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The Association Of Co-Morbid 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 show 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 US Veterans Health Administration hospitals was conducted using the national Veterans Affairs corporate data warehouse. Depression was measured using concurrent ICD-9 diagnosis codes six 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.

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Results—Depression was present in 16% of the cohort, with the occurrence of 9,517 amputations and 63,287 deaths (Median follow-up 5.9 years). Unadjusted HRs of comorbid depression for amputations and all-cause mortality were 1.32 (1.25, 1.39) and 1.02 (0.99, 1.04), respectively. After adjusting 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 as compared to 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 (1.27, 1.58)] as compared to those without depression. Patients taking antidepressants for depression still had increased risk of amputation but only 10% higher compared to those without depression [HR 1.10 (1.03, 1.17)]. Interstingly, patient taking antidepressants for other indications also had a higher risk of amputation compred to those not having depression or not on antidepressants [HR 1.08 (1.03, 1.14)]. Having any diagnosis of depression or the need for antidepressants increased the mortality risk by 18-25% in the PAD cohort compared to those without depression and not on antidperessants 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.

Table of contents summary

In this population-based study of 155,647 veterans with incident PAD from 2003-2014, co-morbid depression was associated with an increased risk of death and amputation, particularly among depressed patients not taking antidepressants. The finding that use of anti-depressantss could mitigate the increased amputation risk in PAD patients with co- morbid depression warrants further investigation.

INTRODUCTION

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

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[12–16]. It has been previously demonstrated that patients with depressive symptoms had a higher risk of prospective PAD occurrence over a period of 7 years[10]. Depression in the setting of PAD also leads to decreased functional outcomes and walking capacity[17, 18], worse patency rates after revascularization[19], and increased progression of PAD[20]. McDermott et al also recently demonstrated a higher association for all-cause mortality and CV mortality in PAD patients with depression[21].

The impact of co-morbid 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. The present analysis sought to characterize the association of co-morbid 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 using Veterans Health Administration (VHA) data from 2003-2014 (N=155,647) using a validated algorithm [ICD-9 diagnosis code for PAD and any one of three criteria: 1) Two ankle brachial indices (ABIs) in 14 months, 2) two visits to a vascular surgeon/clinic in 14 months, or 3) any PAD procedure code.][22] Patients with a PAD diagnosis code in 2 years prior (2000-2002) were excluded to capture incident cases. A comprehensive list of covariates were 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 (ZCTA)], body mass index (BMI), serum creatinine and comorbidities such as diabetes mellitus (DM), hypertension, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), atrial fibrillation (AF), carotid disease, chronic kidney disease (CKD), and end-stage renal disease (ESRD). Smoking status (using a validated method[23]) and use of the following medications were assessed: antiplatelet agents, statins, cilostazol, antiglycemics, and antidepressants. All covariates were measured within a 6-month timeframe (before or after) of the PAD diagnosis date from the national Veterans Affairs (VA) Corporate Data Warehouse (CDW) and VA Medical SAS administrative databases.

Study Exposure and Outcome

Co-morbid depression was defined as having an ICD-9 diagnosis code of 293.83, 296.2×, 296.3×, 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 of the PAD diagnosis date (See Supplemental table I, definition based on data from prior VA studies)[24–26]. Antidepressant use was obtained from the VA pharmacy files for prescriptions filled at a VA pharmacy as well as the non-VA medication file – which holds data on medications filled by veterans and covered by the VA regardless of where it was filled. Antidepressants were classified as selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCA), monoamine-oxidase inhibitor (MAOI), and others (see supplemental Table I for the full list). Patients could be on multiple medications, but no differentiation was made between subjects on one or more drugs within

a given category. In patients without a diagnosis for 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, obesity etc].

The outcomes of interest were incident major amputation (below and above knee) and death after the PAD diagnosis date. Specific amputation codes are defined in supplemental Table I, while long-term survival of the cohort was extracted from the VA vital status file. The follow-up continued through outcome occurrence, death (censoring event in the case of amputations), or December 31, 2015 (whereupon the subject was censored). Patients with prior amputations were included in the analysis but incident amputation was defined as the first amputation after the PAD diagnosis date.

Statistical Analysis

Demographic and clinical variables were assessed for the entire cohort and stratified by depression. Continuous variables were expressed as means (± standard deviations (SD)) or as medians (± interquartile ranges (IQR)) if they were not normally distributed. These were compared using independent sample t-tests or the Wilcoxon rank sum test. Discrete variables were compared using χ^2 tests for proportions. Proportions of missing data were also calculated with no variables missing over 15% except smoking (36.6%). Kaplan-Meier curves were used to compare overall survival (OS) by depression status. Cumulative incidence function (CIF) curves, instead of KM curves, were used to compare amputation-free survival (AFS) by depression status so as to account for death as a competing risk for patients since it precludes them from experiencing an amputation. Treating death as independent or non-informative censoring (as done in KM curves) would produce overestimation of the probability of amputation. Cause- specific Cox proportional hazards regression models were then constructed to calculate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for amputation and death by depression status alone, and then while allowing for interaction by antidepressant use. The models adjusted for the covariates listed in Table I. All variables were found to meet the proportional hazards assumption via log-log survival curves for amputation and mortality. Wald confidence limits were constructed for all hazard ratios. The statistical analysis was done using SAS version 9.4 (SAS Institute, Cary, NC). Two-sided p-values < 0.05 were considered statistically significant. This study was approved by the Emory University IRB and Atlanta VAMC Research and Development Committee. Informed consent was waived for a retrospective cohort study design with no human subject contact and minimal privacy risks.

RESULTS

The cohort consisted of 155,647 veterans with incident clinical PAD and a median follow-up of 5.9 years. The majority of the cohort was male (97.9%) with a mean age of 66.7 years (SD 9.9). There were 9,517 amputations and 63,287 deaths identified during the follow-up period. Of the total, 24,895 (16.0%) carried a diagnosis of depression. The demographics of the cohort are listed in Table I. Amongst patients with depression, 21,090 (84.7%) were on

antidepressants [15,353 (61.7%) were on SSRI, 2,373 (9.5%) were on SNRI, 2,565 (10.3%) were on TCAs, 13 (0.1%) were on MAOI and 11,349 (45.6%) were on other meds] while 3,805 (15.3%) were not on antidepressants. Amongst patients who did not carry a diagnosis of depression, 27% were on some form of antidepressant medication likely for other indications (e.g. PTSD, OCD, smoking cessation etc).

Unadjusted associations of depression with amputation and mortality

In unadjusted Cox models, the risk of amputation was 32% higher [HR 1.32 (1.25, 1.39)] for patients with depression as compared to those without. Depression had no association with mortality risk [HR 1.02 (0.99, 1.04)] in unadjusted analysis. Additionally, the association of depression with amputation and mortality was further explored by stratifying by use of antidepressants. CIF curves showed that AFS among those with depression was worse for those not taking antidepressants as compared to those without depression as well as those with depression on antidepressants (Gray's test, $p<0.0001$) [Figure I]. In terms of absolute risk, the 1- year, 3-year and 5-year AFS for patients with depression and not on antidepressants was 93.6%, 91.5% and 89.8%, respectively, compared to 97.8%, 96.3% and 95.2% AFS for patients without depression, respectively. Patients with depression on antidepressants or those without a diagnosis of depression but on antidepressants for other indications still had a significantly worse AFS as compared to those without depression ($p<0.001$). The absolute AFS at 1-year, 3-years and 5- years was 96.9%, 95.3% and 94.0% for depressed patients on antidepressants and 97.4%, 95.7% and 94.5% for those on antidepressants for other indications but better than those with untreated depression. With respect to mortality [Figure II], patients with untreated depression had a significantly lower OS [89.5% at 1 year, 76.3% at 3 years and 64.3% at 5 years] compared to the other three groups: patients without depression [94.4% at 1 year, 83.30% at 3 years and 71.5% at 5 years], patients on antidepressants for other indications [94.0% at 1 year, 82.2% at 3 years and 70.9% at 5 years] or those with depression but taking antidepressants [94.0% at 1 year, 81.9% at 3 years and 70.1% at 5 years] ($p<0.001$). Patients with depression on antidepressants had no significant difference in mortality as compared to those without depression, whether on antidepressants or not ($p= 0.08$).

Adjusted associations of depression with amputation and mortality

After adjusting for covariates (outlined in methods) in a Cox model [Table II], the hazard of death was 17% higher for depressed subjects versus non-depressed subjects [HR 1.17, 95% CI 1.14-1.20]. Additionally, the risk of amputation was 13% higher for depressed subjects [HR 1.13, 95% CI 1.07-1.19]. Female sex [HR for death 0.82, HR for amputation 0.44], higher BMI [HR for death 0.97, HR for amputation 0.96], Statin use [HR for death 0.77, HR for amputation 0.74], antiplatelet use [HR for death 0.71, HR for amputation 0.87], and Cilostazol use [HR for death 0.92, HR for amputation 0.77] were all associated with lower risks of death and amputation. Black race (vs white) was a significant predictor for increased risk of amputation [HR 1.42] but had a survival advantage in terms of mortality [HR 0.83] while low SES [HR for death 1.37, HR for amputation 1.15] had independently higher risk of mortality and amputation. Traditional atherosclerotic risk factors were associated with higher risk of mortality and amputation such as diabetes [HR for death 1.18, HR for amputation 1.74], hypertension [HR for death 1.11, HR for amputation 1.27] and current

smoking [HR for death 1.28, HR for amputation 1.17]. Of note, CHF [HR for death 1.91, HR for amputation 1.52] and CKD/ESRD [HR for death 1.47, HR for amputation 1.68] were also significant predictors of poor outcomes in PAD. PAD severity in terms of late presentation as rest pain or tissue loss (vs claudication) had a very strong association with death and major amputation [HR for death 1.19 and 1.71 respectively, HR for amputation 2.58 and 8.19 respectively].

Interaction of depression and use of antidepressants and its association with amputation and mortality

There was a statistically significant interaction between depression and antidepressant medications with regards to amputation ($p<0.0001$) [Table III, supplemental Table II]. After adding an interaction term to stratify by antidepressant use, depressed subjects not taking antidepressants had significantly elevated hazards of amputation [HR 1.42, 95% CI 1.27-1.58] relative to non-depressed patients and not on any antidepressants. Depressed patients on antidepressants as well as nondepressed patients but on antidepressants for other indications had a moderately higher risk of amputations compared to the non-depressed PAD patients [HR 1.08, 95% CI 1.03-1.14 and HR 1.10, 95% CI 1.03-1.17, respectively], but not to the same degree as untreated depression. Mortality risk was 18-25% higher for patients with depression (with or without use of antidperessants) or on antidepressants for other indications compared to those who were not depressed and not needing antidepressants for any other diagnoses. However, between these three groups, there was no significant difference in mortality for PAD patients [No depression on antidepressants for other indications (HR 1.18, 95% CI 1.16-1.21), depression with antidepressant use (HR 1.22, 95% CI 1.19-1.26) and without antidepressant use (HR 1.25, 95% CI 1.18-1.33)].

DISCUSSION

In this large cohort of veterans with incident PAD, the present study found that patients with co- morbid depression had a significantly higher risk of amputation (13%) and all-cause mortality (17%) than PAD patients without depression, after adjusting for covariates. There was a significant interaction of antidepressant use on the risk of amputation in PAD patients with depression but not so much on mortality. Being on prescription antidepressants for depression was associated with a significantly lowered risk for amputation (10% higher than non-depressed patients, not on antidepressants) in contrast to those with depression and not on antidepressants (42% higher than non-depressed patients, not on antidepressants). Interestingly, patients on antidepressants for other diagnoses (e.g. PTSD, OCD, anxiety etc) were also at a slightly higher risk of amputation (8% higher than non-depressed, not on antidepressants). Having any diagnosis of depression or the need for antidepressants increased the mortality risk by 18-25% in the PAD cohort. The data underline the negative impact of depression on prognosis of patients with PAD. Although causality is not established, the results presented also highlight the importance of further investigating depressive treatment options in the care of PAD patients suffering from depression.

Association between PAD and Depression

While the evidence base for the relationship between depression and heart disease is growing[12–16], the relationship between depression and PAD is still less well understood. In the Atherosclerosis Risk in Communities Study, Wattanakit et al. demonstrated that depression and anger proneness were associated with greater incident PAD independent of other PAD risk factors[27]. Using data from a large elderly Asian population, Wong et al. demonstrated that depressive symptoms were associated with subclinical PAD even after adjusting for stroke and other cardiovascular diseases[28]. McDermott et al. found that depression was present in 22% of patients with PAD, and an increasing number and severity of depressive symptoms were associated with greater impairment in lower extremity functioning[29]. Other investigators have demonstrated that PAD patients with greater depressive symptoms have more dramatic annual declines in functional performance[30], including reduced walking distance and fast walking velocity. Smolderen et al. found that depression was associated with less improvement in health status after undergoing revascularization[31]. Cherr and colleagues demonstrated that patients with depression are at increased risk for cardiovascular events and progression of contralateral PAD after undergoing lower extremity revascularization[20]. The results of the current study provide further evidence of a clear association between depression and PAD by demonstrating that depression is a significant risk factor for the endpoints of amputation and mortality in the management of PAD. In the cohort, depressed patients initially did not appear to have any mortality difference in unadjusted KM analysis. However, they were on average younger than non-depressed patients with more prevalence of current smoking and other comorbidities such as diabetes, CAD, CHF, COPD and kidney disease. Upon adjustment for these confounders, there was a strong association in terms of 17% increased risk of mortality with depression. To our knowledge, it is the first time that the association of depression on PAD outcomes has been demonstrated in such a large cohort and we also demonstrate an intriguing association between anti-depressant treatment and amputation. These findings deserve further investigation as they have the potential to improve health outcomes in a large population.

Mechanistic Pathways

The association between depression and PAD adverse outcomes may likely to be explained by a composite of behavioral and biological mechanisms as has been previously reported[10]. In the Cardiovascular Health Study, 25% of cardiovascular mortality in patients with depression was attributed to physical inactivity[32], supporting findings by Whooley et al. that adjusting for behavioral mediators, particularly physical inactivity, eliminated the 31% association between depression and cardiovascular events in patients with stable CAD[33]. In a prospective cohort of veterans, the Heart and Soul Study found that 12% of patients with depressive symptoms were shown to have prevalent PAD compared to 7% of patients without depressive symptoms[10]. After exclusion of patients with a self-reported history of PAD, incident PAD events occurred in 7% of patients with depressive symptoms and 5% of patients without depressive symptoms. Factors explaining >5% of the association between depression and incident PAD events included race/ethnicity, diabetes, congestive heart failure, high-density lipoprotein, triglyceride levels, serum creatinine, inflammation (CRP, IL-6, TNF-α), smoking, and levels of physical activity.

Several investigators have reported the association of depression with different physiological systems, which may have mechanistic implications for the present study's findings. These include autonomic dysfunction due to excessive sympathetic or insufficient parasympathetic activity[34, 35], alterations in the hypothalamic-pituitary-adrenal axis resulting in elevated cortisol level and dexamethasone nonsuppression[36, 37], and platelet hyperaggregability related to elevated plasma levels of platelet factor 4 and beta thromboglobulin.[38–40] Endothelial dysfunction associated with reduced levels of endothelial progenitor cells and attenuated flow mediated dilation[41–43] may also be involved as well as a heightened inflammatory response indicated by elevated inflammatory markers such as CRP, TNF-a, and IL-6.[44–47] Investigations thus far support a relative contribution of both physiological and behavioral factors driving the association between depression and vascular disease. The results support the role of more research to better understand the mechanisms involved in the reported association in order to help direct treatment regimens.

Role of Anti-depressants

The findings from this study suggest that antidepressant therapy may alleviate the morbid burden of depression on PAD outcomes related to limb loss but not mortality, although causality remains to be determined. Possible explanations for these findings include a physiological effect of anti-depressants on limb loss in PAD (true causality) or residual confounding from care utilization. In terms of healthcare access and utilization, depressed patients were more likely to be Caucasian, present with tissue loss at PAD diagnosis, and slightly higher chance of being in the lowest SES stratum. However, they had higher prescription rates of antiplatelet, statin and diabetic medications but lower prescription of cilostazol. Despite adjustment for these markers, there was significant effect modification of amputation risk by treatment of depression. Furthermore, nondepressed patients who were on antidepressants for other indications had a moderately higher risk of amputations compared to the non-depressed PAD patients [HR 1.10] which was similar for treated depressed patients [HR 1.08]. This group of patients likely had other mental illnesses necessitating use of antidepressants. There are newer studies suggesting the increased vascular dysfunction in disorders such as PTSD that are treated with antidperessants[48, 49]. Some of the mechanisms of action of antidepressants involve pathophysiological processes in PAD and CV diseases, such as platelet activation.[50] In fact, the impairment of primary hemostasis induced by SSRIs may result in a reduction in thrombotic risk.[51]

The present study's findings bring more data in an area where controversy remains related to the effect of antidepressants on the incidence of CV events. In fact, several randomized studies have taken place on the use of antidepressant in patients with CV disease, with mixed results.[52] It is felt that a large trial on the use of antidepressant therapy vs. placebo would bring ethical concerns because depression in itself requires treatment. With regards to PAD, studies examining the role of antidepressants are limited (or non-existent) and the present study qualifies the potential benefit antidepressants may have in PAD patients with depression. Future studies are needed to support this finding that antidepressants are related to decreased limb loss in patients with PAD with depression and whether depression should be more aggressively treated in patients with cardiovascular disease. Also future studies are

needed in ascertaining the risk of other mental illnesses and their treatement (PTSD, OCD, anxiety etc) on PAD outcomes.

Limitations

This study has several limitations. First, this is an observational study using administrative data, which come from clinical care records, and the analysis may be susceptible to residual confounding. A significant effort was made to account for accurate PAD diagnosis as well as performing a comprehensive Cox model. Additionally, careful handling of missing data were done to minimize and investigate the possibility of bias. Right censoring was done at occurrence of outcomes (death/amputation) [which are fairly accurately reported given the multiple data sources used] or the end of the followup in the study but we could miss the occurrence of amputations in a small percentage of patients who sought all their care outside the VA system and did not use VA coverage (fee-basis). The study did not assess for severity of depression or response to treatment, which represents another limitation. With regards to treatment of depression, it is possible that patients treated for depression were treated with psychotherapy which was not captured in the analysis. Amongst patients on antidepressants we couldn't assess medication compliance. If there is a direct medication effect on amputation risk, data on compliance could help delineate that effect. We also did not investigate the indications for use of anti-depressants in patients who did not carry a diagnosis of depression. We therefore cannot comment on the role of other mental illnesses on PAD amputation risk but it would be something to explore in future manuscripts. Additionally, the study is based on VHA data and it is overwhelmingly comprised of male patients. Therefore, results may differ in a non-VA or female population.

CONCLUSION

The clinical significance of co-morbid depression on PAD is becoming more recognized. The findings of the present study demonstrate that PAD patients with depression are at a higher risk of long-term death and amputation, and that amputation risk may be modifiable based on treatment of depression. The 2016 American Heart Association guidelines for the management of patients with lower extremity PAD have called for new medical therapies for patients PAD.[53] We suggest raised awareness related to mental health issues in this population. We also press for continued investigation into mechanisms involved in worse outcomes for those with depression (mechanisms specific to both overall survival and limb salvage) as well as treatment strategies to alleviate this risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Take Home Message

In 155,647 veterans with peripheral artery disease (PAD), co-morbid 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 PAD be evaluated for depression and receive treatment if depression is identified.

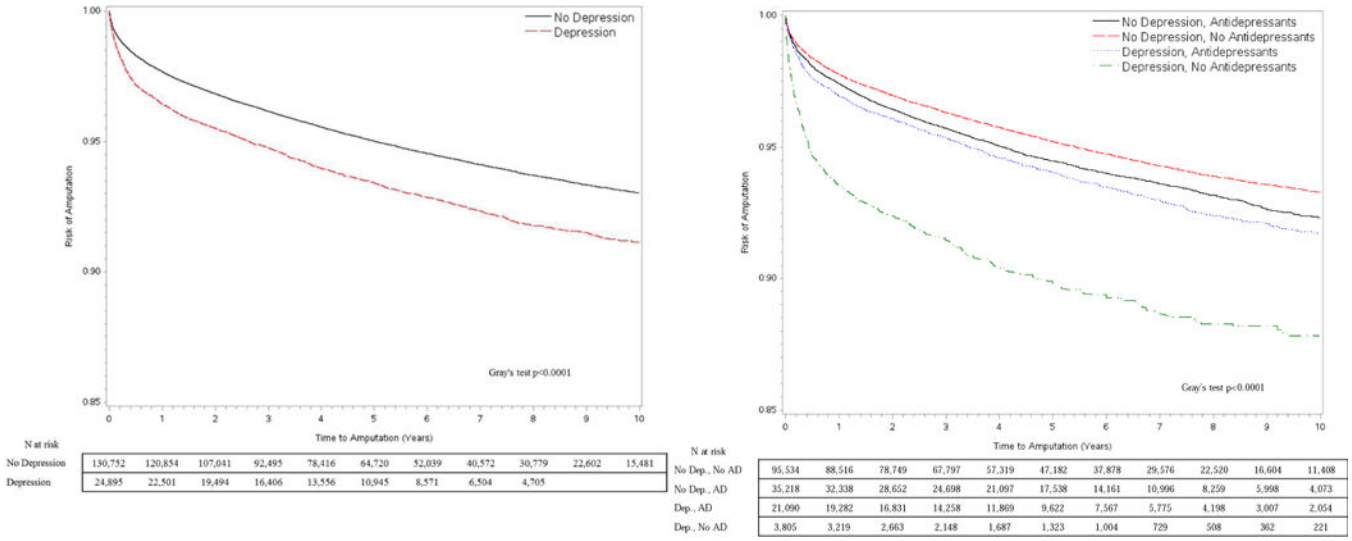

Figure I. Cumulative incidence function (CIF) curves to compare amputation-free survival (AFS) by depression status (A) and use of antidepressants (B)

Death was a competing risk and subjects were censored on December 31, 2015.

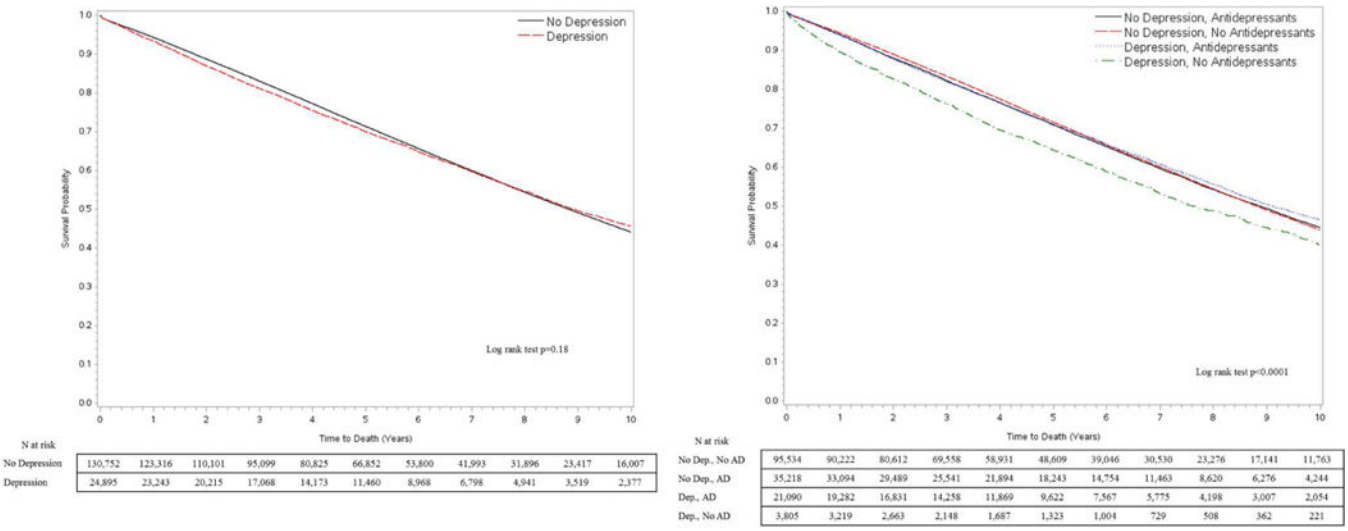

Figure II. Kaplan Meier (KM) curves to compare Overall Survival (OS) by depression status (A) and use of antidepressants (B)

Subjects were censored on December 31, 2015.

Table I

Demographics of full cohort and stratifications by depression for N = 155,647 patients meeting the PAD algorithm from 2003-2014.

Variable	All	Depression	No Depression	p-value
PAD patients in study, No.	155,647	24,895	130,752	
Age, Mean (SD), years	66.7 (9.9)	63.6 (9.4)	67.3 (9.8)	<0.0001
Sex, % Male	98	96	98	<0.0001
Median Followup time (years)	5.9	5.5	6.0	<0.0001
Race, %				0.0234
White	83	83	83	
Black	16	16	16	
Other	1	1	1	
Smoking, %				<0.0001
Current	45	50	44	
Former	41	37	42	
Never	14	13	14	
BMI, Mean (SD), kg/m2	28.6 (6.2)	29.1 (6.7)	28.5 (6.1)	<0.0001
Creatinine, Median (IQR), mg/dL	1.1 (0.9-1.4)	1.1 (0.9-1.3)	1.1(0.9-1.4)	0.0002
Comorbidities, %				
Diabetes	45.5	48.8	44.9	<0.0001
Hypertension	84.2	85.0	84.1	0.0002
CAD	46.3	49.4	45.7	<0.0001
CHF	16.4	19.3	15.9	<0.0001
COPD	8.5	11.2	8.0	<0.0001
AF	12.0	12.1	12.0	0.68
Carotid Disease	63.8	66.8	63.2	<0.0001
CKD or ESRD	7.4	8.0	7.2	<0.0001
Statins, %	72.1	73.7	71.7	<0.0001
Antiplatelets, %	79.4	80.5	79.1	<0.0001
Antidiabetic medications, %	39.7	43.0	39.1	<0.0001
Cilostazol, %	8.0	7.0	8.2	<0.0001
Antidepressant (% taking any)	36.2	84.7	26.9	<0.0001
Median Household Income of Residential Zip Code, %				0.02
<=$25,000	3.3	3.4	3.3	
$25,001-$40,000	27.6	28.0	27.5	
$40,001-$75,000	59.4	59.4	59.4	
$75,001+	9.8	9.3	9.9	
PAD severity, %				<0.0001
Not Specified (per ICD-9 codes)	68.5	68.0	68.6	
Claudication	20.2	19.5	20.3	

Variable	All	Depression	No Depression	p-value
Rest Pain	3.9	4.0	3.9	
Ulceration/Gangrene	7.3	8.5	7.1	

Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; CKD, chronic kidney disease; ESRD, end stage renal disease; mg, milligram; dL, deciliter.

Table II

Cox proportional hazards model for effect of depression on mortality and amputations in PAD patients (N=129,157).

Variable	Death	Amputation
	HR (95% CI)	HR (95% CI)
Depression (Ref. No Depression)	1.17 (1.14, 1.20)	1.13 (1.07, 1.19)
Age (1-year increase)	1.05 (1.05, 1.05)	0.98 (0.98, 0.98)
Race	–	–
White	Ref.	Ref.
Black	0.83 (0.81, 0.85)	1.42 (1.35, 1.50)
Other	0.87 (0.81, 0.95)	1.14 (0.94, 1.37)
Sex (Ref. Male)	0.82 (0.76, 0.88)	0.44 (0.35, 0.54)
Smoking		
Never	Ref.	Ref.
Current	1.28 (1.23, 1.32)	1.17 (1.07, 1.28)
Former	1.08 (1.03, 1.12)	0.95 (0.86, 1.05)
Unknown	1.14 (1.10, 1.19)	1.00 (0.91, 1.10)
BMI (1 kg/m2 increase)	0.97 (0.97, 0.97)	0.96 (0.96, 0.97)
Creatinine (1 mg/dL increase)	1.09 (1.09, 1.10)	1.02 (1.00, 1.03)
Comorbidities (Ref. = No)		
Diabetes	1.18 (1.14, 1.23)	1.74 (1.58, 1.91)
Hypertension	1.11 (1.08, 1.14)	1.27 (1.18, 1.37)
CAD	1.20 (1.18, 1.23)	1.05 (1.00, 1.10)
CHF	1.91 (1.87, 1.95)	1.52 (1.44, 1.61)
COPD	1.34 (1.31, 1.38)	0.91 (0.84, 0.99)
AF	1.37 (1.33, 1.40)	1.27 (1.18, 1.35)
Carotid Disease	1.09 (1.07, 1.11)	1.16 (1.10, 1.22)
CKD or ESRD	1.47 (1.42, 1.53)	1.68 (1.54, 1.83)
Statin (Ref. None)	0.77 (0.75, 0.78)	0.74 (0.71, 0.78)
Antiplatelets (Ref. None)	0.71 (0.69, 0.72)	0.87 (0.83, 0.93)
Antiglycemics (Ref. None)	1.17 (1.13, 1.21)	1.36 (1.24, 1.49)
Cilostazol (Ref. No)	0.92 (0.89, 0.95)	0.77 (0.69, 0.85)
Antidepressants (Ref. None)	–	–
Median Income (Household) of Residential ZCTA (Ref. >$75,000)		
<=$25,000	1.37 (1.30, 1.45)	1.15 (1.01, 1.31)
$25,001-$40,000	1.16 (1.12, 1.19)	1.15 (1.05, 1.25)
$40,001-$75,000	1.09 (1.06, 1.12)	1.04 (0.96, 1.13)
PAD Severity (Ref. = Claudication)		
Not Specified	1.01 (0.99, 1.04)	1.16 (1.07, 1.24)
Rest Pain	1.19 (1.13, 1.25)	2.58 (2.31, 2.88)

Variable	Death	Amputation
	HR (95% CI)	HR (95% CI)
Ulceration/Gangrene	1.71 (1.65, 1.77)	8.19 (7.59, 8.85)

Abbreviations: HR, hazard ratio; CI, confidence interval, SD, standard deviation; IQR, interquartile range; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; CKD, chronic kidney disease; ESRD, end stage renal disease; mg, milligram; dL, deciliter; ZCTA, zip code tabulation area.

Table III

Cox proportional hazard model results for effect of depression on mortality and amputations: unadjusted hazards, primary model, primary model with interaction for antidepressants.

	Mortality	Amputation
	HR (95% CI)	HR (95% CI)
Unadjusted hazards (N=129,157)		
Depression, Yes vs. No	1.02 (0.99, 1.04)	1.32 (1.25,1.39)
Primary model[a] (N=129,157)		
Depression, Yes vs. No	1.17 (1.14, 1.20)	1.13 (1.07, 1.19)
Primary model[a], with interaction by antidepressant status (N=129,157)		
Depression and Antidepressants interaction		
No Depression, No Antidepressants	Ref.	Ref.
No Depression, Antidepressants for other indications	1.18 (1.16, 1.21)	1.08 (1.03, 1.14)
Depression, Antidepressants	1.22 (1.19, 1.26)	1.10 (1.03, 1.17)
Depression, No Antidepressants	1.25 (1.18, 1.33)	1.42 (1.27, 1.58)

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a]Model adjusting for age at entry into cohort, year of entry into cohort, race, sex, socio-economic status, body mass index, PAD severity (claudication, unspecified, rest pain, ulceration/gangrene), comorbidities [Diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, atrial fibrillation, carotid disease, chronic kidney disease and end stage renal disease], antiplatelet medications, cilostazol, antiglycemics, statins, serum creatinine.