidity, but a rather low risk of progression of leg symptoms. These risk estimations are largely taken from cohort studies performed 20 years ago. To test the validity of this, available data were systematically reviewed and attempts were made to perform meta-analyses of CV risk and disease progression.
Methods: A database literature search was conducted of the period 1990–2015 using related subject headings. Inclusion criteria were cohort studies for PAD, sample size >100 subjects, follow up time ≥1 year, and studies presenting endpoints covering mortality and/or CV events. Analyses were performed for a reference population, as well as groups with asymptomatic PAD (APAD), symptomatic PAD, and subjects with ankle brachial index <0.9.
Results: Of 354 identified articles, 35 were eligible for systematic review. Sample size varied between 109 and 16,440 subjects. Mean age in the cohorts ranged from 56 to 81 years (SD 10.8) and mean follow up was 6.3 years (range 1–13). Most included patients with symptomatic PAD had IC (91%). Symptomatic PAD subjects had higher 5 year cumulative CV mortality than the reference population, 13% versus 5%. During follow up, approximately 7% of APAD patients progressed to IC, and 21% of IC patients were diagnosed as having critical limb ischemia, with 4–27% undergoing amputations.
Conclusion: The risk to the limb is underestimated in PAD patients, whereas the CV related morbidity is more moderate than stated in the guidelines. The latter observation is especially valid for IC patients. These findings should be considered when evaluating patients for treatment.

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INTRODUCTION

Peripheral arterial disease (PAD) may be suspected by symptoms and is diagnosed by ankle brachial index (ABI) measurements. PAD is common in older people, with about 20% of those afflicted >60 years of age, increasing to nearly 50% in those aged ≥85 years. Most PAD is asymptomatic, but about 35% have symptoms such as intermittent claudication (IC) or critical limb ischemia (CLI).[1]

The prevalence is likely to increase even further in the future with the growing number of older people in society. PAD is associated with the lowest quality of life of all symptomatic cardiovascular (CV) disease manifestations,[2–4] and is also the most costly.[5] Accordingly, from a public

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health perspective it is important to have solid data on the epidemiology and the natural course of PAD.

All PAD stages are associated with an increased risk of CV mortality and morbidity besides the probability of deterioration of leg symptoms. The scientific support for this comes largely from patient cohorts followed in the 1980s and early 1990s, before the era of risk factor modification and endovascular treatment options. In particular, it seems that data on natural course of PAD are based mainly on publications from the early 1990s.[6,7]

The aim of this systematic review was to improve assessment of risks associated with PAD by gathering all current reliable data on long-term risk of leg symptom deterioration and CV morbidity associated with PAD. A secondary aim was to assess if these risks differed among the sexes.

METHODS

Search strategy

An electronic literature search was conducted in December 2010 using the MEDLINE database. A second literature search was performed on 24 April 2015 using MEDLINE Web of Science, Science direct and Cochrane database. Three more articles were identified for inclusion in the analysis. The search strategy included basic medical subject headings: peripheral vascular disease, intermittent claudication, lowers extremity ischemia and poly-vascular disease, which were followed by the headings: prognosis and natural history. The results were combined to capture all articles encompassing these two topics. Retrieved papers were limited to English language and human studies. Two investigators were responsible for the search and data extraction.

Selection

The titles of the identified articles were reviewed for relevance followed by assessment of the abstracts for topic significance. Finally, the full texts of selected articles were studied. Additional relevant citations identified from reviewed articles were also gathered. All types of study designs were accepted (Fig. 1). Inclusion criteria were: cohort studies covering PAD patients, sample size $\geq$100 subjects, clear presentation of mortality and/or CV events and endpoint data, and follow up $\geq$1 year.

Review articles, interventional studies, and publications without relevant endpoints were excluded as were studies in which PAD was diagnosed without the use of an objective method and based on symptoms only. For studies reporting data from the same population several times, the publication with the longest follow up time was used.

Data extraction and data processing

The content of selected studies was described and presented to summarize inclusion criteria, concomitant risk factors, baseline medication use, and outcome. Follow up time was estimated as mean follow up time or total follow up time depending on available data. Three studies reported median follow up time. For each included study the following data were extracted: population characteristics (sample size, number of men and women, mean age with standard deviation when available), baseline characteristics (smoking, diabetes mellitus (DM), hypertension (HT), previous CV events, and medication), endpoints (CV and non-CV mortality and all-cause mortality), CV events during follow up, and PAD stage at baseline. The study populations were classified into six groups based on baseline disease stage (Table 1): (1) reference, no PAD (defined by no/unknown PAD or $0.9 \leq$ ABI ≤ 1.4); (2) asymptomatic PAD (ABI $<$0.9 without clinical manifestations); (3) symptomatic PAD (diagnosed IC or CLI); (4) ABI based group (subjects with ABI < 0.9 without information on symptoms); (5) total PAD cohort (all subjects with PAD regardless of stage or with ABI < 0.9); and (6) PAD subjects separated by sex.

For analysis of incidence, incidence rates were collected when reported, otherwise raw numbers and follow up time were used.

The cohorts analyzed consisted of different studies. For description of PAD stages, analyses were based on 23 studies that displayed baseline data on clinical diagnoses (included in reference, asymptomatic, and/or symptomatic PAD groups). The remaining studies based PAD diagnosis on ABI without presenting symptoms. Data on disease progression was presented in eight studies, while revascularization and amputation rates were given in six and nine studies, respectively. Only five studies separated analyses by sex. In all but two studies (one using age only and one unadjusted) adjustments were made for age, gender, BMI, and risk factors as smoking, DM, HT, and prevalent CV disease (Table 2).

Validation

All studies fulfilling the inclusion criteria were critically assessed by two investigators to ensure reporting of relevant information. Study design, selected population, sample size, sex, and follow up time frame were summarized and evaluated in concordance with PRISMA guidelines.[8]

Statistical analyses

Study characteristics such as inclusion criteria, concomitant risk factors, medication use, follow up time, and outcome were tabulated. For each study the extracted data covered both the entire reported population and sub-populations defined by disease stage as described above. Incidence ratio with confidence intervals was extracted when possible. In studies not presenting incidence in events per person years, person year exposure was computed from available sources (mean follow up time, total follow up time). Incidences with confidence intervals (CI) for mortality endpoints were computed for each subgroup and plotted in Forest plots with or without pooled estimates using a random effects model.[9] Because of data heterogeneity, 95% CI were calculated and random effect models used to pool