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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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26

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 T2DM¹. 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 ^{2,3}. 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 ⁴.
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 factors⁵. The incidence of myocardial
76 infarction is multiplied by 2 to 4 in the case of T2DM and is associated with a higher
77 mortality⁶.

78 Similarly, the risk of stroke is multiplied by 1.5 to 2 with more severe forms and higher
79 mortality^{7,8} 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 patients⁹⁻¹¹. In addition, there are
90 more complications after revascularization with higher cardiovascular morbidity⁹⁻¹².
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 ulcer¹³⁻¹⁷. 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 ± 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 ± 10 years vs. 70 ± 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 glyceimic
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 ^{3,18-21}.

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 ^{18,22}. 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 found²³.
279 Using imaging, metformin is also negatively and independently associated with lower-
280 limb arterial calcification²⁴. 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 process²⁵. 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 ^{23,26}.

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 TcPO₂ 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.

320 V. References

- 321 1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and
322 regional diabetes prevalence estimates for 2019 and projections for 2030 and
323 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th
324 edition. *Diabetes Res Clin Pract.* 2019 Nov 1;157:107843.
- 325 2. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Vol. 389, *The Lancet.* Lancet;
326 2017. p. 2239–51.
- 327 3. Gaede P, Vedel P, Larsen N, Jensen GVHH, Parving H-H, Pedersen O, et al.
328 Multifactorial intervention and cardiovascular disease in patients with type 2
329 diabetes. *N Engl J Med.* 2003 Jan 30;348(5):383–93.
- 330 4. Fowler MJ. Microvascular and macrovascular complications of diabetes. Vol. 26,
331 *Clinical Diabetes.* American Diabetes Association; 2008. p. 77–82.
- 332 5. Franco OH, Steyerberg EW, Hu FB, Mackenbach J, Nusselder W. Associations of
333 Diabetes Mellitus With Total Life Expectancy and Life Expectancy With and
334 Without Cardiovascular Disease. 2007 Jun 11;167(11).
- 335 6. Franklin K, Goldberg RJ, Spencer F, Klein W, Budaj A, Brieger D, et al. Implications
336 of Diabetes in Patients With Acute Coronary Syndromes: The Global Registry of
337 Acute Coronary Events. 2004 Jul 12;164(13).
- 338 7. Stegmayr B, Asplund K. Diabetes as a risk factor for stroke. A population
339 perspective. *Diabetologia.* 1995 Sep;38(9).
- 340 8. Tuomilehto J, Rastenyté D, Jousilahti P, Sarti C, Vartiainen E, Rastenyte D, et al.
341 Diabetes Mellitus as a Risk Factor for Death From Stroke. *Stroke.* 1996 Feb;27(2).
- 342 9. Marso SP, Hiatt WR. Peripheral arterial disease in patients with diabetes. *Journal*
343 *of the American College of Cardiology J Am Coll Cardiol;* Mar 7, 2006 p. 921–9.
- 344 10. Jude EB, Eleftheriadou I, Tentolouris N. Peripheral arterial disease in diabetes - A

- 345 review. Vol. 27, Diabetic Medicine. Diabet Med; 2010. p. 4–14.
- 346 11. Thiruvoipati T, Kielhorn CE, Armstrong EJ. Peripheral artery disease in patients
347 with diabetes: Epidemiology, mechanisms, and outcomes. World J Diabetes. 2015
348 Jul 10;6(7):961.
- 349 12. Clark N. Peripheral Arterial Disease in People with Diabetes. Vol. 26, Diabetes
350 Care. Diabetes Care; 2003. p. 3333–41.
- 351 13. Eshcol J, Jebarani S, Anjana RM, Mohan V, Pradeepa R. Prevalence, incidence and
352 progression of peripheral arterial disease in Asian Indian type 2 diabetic patients.
353 2014;28(5).
- 354 14. Meloni M, Izzo V, Giurato L, Gandini R, Uccioli L. Below-the-ankle arterial disease
355 severely impairs the outcomes of diabetic patients with ischemic foot ulcers. 2019
356 Jun;152:9–15.
- 357 15. Morbach S, Furchert H, Gröblinghoff U, Hoffmeier H, Kersten K, Klauke G-TT, et al.
358 Long-Term Prognosis of Diabetic Foot Patients and Their Limbs: Amputation and
359 death over the course of a decade. 2012 Oct;35(10).
- 360 16. Ghanassia E, Villon L, Thuan Dit Dieudonné J-F, Boegner C, Avignon A, Sultan A, et
361 al. Long- Term Outcome and Disability of Diabetic Patients Hospitalized for
362 Diabetic Foot Ulcers: A 6.5-year follow-up study. 2008 Jul;31(7).
- 363 17. Wilcox T, Newman JD, Maldonado TS, Rockman C, Berger JS. Peripheral vascular
364 disease risk in diabetic individuals without coronary heart disease.
365 Atherosclerosis. 2018;275:419–25.
- 366 18. Turner R. Effect of intensive blood-glucose control with metformin on
367 complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet.
368 1998 Sep 12;352(9131):854–65.
- 369 19. Turner R. Intensive blood-glucose control with sulphonylureas or insulin

- 370 compared with conventional treatment and risk of complications in patients with
371 type 2 diabetes (UKPDS 33). *Lancet*. 1998 Sep 12;352(9131):837–53.
- 372 20. Margolis KL, O'Connor PJ, Morgan TM, Buse JB, Cohen RM, Cushman WC, et al.
373 Outcomes of combined cardiovascular risk factor management strategies in type 2
374 diabetes: the ACCORD randomized trial. *Diabetes Care*. 2014 Jun;37(6):1721–8.
- 375 21. Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, et al.
376 Association of glycaemia with macrovascular and microvascular complications of
377 type 2 diabetes (UKPDS 35): Prospective observational study. *Br Med J*. 2000 Aug
378 12;321(7258):405–12.
- 379 22. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-Year Follow-up of
380 Intensive Glucose Control in Type 2 Diabetes. *N Engl J Med*. 2008 Oct
381 9;359(15):1577–89.
- 382 23. Kooy A, de Jager J, Lehert P, Bets DDD, Wulffelé MG, Donker AJMM, et al. Long-
383 term effects of metformin on metabolism and microvascular and macrovascular
384 disease in patients with type 2 diabetes mellitus. *Arch Intern Med*. 2009 Mar
385 23;169(6):616–25.
- 386 24. Mary A, Hartemann A, Liabeuf S, Aubert CE, Kemel S, Salem JE, et al. Association
387 between metformin use and below-the-knee arterial calcification score in type 2
388 diabetic patients. *Cardiovasc Diabetol*. 2017 Dec 15;16(1):24.
- 389 25. Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Metformin: from mechanisms
390 of action to therapies. *Cell Metab*. 2014 Dec 2;20(6):953–66.
- 391 26. de Jager J, Kooy A, Schalkwijk C, van der Kolk J, Lehert P, Bets D, et al. Long-term
392 effects of metformin on endothelial function in type 2 diabetes: a randomized
393 controlled trial. *J Intern Med*. 2014 Jan;275(1):59–70.

394

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396 No funding.

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.

Patients	Patients (n=100)
Age (years)	70.9 ±9.2
Male gender	86
Overweight and obesity	61
Obesity	24
BMI (kg/m ²)	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
Medical history	
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
Diabetes mellitus history and complications	
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

PAD profile	
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

	At M6 N=100	At M12 N=100
Patients with new leg ulcers	29	39
Patients with at least one Local infection	30	38
At least one hospitalization	54	73
Patients with MALE	32	37
Lower limb revascularization	31	36
Any lower limb amputation	13	16
Major lower limb amputation	2	4
Minor lower limb amputation	11	12
Patients with MACE	10	13
Myocardial infarction	5	6
Ischemic stroke	1	1
Cardiovascular deaths	8	10
All-cause deaths	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	4 (10.8%)	0 (0%)	0.017
Minor amputation	12	11 (29.7%)	1 (1.6%)	0.001
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	36 (97.3%)	0 (0%)	0.001
MACE	13	6 (16.2%)	7 (11.1%)	0.464
Leg ulcer	39	22 (59.5%)	17 (27.0%)	0.001
Local infection	38	21 (56.8%)	17 (27.0%)	0.003
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

Covariate	Whole sample (N=100)	Patients with MACE (N=13)	Patients without MACE (N=87)	P-value
Major amputation	4	0 (0%)	4 (4.6%)	1
Minor amputation	12	4 (30.8%)	8 (9.2%)	0.048
All-cause Death	14	10 (76.9%)	4 (4.6%)	0.001
Cardiovascular death	10	10 (76.9%)	0 (0%)	0.001
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	6 (46.1%)	0 (0%)	0.001

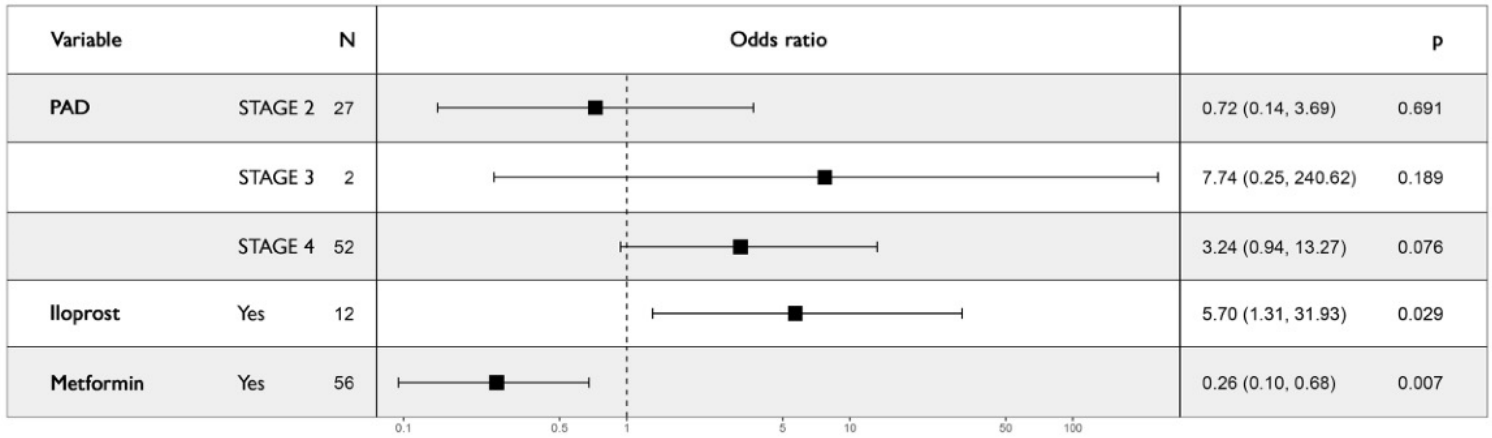
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426 **V. Figure 1.**

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

428 PAD: peripheral arterial disease.



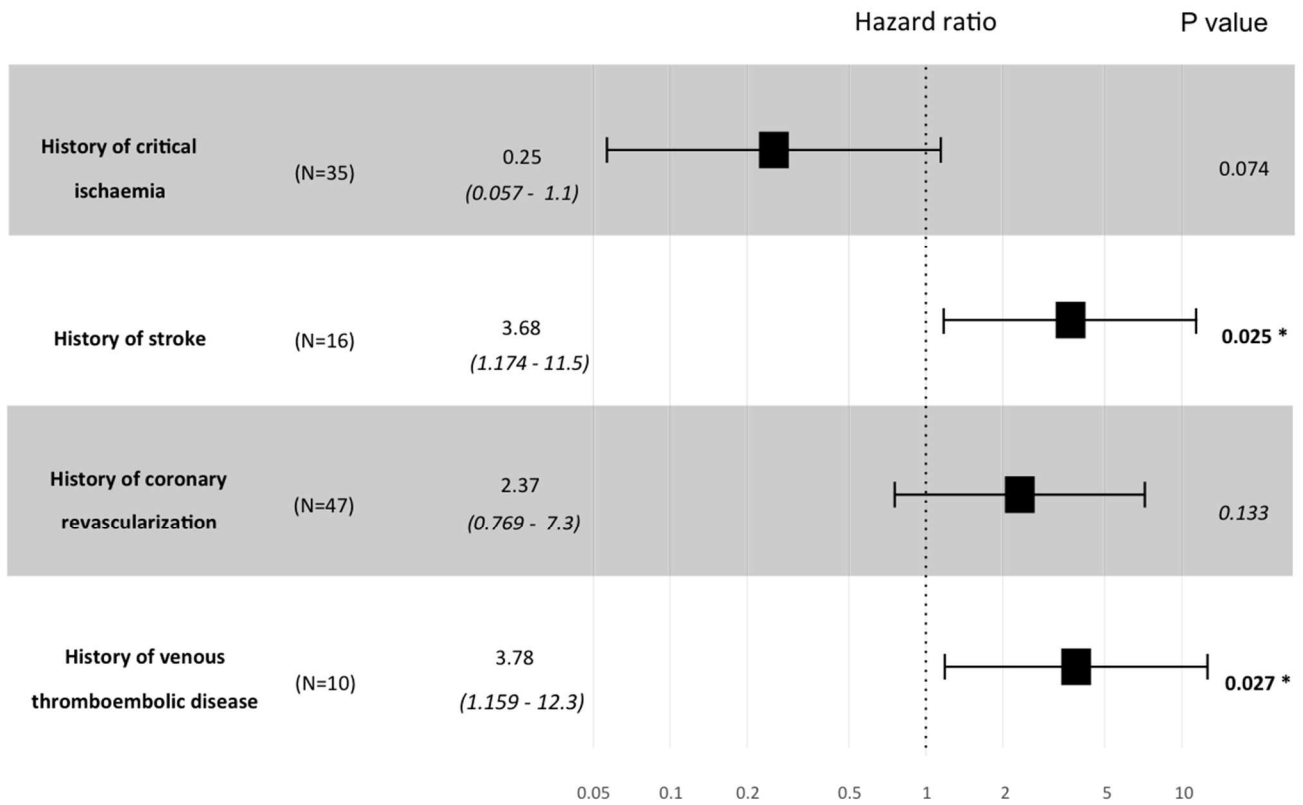
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432 **VI. Figure 2.**

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**

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

439

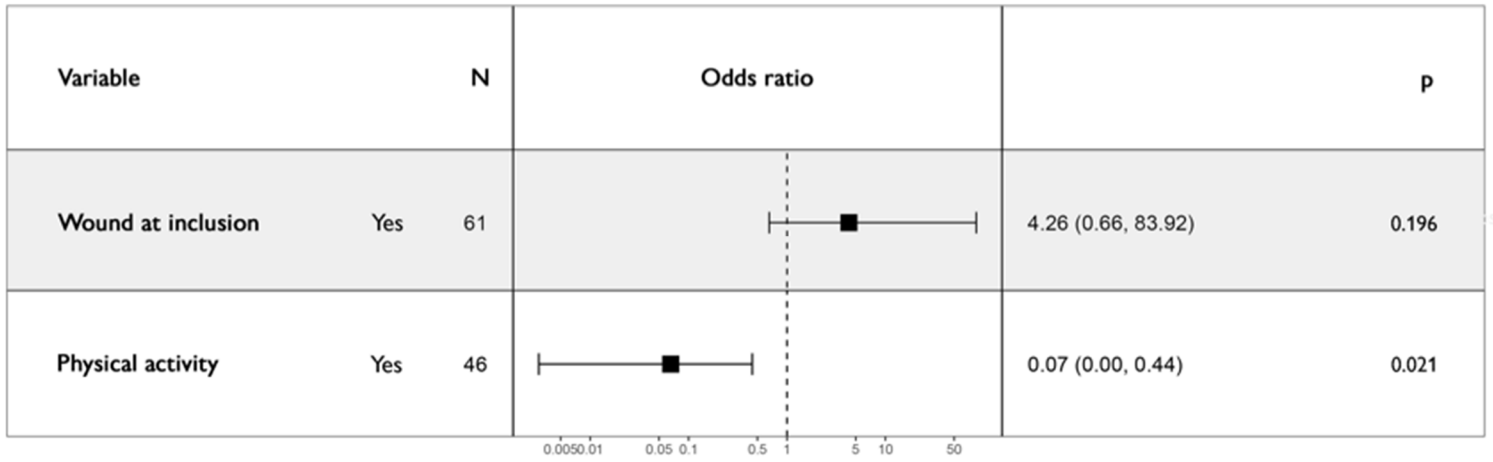
440 ACE: angiotensin conversion enzyme. GLP-1: glucagon-like peptide 1. SGLT-2: Sodium/glucose

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	14 (100%)	0 (0.0%)	0.001
Cardiovascular death	10	10 (71.4%)	0 (0.0%)	0.001
Non cardiovascular death	4	4 (28.6%)	0 (0.0%)	0.001
MACE	13	10 (71.4%)	3 (3.5%)	0.001
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	3 (21.4%)	3 (3.5%)	0.034

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

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

454