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Impact of diabetes on the outcomes in patients undergoing contemporary percutaneous coronary intervention: Analysis from the GLOBAL LEADERS study

Ply Chichareon MD^{a,b}, Rodrigo Modolo MD^{a,c}, Norihiro Kogame MD^a, Hidenori Komiyama MD^a, Kuniaki Takahashi MD^a, Chun-Chin Chang MD^d, Mariusz Tomaniak MD^{d,e}, Christopher Raffel MD^f, Roberto Botelho MD^g, Eric Eeckhout MD^h, Sjoerd Hofma MD, PhDⁱ, Diana Trendafilova-Lazarova MD^j, Zsolt Kőszegi MD^k, Andres Iñiguez MD^l, Iván Horváth MD^m, Joanna Wykrzykowska MD, PhD^a, Jan J. Piek MD, PhD^a, Scot Garg MBChB, PhDⁿ, Christian Hamm MD^o, Philippe Gabriel Steg MD^{p,q}, Peter Jüni MD^r, Pascal Vranckx MD, PhD^s, Marco Valgimigli, MD, PhD^t, Stephan Windecker, MD, PhD^l, Yoshinobu Onuma, MD, PhD^{d,u}, Patrick W. Serruys MD, PhD^v

- a. Amsterdam UMC, University of Amsterdam, Heart Center; Department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Meibergdreef 9, Amsterdam, the Netherlands.
- b. Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand.
- c. Department of Internal Medicine, Cardiology Division. University of Campinas (UNICAMP). Campinas, Brazil.
- d. Erasmus Medical Center, Erasmus University, Rotterdam, the Netherlands.
- e. First Department of Cardiology, Medical University of Warsaw, Warsaw, Poland.
- f. Department of Cardiology, Prince Charles Hospital, Brisbane, Australia; and the Faculty of Medicine, University of Queensland, Brisbane, Australia.
- g. CT / Instituto Do Coracao Do Triangulo Mineiro, Uberlandia, Brazil
- h. Department of Cardiology, Lausanne University Hospital, Switzerland
- i. The Department of Cardiology, Medical Center Leeuwarden, Leeuwarden, The Netherlands.
- j. "St. Ekaterina" university Hospital, Sofia, Bulgaria
- k. Jósá András Szabolcs-Szatmár-Bereg County Hospitals and University Teaching Hospital, Nyíregyháza, Hungary
- l. Interventional Cardiology Department, Hospital do Meixoeiro, Vigo, Spain
- m. University of Pécs-Heart Institute, Pécs, Hungary
- n. East Lancashire Hospitals NHS Trust, Blackburn, Lancashire, United Kingdom.
- o. Kerckhoff Heart Center, Campus University of Giessen, Bad Nauheim, Germany.
- p. Université Paris-Diderot, Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, INSERM U-1148, FACT (French Alliance for Cardiovascular Trials) Paris, France.
- q. National Heart and Lung Institute, Royal Brompton Hospital, Imperial College, London, United Kingdom.
- r. Applied Health Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, Department of Medicine, University of Toronto, Toronto, Canada.
- s. Jessa Ziekenhuis, Faculty of Medicine and Life Sciences at the Hasselt University, Hasselt, Belgium
- t. Department of Cardiology, Bern University Hospital, Bern, Switzerland.
- u. Cardialysis Clinical Trials Management and Core Laboratories, Westblaak 98, Rotterdam, the Netherlands.
- v. NHLI, Imperial College London, London, United Kingdom.

Address for correspondence:

Professor Patrick W. Serruys, MD. PhD.

P.O. Box 2125, 3000 CC Rotterdam, the Netherlands.

Tel: +31-10-4635260, Fax: +31-10-4369154

E-mail: patrick.w.j.c.serruys@gmail.com

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50

51 **Abstract (250 words)**

52 **Background**

53 Diabetes has been well recognized as a strong predictor for adverse outcomes after
54 percutaneous coronary intervention (PCI), however, studies in the era of drug-eluting stent
55 and potent P2Y12 inhibitors have shown conflicting results. We assessed ischemic and
56 bleeding outcomes after contemporary PCI according to diabetic status.

57

58 **Methods and results**

59 We studied 15,957 patients in the GLOBAL LEADERS study with known baseline
60 diabetic status. The primary endpoint was all-cause death or new Q-wave myocardial
61 infarction at 2 years. The secondary safety endpoint was major bleeding defined as bleeding
62 academic research consortium (BARC) type 3 or 5.

63 Out of 15957 patients with known diabetic status before PCI, 4,038 patients (25.1%)
64 were diabetes. Patients with diabetes had significantly higher risk of primary endpoint at 2
65 years than non-diabetes (adjusted hazard ratio [HR] 1.36; 95% confidence interval [CI] 1.14-
66 1.61). The difference was driven by a significantly higher risk of all-cause mortality at 2
67 years in diabetes than non-diabetes (adjusted HR 1.44, 95% CI 1.18-1.75). The risk of BARC
68 3 or 5 bleeding was not different between the two groups (adjusted HR 1.18, 95% CI 0.92-
69 1.50). The effect of antiplatelet strategy (experimental versus reference strategy) on the
70 primary endpoint and secondary safety endpoint at 2 years were not different between
71 diabetes and non-diabetes.

72

Conclusions

Diabetic patients had higher risk of ischemic events after PCI than non-diabetic patients. The bleeding risk was not different between diabetes and non-diabetes. The outcomes of diabetic patients following PCI was not affected by the two different antiplatelet strategies.

98 **Introduction**

99 Diabetes mellitus is a chronic disease associated with a high morbidity and mortality.
100 It is also a well-known risk factor for coronary artery disease (CAD).¹ Unsurprisingly, CAD
101 is a major cause of death in diabetic patients. Incidence of diabetes has increased worldwide²
102 and its prevalence in CAD patients undergoing percutaneous coronary intervention (PCI) has
103 been reported to be as high as 20-30%.³⁻⁵

104 Diabetes has been well recognized as a strong predictor for adverse outcomes after
105 PCI. In large pooled randomized trials, diabetes with or without insulin treatment was
106 identified as independent predictor of major adverse cardiac events, cardiac death, and
107 myocardial infarction (MI) after PCI trials⁶. However, recent studies have shown no
108 difference in the risk of MI^{5,7} and cardiac death⁵ between diabetic and non-diabetic patients.
109 It could be hypothesized that treatment with potent antiplatelet therapy together with the
110 improvement in PCI practice may mitigate the negative impact of diabetes on adverse
111 ischemic events⁸.

112 The evidence on the risk of bleeding in diabetic patients treated with antiplatelet
113 therapy was less well studied than the risk of ischemic event. In the Platelet Inhibition and
114 Patient Outcomes (PLATO) study, diabetic patients presenting with acute coronary syndrome
115 were associated with higher bleeding risk than non-diabetic patients regardless of the choice
116 of P2Y₁₂ receptor inhibitor (clopidogrel or ticagrelor)⁹. However, the studies in the setting of
117 PCI has shown that diabetes was not associated with an increased risk of bleeding during dual
118 antiplatelet therapy (DAPT)¹⁰. Furthermore, novel risk scores to predict bleeding after PCI
119 did not identify the predictive value of diabetes^{11,12}. In the GLOBAL LEADERS study, when
120 compared with conventional DAPT, long-term ticagrelor monotherapy tended to lower the
121 risk of all-cause mortality or new Q wave MI after PCI with similar risk of bleeding at 2

122 years¹³. The effect of antiplatelet strategy on the ischemic and bleeding outcomes may differ
123 between diabetic and non-diabetic patients undergoing PCI.

124 Therefore, we aimed to compare the ischemic and bleeding outcomes after
125 contemporary PCI in patients with or without diabetes. In addition, the impact of diabetes on
126 the effect of two antiplatelet strategies in the GLOBAL LEADERS study was also assessed.
127

128 **Methodology**

129 **Study design and population**

130 The GLOBAL LEADERS study was an investigator-initiated, randomized, multi-
131 center, open-label trial comparing two strategies of antiplatelet therapy after PCI using
132 uniformly bivalirudin and biolimus A9 eluting stents (Biomatrix) in all-comers patients¹³. In
133 the experimental strategy, patients received aspirin 75-100 mg once daily in combination
134 with ticagrelor 90 mg twice daily for one month; followed by ticagrelor 90 mg twice daily
135 alone for 23 months (irrespective of the clinical presentation). In the reference strategy,
136 patients received aspirin 75-100 mg daily in combination with either clopidogrel 75 mg once
137 daily in patients with stable CAD or ticagrelor 90 mg twice daily in patients with acute
138 coronary syndrome (ACS) for 1 year; followed by aspirin 75-100 mg once daily alone for the
139 following 12 months (from 12 to 24 months after PCI).

140 The main study enrolled 15,991 patients between July 2013 to November 2015 in an
141 “all-comers” design¹³: no restriction regarding clinical presentation, complexity of the lesions
142 or number of stents used. Since 23 patients withdrew consent and requested data deletion
143 from the database, a total of 15,968 patients remained in the study. Patients were followed up
144 at 30 days and 3, 6, 12, 18 and 24 months after the index PCI. Electrocardiogram (ECG) was
145 obtained at discharge, 3-month and 2-year follow up and during the follow up if there was
146 suspected ischemic events or repeat revascularization. All ECGs were analyzed at the core

laboratory (Cardialysis, Rotterdam, Netherlands) by technicians who were blinded to the treatment assignments.

Patients with diabetes mellitus was a pre-specified subgroup of the GLOBAL LEADERS study. In the present study, patients were stratified according to status of diabetes mellitus before PCI. Patients with diabetes mellitus were also stratified into non-insulin treated diabetes or insulin-treated diabetes. Patients were classified as insulin-treated diabetes if they received any kind of insulin therapy, and non-insulin treated diabetes if they were treated with oral hypoglycemic drug or lifestyle modification. The analysis was based on the intention-to-treat population. The GLOBAL LEADERS study was approved by the institutional review board at each participating institution. All patients provided informed consent. The study complied with the Declaration of Helsinki and Good Clinical Practices. An independent data and safety monitoring committee oversaw the safety of all patients.

Objectives and endpoints

The present study aimed to assess the risk of diabetic patients with CAD undergoing contemporary PCI treatment and to evaluate interaction between diabetes and antiplatelet strategies on the outcomes after PCI.

The primary ischemic endpoint was all-cause death or new Q wave MI at 2 years. The secondary safety endpoint was major bleeding defined as bleeding academic research consortium (BARC) type 3 or 5¹⁴. The additional secondary endpoints were cardiac death, patient-oriented composite endpoint (POCE) and net adverse clinical endpoint (NACE). POCE was defined as composite endpoint of all-cause death, any stroke, any MI and any revascularization¹⁵. NACE included POCE plus BARC 3 or 5 bleeding. Time to first event analysis was used for the analysis of composite endpoint. Individual components of POCE

171 and NACE, definite or probable stent thrombosis according to academic research consortium
172 were reported¹⁶.

173

174 **Statistical analysis**

175 Continuous variables are presented as mean \pm standard deviation and were compared
176 using independent t test. Categorical variables are presented as counts and percentage and
177 were compared using Chi square test. Cumulative rates of events were estimated using the
178 Kaplan-Meier method and compared using the log-rank test. Multivariable Cox regression
179 was used to determine if diabetes was an independent predictor for the outcomes at 2 years.
180 The covariables included in the model were age, sex, body mass index (BMI), peripheral
181 vascular disease (PVD), prior MI, chronic obstructive pulmonary disease (COPD), renal
182 impairment (defined as estimate glomerular filtration rate < 60 ml/min using the Modification
183 of Diet in Renal Disease equation¹⁷) and acute coronary syndrome as a clinical presentation.
184 Interaction analysis between diabetes and antiplatelet strategy on the outcomes was assessed
185 in the Cox regression model including main effect (diabetes and antiplatelet strategy) and
186 interaction terms. Analyses were performed in R version 3.4.2 (R foundation, Vienna,
187 Austria). All p values were two-sided and the statistical significance was considered if the
188 value was less than 0.05.

189

190 **Results**

191 Of 15957 patients with known diabetic status before PCI, 4,038 patients (25.1%) were
192 diabetes. Of 4002 diabetic patients with known insulin treatment status, 2779 patients were
193 non-insulin treated diabetes and 1223 patients were insulin-treated diabetes. Compared with
194 non-diabetes, diabetic patients were older, had higher mean BMI and higher prevalence of
195 comorbidities such as hypertension, hypercholesterolemia, PVD, COPD, impaired renal

196 function, previous stroke, history of previous PCI or coronary artery bypass grafting (CABG)
197 and previous MI (table 1). Non-diabetic patients were more likely to be current smoker and to
198 present with MI than diabetic patients. There was no difference in the number of lesions
199 treated, percentage of multivessel PCI and mean stent length between diabetes and non-
200 diabetes. Compared with non-diabetes, the average number of stent was higher whereas the
201 average stent diameter and the percentage of bifurcation PCI were lower in diabetes.

202 Compared with non-insulin treated diabetes, patients with insulin-treated diabetes had
203 higher mean BMI and higher prevalence of PVD, impaired renal function, previous stroke,
204 previous MI, previous PCI and previous CABG and were more likely to present with stable
205 CAD. The mean stent diameter in insulin-treated diabetes was lower than non-insulin treated
206 diabetes.

207
208 **Two-year outcomes between diabetes and non-diabetes**

209 The outcomes at 2 years are shown in figure 1. Patients with diabetes had
210 significantly higher risk of primary endpoint at 2 years than non-diabetes (adjusted hazard
211 ratio [HR] 1.36; 95% confidence interval [CI] 1.14-1.61). The difference was driven by the
212 significantly higher risk of all-cause mortality at 2 years in diabetes than non-diabetes
213 (adjusted HR 1.44, 95% CI 1.18-1.75). The two-year risk of ischemic stroke, any MI, any
214 revascularization, POCE, and NACE was significantly higher in diabetes than non-diabetes
215 (figure 1). The risk of stent thrombosis and the risk of bleeding either BARC 2,3 or 5
216 bleeding or BARC 3 or 5 bleeding was not different between the two groups.

217
218 **Insulin-treated versus non-insulin treated diabetes**

219 Two-year outcomes between insulin-treated diabetes, non-insulin treated diabetes and
220 non-diabetes are presented in table 2. Compared with non-diabetes, insulin-treated diabetes

221 had significantly higher risk of primary endpoint at 2 years (adjusted HR 1.75; 95% CI 1.38-
222 2.23). The difference was driven by the significantly higher risk of all-cause mortality at 2
223 years in the insulin-treated diabetes than the non-diabetes (adjusted HR 1.93, 95% CI 1.47-
224 2.53). The risk of primary endpoint and all-cause mortality were not different between non-
225 insulin treated diabetes and non-diabetes (primary endpoint; adjusted HR 1.18, 95% CI 0.96-
226 1.45, all-cause mortality; adjusted HR 1.22, 95% CI 0.96-1.54). Compared with non-diabetic,
227 the adjusted hazard ratio for POCE at 2 years was 1.28 (95% CI 1.15-1.43) to 1.54 (95% CI
228 1.34-1.77) in non-insulin treated diabetes and insulin-treated diabetes respectively. Similar
229 increases in the hazard ratio for NACE, ischemic stroke, any MI and any revascularization
230 were observed in non-insulin treated and insulin-treated diabetes when compared with non-
231 diabetes. The risk of definite, definite or probable stent thrombosis, and BARC 3 or 5
232 bleeding were not different among the three groups.

233

234 **Impact of diabetic status and allocated antiplatelet strategies on outcomes after PCI**

235 The effect of antiplatelet strategy (experimental versus reference strategy) on the
236 primary endpoint and other outcomes at 2 years were not different between diabetes and non-
237 diabetes (figure 2). The results were not changed when the interaction analysis was
238 performed according to the stratification by the insulin treatment status (supplementary figure
239 2).

240

241 **Discussion**

242 We studied the outcomes and the effect of different antiplatelet strategies in diabetic
243 patients stratified by the status of insulin treatment in the large all-comers population
244 undergoing contemporary PCI worldwide. The salient findings from the present study are 1)
245 patients with diabetes either treated with insulin or not had significantly higher risk of

Commented [PV1]: The discussion section is extremely long, has more to do with the literature per se rather than the findings put into context.

246 ischemic event after contemporary PCI treatment. 2) The risk of stent thrombosis was similar
247 among the three groups. 3) Bleeding risk after PCI were not different among non-diabetes,
248 non-insulin treated and insulin-treated diabetes. 4). The outcomes of diabetic patients
249 following PCI was not affected by the two different antiplatelet strategies.

250

251 **Ischemic risk after PCI in diabetes**

252 Drug-eluting stents improved the outcomes in patients with CAD undergoing PCI
253 when compared with bare-metal stent¹⁸. In addition, the newer-generation DES with
254 biocompatible polymer has shown to reduce the risk of composite ischemic endpoint and
255 stent thrombosis when compared with the first-generation DES^{19,20}. Treatment with potent
256 P2Y12 receptor inhibitor in ACS patients undergoing PCI improved survival and lowered the
257 composite ischemic endpoint when compared with clopidogrel⁹.

258 The current PCI practice using newer-generation DES, potent P2Y12 inhibitors in
259 ACS patients and guideline-directed optimal therapy has improved the outcomes of patients
260 undergoing PCI²¹. The improvement has been demonstrated in both diabetic and non-diabetic
261 patients⁹. In the pooled analysis of 6081 patients treated with new-generation DES by
262 Koskinas et al, although the diabetic patients experienced higher risk of repeat target lesion
263 revascularization than non-diabetic patients, the risk of cardiac death, MI and stent
264 thrombosis were not different between the two groups⁵. In the analysis from the BIONICS
265 randomized trial, the rate of target lesion failure at 1 year in diabetes was higher than non-
266 diabetes while the rate of cardiac death, MI and stent thrombosis did not differ between the
267 two groups⁷. In a registry of 4812 consecutive patients treated with second-generation DES,
268 the risk of patient-oriented composite outcome in non-insulin treated diabetes was higher
269 than non-diabetes (adjusted HR 1.21, 95% CI 1.00-1.47, p value 0.049), however, the lower
270 end of confidence interval and p value were close to the level of no difference⁴. The risk of

271 all-cause death, cardiac death, and stent thrombosis were similar between non-diabetes and
272 non-insulin treated diabetes while the risk of these events and patient-oriented composite
273 outcomes were significantly higher in insulin-treated diabetes when compared with the two
274 groups⁴. Recently, in patients with three-vessel disease treated with state-of-the-art PCI, the
275 rate of major adverse cardiac and cerebrovascular events at 2 years was not different between
276 diabetes and non-diabetes (15.0% vs. 12.5%, $p = 0.50$)²².

277 In the present study, although the risk of primary efficacy endpoint and its
278 components were not different between non-diabetes and non-insulin treated diabetes, the
279 risk of POCE, ischemic stroke, any MI, and any revascularization were significantly higher in
280 non-insulin treated diabetes than non-diabetes. The risk of these events was even higher in
281 insulin-treated diabetes when compared with non-diabetes. To date, the present study is the
282 largest cohort of all-comers patients that received contemporary PCI treatment. Although the
283 randomization was not stratified by diabetic status and sample size calculation was not based
284 on the information in diabetes, the large number of diabetic patients in the GLOBAL
285 LEADERS study improved the precision and the power of the analysis. This fact could be an
286 explanation why the risk difference in some outcomes were not demonstrated in the previous
287 studies. Our study is unique in the sense that the PCI in the GLOBAL LEADERS study was
288 standardized since 87.3% of patients received bivalirudin-assisted PCI and almost 95% of
289 lesion were treated with biolimus-A9 eluting stent¹³. Furthermore, ACS patients were treated
290 with potent P2Y12 inhibitor (ticagrelor). The confounding effect of different type of stent and
291 periprocedural antithrombotic medication seen in previous studies were eliminated from the
292 present analysis. Hence, our results emphasize that diabetic patients regardless of the status of
293 the insulin treatment were still experiencing higher risk of major ischemic events after
294 contemporary PCI and the intensive care to reduce the risk in this high-risk subgroup is
295 mandatory.

Commented [PV2]: The endpoint may be criticized

296 Intriguingly, the risk of stent thrombosis either definite or probable stent thrombosis
297 was not different among the three groups. Diabetes has been long recognized as a well-
298 known predictor for stent thrombosis^{23,24}. The risk of stent thrombosis in diabetic patients
299 treated with first-generation DES were 3.71 time higher than non-diabetes²⁵ whereas the
300 hazard ratio of diabetes versus non-diabetes for definite stent thrombosis was lower (HR
301 1.79, 95% 0.99-3.24) in the era of second-generation DES⁶. Although it could be argued that
302 our analysis may be underpowered to detect the difference in the risk of stent thrombosis, the
303 similar risk of definite stent thrombosis among diabetes and non-diabetes in the present study
304 is in line with the other recently published data^{7,26}.

305

306 **Bleeding risk after PCI in diabetes**

307 Platelets of diabetic patients are more reactive in adhesion, activation, degranulation
308 and aggregation than the platelets of healthy controls²⁷. The turnover rate and the number of
309 reticulated platelets in diabetic patients were also higher which resulted in the increased
310 endothelial cell adhesion²⁸. Moreover, platelets of diabetic patients were more resistant to
311 antiplatelet agent^{29,30}. From these evidences, it could be hypothesized that the bleeding risk of
312 diabetic patients treated with antiplatelet would be at least similar or even lower than non-
313 diabetic patients.

314 Recent studies have shown that diabetes was not an independent predictor for
315 bleeding after PCI in the era of DES. A large individual patient data meta-analysis of 11,473
316 patients studying the outcomes between short-term or long-term DAPT after DES
317 implantation according to the diabetic status showed similar bleeding risk between diabetic
318 and non-diabetic patients²⁶. Diabetic patients even experienced lower bleeding risk than non-
319 diabetic patients after PCI in a multicenter US registry of consecutive PCI patients³¹.
320 Nonetheless, most of the patients in these studies received clopidogrel as a P2Y₁₂ inhibitor.

321 The present study assessed the risk of bleeding according to diabetic status in patients
322 undergoing contemporary PCI treatment in which majorities of the patients received potent
323 P2Y12 inhibitor. Our findings were similar to the results from the previous studies of diabetic
324 patients treated with DAPT after PCI in which the risk of bleeding at 2 years was not
325 different among diabetes and non-diabetes.

326

327 **Impact of antiplatelet strategies on PCI results in diabetes**

328 Considering that diabetic patients are at higher risk of ischemic event and similar
329 bleeding risk to the non-diabetic patients undergoing PCI, diabetic-specific antiplatelet
330 regimens may be needed³². The more aggressive and potent antiplatelet regimens in diabetic
331 patients might theoretically reduce the ischemic risk without increasing the risk of bleeding⁸.
332 However, our results did not support the above hypothesis since no significant interaction
333 between diabetic status and antiplatelet strategies on any outcomes was observed.

334 The complexity of CAD could affect the outcomes of diabetic patients treated with
335 PCI. The pooled analysis of randomized trials in 18441 patients has shown that the risk of
336 repeat revascularization in diabetic patients was dependent on the coronary lesion complexity
337 as defined by American College of Cardiology and American Heart Association
338 classification⁶. Hence, the outcomes and selection of the optimal platelet strategy may not
339 solely depend on the diabetic status but may also depend on complexity of CAD or other
340 comorbidities. The ongoing TWILIGHT study (NCT 02270242) is comparing two
341 antiplatelet strategies in high-risk patients after PCI. High-risk patient is defined as having at
342 least one high-risk angiographic criteria and at least one high-risk clinical characteristics.
343 Medically treated diabetes is one of the clinical criteria of high-risk patients. The THEMIS
344 study (NCT 01991795) is testing the impact of ticagrelor in diabetic patients with stable CAD

345 without prior MI. Both studies may provide the information added to the literature on the
346 optimal antiplatelet strategy after PCI in diabetic patients.

347
348 **Limitations**

349 First, our analyses are considered exploratory and statistical adjustment for multiple
350 testing was not performed. Therefore, the results should be interpreted with caution and
351 considered as hypothesis-generating.³³ Secondly, the randomization in the GLOBAL
352 LEADERS study was not stratified by diabetic status. Hence, the results on the effect of
353 antiplatelet strategy and diabetic status on the outcomes are at risk for a type II error. Finally,
354 there was no adjudication for serious adverse events due to limited financial resources and
355 the endpoints were site-reported with the exception of primary endpoint: all-cause death and
356 new Q wave MIs assessed by an independent ECG core lab. Nevertheless, there was regular
357 monitoring and on-site visits for consistency of event definitions and underreport of the
358 events.

359
360 **Conclusions**

361 In this subgroup analysis of the GLOBAL LEADERS study, diabetic patients with or
362 without insulin therapy still had higher risk of adverse ischemic events than non-diabetic
363 patients. The outcomes of diabetic patients following PCI was not affected by the two
364 different antiplatelet strategies.

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370 **Table and figure legends**

371 Table 1: Clinical, angiographic and procedural characteristics of patients with or without
372 diabetes mellitus

373
374 Table 2: Two-year outcomes among non-diabetes, non-insulin treated diabetes and insulin-
375 treated diabetes

376
377 Figure 1: Two-year outcomes between patients with or without diabetes mellitus

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379 Figure 2: Two-year outcomes in patients with or without diabetes mellitus according to
380 antiplatelet strategy

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382 Supplementary figure 1: two-year outcomes among non-diabetes, non-insulin treated and
383 insulin-treated diabetes according to antiplatelet strategy

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Table 1: Clinical, angiographic and procedural characteristics of patients with or without diabetes mellitus

Variable	Non-diabetes (N= 11919)	Diabetes (N=4038)	P value†	Non-insulin treated diabetes (N=2779)	Insulin-treated diabetes (N=1223)	P value‡
Mean age (years) ± SD	63.93±10.50	66.33±9.48	<0.0001	66.27±9.44	66.51±9.61	0.4647
Mean body-mass index (kg/m²) ± SD	27.69±4.33	29.66±5.01	<0.0001	29.45±4.85	30.13±5.34	0.0001
Hypertension	8211 (69.16)	3497 (86.69)	<0.0001	2397 (86.32)	1067 (87.39)	0.3862
Hypercholesterolemia	7699 (66.65)	3064 (78.38)	<0.0001	2112 (78.40)	933 (78.87)	0.7746
Current smoker	3364 (28.22)	800 (19.81)	<0.0001	565 (20.33)	229 (18.72)	0.2581
Peripheral vascular disease	604 (5.11)	401 (10.04)	<0.0001	254 (9.23)	141 (11.67)	0.0214
Chronic obstructive pulmonary disease	572 (4.82)	249 (6.20)	0.0007	159 (5.75)	87 (7.18)	0.0986
Previous major bleeding	74 (0.62)	24 (0.60)	0.9480	17 (0.61)	7 (0.57)	1
Impaired renal function	1332 (11.25)	838 (20.81)	<0.0001	484 (17.47)	352 (28.83)	<0.0001
Previous stroke	257 (2.16)	164 (4.07)	<0.0001	92 (3.32)	70 (5.73)	0.0005
Previous MI	2623 (22.06)	1086 (27.00)	<0.0001	668 (24.11)	406 (33.39)	<0.0001
Previous PCI	3596 (30.20)	1623 (40.22)	<0.0001	1046 (37.67)	556 (45.50)	<0.0001
Previous CABG	570 (4.79)	373 (9.25)	<0.0001	232 (8.36)	139 (11.37)	0.0030
Clinical presentation			<0.0001			0.0485
Stable coronary artery disease	6041 (50.68)	2434 (60.28)		1647 (59.27)	772 (63.12)	
Unstable angina	1479 (12.41)	542 (13.42)		362 (13.03)	163 (13.33)	
Non-ST-elevation MI	2644 (22.18)	727 (18.00)		524 (18.86)	200 (16.35)	
ST-elevation MI	1755 (14.72)	335 (8.30)		246 (8.85)	88 (7.20)	
Number of lesion treated, mean ± SD	1.43 ± 0.74	1.46 ± 0.75	0.0503	1.45 ± 0.74	1.48 ± 0.77	0.1319
Lesions treated per patient			0.0513			0.0649
One lesion	8118 (68.62)	2665 (66.56)		1860 (67.49)	778 (64.19)	
Two lesions	2672 (22.59)	969 (24.20)		640 (23.22)	323 (26.65)	
Three or more lesions	1040 (8.79)	370 (9.24)		256 (9.29)	111 (9.16)	
Left main PCI	312 (2.64)	117 (2.92)	0.3666	79 (2.87)	38 (3.14)	0.7194
RCA PCI	4476 (37.84)	1474 (36.81)	0.2559	1041 (37.77)	419 (34.57)	0.0587
LAD PCI	6089 (51.47)	1961 (48.98)	0.0067	1350 (48.98)	599 (49.42)	0.8259
LCX PCI	3666 (30.99)	1340 (33.47)	0.0038	904 (32.80)	419 (34.57)	0.2925
Bypass graft PCI	118 (1.00)	100 (2.50)	<0.0001	66 (2.39)	34 (2.81)	0.5157
Stent number per patient, mean ± SD	1.71 ± 1.08	1.75 ± 1.09	0.0323	1.75 ± 1.10	1.76 ± 1.08	0.7433
Multivessel PCI	2645 (22.36)	930 (23.23)	0.2652	647 (23.48)	277 (22.85)	0.6997
Bifurcation PCI	1905 (16.10)	590 (14.74)	0.0425	416 (15.09)	169 (13.94)	0.3719
Stent length per patient (mm), mean±SD	24.88 ± 12.91	25.26 ± 13.70	0.1141	25.46 ± 13.87	24.82 ± 13.40	0.1871
Stent diameter per patient (mm), mean±SD	3.01 ± 0.43	2.96 ± 0.43	<0.0001	2.98 ± 0.43	2.92 ± 0.41	0.0001

Values shown are % (n) otherwise indicated

†comparison between diabetes and non-diabetes

‡comparison between non-insulin treated diabetes and insulin-treated diabetes

Commented [PV3]: This may be a totally different patient population

Circ cardiovasc intervention 2015; 8.

2200patients may be not bad to look for the impact on outcome. Are patients with diabetes and real dysfunction doing worse than others. Is there an impact from the treatment strategy?

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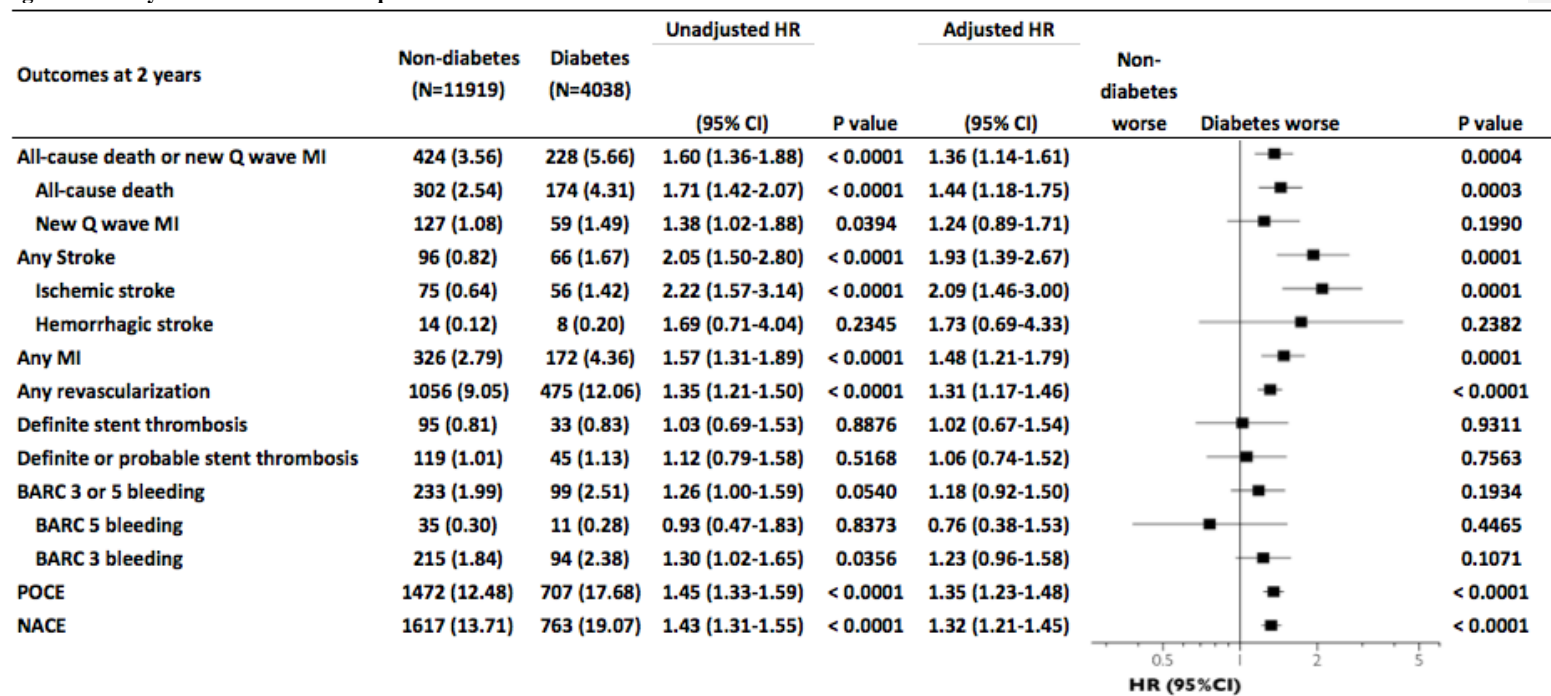
404 Table 2: Two-year outcomes among non-diabetes, non-insulin treated diabetes and insulin-treated diabetes
405

Outcomes at 2 years	Non-diabetes	Non-insulin treated diabetes	Insulin-treated diabetes	Unadjusted HR (95% CI)		Adjusted HR (95% CI)	
	(N=11919)	(N=2779)	(N=1223)	Non-insulin treated diabetes/Non-diabetes	Insulin-treated diabetes/Non-diabetes	Non-insulin treated diabetes/Non-diabetes	Insulin-treated diabetes/Non-diabetes
All-cause death or new Q wave MI	424 (3.56)	132 (4.76)	94 (7.69)	1.34 (1.10-1.63)	2.20 (1.76-2.75)	1.18 (0.96-1.45)	1.75 (1.38-2.23)
All-cause death	302 (2.54)	97 (3.50)	75 (6.13)	1.38 (1.10-1.74)	2.46 (1.91-3.16)	1.22 (0.96-1.54)	1.93 (1.47-2.53)
New Q wave MI	127 (1.08)	38 (1.40)	21 (1.76)	1.29 (0.90-1.85)	1.64 (1.03-2.60)	1.16 (0.80-1.70)	1.44 (0.89-2.33)
Any Stroke	96 (0.82)	39 (1.44)	27 (2.27)	1.75 (1.21-2.54)	2.80 (1.83-4.29)	1.67 (1.15-2.45)	2.61 (1.67-4.09)
Ischemic stroke	75 (0.64)	32 (1.18)	24 (2.02)	1.84 (1.21-2.78)	3.18 (2.01-5.04)	1.75 (1.15-2.66)	3.03 (1.87-4.91)
Hemorrhagic stroke	14 (0.12)	5 (0.19)	3 (0.25)	1.53 (0.55-4.26)	2.12 (0.61-7.36)	1.68 (0.59-4.81)	1.88 (0.51-6.98)
Any MI	326 (2.79)	113 (4.15)	58 (4.89)	1.50 (1.21-1.85)	1.77 (1.34-2.34)	1.48 (1.19-1.84)	1.49 (1.11-2.01)
Any revascularization	1056 (9.05)	315 (11.58)	156 (13.18)	1.29 (1.14-1.47)	1.49 (1.26-1.76)	1.28 (1.12-1.46)	1.39 (1.17-1.66)
Definite stent thrombosis	95 (0.81)	24 (0.87)	8 (0.67)	1.09 (0.69-1.70)	0.83 (0.40-1.70)	1.10 (0.69-1.74)	0.77 (0.37-1.62)
Definite or probable stent thrombosis	119 (1.01)	34 (1.23)	10 (0.83)	1.23 (0.84-1.80)	0.83 (0.43-1.57)	1.18 (0.80-1.76)	0.74 (0.38-1.44)
BARC 3 or 5 bleeding	233 (1.99)	62 (2.27)	37 (3.11)	1.14 (0.86-1.51)	1.57 (1.11-2.22)	1.09 (0.82-1.44)	1.42 (0.99-2.03)
BARC 5 bleeding	35 (0.30)	6 (0.22)	5 (0.43)	0.74 (0.31-1.75)	1.41 (0.55-3.59)	0.64 (0.27-1.54)	1.03 (0.39-2.74)
BARC 3 bleeding	215 (1.84)	60 (2.20)	34 (2.85)	1.20 (0.90-1.60)	1.56 (1.09-2.24)	1.16 (0.86-1.55)	1.44 (0.99-2.09)
POCE	1472 (12.48)	452 (16.41)	250 (20.68)	1.34 (1.20-1.49)	1.73 (1.51-1.98)	1.28 (1.15-1.43)	1.54 (1.34-1.77)
NACE	1617 (13.71)	489 (17.75)	269 (22.23)	1.32 (1.19-1.46)	1.69 (1.49-1.93)	1.26 (1.13-1.39)	1.50 (1.31-1.72)

406
407 BARC: bleeding academic research consortium, CI: confidence interval, HR: hazard ratio, MI: myocardial infarction, NACE; net adverse
408 clinical events, POCE; patient-oriented composite endpoints.

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Figure 1: Two-year outcomes between patients with or without diabetes mellitus



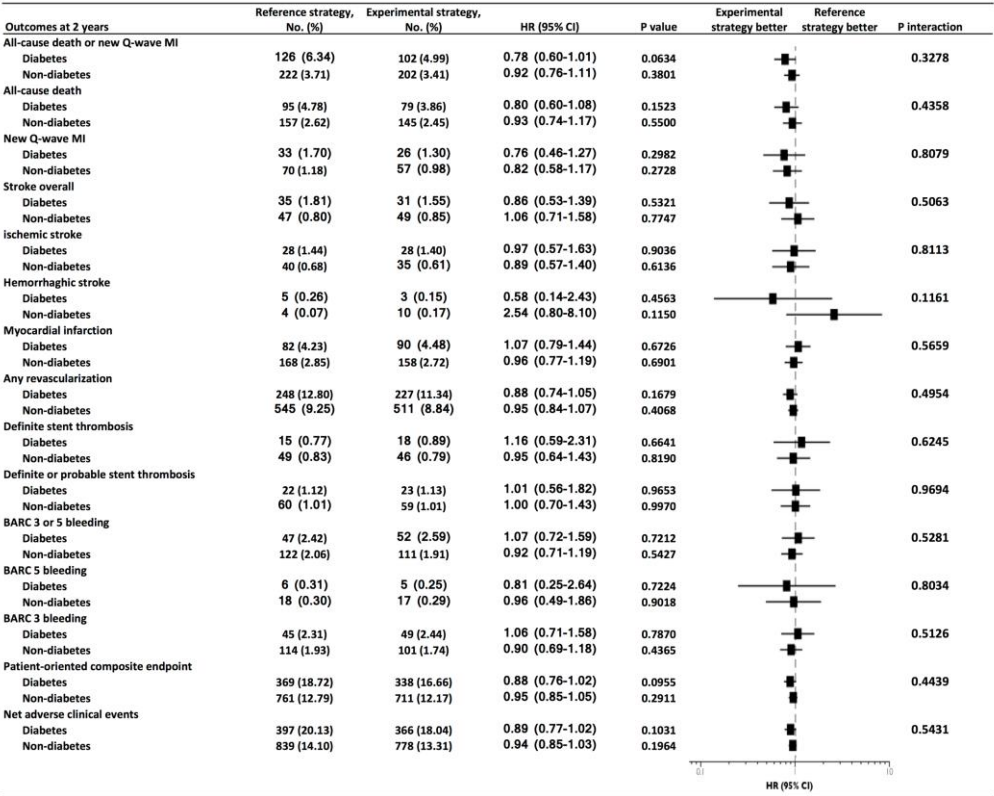
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412 BARC: bleeding academic research consortium, CI: confidence interval, HR: hazard ratio, MI: myocardial infarction, NACE; net adverse

413 clinical events, POCE; patient-oriented composite endpoints.

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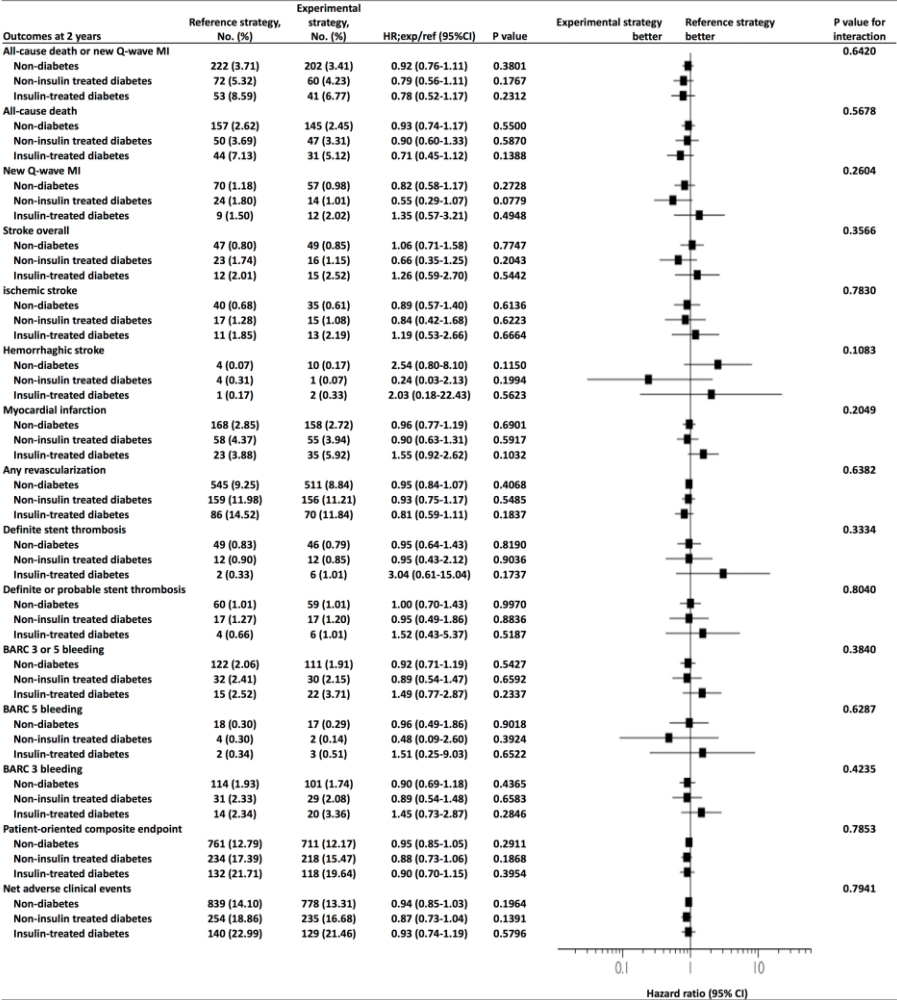
Figure 2: Two-year outcomes in patients with or without diabetes mellitus according to antiplatelet strategy



BARC: bleeding academic research consortium, CI: confidence interval, HR: hazard ratio,

MI: myocardial infarction

Supplementary figure 1: two-year outcomes among non-diabetes, non-insulin treated and insulin-treated diabetes according to antiplatelet strategy



BARC: bleeding academic research consortium, CI: confidence interval, HR: hazard ratio, MI: myocardial infarction, NACE; net adverse clinical events, POCE; patient-oriented composite endpoints.

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