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## Occurrence of Major Local Lower Limb Events in Type 2 Diabetic Patients with Lower Extremity Arterial Disease: Impact of Metformin

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1 Occurrence of major local lower limb events in type  
2 2 diabetic patients with lower extremity arterial  
3 disease: impact of metformin

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23

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## Article Highlights

27 **Type of Research:**

28 Single center retrospective study of prospectively collected registry data (Registry:  
29 DIAPA (DIAbetes and Peripheral Artery disease).

30

31 **Key Findings:**

32 Investigation of predictive factors for Major Adverse Limb events in a population of 100  
33 diabetic patients with peripheral arterial disease identified Metformin as a protective  
34 agent (OR=0.26; 95%CI [0.10; 0.68]; p=0.007).

35

36 **Take home Message:**

37 Metformin protects against local complications in people with diabetes with PAD and  
38 should be prescribed in all diabetic patients with peripheral artery disease at an early  
39 stage.

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## Abstract

**Introduction:** patients with type 2 diabetes mellitus (T2DM) are particularly at risk of developing major cardiovascular events (MACE) and peripheral artery disease (PAD) due to an acceleration of the atherosclerotic process linked to hyperglycemia and inflammation with a greater risk of local complications. We aimed to identify the predictive factors for major adverse limb events (MALE) in T2DM patients with PAD to manage modifiable factors at an early stage.

**Methods:** This is a prospective study in which T2DM patients with PAD were included from November 2017 to May 2018 and followed over 12 months. The predictive factors for the onset of MALE, MACE, and death from all causes have been identified.

**Results:** a total of 100 patients were included; 37% of the patients developed a MALE. After multivariate analysis, metformin was associated with a decrease of MALE (OR=0.26; 95%CI [0.10; 0.68]; p=0.007), and a history of the treatment of intravenous iloprost was associated with an increased risk of MALE (OR=5.70; 95%CI [1.31; 31.92]; p =0.029). Regular physical activity was associated with a decreased risk of MACE (OR=0.07; 95%CI [0;0.44]; p=0.021). A history of stroke and a history of venous thromboembolism were associated with an increased all-cause mortality risk with OR=3.68; 95%CI [1.17;11.5]; p=0.025 and OR=3.78; 95%CI [1.16; 12.3]; p=0.027.

**Conclusion:** Metformin is protective against local complications in people with diabetes with PAD and should be prescribed to all diabetic patients with PAD at an early stage.

## 61 I. Introduction

62 The number of adults with Type 2 diabetes mellitus (T2DM) has doubled worldwide in  
63 the past 30 years and continues to grow exponentially. In 2019 more than 463 million  
64 people had DM, representing 9.3% of the world's population, and projections by 2045  
65 estimate that the number of DM patients will reach 700 million by 2045, with 90% of  
66 T2DM<sup>1</sup>. In 2017, 5 million deaths were attributed to T2DM, and this health burden is  
67 mainly due to the cardiovascular complications of the disease. DM is among the top ten  
68 causes of death worldwide associated with cardiovascular mortality <sup>2,3</sup>. The  
69 pathophysiology of diabetic vasculopathy is particularly complex and multifactorial. It  
70 combines vascular aggression, especially at the endothelial level, and inhibition of  
71 cellular defense or repair mechanisms related to hyperglycemia and inflammation <sup>4</sup>.  
72 This accelerates the atherosclerotic processes, leading to a more advanced, more  
73 extensive, and therefore more severe disease. T2DM is a major independent  
74 cardiovascular risk factor, doubling or tripling the risk of a cardiovascular event  
75 independently of other frequently associated risk factors<sup>5</sup>. The incidence of myocardial  
76 infarction is multiplied by 2 to 4 in the case of T2DM and is associated with a higher  
77 mortality<sup>6</sup>.

78 Similarly, the risk of stroke is multiplied by 1.5 to 2 with more severe forms and higher  
79 mortality<sup>7,8</sup> and by 5 to 10 for the lower extremity arterial disease (LEAD). LEAD affects  
80 20 to 30% of T2DM patients. Diagnosis in these patients is often delayed due to the  
81 T2DM-associated peripheral neuropathy that makes the disease poorly symptomatic.  
82 Very often, arterial damage is already advanced at the time of diagnosis. In T2DM,  
83 arterial calcifications are extensive and associated with the development of leg ischemia  
84 due to arterial obstruction and loss of the capacity to react to vasodilatory stimuli. By  
85 adding an increased risk of skin lesion infections due to the altered immunity response

86 related to the duration and extent of chronic hyperglycemia, T2DM patients are six times  
87 more likely to develop Chronic Limb-Threatening Ischemia (CLTI) and 5 to 12 times  
88 more likely to undergo major lower limb amputation. In the case of CLTI on one leg,  
89 CLTI on the other leg will be diagnosed in 50% of patients<sup>9-11</sup>. In addition, there are  
90 more complications after revascularization with higher cardiovascular morbidity<sup>9-12</sup>.  
91 Predictive factors for major lower limb events (MALE) in T2DM patients with LEAD are  
92 little known.  
93 Very few studies addressed this question, and the currently known predictive factors of  
94 poor local outcomes are the HbA1c level, age, distal artery involvement, renal failure,  
95 active smoking, insulin dependence, popliteal stenosis, and a history of a diabetic  
96 wound, peripheral revascularization, and amputation or leg ulcer<sup>13-17</sup>. In this study, we  
97 aimed to prospectively evaluate the known predictive factors for major local lower limb  
98 events (MALE: major adverse limb events: critical ischemia leading to major amputation  
99 or revascularization) in type 2 diabetic patients with PAD. We also wished to assess the  
100 impact of patient treatment, in particular oral antidiabetic drugs, on the occurrence of  
101 MALE, major adverse cardiovascular events (MACE), and all-cause mortality in this  
102 population.

## 103 **II. Methods**

### 104 **a. Population**

105 The study was conducted in the Vascular Medicine Department, the Vascular  
106 Rehabilitation Department of the Georges-Pompidou European hospital, and Coentim-  
107 Celton hospital (Paris). DIAPA (DIAbetes and Peripheral Artery disease) is a prospective  
108 registry including patients with T2DM and LEAD. Patients under 18 years of age or with  
109 non-type 2 DM are not included in this registry. LEAD is defined by an ankle-brachial

110 index (ABI) < 0.9, or either a history of endovascular or surgical lower extremity  
111 revascularization or the presence of atherosclerotic plaque determined by a thickness  $\geq$   
112 1.5mm on arterial Doppler ultrasound or computed tomography angiography (CTA) of  
113 the abdominal aorta or the lower limb arteries.

114 The local ethical committee waived patient consent, but a non-opposition for using their  
115 medical data is required to include a patient in DIAPA. Biological and clinical parameters  
116 were collected at the date of inclusion, including the stage of LEAD and concomitant  
117 treatments. Follow-up visits at 6 and 12 months were scheduled. At each visit, the  
118 occurrence of MACE (myocardial infarction, stroke, or cardiovascular death), MALE  
119 (CLTI leading to revascularization of a lower limb, or major amputation), minor  
120 amputations, all-cause death, microvascular complications of T2DM and treatment  
121 changes since the last visit were collected in a standardized electronic record (Redcap®,  
122 USA). The primary outcome of this study was the occurrence of MALE at the last follow-  
123 up. Secondary outcomes were the occurrence of MACE and death from any cause at the  
124 last follow-up. Based on the data collected at baseline and the history, we identified  
125 predictive factors associated with the presence of MALE at 12 months in these patients  
126 with PAD and T2DM. The second objective of this study was to identify factors related to  
127 the presence of MACE and the occurrence of all-cause death at 12 months in this  
128 population.

## 129 **b. Statistical analysis**

130 Results are presented as a mean  $\pm$  standard deviation or number and frequency (n(%)).  
131 The variables analyzed were those at inclusion and the history of patients with less than  
132 20% missing data. There were no patients excluded. In the bivariate analyses,  
133 quantitative variables were compared between patients with or without  
134 MALE/MACE/death using a Student's T-test if the distribution was normal and a Mann-

135 Whitney test in all cases. When the p-value of the parametric test differed from that of  
136 the non-parametric test, the non-parametric p-value was considered for further  
137 analyses. Qualitative variables were compared between patients with or without  
138 MALE/MACE/death using a Chi-square test and a Fisher test when numbers permitted.  
139 Based on this bivariate analysis, we pre-selected the variables associated with the  
140 criterion MALE/MACE/death, whose p-value is significant at the 20% threshold.  
141 Variables with missing data were not retained.  
142 We then proceeded to the final selection of independent variables associated with the  
143 presence of MACE/MALE at 12 months by a multivariate analysis based on logistic  
144 regression modeling with stepwise variable selection. The results are presented as odds  
145 ratio (OR) with a 95% confidence interval (CI). We selected the independent variables  
146 that explain the occurrence of all-cause deaths using a Cox proportional risk model with  
147 stepwise variable selection. The results are presented as a Hazard Ratio (HR) with a  
148 95% CI. Residuals were verified by the Schoenfeld method. The Kaplan-Meier method  
149 was used to compare patient survival with/without MACE and with/without MALE. The  
150 results for each criterion are shown graphically as Forest plots. Lastly, to avoid a  
151 potential confounding bias of no metformin prescription in severe renal failure, we  
152 performed a bivariate analysis of the severe renal failure variable at inclusion (M0)  
153 between patients who developed MALE vs. Non-MALE during follow-up.

### 154 **III. Results**

155 One hundred consecutive patients were included from November 2017 to May 2018.  
156 The mean age was  $70.9 \pm 9.2$  years, and men represented 86% of the patients. Table 1  
157 presents the characteristics of the patients at inclusion. All patients had hypertension,  
158 98% had dyslipidemia, 12% were active smokers and, 49% former smokers, 65% were

159 overweight. The mean duration of diabetes since initial diagnosis was 17.4 years, with a  
160 mean HbA1c of 7.3%. There was no difference in glycemic control between patients on  
161 metformin and patients without metformin, with HbA1c not significantly different  
162 between the two groups: median HbA1c was 7.1% [6.3-8.4] for patients taking  
163 metformin vs. 6.8 [6.3–7.6] for patients without metformin (p=0.412).

164 More than half of the patients had at least one microvascular complication of diabetes:  
165 79% had diabetic neuropathy (64% of which were complicated by diabetic wounds);  
166 41% had diabetic retinopathy (19% of which was at the stage of proliferative  
167 retinopathy), and 89% had diabetic nephropathy (54% of which had chronic renal  
168 failure defined by a glomerular filtration rate below 60mL/min).

169 The average duration of the PAD was 4.7 years. More than two-thirds of the patients had  
170 symptomatic PAD, of which 33% with claudication and 67% had critical ischemia (96%  
171 leg ulcer or necrosis). 39% had already had at least one hospitalization for a PAD. 35%  
172 had already had a history of healed critical ischemia. 75% had already been  
173 revascularized by surgery or angioplasty, and 42% had been amputated, of which 6%  
174 were major amputations. 12% had had at least one treatment with venous iloprost in  
175 the past.

176 Regarding treatment, 78% of patients were on triple vasculoprotective therapy with an  
177 ACE inhibitor or ARA2 in combination with a statin (95%) and an antiplatelet agent  
178 (mainly aspirin in 90%) (Supplementary data).

179 66% of patients were on oral anti-diabetic drugs (OADs), mainly metformin (56%), and  
180 58% were on insulin alone or in combination with OADs.

181 All the cardiovascular events that occurred during the follow-up period, the first six  
182 months and up to 1 year, are presented in Table 2. At 12 months of follow-up, among the  
183 patients alive, 44% had critical ischemia, with 3% at stage III and 41% at stage IV of the

184 Fontaine classification. 22% of the patients had an asymptomatic PAD, and 34% had  
185 intermittent claudication. During this follow-up, the total occurrence of MALE was 37%,  
186 lower limb revascularization 36%, and major amputation 4%.

187 Among the patients who had a MALE during follow-up, 97.3% were revascularized for  
188 critical ischemia, 10.8% had a major amputation, 29.7% had a minor amputation, and  
189 16% had a MACE. Patients with a MALE did not die more than non-MALE and did not  
190 have more MACE (Table 3).

191 MACE, myocardial infarction, ischemic stroke, and cardiovascular death were  
192 respectively 13%, 6%, 1%, and 10% when considering deaths secondary to  
193 complications related to the PAD itself. Among the patients with MACE, 46% had MI,  
194 7.7% had a stroke, 77% had cardiovascular death, and 46% had a MALE. Patients who  
195 developed a MACE during follow-up did not have more MALE (Table 4).

196 At the end of the follow-up, 14% of the patients had died, with 71.4% from  
197 cardiovascular causes. 71% of these patients had presented a MACE, 21% a MI, and 35%  
198 a MALE. Patients who died did not have more MALE during follow-up than patients who  
199 were still alive (Supplementary data).

#### 200 **a. Factors associated with the occurrence of MALE**

201 During the one-year follow-up, 37% of the patients had experienced a MALE. After  
202 multivariate analysis, the independent factors associated with the occurrence of MALE  
203 at one year were the following (Figure 1):

204 - The use of metformin and the history of intravenous iloprost treatment. Metformin  
205 appeared to be a protective factor against the occurrence of MALE with an Odds Ratio  
206 (OR) of 0.26; 95%CI [0.10;0.68] (p=0.007). Characteristics of patients with metformin  
207 vs. without metformin are provided in supplementary data.

208 - A history of intravenous iloprost treatment appeared to be a risk factor for the  
209 occurrence of MALE with an OR of 5.70 95%CI [1.31; 31.92] (p=0.029).

210 Critical ischemia stage 4 at M0 was associated with an increase in MALE but not  
211 significantly, with an OR of 3.24 95%CI [0.94;13.26] and a p=0.076. Severe renal failure  
212 was not related to the occurrence of MALE in neither bivariate (p=0.132) nor  
213 multivariate analysis (OR=0.73; 95%CI [0.26;2.07] p=0.620).

#### 214 **b. Factors associated with the occurrence of MACE**

215 During the one-year follow-up, 13% of the patients had developed a MACE.

216 The factors identified as being associated with the occurrence of MACE at one year in a  
217 bi-variate analysis at the significance level (p<0.05) were as follows:

218 - Presence of a trophic disorder at inclusion (p=0.014): among patients who had a MACE  
219 at one year, 92.3% had a lower limb ulcer or necrosis at inclusion vs. 56.32% among  
220 patients without a MACE at one year

221 - Regular physical activity (p=0.003): 51.7% of patients without MACE were active  
222 versus 7.7% of patients with MACE at one year

223 After multivariate analysis, only one independent factor associated with the occurrence  
224 of MACE at the significance level of p<0.05 was identified (Supplementary figure):  
225 regular physical activity with an OR of 0.066 (p=0.021), appearing to be a protective  
226 factor against the occurrence of MACE throughout the follow-up.

#### 227 **c. Factors associated with the occurrence of death from any cause at one** 228 **year**

229 During the one-year follow-up, 14 patients died for any reason. The factors identified as  
230 being related to the event of death from any cause at one year in bi-variate analysis at  
231 the significance level of p<0.05 were:

232 1. Age: patients who died during follow-up were older ( $75\pm 10$  years vs.  $70\pm 9$  years on  
233 average) ( $p=0.046$ ).

234 2. A reason for hospitalization for treatment of a lower limb wound; the other reasons  
235 were a follow-up of PAD without trophic disorder and follow-up of diabetes. All patients  
236 who died were hospitalized for a lower limb wound vs. 58.1% of patients still alive at  
237 one year ( $p=0.003$ ).

238 3. The Fontaine classification stage of PAD at inclusion ( $p=0.021$ ): patients who died at  
239 one year had stage IV at inclusion in 85.7% of cases vs. 46% of patients alive at one year.

240 4. Presence of any kind of leg wound ( $p=0.001$ ): 100% of patients who died had a wound  
241 at inclusion vs. 54.7% of patients alive at one year

242 5. Physical activity ( $p=0.018$ ): 14.3% of the deceased patients practiced regular physical  
243 activity at inclusion vs. 51.2% of patients alive at one year

244 6. A history of stroke ( $p=0.03$ ): 35.7% of the deceased patients had a history of stroke  
245 versus 12.8% of the patients still alive at one year

246 7. A history of venous thrombo-embolic event (VTE) ( $p=0.032$ ): 28.6% of patients who  
247 died had a history of VTE versus 6.9% of patients still alive at one year

248 8. OAD use ( $p=0.049$ ): 42.9% of deceased patients were on OAD at inclusion vs. 69.8% of  
249 living patients.

250 After multivariate analysis, the independent factors associated with the occurrence of  
251 all-cause death at one year at the significance level were:

252 1. A history of VTE ( $p=0.027$ ) with an HR of 3.8; 95%CI [1.16; 12.3]  
253 2. A history of stroke ( $p=0.025$ ) with an HR of 3.7; 95%CI [1.17;11.50]

254 However, a history of CTLI was not significantly associated with a decrease in all-cause  
255 mortality but with a trend towards a higher mortality rate ( $p=0.074$ ). Figure 2 shows the  
256 Forest plot of the independent factors related to all-cause death. Patients with MALE

257 during follow-up did not die more than those without MALE at the end of follow-up, with  
258 13.5% and 14.3% of deaths for MALE and non-MALE with a  $p=0.914$  at the end of  
259 follow-up.

## 260 **IV. Discussion**

261 We aimed to identify and assess the predictive factors for major local events of the lower  
262 limbs during a 12-month follow-up in a population of T2DM patients with PAD. At the  
263 end of the 12-month follow-up, metformin was associated with a decrease in MALE and  
264 appeared to be a protective factor with an  $OR=0.2$ . Few studies have looked at the  
265 predictive factors for the progression of PAD, and even fewer in this population. Most  
266 studies were interventional studies comparing intensive vs. conventional glyceic  
267 control or different management of cardiovascular risk factors (hypertension,  
268 dyslipidemia) on the occurrence of MACE and microvascular complications with little  
269 data on macrovascular damage to the lower limb<sup>3,18-21</sup>.

270 In the UKPDS 34 study in newly diagnosed T2DM diabetes patients with no prior  
271 cardiovascular history over a 10-year follow-up, metformin was associated with a 32%  
272 reduction in the risk of diabetes-related events, including lower limb amputations, a  
273 36% reduction in the risk of all-cause death. Regarding macrovascular events (MI,  
274 sudden death, PAD, stroke), metformin reduced the risk by 30% compared to  
275 conventional treatment<sup>18,22</sup>. Similar results were found in the HOME randomized trial of  
276 insulin-requiring T2DM patients, comparing treatment with metformin + insulin vs.  
277 placebo + insulin during a 4-year follow-up. A 39% reduction in the risk of  
278 macrovascular events, including non-traumatic lower limb amputations, was found<sup>23</sup>.  
279 Using imaging, metformin is also negatively and independently associated with lower-  
280 limb arterial calcification<sup>24</sup>. UKPDS and HOME randomized trials found a decrease in

281 cardiovascular events and a more significant weight loss associated with metformin.  
282 This weight loss potentiates the effect of insulin on its target organs by decreasing the  
283 adipose mass and consequently allows a decrease in HbA1c. The HOME trial also  
284 demonstrated a reduction in biological markers of inflammation (such as C reactive  
285 protein) and markers of endothelial dysfunction such as Tissue Plasminogen Activator  
286 or the Plasminogen activator inhibitor 1, which may explain the decrease in major  
287 adverse events due to the reduction of atherosclerosis progression in patients taking  
288 Metformin.

289 The complex mechanisms by which metformin would have a beneficial effect on  
290 macrovascular damage include a decrease in endothelial dysfunction by increasing  
291 Nitric oxide production, a reduction of oxidative stress by reducing the production of  
292 oxygenated reagents, and advanced glycation products. In addition, metformin lowers  
293 triglyceride levels and slows down the atherosclerotic process<sup>25</sup>. It may be thus  
294 worthwhile to prescribe metformin in patients newly diagnosed with type 2 diabetes  
295 but also to continue metformin in the absence of severe renal impairment  
296 (GFR<30ml/min) even in insulin-dependent patients because of the potentially vascular  
297 protection effect of metformin and to potentiate the effects of insulin <sup>23,26</sup>.

## 298 **Limitations**

299 The first limitation is the short follow-up period of one year, which did not allow the  
300 detection of sufficient MALE to identify further predictive factors for complications of  
301 PAD. In addition, the study included only 100 patients, which may also have prevented  
302 the identification of other factors associated with MALE. We were also unable to  
303 characterize the severity of PAD due to technical problems in measuring the pressure of  
304 the big toes and TcPO<sub>2</sub> in patients with arterial calcifications. Similarly, most patients  
305 had significant distal medial arterial calcification due to the duration of diabetes and the

306 presence of renal insufficiency, making complementary imaging examinations  
307 challenging to interpret. Nevertheless, the exhaustive nature of the data collection at  
308 inclusion and of the history allowed us to confirm the predictive factors already known  
309 for the occurrence of MALE but also to identify protective factors such as the use of  
310 metformin. Lastly, few patients were on GLP1 analogs (7%) and none on SGLT2  
311 inhibitors, preventing our cohort's evaluation of these treatments.

## 312 **Conclusion**

313 We have identified and evaluated the predictive factors for the occurrence of MALE in  
314 patients with advanced T2DM with arterial disease and at very high cardiovascular risk.  
315 Metformin seems to protect against local complications even in people with diabetes  
316 with severe arterial disease. Metformin should be prescribed for all diabetic patients  
317 with arterial disease and used early after diagnosing PAD. Regular physical activity, 30  
318 minutes a day at least three times a week, is associated with reducing major  
319 cardiovascular events and should be encouraged and maintained in this population.

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394

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397 **VII. Conflict of interest**

398 No conflict of interest

399 **VIII. Author contributions**

400 ST, AG, GM, and EM conceived and supervised the study. ST, NM, LG, GD, and GG  
401 collected the data. YT and HM performed the statistical analysis. AA and TM ran the  
402 statistical analysis. ST and GG wrote the manuscript. All authors interpreted the data,  
403 drafted and revised the manuscript, and approved the final version.

404 **IX. Tables and figures**

405 **I. Table 1. Patient characteristics**

406 BMI: Body mass index. CKD: Chronic Kidney Disease. LDL: Low-density lipoprotein. PAD:  
 407 Peripheral arterial disease. A diabetic wound refers to a foot wound secondary to diabetic  
 408 neuropathy.

<b>Patients</b>	<b>Patients (n=100)</b>
Age (years)	70.9 ±9.2
Male gender	86
Overweight and obesity	61
Obesity	24
BMI (kg/m <sup>2</sup> )	27.0 ±5.1
Active smoking	12
Systolic blood pressure (mmHg)	138.1 ±18.1
Diastolic blood pressure (mmHg)	72.2 ± 14.7
LDLc (mmol/L)	1.8 ±0.9
Triglycerides (mmol/L)	1.9 ±1.0
HBA1c (%)	7.3 ±1.7
<b>Medical history</b>	
Hypertension	100
Dyslipidaemia	98
Abdominal aortic aneurysm	6
Stroke	16
Carotid artery disease	67
Coronary artery disease	55
Coronary revascularisation	47
Heart failure	19
Atrial fibrillation	22
<b>Diabetes mellitus history and complications</b>	
Duration of diabetes (year)	17.4 ± 10.4
Diabetic wound (number)	64
Diabetic neuropathy	79
Diabetic retinopathy	41
Proliferating diabetic retinopathy	19
Diabetic nephropathy	89
Microalbuminuria (30-300mg/24h)	38
Proteinuria (≥300mg/24h)	31
CKD (DFG<60ml/min)	53
CKD stage 3 (GFR: 30–59 ml/min)	32
CKD stage 4 (GFR: 15–29 ml/min)	6
CKD stage 5 (GFR<15 ml/min)	15
Dialysis	14

<b>PAD profile</b>	
Stage 1=asymptomatic	19
Stage 2=claudication	27
Stage 3=resting pain	2
Stage 4=arterial trophic disorder	52

409

410 **II. Table 2. Monitoring of cardiovascular events and deaths from all causes**

411 MACE: Major Adverse Cardiovascular Events. MALE: Major Adverse Limb Events.

412

	<b>At M6 N=100</b>	<b>At M12 N=100</b>
<b>Patients with new leg ulcers</b>	29	39
<b>Patients with at least one Local infection</b>	30	38
<b>At least one hospitalization</b>	54	73
<b>Patients with MALE</b>	32	37
<b>Lower limb revascularization</b>	31	36
<b>Any lower limb amputation</b>	13	16
<b>Major lower limb amputation</b>	2	4
<b>Minor lower limb amputation</b>	11	12
<b>Patients with MACE</b>	10	13
<b>Myocardial infarction</b>	5	6
<b>Ischemic stroke</b>	1	1
<b>Cardiovascular deaths</b>	8	10
<b>All-cause deaths</b>	11	14

413

414

415 **III. Table 3. Events at complete follow-up (12 months) in patients with Major**  
 416 **Adverse Limb Events (MALE) vs. without MALE.**

417 MACE: Major Adverse Cardiovascular Events.

418

Covariate	Whole sample (N=100)	Patients with MALE (N=37)	Patients without MALE (N=63)	P-value
Major amputation	4	<b>4 (10.8%)</b>	<b>0 (0%)</b>	<b>0.017</b>
Minor amputation	12	<b>11 (29.7%)</b>	<b>1 (1.6%)</b>	<b>0.001</b>
All-cause Death	14	5 (13.5%)	9 (14.3%)	0.914
Cardiovascular death	10	5 (13.5%)	5 (7.9%)	0.369
Non cardiovascular death	4	0 (0%)	4 (6.5%)	0.294
Lower limb arterial Revascularization	36	<b>36 (97.3%)</b>	<b>0 (0%)</b>	<b>0.001</b>
MACE	13	6 (16.2%)	7 (11.1%)	0.464
Leg ulcer	39	<b>22 (59.5%)</b>	<b>17 (27.0%)</b>	<b>0.001</b>
Local infection	38	<b>21 (56.8%)</b>	<b>17 (27.0%)</b>	<b>0.003</b>
Ischemic stroke	1	0 (0%)	1 (1.6%)	1.000
Myocardial infarction	6	4 (10.8%)	2 (3.2%)	0.190

419

420

421 **IV. Table 4. Events at complete follow-up in patients with Major Adverse**  
 422 **Cardiovascular Events (MACE) vs. without MACE.**

423

<b>Covariate</b>	<b>Whole sample (N=100)</b>	<b>Patients with MACE (N=13)</b>	<b>Patients without MACE (N=87)</b>	<b>P-value</b>
Major amputation	4	0 (0%)	4 (4.6%)	1
Minor amputation	12	<b>4 (30.8%)</b>	<b>8 (9.2%)</b>	<b>0.048</b>
All-cause Death	14	<b>10 (76.9%)</b>	<b>4 (4.6%)</b>	<b>0.001</b>
Cardiovascular death	10	<b>10 (76.9%)</b>	<b>0 (0%)</b>	<b>0.001</b>
Non cardiovascular death	4	0 (0%)	4 (4.6%)	1
Lower limb arterial Revascularization	36	6 (46.1%)	30 (34.5%)	0.414
Leg ulcer	39	8 (61.5%)	31 (35.6%)	0.074
Local infection	38	7 (53.8%)	31 (35.6%)	0.207
Ischemic stroke	1	1 (7.7%)	0 (0%)	0.13
Myocardial infarction	6	<b>6 (46.1%)</b>	<b>0 (0%)</b>	<b>0.001</b>

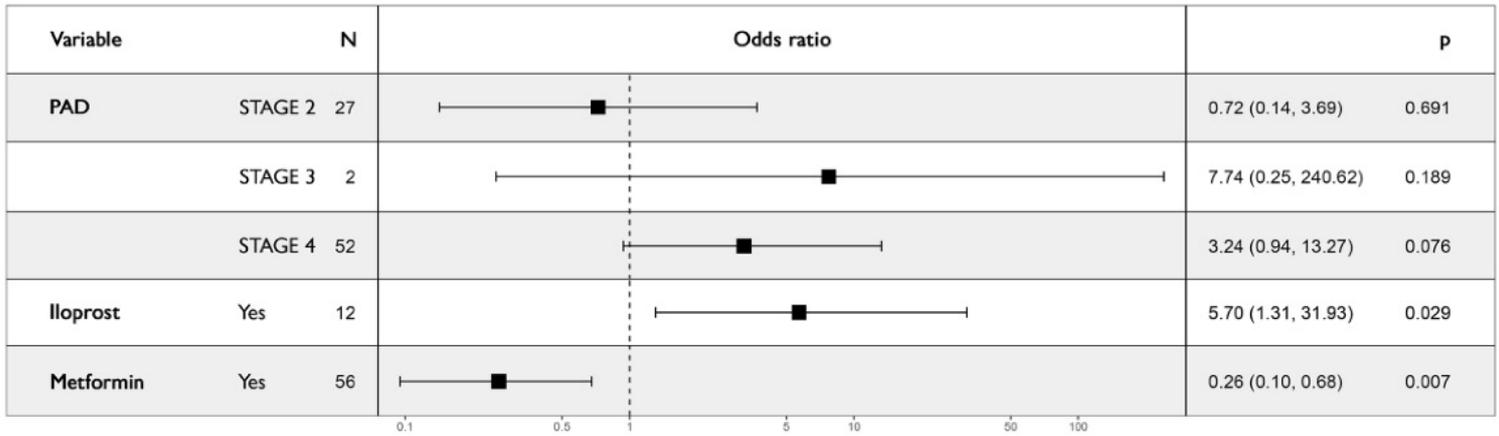
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426 **V. Figure 1.**

427 Forest plot of independent factors associated with Major Adverse Limb Events (95% CI).

428 PAD: peripheral arterial disease.



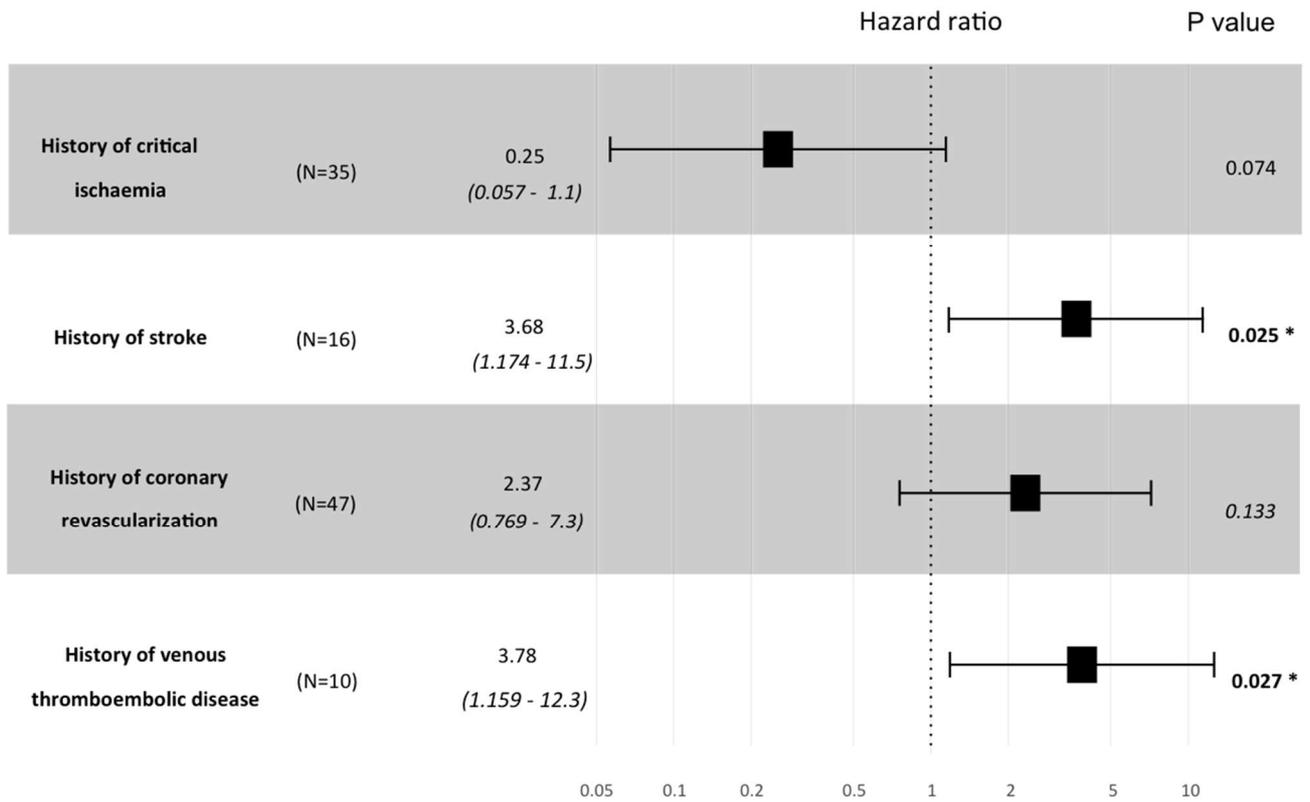
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432 **VI. Figure 2.**

433 Forest plot of independent factors associated with all-cause death in multivariate  
434 analysis



435

436

437 **X. Supplementary material**

438 **I. Supplementary data 1. Drug treatment of patients**

<b>Medication</b>	<b>Patients (n=100)</b>
<b>ACE inhibitors or ARB2</b>	91
<b>Statin</b>	95
<b>Anti-platelet therapy</b>	90
<b>Anticoagulant</b>	18
<b>Anti-platelet therapy or anticoagulant</b>	98
<b>Anti-platelet therapy and anticoagulant</b>	10
<b>Oral antidiabetic drug</b>	66
<b>GLP-1 analogue</b>	7
<b>Gliptin</b>	19
<b>Sulfamide</b>	18
<b>Glinide</b>	8
<b>Metformin</b>	56
<b>SGLT-2 inhibitors</b>	0
<b>Alpha Glucosidase Inhibitor</b>	1
<b>Insulin</b>	58
<b>Antibiotic</b>	14

439

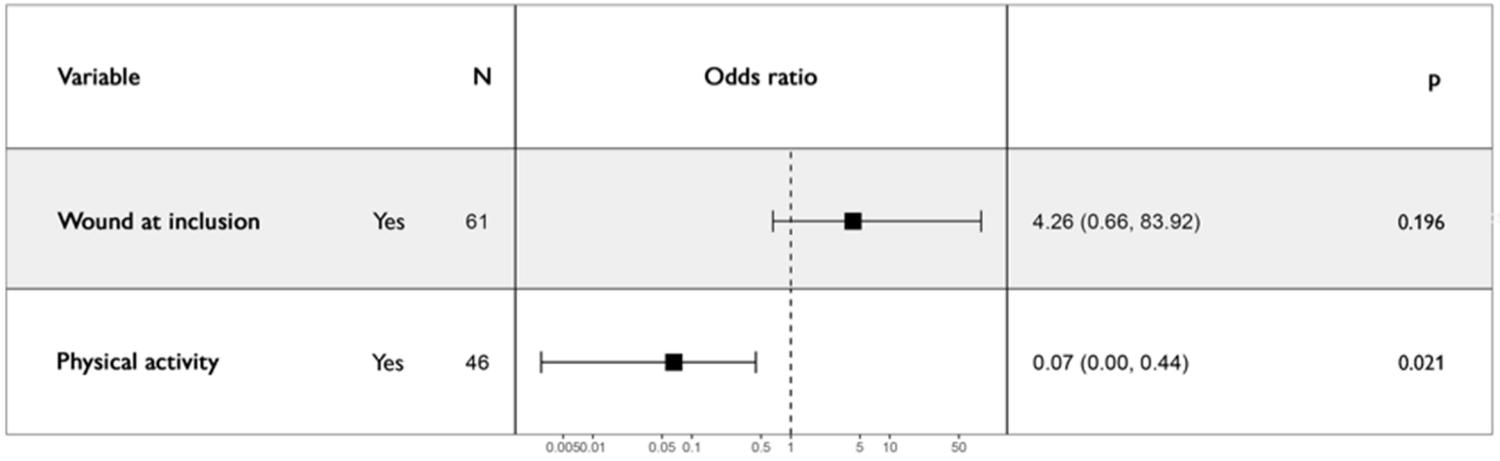
440 ACE: angiotensin conversion enzyme. GLP-1: glucagon-like peptide 1. SGLT-2: Sodium/glucose

441 cotransporter 2.

442

443 **II. Supplementary data 2. Forest plot of independent factors associated with**

444 **MACE at one year**



445

446

447 **III. Supplementary data 3. Events at complete follow-up in patients with death**  
 448 **during follow-up vs. patients still alive.**

449

Covariate	Whole sample (N=100)	Deceased patients (N=14)	Still alive patients (N=86)	P-value
Major amputation	4	0 (0%)	4 (4.6%)	1
Minor amputation	12	3 (21.4%)	9 (10.5%)	0.367
All-cause Death	14	<b>14 (100%)</b>	<b>0 (0.0%)</b>	<b>0.001</b>
Cardiovascular death	10	<b>10 (71.4%)</b>	<b>0 (0.0%)</b>	<b>0.001</b>
Non cardiovascular death	4	<b>4 (28.6%)</b>	<b>0 (0.0%)</b>	<b>0.001</b>
MACE	13	<b>10 (71.4%)</b>	<b>3 (3.5%)</b>	<b>0.001</b>
Lower limb arterial Revascularization	36	5 (35.7%)	31 (36%)	0.981
Leg ulcer	39	8 (57.1%)	31 (36%)	0.133
Local infection	38	7 (50%)	31 (36%)	0.319
Ischemic stroke	1	1 (7.1%)	0 (0%)	0.14
Myocardial infarction	6	<b>3 (21.4%)</b>	<b>3 (3.5%)</b>	<b>0.034</b>

450

451

452 **IV. Supplementary data 4. Clinical data, treatments, and outcomes of patients with**  
 453 **metformin vs. without metformin.**

Covariate	Patients without metformin (n=44)	Patients with metformin (n=56)	P-value
Age (years)	74.2 (9.57)	68.3 (8.14)	0.001
Male gender	37 (84.1 %)	49 (87.5%)	0.626
CKD (DFG<60ml/min)	34 (79.1%)	19 (33.9 %)	<0.001
CKD stage 3 (GFR: 30-59 ml/min)	14 (34.1%)	18 (34%)	0.985
CKD stage 4 (GFR: 15-29 ml/min)	6 (14.6%)	0 (0%)	<0.006
CKD stage 5 (GFR<15 ml/min)	15 (36.6%)	0 (0%)	<0.001
Statin	40 (90.9%)	55 (99.2%)	0.166
Anti-platelet therapy	40 (90.9%)	50 (89.3%)	1
GLP-1 analogue	0 (0%)	7 (12.5%)	0.017
Gliptin	4 (9.1%)	15 (26.8%)	0.038
Sulfamide	2 (4.6%)	16 (28.6%)	0.002
Glinide	5 (11.4%)	3 (5.4%)	0.295
SGLT-2 inhibitors	0 (0%)	0 (0%)	1
Alpha Glucosidase Inhibitor	0 (0%)	1 (1.8%)	1
Insulin	34 (77.3%)	24 (42.9%)	0.001
Major amputation	2 (4.5%)	2 (3.6%)	1
Minor amputation	7 (15.9%)	5 (8.9%)	0.286
All-cause Death	9 (20.4%)	5 (8.9%)	0.099
Cardiovascular death	6 (13.6%)	4 (7.1%)	0.328
Non cardiovascular	3 (6.8%)	1 (1.8%)	0.317

<b>death</b>			
<b>Lower limb arterial Revascularization</b>	<b>23 (52.3%)</b>	<b>13 (23.2%)</b>	<b>0.003</b>
<b>MACE</b>	8 (18.2%)	5 (8.9%)	0.172
<b>Leg ulcer</b>	<b>22 (50.0%)</b>	<b>17 (30.4%)</b>	<b>0.046</b>
<b>Local infection</b>	<b>22 (50.0%)</b>	<b>16 (28.6%)</b>	<b>0.028</b>
<b>Ischemic stroke</b>	1 (2.3%)	0 (0%)	0.440
<b>Myocardial infarction</b>	5 (11.4%)	1 (1.8%)	0.084

454