

CLINICAL INVESTIGATIONS

Impact of diabetes on mortality in peripheral artery disease: a meta-analysis

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Background: There are accumulating studies showing the association between diabetes and all-cause mortality in peripheral vascular disease. However, the results in these studies are conflicting regarding the impact of diabetes on outcome.

Hypothesis: Diabetes is associated with increased risk of mortality in peripheral artery disease.

Methods: Using MEDLINE and Scopus, we searched for studies published before January 2016. Additionally, studies were identified by manual search of references of original articles or review studies on this topic. Of the 1072 initially identified records, 21 studies with 15,857 patients were included in the final analysis.

Results: Diabetes was associated with a statistically significant increased risk of all-cause mortality (odds ratio: 1.89, 95% confidence interval: 1.51-2.35, $P < 0.001$), without detected publication bias (Egger bias = 0.75, $P = 0.631$). The stronger effect on outcome was obtained in patients with critical limb ischemia (odds ratio: 2.38, 95% confidence interval: 1.22-4.63, $P < 0.001$) as the most severe form of peripheral vascular disease.

Conclusions: Diabetes is associated with an increased risk of mortality in peripheral vascular disease, and the effect is even more pronounced in patients with critical limb ischemia.

KEYWORDS

peripheral artery disease, critical limb ischemia, diabetes, mortality, meta-analysis

1 | INTRODUCTION

Due to the decrease in smoking globally, diabetes is fast becoming the major risk factor for peripheral artery disease (PAD).¹ Clustering of cardiovascular risk factors and metabolic changes that often accompany diabetes with subsequent increase in vascular inflammation contribute to the accelerated atherosclerosis and high risk for cardiovascular events.^{2,3} Both the duration of diabetes and degree of diabetic control are related to incidence and severity of PAD.⁴ Peripheral neuropathy, commonly associated with diabetes, is responsible for later clinical presentation of the disease, with more severe manifestations, such as critical limb ischemia (CLI).⁵ Therefore, patients with diabetes have higher PAD prevalence (range, 20%-30%) and are exposed to premature mortality mostly due to cardiovascular diseases.⁵ Conflicting data were published regarding the prognostic implication of diabetes on all-cause mortality in PAD patients.⁶⁻²⁶ We performed a comprehensive systematic review and meta-analysis of available studies to assess the prognostic

significance of diabetes to predict all-cause mortality in PAD patients. Additionally, we separately analyzed the impact of diabetes on fatal outcome in patients with CLI as the most severe form of peripheral vascular disease, frequently called acute coronary syndrome of the leg.

2 | METHODS

During the conduct of this meta-analysis we followed the Meta-Analysis of Observational Studies in Epidemiology guidelines. We performed a systematic literature search of MEDLINE and Scopus for all studies published between January 1993 and January 2016, without language restriction, using the following medical subject headings: "diabetes," "diabetic," "peripheral artery disease," "peripheral vascular disease," "critical limb ischemia," and "mortality." Additional studies were identified by manual search of references of original studies or review studies. Studies meeting inclusion criteria were those

comparing all-cause mortality rates in patients with intermittent claudication and/or CLI and a follow-up period of at least 1 year. Study selection and data extraction were conducted independently by 2 investigators (K.V., M.V.). Any disagreements or differences in the data extraction between the 2 authors were resolved through consensus after rechecking the source data and consultations with additional investigators (A.V.P., D.F., M.M.). The completed database contained the following data: name of the first author, year of publication, country of origin, study design, total number of patients in each study, the number of patients with diabetes and CLI, the definition of PAD, the proportion of patients with coronary artery disease (CAD), the number of patients who died in each group (with and without diabetes), the follow-up period, conduction of multivariate analysis, and confounding factors. PAD was generally defined according to the ankle-brachial index at <0.9 . Five studies included only patients with CLI, and the rest of the studies included those suffering from CLI together with patients with severe claudication (Rutherford stage 3) and indication for either vascular bypass surgery or endovascular treatment. Study quality was assessed using the validated Newcastle-Ottawa Scale for assessment of nonrandomized and observational studies, and studies were evaluated based on subject selection, comparability of study groups, and assessment of the outcome.

Statistical heterogeneity was assessed using the Cochran Q test and I^2 statistic. Statistically significant heterogeneity was considered present at $P < 0.10$ and $I^2 > 50\%$. Meta-analysis of outcome was reported using a random-effects model, and pooled odds ratio (OR) was reported with 95% confidence interval (CI). Egger's test was used to assess risk for publication bias. Sensitivity analysis was performed by excluding trials 1 at a time to assess the contribution of each study to the pooled estimates. Analyses were conducted using statistical software Stats Direct version 3.0.165 (Stats Direct Ltd., Altrincham, United Kingdom).

3 | RESULTS

A total of 1072 citations were obtained from the electronic search. After reading titles and abstracts, followed by review of potentially relevant studies, 21 studies were included in the final analysis, including a total of 15857 patients (Figure 1). The study characteristics are listed in the Table 1. The mean age of the population was 69.8 years, 68.8% were males, 54.3% had CLI, 44.1% had CAD, and 43.6% patients had diabetes. Ten studies were retrospective and 11 were prospective in nature. Multivariate statistical analysis was performed in 19 studies. Using the Newcastle-Ottawa scoring system, for included studies the mean score was 7.38, the median was 8.0, with the interquartile range was 7.0–8.0. A total of 28.7% of patients died during median follow-up period of 2.9 years. Eight studies^{8,10–12,16,21–23} reported the cause of death, and cardiovascular death comprised 54% (range, 33%–75%) and noncardiovascular death 46% (range, 25%–67%). In pooled analysis, 37.3% of PAD patients with diabetes died compared with 22.2% of PAD patients without diabetes (OR: 1.89, 95% CI: 1.51–2.35) (Figure 2A). The analysis of pooled studies showed a significant heterogeneity ($I^2 = 84.9\%$,

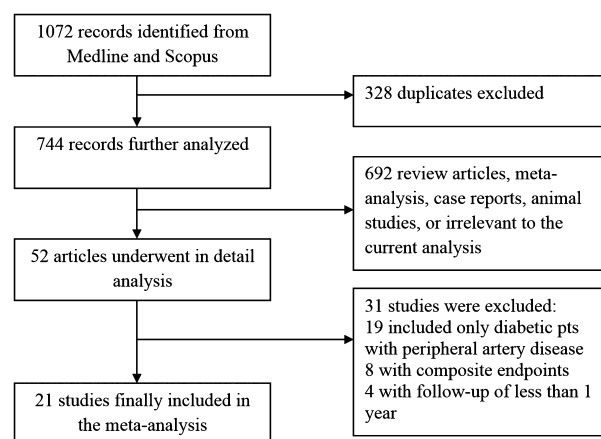


FIGURE 1 Study flow diagram.

Cochran $Q = 132.5$, $P < 0.001$), but no publication bias was detected (Egger: bias = 0.75, $P = 0.631$). Sensitivity analysis indicated that none of the studies had a significant influence on the risk of mortality, and similar results to the main findings were obtained. Additional analyses of studies with performed multivariate analysis (OR: 1.89, 95% CI: 1.51–2.37, $I^2 = 84.3\%$) and of prospective studies with performed multivariate analysis that included 7868 patients (OR: 1.82, 95% CI: 1.35–2.45, $I^2 = 84\%$), revealed similar results. Meta-analysis of 8 prospective studies^{8,12–14,16,18,21,22} (5628 patients) with performed multivariate analysis and with the exclusion of studies that included only patients with CLI, showed substantially reduced level of heterogeneity (OR: 1.68, 95% CI: 1.37–2.08, $I^2 = 49.8\%$) without publication bias (Egger: bias = 0.38, $P = 0.857$) (Figure 2B). Five studies^{11,19,20,24,26} analyzed exclusively patients with CLI with a total of 3523 patients. Meta-analysis of those studies showed a stronger impact of diabetes on outcome (OR: 2.38, 95% CI: 1.22–4.63, $I^2 = 93\%$), without detected publication bias ($P = 0.778$) (Figure 2C). Finally, a meta-analysis was also conducted including 4 Caucasian studies with CLI, which exhibited an even stronger effect of diabetes on outcome, with a lower level of heterogeneity (OR: 2.96, 95% CI: 1.77–4.97, $I^2 = 79.5\%$) (Figure 2D).

4 | DISCUSSION

The prognostic role of diabetes, although well established in ischemic heart disease and cerebrovascular disease, was not extensively studied in PAD patients.^{27,28} According to our meta-analysis, the coexistence of PAD and diabetes identified patients at high risk of mortality, and patients with diabetes and CLI had even worse prognoses.

PAD is a marker of advanced atherosclerosis, and polyvascular involvement is often present in PAD patients.^{29,30} Diabetes accelerates atherosclerosis by mechanisms that include increased platelet activity, increased levels of coagulation factors, and inflammatory biomarkers.³¹ In this way, patients with diabetes and PAD harbor a proinflammatory and prothrombotic milieu associated with unfavorable cardiovascular outcomes. In addition, due to peripheral neuropathy, PAD is usually asymptomatic at earlier stages, and patients usually lack the typical symptoms of angina when concomitant

TABLE 1 Characteristics of studies included in meta-analysis

Author, Year	Country	Patients (No.)	Age (Years)	Male (%)	Type of Study	Follow-up (Years)	DM (%)	CAD (%)	Mortality (%)	Mortality: DM vs Non-DM (%)	PAD Definition	ABI	CLI (%)	Multivariate Analysis	Confounders
Abularrage, 2010	USA	920	71.2	64.3	R	2.9 ¹	49.9	61.5	46.5	49 vs 44	Stage 3, CLI	—	41.7	Yes	Age, sex, CAD, HT, CKD
Akbari, 2000	USA	962	68.4	61.9	P	5	34.5	45.8	41.8	41.8 vs 41.9	Stage 3, CLI	—	92	No	—
Cheng, 2000	China	665	71.1 ± 11.1	60.3	P	2.3	42	35.8	44.2	47 vs 42	ABI ²	—	62.4	Yes	Age, sex, CAD, HT, CKD, smoking, HLP
Collins, 2007	USA	796	64.7 ± 9.9	99	R	1.4	61.3	—	44.5	46.9 vs 40.6	ABI	0.57 ¹	16.5	Yes	Age, sex, CAD, HT, CKD, smoking, HLP, medications
Dawson, 1993	Netherlands	376	63.9 ± 11.5	83.5	R	5.9	24.2	45.5	30.9	52.7 vs 23.9	Stage 3, CLI	—	58.8	Yes	Age, sex, CAD, HT, CKD, smoking
Dick, 2007	Switzerland	400	75.5 ± 10.9	57.7	P	1	46.3	—	30.5	35.1 vs 26.5	CLI	—	100	Yes	Age, sex, HT, CKD, smoking, HLP
Garg, 2006	USA	460	71.9 ± 8.4	59.4	P	4.8 ¹	31.1	35.7	29.1	40.6 vs 24	ABI	0.64 ± 0.15	81.2	Yes	Age, sex, CAD, HT, CKD, smoking, HLP
Gollge, 2014	Australia	1177	71 ¹	74.1	P	1.7 ¹	44.4	52.2	11.5	12.6 vs 10.5	Stage 3, CLI	—	12.3	Yes	Age, sex, CAD, HT, CKD, smoking, medications
Goodney, 2010	Lebanon	2036	73	67	P	1	53	40	10.2	13 vs 7	Stage 3, CLI	—	75	Yes	Age, CAD, CKD, smoking, medications
Jude, 2001	United Kingdom	136	64.7 ± 10.8	59.6	R	4.5 ¹	42.6	39	36.8	51.7 vs 25.6	Stage 3, CLI	—	37.5	Yes	Age, sex, CAD, HT, CKD, smoking
Kalman, 1997	Canada	358	68 ± 10	68	P	5	38	47	54.2	67.6 vs 45.9	ABI	0.35 ± 0.21	79.1	Yes	Age, sex, CAD, CKD
Karacagil, 1995	Sweden	267	68.5 ± 12	67.9	R	3	34.5	—	22.1	38 vs 13.7	ABI	—	75.6	No	—
Leibson, 2004	USA	335	61.2 ± 5.3	63.6	P	23	55.5	26	78.5	81.7 vs 74.5	ABI	0.75 ± 0.26	NM	Yes	Age, sex, CAD, HT, smoking
Luther, 1997	Finland	188	72.5	53.2	R	5	47.3	—	43.1	58.4 vs 29.3	CLI	—	100	Yes	Age, sex, HT, smoking, HLP
Malmstedt, 2008	Sweden	1840	76.2 ± 9.5	53.1	P	2.2 ¹	40.3	59	47	65.5 vs 34.4	CLI	—	100	Yes	Age, sex, CAD, HT, CKD, smoking
Missouri, 2004	United Kingdom	110	70.8 ± 10	60	P	6.1	21.8	—	55.5	58.3 vs 54.7	ABI	—	0	Yes	Age, sex, HT
Miura, 2014	Japan	2930	71.5 ± 8.9	78.7	R	2.7	16.4	50.5	8.3	11.2 vs 7.7	ABI	0.6 ± 0.2	0	Yes	Age, sex, CAD, HT, CKD, smoking, medications
Mueller, 2014	Austria	487	70 ¹	69.8	P	5	34.7	31	23.4	32 vs 18.9	ABI	0.62 ¹	19	Yes	Age, sex, HT, smoking, HLP
Suzuki, 2013	Japan	884	71.4 ± 10.2	69.2	R	1.5	70.9	51	42	41.9 vs 42	CLI	—	100	Yes	Age, sex, CAD, HLP, medications
Vrsalovic, 2016	Croatia	319	71 ¹	66.5	R	2 ¹	53.9	41	11.9	16.3 vs 6.8	ABI	0.58 ± 0.14	42	Yes	Age, sex, CAD, HT, CKD, smoking, HLP, medications
Wöfle, 2003	Germany	211	69 ¹	65.4	R	1	44.5	—	12.8	22.3 vs 5.1	CLI	—	100	Yes	Age, sex, CAD, HT, smoking, HLP

Abbreviations: ABI, ankle-brachial index; CAD, coronary artery disease; CKD, chronic kidney disease; CLI, critical limb ischemia; DM, diabetes mellitus; HT, hypertension; NM, not mentioned; P, prospective; PAD, peripheral artery disease; R, retrospective.

¹ Median.

² ABI < 0.9.

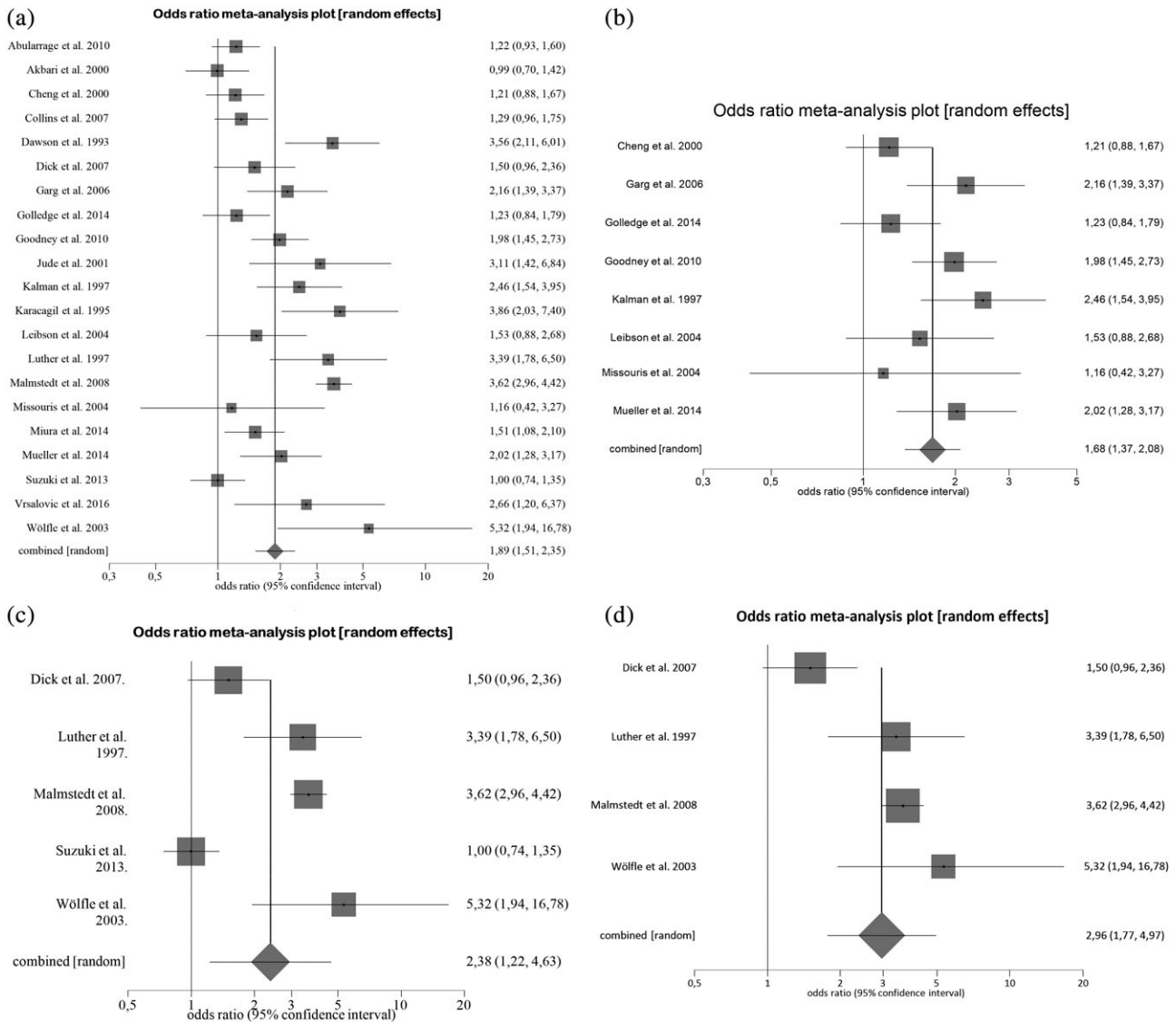


FIGURE 2 Meta-analysis (random effects model) testing the association between diabetes and all-cause mortality in (a) all studies with peripheral artery disease, (b) prospective studies with performed multivariate analysis without critical limb ischemia, (c) all studies with critical limb ischemia, and (d) Caucasian studies with critical limb ischemia.

ischemic heart disease is present.⁵ Therefore, sudden death may be the first clinical presentation of the associated CAD in PAD patients with diabetes. In our meta-analysis, the high mortality rates in CLI that exceed other patients with PAD most probably reflect the systemic atherosclerotic burden associated with CLI (ie, frequently associated CAD).¹ Our group has recently reported that the coexistence of CLI and diabetes synergistically increased the risk of all-cause mortality in patients with symptomatic PAD and preserved left ventricular ejection fraction.²⁵

Because PAD is a marker of generalized atherosclerosis, affecting multiple vascular beds and due to the absence of typical angina symptoms in diabetes (silent myocardial ischemia), comprehensive diagnostic evaluation should be considered in this subpopulation that is at a very high risk for fatal outcome. Special attention should be paid to patients with CLI, where an even stronger effect of diabetes on worse clinical outcome was obtained.

The results of our systematic review and meta-analysis, which included high-quality studies, for the first time clearly showed the

increased risk of all-cause mortality associated with diabetes in PAD. These findings are in line with previously published meta-analysis on the prognostic role of diabetes in ischemic heart disease and cerebrovascular disease.^{27,28}

Further prospective studies are needed to evaluate the prognostic role of diabetes in the whole spectrum of symptomatic and asymptomatic patients with peripheral vascular disease.

4.1 | Study limitations

Only diabetic patients who had symptomatic PAD of the lower extremities were included; therefore, asymptomatic diabetics and those with PAD of other arteries than lower limbs were not evaluated in this systematic review. Due to the study designs, cardiovascular death was rarely reported, and all-cause mortality was the most common outcome. Only 1 study¹⁰ reported the relative risk rate for cardiovascular cause of death in diabetic patients. Although the prevalence of CAD was reported in most of the studies, a subset of

patients having both CAD and PAD with or without associated diabetes were not separately analyzed. We acknowledge moderate heterogeneity noted in the analysis. The level of heterogeneity could be attributed to the differences in the study population—mean age, diabetes duration, severity of PAD (ie, proportion of patients with CLI), prevalence of CAD, and length of follow-up period.

5 | CONCLUSION

This meta-analysis showed that diabetes is associated with an increased risk of mortality in PAD, with a more pronounced effect in patients with CLI as the most serious manifestation of the disease.

5.1 | Conflict of interests

The authors declare no potential conflict of interests.

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