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FOR DEBATE

# Ten Year Mortality in Different Peripheral Arterial Disease Stages: A Population Based Observational Study on Outcome☆

**Fredrik Sartipy** [a,*], **Birgitta Sigvant** [b], **Fredrik Lundin** [c], **Eric Wahlberg** [d]

[a] Section of Vascular Surgery, Department of Clinical Science and Education, Karolinska Institutet at Södersjukhuset, Stockholm, Sweden
[b] Department of Surgical Sciences, Uppsala University, Uppsala, Sweden
[c] Centre of Clinical Research, County Council of Värmland, Karlstad, Sweden
[d] Department of Medicine and Health, Linköping University, Linkoping University Hospital, Linköping, Sweden

**WHAT THIS PAPER ADDS**

This cohort study provides up to date long-term follow-up data on mortality for different PAD stages in a population based setting. Age adjusted risks for cardiovascular and all cause mortality are presented separately for subjects with different PAD stages and compared with a reference population. PAD subjects were still found to have a high mortality risk, similar to that presented almost two decades ago. Asymptomatic PAD (APAD) confers similar risk of cardiovascular death as symptomatic subjects. These findings highlight the need for awareness and preventive strategies for all PAD stages, including APAD subjects.

**Objective:** The aim was to determine long-term mortality rates and the underlying cause of death for subjects with different peripheral arterial disease (PAD) stages in a population based setting.

**Methods:** A randomly selected population sample of 5080 subjects was enrolled in the study in 2004–2005. Participants completed health state questionnaires and underwent ankle brachial index (ABI) measurements for classification into PAD severity stages and reference subjects. A follow-up was conducted by the end of 2015 using data from Swedish governmental national registers for cause of death, which was then compared with PAD stage determined at baseline in 2005.

**Results:** The 10 year all cause mortality was 27% for reference cases, 56% for asymptomatic PAD (APAD), 63% for intermittent claudication (IC), and 75% for severe limb ischaemia (SLI). Among all PAD subjects, cardiovascular (CV) causes were the most common main cause of death (45%) and a CV event was present as either the main or one of the three most common contributing causes of death in 64% of the cases. The age adjusted hazard ratios for a main cause of death by a CV event were 1.9 (95% CI 1.5–2.3) for APAD, 2.6 (95% CI 2.1–3.4) for IC, and 3.5 (95% CI 2.3–5.2) for SLI.

**Conclusion:** PAD subjects, including the APAD subjects, are still at high risk of CV death. The mortality risks are more than doubled in symptomatic PAD patients compared with reference subjects and increase by severity of PAD stage. Awareness and improved risk reduction management of PAD are still warranted.



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## INTRODUCTION

Peripheral arterial disease (PAD) is a major healthcare issue worldwide with a prevalence that increased by 23% between 2000 and 2010.[1] Patients with PAD have an increased risk of cardiovascular (CV) mortality.[2,3] Knowledge of PAD risk levels is mainly based on studies performed over 10 years ago,[4–6] with few being population based and covering all stages of PAD. Treatment of risk factors such as smoking, hypertension, diabetes, and dyslipidaemia has improved since then and there are recent reports suggesting that mortality rates for the comparable illnesses coronary artery disease (CAD) and stroke are

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* Corresponding author. Kirurgkliniken, Sjukhusbacken 10, 118 83 Stockholm, Sweden.
*E-mail address:* fredrik.sartipy@sll.se (Fredrik Sartipy).



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declining.[7–9] Over the last two decades, in Sweden, CAD mortality has decreased by approximately two thirds,[8] mainly due to reduction in major risk factors such as high cholesterol.[10]

Up to date information on morbidity and mortality rates in PAD is essential in decision making for vascular procedures and other treatments. From a societal perspective it is important for prioritisation and allocation of resources since PAD affects large populations for a long time period.[11] Accordingly, there is a need for updated information on the risks associated with PAD.

Besides being more reliable for assessing mortality from a societal perspective, prospective population based cohort studies have the advantage of enabling quantification and duration of risk factors influencing the variability of the disease. Such cohorts can also identify subgroups at risk that could benefit from improved prophylactic treatment. More widespread implementation of the latter is likely to result in better patient survival, but needs to be verified by epidemiological data.

The aim of this prospective population based observational study was to determine current mortality rates for all PAD stages. The hypothesis was that mortality for PAD has tended to decline compared with the rates reported from the 20th century.

## METHODS

### Study design

The study was conducted as a prospective observational population based cohort study using physical examinations and questionnaires at baseline, and register data at the end of the observation time 10 years later. The study was a long-term follow-up of the original cohort, published and described in 2007.[12]

### Study population

The cohort was assembled between August 13, 2004, and January 13, 2005, through invitation of 8000 randomly selected men and women aged 60–90 years from the Swedish tax register from four different regions in Sweden. The sample had the same distribution of age and gender as the general population in this age group. Four regions were enrolled (Malmö, Karlstad, Älvkarleby, and Skellefteå) to obtain representation from urban, industrial, rural, and agricultural districts. In each region, 2000 subjects were invited and in total 5080 subjects agreed to participate and each provided written informed consent. The observation period ended in December 31, 2015, when individual patient register data from Swedish national registers covering 2004–2015 were retrieved, thus rendering an observation time of 10 years.

### Data collection

In 2004 all subjects were invited to participate by a letter. Three self administered questionnaires that assessed risk factors for PAD, current pharmacological treatment, concomitant diseases, present and former smoking habits, leg symptoms, and walking ability were enclosed with the invitation. Walking ability covered the questions in the Rose's World Health Organisation (WHO) questionnaire and Walking Impairment Questionnaire (WIQ).[13,14] The participants were invited to a primary healthcare clinic where specially trained nurses performed bilateral ankle brachial index (ABI) measurements and assisted in completion of the questionnaires when necessary. The procedure has been described in detail previously.[12] The subjects were divided into the following subgroups by ABI and symptomatic severity stage of PAD: asymptomatic PAD (APAD), intermittent claudication (IC), or severe limb ischaemia (SLI). Subjects with normal ABI and no qualifying symptoms were classified as the reference group (Ref). SLI was used as a proxy for critical limb ischaemia,[12] which was difficult to assess in an epidemiological study of this kind which relied on questionnaire data. Subjects who were diagnosed and considered at risk of critical limb ischaemia or who had a brachial blood pressure above 180 mmHg were referred to their general practitioner, but no other intervention was made during the assessment period.

### Definitions of PAD stages

APAD: subjects with an ABI $<0.9$ without qualifying answers in the questionnaire (i.e., no pain in the calf or thigh when walking).

IC: subjects with an ABI $<0.9$ and qualifying answers in the questionnaire (i.e., pain in calf or thigh when walking with relief at rest).

SLI: all subjects with lowest ankle blood pressure $\leq 70$ mmHg.

Ref: subjects with an ABI $\geq 0.9$ and no symptomatic qualifying answers.

### Register data

Healthcare is mainly organised, administered, and funded by the government in Sweden, which also keeps a variety of mandatory healthcare registers. Every citizen has a unique personal registration number that makes it possible to follow each one over time and to cross link data. One of the registers is the National Patient Register (NPR), which includes all diagnoses recorded at Swedish hospitals covering all in and outpatient care since 2001. Beyond the primary discharge diagnosis, an unlimited number of secondary diagnoses can be recorded. The International Classification of Diseases, 10th revision (ICD-10), has been used for diagnosis coding since 1997. The NPR is updated once a year and covers $>99\%$ of all hospital discharges. Cases with a missing main diagnosis are around 1%. The NPR is regularly checked for quality and validity.[15]

The Cause of Death Register (CDR) contains data of all deaths in Sweden since 1961. The data collected include time of death, underlying and contributing causes of death, as well as 30 other variables. The use of CDR, in combination with NPR, has previously been demonstrated to provide highly accurate data in similar patient populations.[16]

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