

# Peripheral artery disease, lower limb revascularization, and amputation in diabetes patients with and without coronary artery disease: a cohort study from the Western Denmark Heart Registry

Kevin Kris Warnakula Olesen <sup>1</sup>, Christine Gyldenkerne,<sup>1</sup> Troels Thim,<sup>1</sup> Reimar Wernich Thomsen,<sup>2</sup> Michael Maeng<sup>1</sup>

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<sup>1</sup>Department of Cardiology, Aarhus Universitetshospital, Aarhus, Denmark

<sup>2</sup>Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

## Correspondence to

Dr Kevin Kris Warnakula Olesen; kevole@clin.au.dk

## ABSTRACT

**Introduction** Patients with diabetes have increased risk of lower limb revascularization and amputation due to higher risk of peripheral artery disease (PAD) and peripheral neuropathy. The additive effect of coronary artery disease (CAD) is less clear. We examined the risk of PAD, lower limb revascularization, and amputation in diabetes and non-diabetes patients with and without CAD in patients examined by coronary angiography (CAG).

**Research design and methods** We included all patients undergoing CAG between 2003 and 2016 in Western Denmark. Patients with previous CAD, PAD, lower limb revascularization, or amputation were excluded. Patients were stratified by diabetes and CAD status and followed for a maximum of 10 years. Outcomes were PAD, lower limb revascularization, and amputation. We estimated 10-year cumulative incidences and adjusted HRs (aHRs) using patients neither diabetes nor CAD as reference.

**Results** A total of 118 787 patients were included, of whom 41 878 (35%) had neither diabetes nor CAD, 5735 (5%) had diabetes alone, 59 427 (50%) had CAD alone, and 11 747 (10%) had both diabetes and CAD. Median follow-up was 6.9 years. Diabetes patients without CAD had higher risk of PAD (3.5%, aHR 1.73, 95% CI 1.51 to 1.97), lower limb revascularization (1.6%, aHR 1.55, 95% CI 1.16 to 2.05), and lower limb amputation (2.4%, aHR 5.51, 95% CI 4.09 to 7.43) compared with patients with neither diabetes nor CAD. CAD was associated with 2.5-fold and 1.8-fold higher risk of PAD and amputation, respectively, among patients without diabetes, and associated with 3.9-fold and 9.5-fold higher risk of PAD and lower limb amputation among patients with diabetes.

**Conclusions** Despite absence of obstructive CAD, patients with diabetes remained at higher risk of PAD, lower limb revascularization, and lower limb amputation. Diabetes was more strongly associated with amputation than CAD, but CAD exacerbated the risks of PAD, revascularization, and amputation in patients with diabetes.

## Significance of this study

### What is already known about this subject?

► Patients with diabetes have increased risk of lower limb amputation due to higher risk of peripheral artery disease and peripheral neuropathy. The role of concomitant coronary artery disease (CAD) is unclear.

### What are the new findings?

► Patients with diabetes are at higher risk of lower limb amputation despite absence of CAD.  
► However, CAD significantly exacerbates amputation risk among patients with diabetes, especially in patient with multivessel CAD.  
► Diabetes patients without CAD were more likely to undergo distal amputations, rather than proximal amputations, which were associated with CAD.

### How might these results change the focus of research or clinical practice?

► Continued screening and treatment of macrovascular and microvascular disease is necessary in all patients with diabetes to reduce the risk of amputation. However, patients with diabetes and CAD may require additional screening, management, and treatment of peripheral artery disease and microvascular disease to reduce the risk of lower limb amputation. This, however, needs to be explored in a randomized setting.

## INTRODUCTION

Diabetes is associated with a higher risk of atherosclerotic cardiovascular disease including ischemic stroke, coronary artery disease (CAD), and peripheral artery disease (PAD).<sup>1 2</sup> Patients with diabetes also have an increased risk of microvascular disease, including peripheral neuropathy, which can

cause foot ulcers. Poor glycemic control, type of diabetes, previous lower limb revascularization, hypertension, and high level of comorbidity are all associated with increased risk of amputation in patients with diabetes.<sup>3</sup> Atherosclerosis in one vascular bed is often associated with presence or development of atherosclerosis in other vascular beds.<sup>4</sup> Considering the combination of increased atherothrombotic risk and the risk of microvascular disease, patients with diabetes have a higher risk of lower limb ischemia and amputation. The absence of obstructive CAD is associated with a low risk of myocardial infarction and an intermediate risk of ischemic stroke in patients with diabetes.<sup>5–7</sup> However, does the absence of obstructive CAD ensure a low risk of PAD, lower limb revascularization, and amputation in patients with diabetes?

We conducted a cohort study of diabetes and non-diabetes patients with and without obstructive CAD to estimate the risk of PAD, lower limb revascularization, and lower limb amputation. We hypothesized that the absence of obstructive CAD by coronary angiography (CAG) would be associated with low risks of PAD, lower limb revascularization, and lower limb amputation in both diabetes and non-diabetes patients.

## METHODS

### Setting

All Danish residents are assigned a unique 10-digit identifier at birth or immigration. This identifier is used throughout every national and regional registry, thus allowing accurate cross-linkage of data between registries. The Civil Registration System contains information on vital status of every resident in Denmark,<sup>8</sup> hereby reducing loss to follow-up (<0.3%).<sup>9</sup> The Danish National Patients Registry records every discharge diagnoses for in-hospital admission and visits to outpatient clinics in national Danish healthcare system.<sup>10</sup> The Danish National Prescription Registry contains information on every dispensed prescription from a Danish pharmacy since 1994.<sup>11</sup> The Western Denmark Heart Registry has registered every cardiac procedure in Western Denmark since 1999, and it contains detailed patient-related and procedural information that includes the presence and extent of CAD.<sup>12</sup>

### Patient selection

We included all patients examined by CAG from 1 January 2003 to 31 December 2016 (figure 1). We excluded patients aged <18 years and patients with previous history of myocardial infarction (MI), percutaneous coronary intervention, or coronary artery bypass grafting (CABG) prior to CAG date to identify patients with a first-time diagnosis of CAD. We also excluded patients diagnosed with PAD, previous lower revascularization, or amputation before start of follow-up. Patients with missing CAD status were not included, as well as patients classified as 'no CAD' but were revascularized within 30 days of CAG.

Lastly, patients who either died or emigrated <30 days after CAG were excluded.

### Diabetes

Diabetes was defined as at least one of the following: (1) dietary treatment for diabetes, oral diabetes treatment, or receiving insulin treatment ( $\pm$ oral diabetes treatment) recorded in the Western Denmark Heart Registry, (2) a previous diabetes diagnosis registered in the Danish National Patient Registry before start of follow-up, or (3) redeeming  $\geq 1$  prescription(s) of insulin or non-insulin diabetes medication 6 months before or 30 days after CAG.

### Coronary artery disease

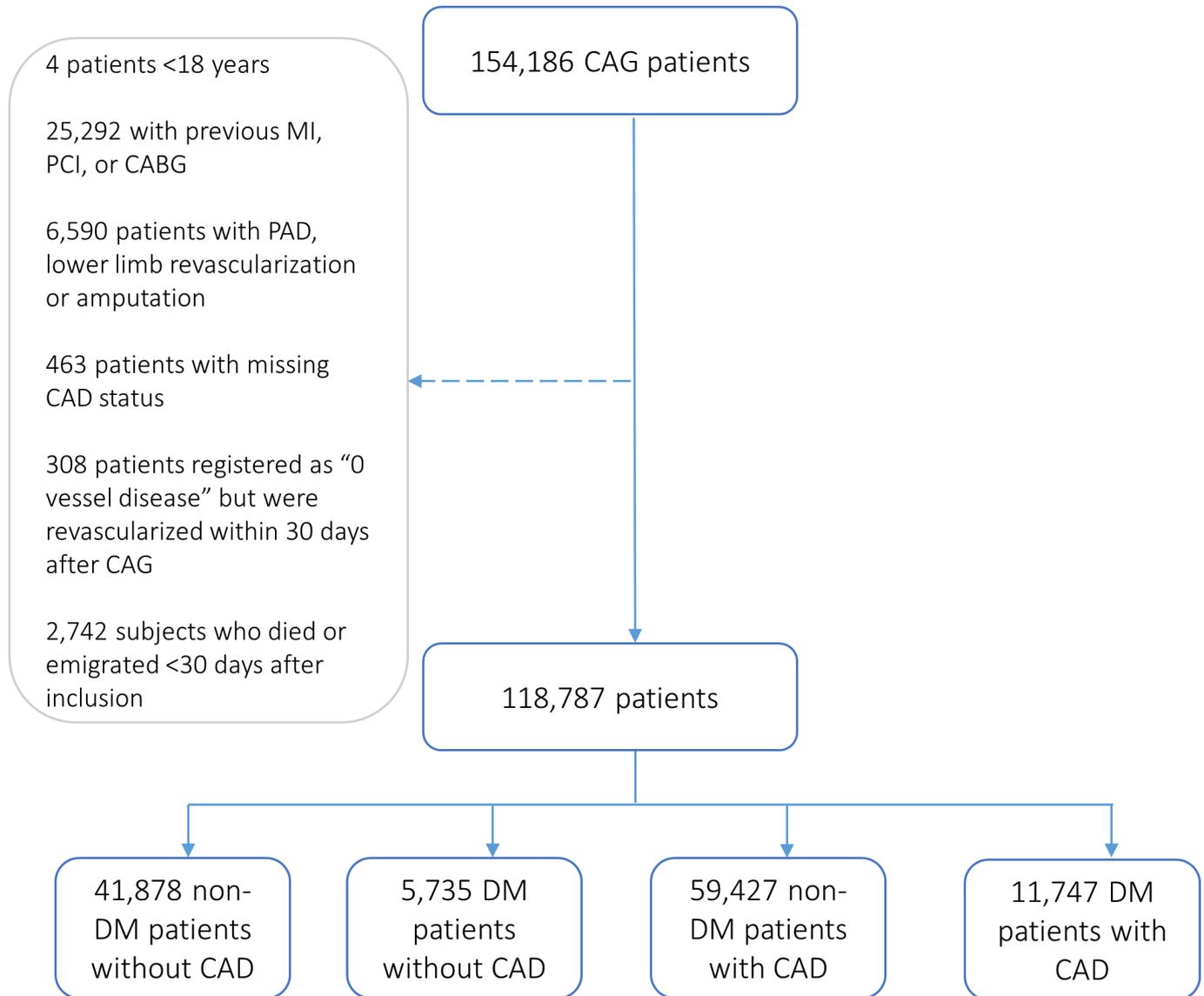
CAD was defined as  $\geq 1$  obstructive stenoses ( $\geq 50\%$  lumen narrowing) or non-obstructive stenosis in  $\geq 2$  coronary vessels by CAG according to the Western Denmark Heart Registry.<sup>12</sup>

### Outcomes

PAD was defined as a primary or secondary discharge diagnoses of PAD during hospitalization or visit to outpatient clinic (online supplemental table S1). Lower limb revascularization was defined as thrombectomy, percutaneous transluminal angioplasty, or arterial bypass surgery distal from the infrarenal aorta. Lower limb amputation was defined as an amputation from hip down.<sup>10</sup> The level of the amputation was evaluated as separate outcomes (hip/femur amputation, knee/lower leg amputation, and ankle/foot/toe amputation).

### Statistical analysis

Follow-up started 30 days after CAG to allow for any CAG-related changes in comorbidities and medications to be registered. Follow-up continued until outcome, emigration, death, end of follow-up (31 December 2018) with a maximum of 10 years of follow-up. Events occurring more than 10 years after start of follow-up were censored. Event rates per 100 person-years were estimated. The 10-year cumulative incidence proportions accounting for the competing risk of all-cause death were calculated. Crude and adjusted HRs (aHRs) were estimated using Cox proportional regression analysis and non-diabetes patients without CAD as reference. The central assumption of proportional hazards was evaluated by log–log plots and found to be satisfied. HR were adjusted for age, sex, hypertension, microvascular disease, active smoking, categorized body mass index ( $<18.5$  kg/m<sup>2</sup>, 18.5–24.9 kg/m<sup>2</sup>, 25–29.9 kg/m<sup>2</sup>,  $\geq 30$  kg/m<sup>2</sup>), oral anticoagulant treatment (vitamin K antagonists or direct oral anticoagulants), antiplatelet treatment (aspirin and/or adenosine diphosphate (ADP) inhibitors), and statin treatment. A total of 19.3% of patients had missing data of either smoking (9.9%) and/or body mass index (14.4%). Missing data were handled through multiple imputation using chained equations, imputing 20 datasets.<sup>13 14</sup>



**Figure 1** Patient selection. CAD, coronary artery disease; CABG, coronary artery bypass grafting; CAG, coronary angiography; DM, diabetes; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

### Diabetes subgroup analysis

We performed stratified analysis of patients with diabetes by: (1) extent of CAD (0 vessel disease (VD), 1 VD, 2 VD, 3 VD, and diffuse VD), (2) type of diabetes treatment, and (3) duration of diabetes (0–4 years, 5–9 years, and  $\geq 10$  years). We tested for trend between extent of CAD and each outcomes in patients with diabetes.

### Amputation distribution

We counted the distribution of type of amputation (hip/femur, knee/lower leg, and ankle/foot/toe), and tested the hypothesis of no difference in distribution of type of amputation using Pearson's  $\chi^2$  test.

### RESULTS

We included 118 787 patients, of whom 41 878 (35%) had neither diabetes nor CAD, 5735 (5%) had diabetes alone, 59 427 (50%) had CAD alone, and 11 747 (10%)

had both diabetes and CAD (figure 1). Median follow-up was 6.9 years (IQR 4.0–10.0).

Regardless of presence or absence of diabetes, patients with CAD were older, more often men, and more often treated with antiplatelet agents and statin (table 1 and online supplemental table S2).

Regardless of CAD, patients with diabetes more often had hypertension, heart failure, previous ischemic stroke, and microvascular disease. Type of diabetes treatment was overall similar between diabetes patients with and without CAD. However, insulin and sulfonylureas were used more frequently among diabetes patients with CAD.

Compared with patients with neither diabetes nor CAD, the risk of PAD and lower limb revascularization was highest in patients who had both diabetes and CAD, followed by patients with CAD alone and patients with diabetes alone (table 2).

**Table 1** Baseline characteristics in patients with and without diabetes by coronary artery status

	No DM, no CAD (n=41 878)		DM, no CAD (n=5735)		No DM, CAD (n=59 427)		DM, CAD (n=11 747)	
	N	%	N	%	N	%	N	%
Median age (IQR)	61 years (52–69)		62 years (53–70)		66 years (58–74)		67 (59–74)	
Female	20 873	49.8	2777	48.4	17 810	30.0	3522	30.0
Active smoker*	8867	21.2	1080	18.8	18 215	30.7	2906	24.7
Mean body mass index* (±SD)	26.9 kg/m <sup>2</sup> ±5.1		30.8 kg/m <sup>2</sup> ±6.5		26.8 kg/m <sup>2</sup> ±4.4		29.4 kg/m <sup>2</sup> ±5.3	
Mean eGFR* (±SD)	89 mL/min (25.6)		92 mL/min (32.2)		86 mL/min (25.1)		86 mL/min (30.2)	
Mean systolic BP* (±SD)	137 mmHg (22)		140 mmHg (22)		139 mmHg (23)		141 mmHg (23)	
Mean diastolic BP* (±SD)	78 mmHg (13)		78 mmHg (13)		78 mmHg (13)		77 mmHg (13)	
Median DM treatment duration, (IQR)			4.0 years (0.5–9.4)				4.8 year (0.6–10.7)	
<b>Cardiovascular disease</b>								
Hypertension	20 157	48.1	4450	77.6	31 761	53.4	9274	78.9
Heart failure	6246	14.9	1113	19.4	9136	15.4	2441	20.8
Ischemic stroke	594	1.4	200	3.5	1190	2.0	501	4.3
Transient ischemic attack	966	2.3	137	2.4	1419	2.4	382	3.3
Carotid stenosis	30	0.1	4	0.1	122	0.2	40	0.3
Atrial fibrillation	6588	15.7	1043	18.2	7048	11.9	1731	14.7
Nephropathy	49	0.1	376	6.6	69	0.1	825	7.0
Retinopathy	31	0.1	808	14.1	30	0.1	1810	15.4
Peripheral neuropathy	81	0.2	275	4.8	126	0.2	643	5.5
<b>Comedication</b>								
Aspirin	21 223	50.7	3553	62.0	50 368	84.8	9838	83.7
ADP inhibitor	2289	5.5	320	5.6	34 370	57.8	5676	48.3
Vitamin K antagonist	5638	13.2	882	15.4	5260	8.9	1388	11.8
Direct oral anticoagulants	1030	2.5	182	3.2	1207	2.0	288	2.5
Statin	17 543	41.9	4149	72.3	51 122	86.0	10 302	87.7
Insulin	0	0.0	1580	27.6	0	0.0	3570	30.4
Non-insulin	0	0.0	3672	64.0	0	0.0	7696	65.5
Metformin			3167	55.2			6480	55.2
Sulfonylureas			1127	19.7			2769	23.6
DPP-4 inhibitor			344	6.0			681	5.8
GLP-1 analogs			243	4.2			435	3.7
SGLT-2 inhibitors			29	0.5			73	0.6
Glitazones			42	0.7			100	0.9
Repaglinide			22	0.4			44	0.4
Acarbose			9	0.2			28	0.2

\*Missing values: smoking (9.9%); BMI (14.3%), eGFR (26.4%), and blood pressure (13.3%).

ADP, adenosine diphosphate; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon like peptide-1; SGLT-2, sodium–glucose cotransporter-2.

Diabetes alone patients had a lower risk of PAD compared with CAD alone patients (figure 2). However, PAD risk did seem to more progressively increase during follow-up among diabetes alone patients reaching a comparable 10-year risk as patients with CAD alone

(diabetes alone: 6.9% vs CAD alone: 7.9%). Patients with both diabetes and CAD had an almost 10-fold increased risk of lower limb amputation when compared with patients with neither diabetes nor CAD (3.8% vs 0.3%, aHR 9.49, 95% CI 7.27 to 12.39). Of note, diabetes alone

**Table 2** Number events, event rates and incidence rate ratios by diabetes status and CAD status

	Events	Events per 100 person years (95% CI)	10-year cumulative incidence* (95% CI)	Unadjusted HR (95% CI)	Adjusted HR† (95% CI)
<i>Peripheral artery disease</i>					
–DM –CAD	1170	0.40 (0.38 to 0.43)	3.53% (3.32 to 4.74)	1	1
+DM –CAD	293	0.81 (0.73 to 0.91)	6.89% (6.11 to 7.73)	1.98 (1.74 to 2.25)	1.73 (1.51 to 1.97)
–DM +CAD	3759	1.02 (0.99 to 1.05)	7.90% (7.65 to 8.16)	2.48 (2.32 to 2.65)	2.20 (2.04 to 2.37)
+DM +CAD	1354	2.10 (1.99 to 2.22)	14.56% (13.80 to 15.34)	5.00 (4.63 to 5.41)	3.90 (3.55 to 4.28)
<i>Lower limb revascularization</i>					
–DM –CAD	289	0.10 (0.09 to 0.11)	0.89% (0.79 to 1.00)	1	1
+DM –CAD	63	0.17 (0.13 to 0.22)	1.56% (1.19 to 2.02)	1.73 (1.31 to 2.27)	1.55 (1.16 to 2.05)
–DM +CAD	1090	0.29 (0.27 to 0.30)	2.39% (2.24 to 2.54)	2.89 (2.54 to 3.29)	2.51 (2.17 to 2.91)
+DM +CAD	399	0.59 (0.53 to 0.65)	4.48% (4.04 to 4.96)	5.88 (5.05 to 6.84)	4.61 (3.85 to 5.52)
<i>Lower limb amputation</i>					
–DM –CAD	104	0.04 (0.03 to 0.04)	0.34% (0.28 to 0.41)	1	1
+DM –CAD	100	0.27 (0.22 to 0.33)	2.42% (1.96 to 3.95)	7.77 (5.91 to 10.23)	5.51 (4.09 to 7.43)
–DM +CAD	248	0.06 (0.06 to 0.07)	0.59% (0.52 to 0.67)	1.84 (1.46 to 2.31)	2.02 (1.57 to 2.60)
+DM +CAD	330	0.48 (0.43 to 0.54)	3.81% (3.40 to 4.25)	13.86 (11.12 to 17.28)	9.49 (7.27 to 12.39)
<i>Hip/femur amputation</i>					
–DM –CAD	45	0.02 (0.01 to 0.02)		1	1
+DM –CAD	24	0.06 (0.04 to 0.10)		4.30 (2.62 to 7.06)	3.31 (1.95 to 5.61)
–DM +CAD	148	0.04 (0.03 to 0.05)		2.54 (1.82 to 3.55)	2.62 (1.81 to 2.79)
+DM +CAD	108	0.16 (0.13 to 0.19)		10.46 (7.39 to 14.82)	7.41 (4.87 to 11.28)
<i>Knee/lower leg amputation</i>					
–DM –CAD	36	0.01 (0.01 to 0.02)		1	1
+DM –CAD	37	0.10 (0.07 to 0.14)		8.26 (5.22 to 13.07)	5.19 (3.13 to 8.62)
–DM +CAD	74	0.02 (0.02 to 0.02)		1.58 (1.06 to 2.36)	1.76 (1.14 to 2.74)
+DM +CAD	123	0.18 (0.15 to 0.21)		14.76 (10.18 to 21.41)	9.00 (5.69 to 14.23)
<i>Ankle/foot/toe amputation</i>					
–DM –CAD	38	0.01 (0.01 to 0.02)		1	1
+DM –CAD	68	0.18 (0.15 to 0.23)		14.48 (9.73 to 21.53)	10.20 (6.64 to 15.67)
–DM +CAD	74	0.02 (0.02 to 0.02)		1.50 (1.02 to 2.22)	1.85 (1.21 to 2.82)
+DM +CAD	199	0.29 (0.25 to 0.33)		22.84 (16.14 to 32.34)	16.67 (11.08 to 25.07)

\*10-year cumulative incidence proportion accounting for the competing risk of death.

†Adjusted for age, sex, hypertension, microvascular disease, active smoking (imputed), body mass index (imputed), oral anticoagulant treatment, antiplatelet treatment, and statin treatment.

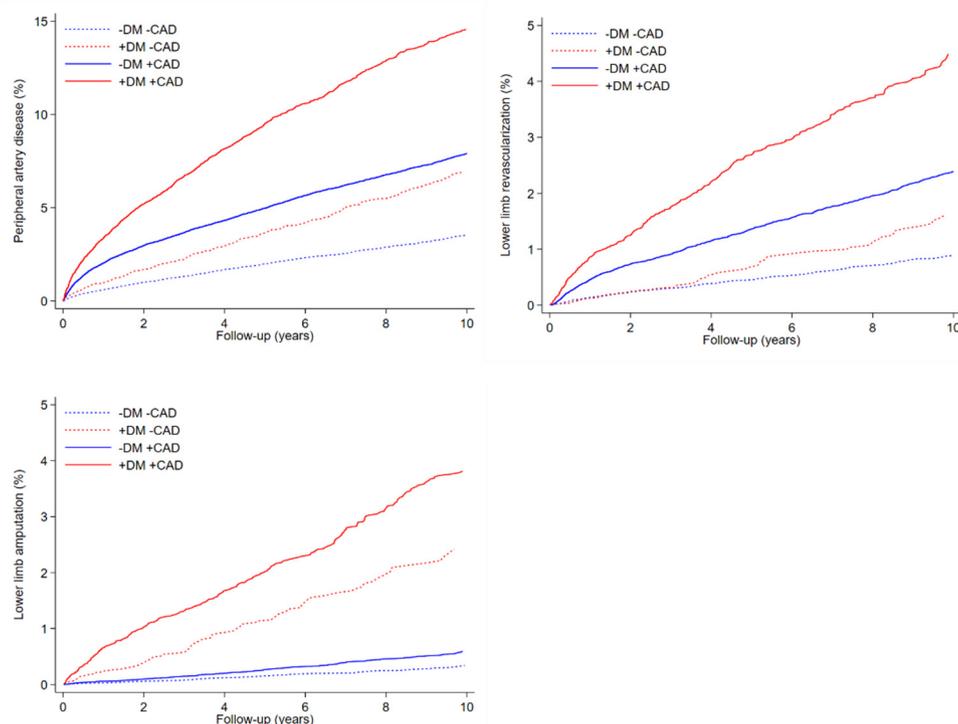
CAD, coronary artery disease; DM, diabetes mellitus.

(2.4%, aHR 5.51, 95% CI 4.09 to 7.43) was also associated with an increased risk of lower limb amputation, which was much higher than for patients with CAD alone (0.6%, aHR 2.02, 95% CI 1.57 to 2.60) compared with patients with neither diabetes nor CAD. Risks of PAD, lower limb revascularization, and amputation increased by extent of CAD in patients with diabetes ( $p_{\text{trend}} < 0.0001$ , figure 3, online supplemental table S3). Insulin-treated patients with had the highest risks of PAD, revascularization, and amputation (figure 3, online supplemental table S4). Duration of diabetes was also associated risk of PAD and amputation but not revascularization (figure 3, online

supplemental table S5). Diabetes patients without CAD more often had distal lower limb amputations (ankle/foot/toe), while non-diabetes patients with CAD more often underwent proximal amputations (hip/femur) (online supplemental figure S1). The distributions of type of amputation differed significantly ( $p < 0.001$ ).

## DISCUSSION

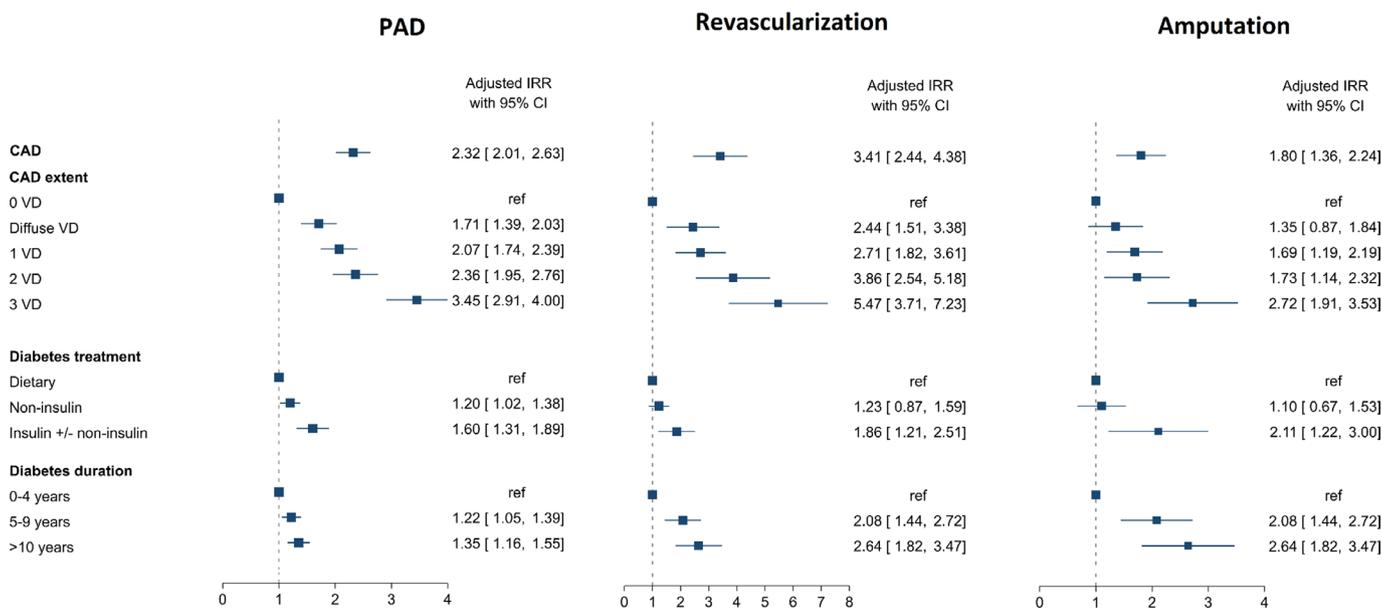
The main findings of the study were that diabetes still infers an increased risk of PAD and lower limb amputation despite the absence of obstructive CAD. Diabetes was



**Figure 2** Ten-year cumulative incidence of peripheral artery disease, lower limb revascularization, and lower limb amputation by diabetes and coronary status. CAD, coronary artery disease; DM, diabetes.

associated with a higher risk of lower limb amputation compared with CAD, but the level of amputation differed between the two exposures. Furthermore, CAD was associated with an incremental risk of PAD and amputation among patients with diabetes. Diabetes patients with obstructive multivessel CAD, receiving insulin treatment, or with a long duration of diabetes had the highest risk. Although CAD alone patients had higher risk of PAD

and lower limb revascularization than those with diabetes alone, diabetes alone patients remained at much higher risk of lower limb amputation than those with CAD alone. Hence, in patients with diabetes, the absence of CAD reduced the risk of lower limb amputation from a 9.5-fold increase to a 5.5-fold increase but did not by any means eliminate their highly elevated risk. Among Danish patients with a high prevalence of lipid-lowering



**Figure 3** Risk of peripheral artery disease, lower limb revascularization, and lower limb amputation in diabetes patient by presence and extent of CAD, diabetes treatment, and duration of diabetes. CAD, coronary artery disease; IRR, incidence rate ratio; PAD, peripheral artery disease; VD, vessel disease.

and antithrombotic treatment, MI risk in diabetes alone patients is low and comparable with patients with neither diabetes nor CAD, while their risk of ischemic stroke was higher.<sup>5 7 15</sup> Hence, the absence of CAD by CAG ensures a sustained low risk of MI in patients with diabetes but does not protect from other cardiovascular outcomes including ischemic stroke, PAD, and lower limb amputation. Although this may not be generalizable to countries outside Denmark, this nevertheless emphasizes the need for continued monitoring and treatment of macrovascular and microvascular disease in patients with diabetes, in particular diabetes patients with CAD.

Patients with diabetes had higher prevalence of microvascular disease, irrespective of CAD status. Patients with diabetes often develop microvascular complications causing visual impairment, loss of sensory function, kidney failure and so on.<sup>16–18</sup> Foot ulcers and amputations are also more frequent among patients with diabetes due to a combination of PAD and peripheral neuropathy.<sup>1</sup> Reduced pain sensitivity may postpone PAD diagnosis in diabetes patients with polyneuropathy. Furthermore, microvascular disease increases the risk of amputation independently of PAD.<sup>19</sup> Diabetes patients with peripheral microvascular disease have a higher risk of disseminated macrovascular atherosclerotic disease in multiple organs, including CAD, PAD, and cerebrovascular disease.<sup>20</sup> Moreover, diabetes is associated with coronary microvascular disease and subsequent risk of adverse ischemic events.<sup>21</sup> Screening for microvascular disease is a central part of diabetes management, and foot evaluations are recommended to prevent development of ulcers and amputation.<sup>22</sup> We found that diabetes was associated with a higher prevalence of microvascular disease, which may both reflect a true higher prevalence as well as surveillance bias caused by routine screening of patients with diabetes in the primary sector. This could, in part, explain the higher amputation risk among patients with diabetes. Diabetes alone was primarily associated with distal amputations, whereas CAD alone was associated with proximal amputations. However, even when adjusting for diagnosed microvascular disease, diabetes alone patients still had higher risk of amputation than CAD alone patients.

CAD was associated with an increased risk of developing PAD and having lower limb revascularization. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial found that microvascular disease increased the risk of PAD and amputation in patients with type 2 diabetes, while macrovascular disease (previous coronary heart disease or cerebrovascular disease) did not affect the risk of PAD or amputation.<sup>23</sup> A recent Danish cohort stratified patients with and without diabetes by extent of CAD by angiography (n=116 491), and similarly found that CAD extent was associated with an increased risk of PAD in patients with diabetes 5 years after CAG, with significant interaction between diabetes and CAD extent ( $p_{\text{interaction}}=0.042$ ).<sup>24</sup> Researchers did not examine lower

limb revascularization or amputation. As a confirmation and extension of the Danish angiographic cohort,<sup>24</sup> we report that the presence of CAD more than doubles the risk of PAD, lower limb revascularization, and lower limb amputation. Our cohort consists of routine clinical care patients undergoing CAG contrary to the ADVANCE trial that included a more selective group of patients with type 2 diabetes. Furthermore, macrovascular disease was associated with revascularization for PAD (HR 1.75, 95% CI 1.13 to 2.73) in the ADVANCE trial too.

More than 8 in 10 patients with CAD received treatment with aspirin. The remaining were almost all treated with oral anticoagulants. Similarly, almost 9 in 10 patients with CAD were in statin treatment. Antiplatelet monotherapy and statin treatment are recommended in patients with symptomatic PAD.<sup>25</sup> Oral anticoagulants are currently not recommended in management of PAD. However, more recently low dose of rivaroxaban in combination with aspirin has been found to reduce cardiovascular risk, including major amputation (HR 0.30, 95% CI 0.11 to 0.80), in patients with stable CAD or PAD.<sup>26 27</sup> Moreover, additional antithrombotic treatment, including low-dose rivaroxaban, should be considered in chronic coronary syndrome patients with diabetes and/or PAD according to European guidelines.<sup>28 29</sup> However, it is unknown whether supplementary antithrombotic medication would reduce amputation risk in diabetes patients with CAD. Sodium/glucose cotransporter (SGLT)-2 inhibitors and glucagon-like peptide (GLP)-1 analogs reduce cardiovascular risk and improve glycemic control in diabetes patients with atherosclerotic cardiovascular disease.<sup>30–35</sup> However, SGLT-2 treatment have either had no impact or have been associated with an increased the risk of amputation.<sup>34 36–38</sup> Among the GLP-1 analogs, liraglutide reduces the risk of amputation semaglutide reduce the risk of lower limb revascularization,<sup>31 37</sup> while exanotide did not reduce amputation nor revascularization.<sup>39</sup> Thus, class effects of GLP-1 analogs on lower limb revascularization and amputation is undetermined. None of the pivotal trials were powered to examine the effect of GLP-1 analogs on lower limb revascularization or amputation, and they only included diabetes patients with established atherosclerotic disease. The role of GLP-1 analogs in reducing amputation risk needs additional investigation in dedicated clinical trials, including examining their effect in diabetes patients without established cardiovascular disease.

### Limitations

We did not have access to hemoglobin A1c in our dataset, and we cannot account for the effect of hyperglycemia in our study. However, we did find that amputation was associated with pseudoindicators of diabetes disease severity such as duration of diabetes and insulin treatment. The use of aspirin and statin was high in patients with CAD, and this may have reduced the relative risk of symptomatic PAD, lower limb intervention, and lower limb amputation. As such, we have likely underestimated the PAD

risk among this subgroup. Our study included symptomatic patients undergoing CAG and may not represent the risk in the general population. Obstructive CAD was defined by 50% stenosis, which no longer reflects the current guidelines. However, in recent years Danish interventional cardiologists have increasingly been using intravascular pressure measurements, such as fractional flow ratio and adenosine-free resting indices, to identify functionally limiting lesions during CAG in accordance with guidelines. Lastly, PAD diagnosis were identified based on hospital and outpatient clinic diagnoses, likely underestimating the true prevalence of PAD.

## CONCLUSIONS

Patients with diabetes had a higher risk of PAD, lower limb revascularization, and lower limb amputation despite the absence of CAD by CAG. Diabetes alone was associated with a higher risk of amputation than CAD alone. Furthermore, CAD was associated with risk of PAD, lower limb revascularization, and lower limb amputation among patients with diabetes, and the risks depend on the CAD extent, type of diabetes treatment, and the duration of diabetes. This emphasizes the need for continued monitoring and treatment of macrovascular and microvascular disease of all patients with diabetes, in particular, diabetes patients with documented CAD. Clinical trials are needed to examine whether newer glucose-lowering medications, such as SGLT-2 inhibitors and GLP-1 analogs, can effectively prevent lower limb amputations in patients with diabetes both with and without established coronary atherosclerosis.

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## ORCID iD

Kevin Kris Warnakula Olesen <http://orcid.org/0000-0002-0560-3615>

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## SUPPLEMENTAL MATERIAL

*Title:* Peripheral Artery Disease, Lower Limb Revascularization, and Amputation in Diabetes Patients with and without Coronary Artery Disease – A Cohort Study from the Western Denmark Heart Registry

Kevin Kris Warnakula Olesen, MD<sup>a</sup>; Christine Gyldenkerne, MD<sup>a</sup>; Troels Thim, MD, PhD<sup>a</sup>;  
Reimar Wernich Thomsen, MD, PhD<sup>b</sup>; Michael Maeng, MD, PhD<sup>a</sup>

<sup>a)</sup> Department of Cardiology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99,  
Aarhus N, Denmark

<sup>b)</sup> Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45,  
Aarhus N, Denmark

**Table S1.** International Classification of Diseases codes 10th revision (ICD-10), Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures Version 1.15, and Anatomical Therapeutic Chemical (ATC) codes used for baseline and outcome definition.

<i>Condition</i>	<i>ICD-10 code</i>
Myocardial infarction	DI21
Ischemic stroke	DI63, DI64
Peripheral artery disease	DI70, DI70.1–DI70.9. DI73.9
Heart failure	DI11.0, DI13.0, DI13.2, DI50
Renal disease	DI12, DI13, DN00–DN05, DN07, DN11, DN14, DN17–DN19, DQ61
Atrial fibrillation/flutter	DI48
Diabetes	DE10–DE14, DH36.0, DO24.0–24.3, DO24.5–24.9
Retinopathy	DE103, DE11.3, DE12.3, DE13.3, DE14.3, DH28.0, DH33.4B, DH34, DH35.0, DH36.0
Peripheral neuropathy	DE10.4, DE11.4, DE12.4, DE13.4, DE14.4, DG56, DG57, DG58, DG59, DG60.9, DG60.3, DG61, DG62, DG63, DG90.0, DG90.9, DG99
Nephropathy	DR80.9, DB28.9A, DE10.2, DE11.2, DE12.2, DE13.2, DE14.2, DE14.3, DN39.1, DN06, DN07, DN08, DN14, DN16, DM10.3, DM35.0E
<i>Procedure</i>	<i>NOMESCO classification</i>
Lower limb revascularization	KPDE-KPDF, KPDH, KPDN, KPDP, KPDQ, KPEE-KPEF, KPEH, KPEN, KPEP, KPEQ, KPFE-KPEG, KPFH, KPFN, KPFP, KPFQ, KPFQ, KPDU74, KPDU84

Lower limb amputation	KNFQ, KNGQ, KNHQ
Percutaneous coronary intervention	KFNG02, KFNG05, KFNG96
Coronary artery bypass grafting	KFNA–KFNE

<i>Drug</i>	<i>Anatomical Therapeutic Chemical code</i>
Aspirin	B01AC06, N02BA01
ADP-inhibitor	B01AC04, B01AC22, B01AC24
Statin	C10AA
Direct oral anticoagulant	B01AF02, B01AE07, B01AF01
Vitamin K-antagonist	B01AA03, B01AA04
β-blokkere	C07*
Angiotensin converting enzyme inhibitors	C09A*, C09B*
Angiotensin-II receptor blockers	C09C*, C09D*
Thiazides	C03AA*, C03AB*
Calcium channel blockers	C08C*, C08D*
Insulin	A10A*
Non-insulin glucose lowering drugs	A10B*

**Table S2.** Procedural baseline characteristics in non-diabetes and diabetes patients by coronary artery status.

	No DM, No CAD (n=41,878)		DM, No CAD (n=5,735)		No DM, CAD (n=59,427)		DM, CAD (n=11,747)	
	n	%	n	%	n	%	n	%
<b>Coronary artery disease extent</b>								
0 VD	41,878	100	5,735	100				
Diffuse VD					9,751	16.4	2,223	18.9
1 VD					26,442	44.5	4,179	35.6
2 VD					12,870	21.7	2,564	21.8
3 VD					10,364	17.4	2,781	23.7
<b>Procedural priority</b>								
Acute	3,234	7.7	298	5.2	16,319	27.5	2,081	17.7
Subacute	9,506	22.7	1,142	19.9	15,222	25.6	3,045	25.9
Elective	29,138	69.6	4,295	74.9	27,885	46.7	6,621	56.4
<b>Procedural indication</b>								
STEMI	1,760	4.2	153	2.7	14,641	24.6	1,769	15.1
NSTEMI	3,295	7.9	395	6.9	10,859	18.3	2,071	17.6
Unstable AP	1,395	3.3	197	3.4	1,714	2.9	352	3.0
Stable AP	17,264	41.2	2,575	44.9	21,127	35.6	4,890	41.6
Arrhythmia	2,031	4.8	224	3.9	1,224	2.1	241	2.1
Valve disease	5,341	12.8	632	11.0	3,570	6.0	848	7.2
Cardiomyopathy	3,854	9.2	593	10.3	2,129	3.6	680	5.8
Other incl. missing	6,938	16.4	966	16.8	4,163	6.9	897	7.6

AP: angina pectoris

NSTEMI: Non-ST segment elevation myocardial infarction

STEMI: ST segment elevation myocardial infarction

VD: vessel disease

**Table S3. Number events, event rates and incidence rate ratios of peripheral artery disease, lower limb revascularization, and lower limb amputation in diabetes patients by presence and extent of coronary artery disease.**

	Events	Events per 100 person years (95% CI)	10-year cumulative incidence (95% CI)	Unadjusted HR (95% CI)	Adjusted HR <sup>†</sup> (95% CI)
<i>Peripheral artery disease</i>					
No CAD				reference	reference
CAD				2.52 (2.22-2.85)	2.32 (2.03-2.65)
Diffuse VD	181	1.60 (1.39-1.86)	15.38 (12.67-18.61)	1.89 (1.57-2.28)	1.71 (1.42-2.06)
1 VD	423	1.75 (1.59-1.93)	15.03 (13.60-16.59)	2.11 (1.82-2.45)	2.07 (1.77-2.42)
2 VD	292	2.04 (1.82-2.28)	16.19 (14.40-18.19)	2.45 (2.08-2.87)	2.36 (1.99-2.80)
3 VD	458	3.13 (2.85-3.43)	24.59 (22.46-26.88)	3.73 (3.22-4.31)	3.45 (2.95-4.04)
					$p_{\text{trend}} < 0.001$
<i>Lower limb revascularization</i>					
No CAD				reference	reference
CAD				3.42 (2.62-4.46)	3.41 (2.58-4.52)
Diffuse VD	51	0.43 (0.33-0.57)	4.29 (3.07-5.97)	2.54 (1.75-3.67)	2.44 (1.68-3.55)
1 VD	111	0.44 (0.36-0.53)	4.35 (3.54-5.34)	2.56 (1.88-3.49)	2.71 (1.96-3.75)
2 VD	94	0.62 (0.51-0.76)	5.78 (4.62-7.22)	3.61 (2.63-4.97)	3.86 (2.76-5.40)
3 VD	143	0.90 (0.77-1.06)	8.30 (6.95-9.90)	5.25 (3.90-7.06)	5.47 (3.98-7.50)
					$p_{\text{trend}} < 0.001$
<i>Lower limb amputation</i>					
No CAD				reference	reference

CAD				1.78 (1.42-2.22)	1.80 (1.41-2.29)
Diffuse VD	47	0.40 (0.30-0.53)	4.42 (3.11-6.25)	1.31 (0.92-1.87)	1.35 (0.95-1.92)
1 VD	103	0.41 (0.33-0.49)	4.20 (3.40-5.18)	1.67 (1.25-2.23)	1.69 (1.26-2.26)
2 VD	65	0.43 (0.33-0.54)	4.11 (3.14-5.36)	1.71 (1.23-2.38)	1.73 (1.24-2.41)
3 VD	115	0.72 (0.60-0.86)	6.73 (5.44-8.16)	2.69 (2.01-3.60)	2.72 (2.03-3.64)
					$p_{\text{trend}} < 0.001$

<sup>†</sup>Adjusted for age, sex, hypertension, microvascular disease, active smoking (imputed), body mass index (imputed), oral anti-coagulant treatment, anti-platelet treatment, statin treatment, diabetes treatment, and diabetes duration.

**Table S4. Number events, event rates and incidence rate ratios by diabetes treatment**

	Patients	Events	Events per 100 person years (95% CI)	Unadjusted HR (95% CI)	Adjusted HR <sup>†</sup> (95% CI)
<i>Peripheral artery disease</i>					
Non-pharmacological treatment	3,457	236	1.09 (0.96-1.24)	1	1
Non-insulin treatment	8,875	722	1.43 (1.33-1.54)	1.30 (1.12-1.50)	1.20 (1.03-1.39)
Insulin treatment	5,150	689	2.43 (2.25-2.61)	2.19 (1.89-2.54)	1.60 (1.33-1.91)
<i>Lower limb revascularization</i>					
Non-pharmacological treatment	3,457	65	0.29 (0.23-0.37)	1	1
Non-insulin treatment	8,875	192	0.37 (0.32-0.42)	1.26 (0.95-1.68)	1.23 (0.92-1.64)
Insulin treatment	5,150	205	0.68 (0.59-0.78)	2.34 (1.77-3.10)	1.86 (1.32-2.62)
<i>Lower limb amputation</i>					
Non-pharmacological treatment	3,457	37	0.16 (0.12-0.23)	1	1
Non-insulin treatment	8,875	123	0.23 (0.20-0.28)	4.27 (3.49-5.24)	1.10 (0.75-1.61)
Insulin treatment	5,150	279	0.90 (0.80-1.01)	16.34 (13.99-19.09)	2.11 (1.40-3.18)

\*10-year cumulative incidence proportion accounting for the competing risk of death.

†Adjusted for age, sex, hypertension, microvascular disease, active smoking (imputed), body mass index (imputed), oral anti-coagulant treatment, anti-platelet treatment, statin treatment, coronary artery disease, and diabetes duration.

CI: confidence interval

CIP: cumulative incidence proportion

**Table S5. Number events, event rates and hazard ratio by duration of diabetes.**

	Patients	Events	Events per 100 person years (95% CI)	Unadjusted HR (95% CI)	Adjusted HR <sup>†</sup> (95% CI)
<i>Peripheral artery disease</i>					
0-4 years	9,185	682	1.20 (1.11-1.29)	1	1
5-9 years	3,683	370	1.82 (1.65-2.02)	1.50 (1.31-1.70)	1.22 (1.06-1.40)
≥10 years	4,614	595	2.56 (2.36-2.77)	2.08 (1.86-2.32)	1.35 (1.17-1.56)
<i>Lower limb revascularization</i>					
0-4 years	9,185	197	0.33 (0.29-0.38)	1	1
5-9 years	3,683	105	0.49 (0.41-0.60)	1.47 (1.16-1.87)	1.13 (0.88-1.46)
≥10 years	4,614	160	0.65 (0.55-0.76)	1.93 (1.57-2.38)	1.09 (0.82-1.43)
<i>Lower limb amputation</i>					
0-4 years	9,185	97	0.16 (0.13-0.20)	1	1
5-9 years	3,683	104	0.49 (0.40-0.59)	3.01 (2.28-3.97)	2.08 (1.54-2.82)
≥10 years	4,614	229	0.93 (0.82-1.06)	5.80 (4.57-7.35)	2.64 (1.94-3.59)

\*10-year cumulative incidence proportion accounting for the competing risk of death.

†Adjusted for age, sex, hypertension, microvascular disease, microvascular disease, active smoking (imputed), body mass index (imputed), oral anti-coagulant treatment, anti-platelet treatment, statin treatment, coronary artery disease, and type of diabetes treatment.

DM: diabetes mellitus

CAD: coronary artery disease

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CI: confidence interval

CIP: cumulative incidence proportion

**Figure S1. Distribution of first lower limb amputation by diabetes and coronary artery disease.**

