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Cardiovascular risk of chronic coronary syndrome patients according to vascular phenotype, diabetes and smoking.

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Despite the widespread use of effective evidence-based secondary prevention medications in patients with chronic coronary syndrome (CCS), there remain some high-risk patient subsets [1,2]. Polyvascular disease is a powerful predictor of major adverse cardiovascular events (MACE) [2,3]. Cigarette smoking and diabetes mellitus are each strongly associated with extensive arterial disease and further increase this risk [4–7]. CCS patients with additional arterial disease probably do not all have the same level of risk and recent real-world data on this population are scarce. The aim of the present analysis was to assess the long-term risk of MACE in CCS outpatients according to their vascular phenotype combined with their diabetic and smoking status.

We analyzed 5-year follow-up data from 32 703 outpatients with CCS enrolled in the international (45 countries) prospeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease (CLARIFY). The rationale and design have been previously described [8]. CCS was defined by at least one of the following criteria: coronary angiography demonstrating ≥1 coronary stenosis >50%, chest pain with proven myocardial ischaemia, myocardial infarction and/or myocardial revascularization >3 months before enrolment. Exclusion criteria were hospitalization for cardiovascular disease <3 months, planned revascularization and conditions potentially affecting 5-year follow-up. Cerebrovascular disease (CVD) was defined by carotid stenosis >50%, carotid stenting or surgery, previous stroke or transient ischaemic attack. Peripheral artery disease (PAD) was defined by significant lower extremity arterial disease or aortic abdominal aneurysm. Diabetes was defined as a history of diabetes mellitus, regardless of medication use. Whether current or former, all smokers were analyzed together. The patients were categorized into three vascular phenotypes: CAD alone, CAD with either CVD or PAD (CAD+1), CAD with both CVD and PAD (CAD+2) and according to four diabetic and smoking profiles. All subgroups were mutually exclusive. The primary outcome was the composite of cardiovascular death, non-fatal myocardial

infarction or non-fatal stroke. Five-year event rates were presented as cumulative incidence function to account for competing risks. Comparisons across subgroups were performed using the Fine and Gray method with adjustment by age, sex and geographic origin.

The demographic characteristics of the entire CLARIFY population were previously reported [8]. Briefly, mean age was 64.2±10.5 years, 77.6% were men and secondary prevention medication were widely used. Median follow-up was 5 years, interquartile range 4.8-5.1. At baseline, 9502 (29.1%) had diabetes, 19186 (58.7%) were current or former smokers and only 9220 (28.2%) were free of these two major risk factors. Regarding vascular phenotype, 26440 (80.8%) patients had CAD alone, 4967 (15.2%) had CAD+1 and 1296 (4%) had CAD+2. The 5-year primary outcome event rate was 9.2% overall (95% confidence interval (CI) 8.9-9.5) increasing according to the number of diseased arterial beds, 8.0% (95% CI 7.6-8.3) vs 13.8% (95% CI 12.8-14.8) vs 17.5% (95% CI 15.4-19.8) respectively for patients with CAD alone, CAD+1 and CAD+2, $P<0.001$. The enriched analyzes according to the diabetic and smoking status are displayed in **Figure 1** and revealed an even greater variation of the 5-year MACE rate ranging from 6.7% (95% CI 6.2-7.2) in patients with CAD alone and neither diabetes or smoking to 20.7% (95% CI 16.5-25.9) in patients with CAD+2 both diabetics and smokers. Patients with CAD alone and diabetes only had an ischaemic risk comparable to that of patients with additional arterial disease without diabetes or smoking, respectively 9.2% (95% CI 8.2-10.4) vs 11% (95% CI 9.3-12.8), $P=0.82$. In smokers, the risk of MACE increased in proportion to the number of arterial beds affected, 7.7% (95% CI 7.2-8.2) vs 12.0% (95% CI 10.6-13.6) vs 18.3% (95% CI 15.3-21.8), respectively for CAD alone, CAD+1 and CAD+2. The combination of smoking and diabetes conferred an additive risk regardless of vascular phenotype.

In this large international cohort, almost one in five CCS outpatients had at least one additional arterial bed affected which was associated with heightened risk of MACE. A second finding is that the overwhelming majority of CCS patients (71.8%) had either diabetes or a

smoking history. The combined analysis of vascular phenotype, diabetes and smoking status allowed stratification into a broad panel of ischaemic risks without even requiring blood test results. Furthermore, although the presence of additional arterial disease identifies a high-risk subset, its impact on risk varies markedly according to the presence of diabetes or smoking. The REduction of Atherothrombosis for Continued Health (REACH) registry had previously shown that both polyvascular and diabetics patients had a higher risk of MACE [2,3]. The present analysis shows that this is still true in contemporary practice with more widespread use of evidence-based secondary prevention therapies. We also found a differential impact of diabetes and smoking on the progression of arterial impairment over time, which likely reflects pathophysiological differences [9,10]. In smokers, ischaemic risk increased gradually according to the number of arterial beds affected, whereas diabetes conferred a maximally increased risk upfront in both CAD+1 and CAD+2 groups. Moreover, diabetics with CAD alone had an ischaemic risk level similar to non-diabetic and non-smoking CAD patients with additional arterial disease. These results clearly show the burden of diabetes even at less advanced stages of atherosclerosis. In other words, CAD patients with diabetes were equivalent to polyvascular patients in terms of ischaemic risk.

In addition to the benefits of the lifestyle change [7,11], several novel secondary prevention strategies have recently emerged with the aim of lowering ischaemic risk in patients with CCS. Interventions such as long-term dual antithrombotic therapies, proprotein convertase subtilisin/kexin type 9 inhibitors or even anti-inflammatory agents have been proposed [12]. Due to their cost or potential adverse effects these strategies cannot be applied to all patients with CCS. The simple risk stratification that we described may easily identify very high-risk groups who could benefit from more intensive treatment.

In conclusion, CCS patients with additional arterial disease appear to be a heterogeneous group of patients, in whom the risk of MACE varied not only according to the number of

diseased arterial beds, but also widely according to the smoking and diabetes status. Combining these three simple and highly prevalent criteria allowed an effective stratification of ischaemic risk in CCS outpatients.

Declaration of interest

AG has nothing to disclose.

GD reports personal fees from Amgen, Astra Zeneca, Bayer, BMS, Janssen, Sanofi, Terumo, non-financial support from Biotronik, outside the submitted work.

YE has nothing to disclose.

KMF has received fees, honoraria and/or travel expenses from Servier, AstraZeneca, CellAegis, Celixir, UCB and Broadview Ventures, outside the submitted work. He is Director of Vesalius Trials.

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MT reports personal fees from Servier, during the conduct of the study; personal fees from Bayer, Cadila Pharmaceuticals, Janssen-Cilag, Kowa, PERFUSE Group, Servier and UCB Pharmaceuticals, outside the submitted work.

LJF has nothing to disclose.

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Author contributions

AG, GD, and PGS contributed to the conception and design of the work. AG, GD, YE, KMF, RF, IF, JCT, MT, LJF and PGS contributed to the acquisition, analysis, or interpretation of data for the work. AG and GD drafted the manuscript. KMF, RF, IF, JCT, MT, LJF and PGS critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

References

1. Sorbets E, Fox KM, Elbez Y, et al. Long-term outcomes of chronic coronary syndrome worldwide: insights from the international CLARIFY registry. *Eur Heart J*. 2020;41:347–356.

2. Bhatt DL, Eagle KA, Ohman EM, et al. Comparative Determinants of 4-Year Cardiovascular Event Rates in Stable Outpatients at Risk of or With Atherothrombosis. *JAMA*. 2010;304:1350–1357.

3. Steg PG, Bhatt DL, Wilson PWF, et al. One-Year Cardiovascular Event Rates in Outpatients With Atherothrombosis. *JAMA*. 2007;297:1197–1206.

4. Joosten MM, Pai JK, Bertoia ML, et al. Associations between conventional cardiovascular risk factors and risk of peripheral artery disease in men. *JAMA*. 2012;308:1660–1667.

5. Bonaca MP, Gutierrez JA, Cannon C, et al. Polyvascular disease, type 2 diabetes, and long-term vascular risk: a secondary analysis of the IMPROVE-IT trial. *Lancet Diabetes Endocrinol*. 2018;6:934–943.

6. Verma S, Mazer CD, Bhatt DL. The perils of polyvascular disease in type 2 diabetes. *The Lancet Diabetes & Endocrinology*. 2018;6:914–916.

7. Bouabdallaoui N, Messas N, Greenlaw N, et al. Impact of smoking on cardiovascular outcomes in patients with stable coronary artery disease. *Eur J Prev Cardiol*. 2020;2047487320918728.

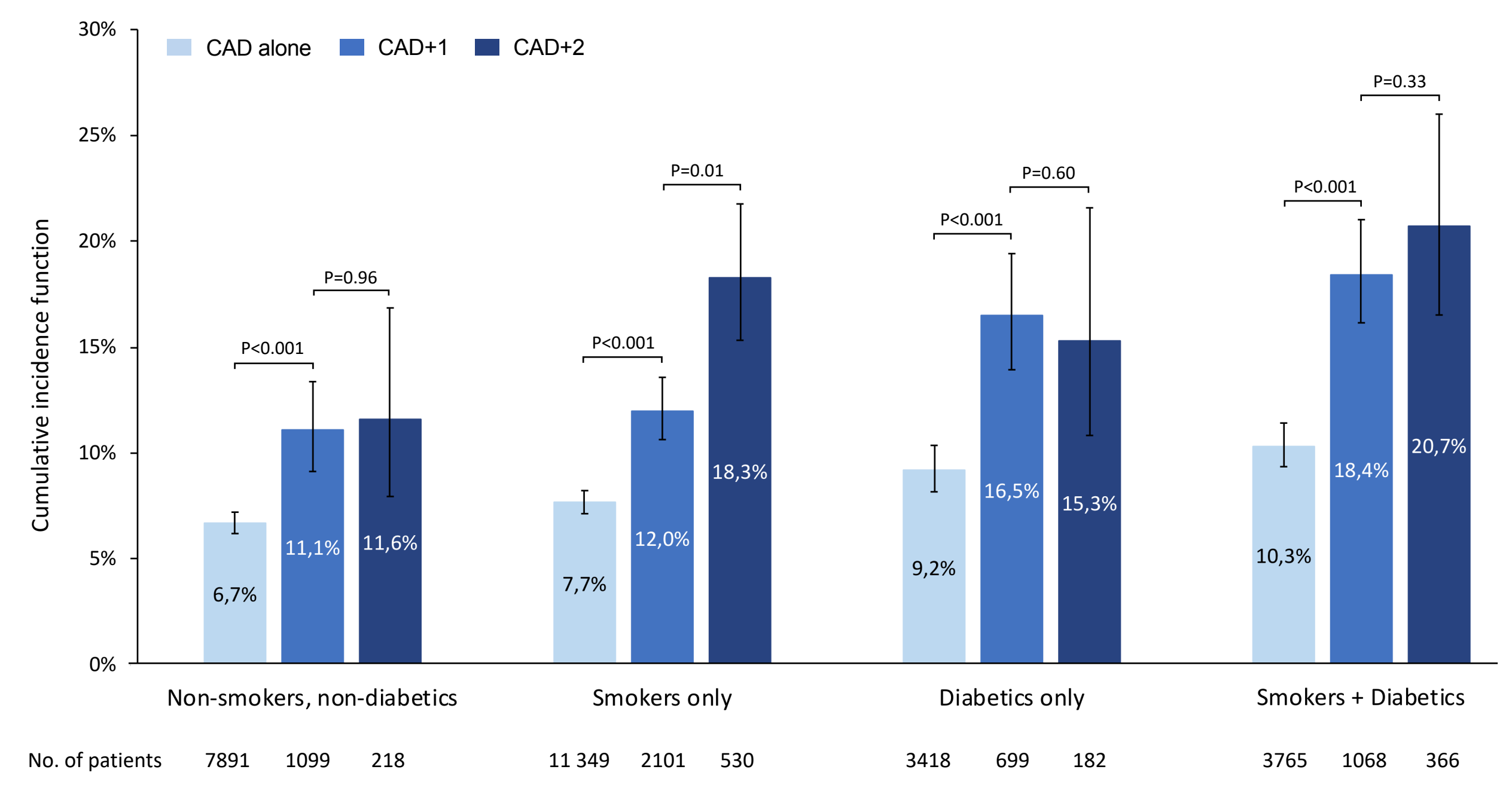
8. Sorbets E, Greenlaw N, Ferrari R, et al. Rationale, design, and baseline characteristics of the CLARIFY registry of outpatients with stable coronary artery disease. *Clin Cardiol*. 2017;40:797–806.

9. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. *Eur Heart J*. 2013;34:2436–2443.

10. Messner B, Bernhard D. Smoking and Cardiovascular Disease: Mechanisms of Endothelial Dysfunction and Early Atherogenesis. *Arterioscler Thromb Vasc Biol*. 2014;34:509–515.

11. Biscaglia S, Campo G, Sorbets E, et al. Relationship between physical activity and long-term outcomes in patients with stable coronary artery disease. *Eur J Prev Cardiol*. 2020;27:426–436.

12. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41:407–477.


CAD alone
CAD+1
CAD+2
Cumulative incidence function
30%
25%
20%
15%
10%
5%
0%
P<0.001
P=0.96
P<0.001
P=0.01
P<0.001
P=0.60
P<0.001
P=0.33
6,7%
11,1%
11,6%
7,7%
12,0%
18,3%
9,2%
16,5%
15,3%
10,3%
18,4%
20,7%
Non-smokers, non-diabetics
Smokers only
Diabetics only
Smokers + Diabetics
No. of patients
7891
1099
218
11 349
2101
530
3418
699
182
3765
1068
366