

# The association of comorbid depression with mortality and amputation in veterans with peripheral artery disease

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## ABSTRACT

**Objective:** Peripheral artery disease (PAD) is an increasing health concern with rising incidence globally. Previous studies have shown an association between PAD incidence and depression. The objective of the study was to determine the association of comorbid depression with PAD outcomes (amputation and all-cause mortality rates) in veterans.

**Methods:** An observational retrospective cohort of 155,647 patients with incident PAD (2003-2014) from nationwide U.S. Veterans Health Administration hospitals was conducted using the national Veterans Affairs Corporate Data Warehouse. Depression was measured using concurrent *International Classification of Diseases, Ninth Revision* diagnosis codes 6 months before or after PAD diagnosis. The main outcomes were incident major amputation and all-cause mortality. Crude associations were assessed with Kaplan-Meier plots. The effects of depression adjusted for covariates were analyzed using Cox proportional hazards models.

**Results:** Depression was present in 16% of the cohort, with the occurrence of 9517 amputations and 63,287 deaths (median follow-up, 5.9 years). Unadjusted hazard ratios (HRs) of comorbid depression for amputations and all-cause mortality were 1.32 (95% confidence interval [CI], 1.25-1.39) and 1.02 (95% CI, 0.99-1.04), respectively. After adjustment for covariates in Cox regression models, a diagnosis of comorbid depression at the time of PAD diagnosis was associated with a 13% higher amputation (HR, 1.13; 95% CI, 1.07-1.19) and 17% higher mortality (HR, 1.17; 95% CI, 1.14-1.20) risk compared with patients with no depression. On stratification by use of antidepressants, depressed patients not taking antidepressants had a 42% higher risk of amputation (HR, 1.42; 95% CI, 1.27-1.58) compared with those without depression. Patients taking antidepressants for depression still had increased risk of amputation but only 10% higher compared with those without depression (HR, 1.10; 95% CI, 1.03-1.17). Interestingly, patients taking antidepressants for other indications also had a higher risk of amputation compared with those not having depression or not taking antidepressants (HR, 1.08; 95% CI, 1.03-1.14). Having any diagnosis of depression or the need for antidepressants increased the mortality risk by 18% to 25% in the PAD cohort compared with those without depression and not taking antidepressants for any other indication.

**Conclusions:** PAD patients with comorbid depression have a significantly higher risk of amputation and mortality than PAD patients without depression. Furthermore, untreated depression was associated with an increased amputation risk in the PAD population, more so than depression or other mental illness being treated by antidepressants. The underlying mechanisms for causality, if any, remain to be determined. The association of antidepressant treatment use with amputation risk should prompt further investigations into possible mechanistic links between untreated depression and vascular dysfunction. (J Vasc Surg 2018;■:1-10.)

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This work was supported by start-up funds from the University of California, San Francisco, and the Northern California Institute for Research and Education. Additional support came from Award No. KL2RR024130 from the National Center for Research Resources, Award No. 1K23HL122446-01 from the National Institute of Health/NHLBI, and a Society for Vascular Surgery Seed Grant and Career Development Award (S.M.G.). Furthermore, the work was also supported by an American Heart Association Mentored Clinical and Population Research Award (15MCPRP25580005), NIH-NIA Award No. 1R03AG050930, and American Geriatric Society/Society for Vascular Surgery Foundation Jahnigen Career Development Award (S.A.). This material is the result of work supported with resources and the use of facilities at the Atlanta VA Medical Center, Decatur, Georgia. The content is solely the responsibility of the authors and does not necessarily

represent the official views of the National Center for Research Resources or the National Institutes of Health. The work does not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government. The funding organizations were not involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Author conflict of interest: none.

Presented at the Twelfth Annual Academic Surgical Congress, Las Vegas, Nev, February 7-9, 2017.

Additional material for this article may be found online at [www.jvascsurg.org](http://www.jvascsurg.org).

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

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<https://doi.org/10.1016/j.jvs.2017.10.092>

Peripheral artery disease (PAD) is a significant health issue with a rising incidence globally.<sup>1</sup> Patients with PAD continue to be threatened with an unacceptably high risk for cardiovascular (CV) events<sup>2,3</sup> and suffer significant morbidity related to claudication and limb loss, resulting in a decreased quality of life.<sup>4,5</sup> Inflammation and endothelial dysfunction play an important role in the pathophysiologic process of PAD. Whereas circulating inflammatory markers are associated with disease progression and mortality,<sup>6</sup> impaired endothelial function independently predicts future CV events.<sup>7,8</sup> More recent evidence suggests that depression, which is associated with inflammation and endothelial dysfunction,<sup>9</sup> should join smoking, diabetes, hyperlipidemia, and hypertension as a recognized risk factor for PAD.<sup>10,11</sup>

Although there has been recognition of the role of depression in the development and progression of CV disease, the relationship remains less well characterized in the PAD population.<sup>12-16</sup> It has been previously demonstrated that patients with depressive symptoms had a higher risk of prospective PAD occurrence during a period of 7 years.<sup>10</sup> Depression in the setting of PAD also leads to decreased functional outcomes and walking capacity,<sup>17,18</sup> worse patency rates after revascularization,<sup>19</sup> and increased progression of PAD.<sup>20</sup> McDermott et al<sup>21</sup> also recently demonstrated a higher association for all-cause mortality and CV mortality in PAD patients with depression.

The impact of comorbid depression on the risk of amputation in patients with PAD is less understood. In addition, the effect of antidepressant treatment on outcomes in this population has not been studied. This analysis sought to characterize the association of comorbid depression and of antidepressant treatment with the risk of limb loss and mortality in the PAD population.

## METHODS

**Sample and database.** Incident PAD patients were identified by Veterans Health Administration data from 2003 to 2014 (N = 155,647) using a validated algorithm (*International Classification of Diseases, Ninth Revision* diagnosis code for PAD and any one of three criteria: two ankle-brachial indices in 14 months, two visits to a vascular surgeon or clinic in 14 months, or any PAD procedure code).<sup>22</sup> Patients with a PAD diagnosis code in the preceding 2 years (2000-2002) were excluded to capture incident cases. A comprehensive list of covariates was obtained: age at PAD diagnosis (estimated using date of birth), sex, race, and socioeconomic status (SES; median household income of the patient's most recent residential ZIP code tabulation area); body mass index; serum creatinine concentration; and comorbidities, such as diabetes mellitus, hypertension, coronary artery disease (CAD), chronic obstructive pulmonary disease, congestive heart failure (CHF), atrial fibrillation, carotid disease, chronic kidney disease, and end-stage renal disease. Smoking status (using a validated method<sup>23</sup>) and use of

## ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective analysis of prospectively collected data from the National Veterans Affairs Corporate Data Warehouse
- **Take Home Message:** In 155,647 veterans with peripheral artery disease, comorbid depression was present in 16%, and it was associated with increased risk of death and amputation, particularly among depressed patients not taking antidepressants.
- **Recommendation:** The authors suggest that all patients with peripheral artery disease be evaluated for depression and receive treatment if depression is identified.

the following medications were assessed: antiplatelet agents, statins, cilostazol, antiglycemics, and antidepressants. All covariates were measured within a 6-month time frame (before or after) of the PAD diagnosis date from the national Veterans Affairs (VA) Corporate Data Warehouse and VA Medical SAS administrative databases.

**Study exposure and outcome.** Comorbid depression was defined as having an *International Classification of Diseases, Ninth Revision* diagnosis code of 293.83, 296.2x, 296.3x, 300.4, or 311 either at least once in an inpatient setting or at least twice within 14 months in an outpatient setting within 6 months before or after the PAD diagnosis date ([Supplementary Table I](#), online only; definition based on data from prior VA studies).<sup>24-26</sup> Antidepressant use was obtained from the VA pharmacy files for prescriptions filled at a VA pharmacy as well as from the non-VA medication file, which holds data on medications filled by veterans and covered by the VA regardless of where the prescription was filled. Antidepressants were classified as selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and others ([Supplementary Table I](#), online only). Patients could be taking multiple medications, but no differentiation was made between subjects taking one or more drugs within a given category. In patients without a diagnosis of depression, we did not explore the indication for use of antidepressant medications for the purpose of this analysis (such as smoking cessation, post-traumatic stress disorder [PTSD], obsessive-compulsive disorder [OCD], anxiety disorders, social phobia, panic disorder, bulimia nervosa, premenstrual dysphoric disorder, borderline personality disorder, and obesity).

The outcomes of interest were incident major amputation (below and above the knee) and death after the PAD diagnosis date. Specific amputation codes are defined in [Supplementary Table I](#) (online only); long-term survival of the cohort was extracted from the VA Vital Status File. The follow-up continued through outcome occurrence,

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