Prevalence of diabetes and impact on cardiovascular events and mortality in patients with chronic coronary syndromes, across multiple geographical regions and ethnicities.

Koon-Hou Mak[1], Emmanuelle Vidal-Petiot[2, 3*], Robin Young[4], Emmanuel Sorbets[3, 5, 6], Nicola Greenlaw[4], Ian Ford[4], Michal Tendera[7], Roberto Ferrari[8, 9], Jean-Claude Tardif[10], Jacob A. Udell[11], Jorge Escobedo[12], Kim M. Fox[13], Philippe Gabriel Steg[3,6,13,14], on behalf of the CLARIFY Investigators

[1]Mak Heart Clinic, Gleneagles Medical Centre, 6 Napier Road#08-13, Singapore 258499

[2]Physiology Department, Assistance Publique-Hôpitaux de Paris, Hôpital Bichat and INSERM U1149, Centre For Research in Inflammation, 46 rue Henri Huchard, 75018 Paris, France

[3]Université de Paris, Paris, France

[4]Robertson Centre for Biostatistics, Boyd Orr Building, University Avenue, University of Glasgow, Glasgow, G12 8QQ United Kingdom

5Centre de Diagnostic et de Thérapeutique, Assistance Publique-Hôpitaux de Paris, Hôpital Hôtel Dieu, 1, place du Parvis Notre Dame, 75004 Paris, France

[6]FACT (French Alliance for Cardiovascular Trials), an F-CRIN network, and INSERM U1148, Laboratory for Vascular Translational Science, 46, rue Henri Huchard, 75018 Paris, France

[7]Medical University of Silesia, School of Medicine in Katowice, Department of Cardiology and Structural Heart Disease, Katowice, Poland

[8]Cardiovascular centre, University of Ferrara, Italy

[9]Maria Cecilia Hospital, GVM Care & Research, Cotignola (RA), Italy

[10]Department of Medicine, Montreal Heart Institute, Université de Montreal, 5000 Belanger street, Montreal H1T1C8, PQ, Canada

[11]Women's College Research Institute, Women's College Hospital, University of Toronto, 76 Grenville St, Toronto, ON M5S 1B1, Canada

[12] Unidad de Investigación en Epidemiología Clínica, Hospital General Regional 1, Instituto Mexicano del Seguro Social, Mexico City, Mexico.

[13]NHLI Imperial College, Dovehouse Street, London SW3 6LP ICMS, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK

[14]Cardiology Department, Assistance Publique-Hôpitaux de Paris, Hopital Bichat, 75018 Paris, France

***Corresponding author**

Dr Emmanuelle Vidal-Petiot
Physiology Department, Bichat Hospital, 46 rue Henri Huchard, 75018 Paris, France
Tel +331 40 25 84 08; Fax +331 40 25 88 56
Email: emmanuelle.vidal-petiot@aphp.fr

Manuscript length:
Main body: 3848 words + 1 figure and 3 tables: total 4848

ABSTRACT (250 words)

Background: In contrast with the setting of acute myocardial infarction, there are limited data regarding the impact of diabetes mellitus on clinical outcomes in contemporary cohorts of patients with chronic coronary syndromes. We aimed to investigate the prevalence and prognostic impact of diabetes according to geographical regions and ethnicity.

Methods: CLARIFY is an observational registry of patients with chronic coronary syndromes, enrolled across 45 countries in Europe, Asia, America, Middle East, Australia and Africa in 2009-2010, and followed-up yearly for 5 years. Chronic coronary syndromes were defined by ≥1 of the following criteria: prior myocardial infarction, evidence of coronary stenosis >50%, proven symptomatic myocardial ischemia, or prior revascularisation procedure.

Results: Among 32,694 patients, 9502 (29%) had diabetes, with a regional prevalence ranging from below 20% in Northern Europe to approximately 60% in the Gulf countries. In a multivariable-adjusted Cox proportional hazards model, diabetes was associated with increased risks for the primary outcome (cardiovascular death, myocardial infarction or stroke) with an adjusted hazard ratio of 1.28 (95% CI 1.18-1.39) and for all secondary outcomes (all-cause and cardiovascular mortality, myocardial infarction, stroke, heart failure and coronary revascularization). Differences on outcomes according to geography and ethnicity were modest.

Conclusion: In patients with chronic coronary syndromes, diabetes is independently associated with mortality and cardiovascular events, including heart failure, which is not accounted by demographics, prior medical history, left ventricular ejection fraction, or use of secondary prevention medication. This is observed across multiple geographic regions and ethnicities, despite marked disparities in the prevalence of diabetes.

ClinicalTrials identifier: NCT00799903

Abstract word count: 250 words

Keywords

CLARIFY registry; diabetes; chronic coronary syndromes; geographical disparities

INTRODUCTION

The global prevalence of diabetes has been rising rapidly and is estimated to have doubled since 1980, from 4.7% to 8.5% among adults.[1] This unfavourable trend has been observed across a broad range of high and low income countries. [2,3]

Today, diabetes is the seventh cause of death worldwide.[4] Age-standardized mortality rates attributable to high blood glucose are highest in the Middle East (which has by far the highest prevalence of diabetes worldwide), South-East Asia, and Africa.[1] In patients without established cardiovascular disease, diabetes is associated with two-fold increase in the occurrence of a wide range of vascular disease independent of other risk factors.[5,6] Among patients at high risk for or with established cardiovascular disease, [7–9] diabetes is independently increases the risk of death and cardiovascular events, including heart failure, by approximately 30 to 40%.[9] After acute myocardial infarction, short- and long-term mortality is higher among those with diabetes.[10–12] In contrast, information is limited in the setting of chronic coronary syndromes.

The use of various evidence-based therapies has improved outcomes following myocardial infarction, including in patients with diabetes.[12–14] In the United States, all-cause mortality for patients with diabetes has been declining by 20% every 10 years since 1985, mainly driven by the reduction of death from vascular causes.[15] Contemporary data regarding the worldwide prevalence of diabetes mellitus and its impact on clinical outcomes of patients with chronic coronary syndromes are needed.

The prospeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease (CLARIFY) registry was established to describe the characteristics, management and outcomes of the broad contemporary spectrum of patients with chronic coronary

syndromes,[16] which include patients with angina, myocardial ischemia or both, patients with previous history of myocardial infarction or history of coronary revascularization and patients with established coronary artery disease who may have no symptoms or ischemia.[17] Patients with chronic coronary syndromes were enrolled from 45 countries in Europe, the Middle East, Asia, Northern, Central and South America, Australia and South Africa, and encompassed diverse ethnic origins. We aimed to describe the prevalence of diabetes among the ethnic and geographical regions, to evaluate the impact of diabetes on adverse cardiovascular outcomes among patients with chronic coronary syndromes, and to study whether the impact of diabetes differed according to region and ethnicity.

METHODS

Study design and subjects

The design and overall results of the CLARIFY study have been described previously.[18,19] Briefly, this international prospective observational registry enrolled stable patients, between November 26, 2009 and June 30, 2010, in whom coronary artery disease has been objectively documented by either previous myocardial infarction (>3 months), a previous coronary revascularization procedure (>3 months), coronary angiography (>50% stenosis) or myocardial ischemia provoked by functional testing in symptomatic individuals. Exclusion criteria were hospital admission for cardiovascular reasons (including revascularization) in the past 3 months, planned revascularisation, or conditions compromising the participation or 5-year follow-up (including severe other cardiovascular disease such as advanced heart failure, severe valve disease, or history of valve repair or replacement). The study was approved by local Ethics

Committees and/or Institutional Review Boards. All subjects provided written informed consent. The clinical trial registration number is ISRCTN43070564.

Data collection

Following recruitment of eligible subjects, demographic characteristics, medical history and current medications (medicines that were administered regularly for at least 7 days before inclusion) were obtained. Participation in the study did not affect routine clinical care and investigation, and participants were managed according to usual practice. No specific tests or treatment were mandated by the study protocol. Participants were followed regularly by at least an annual visit interspersed with telephone calls at 6 months, for 5 years. Major clinical events, such as death and its causes, myocardial infarction, stroke, coronary angiography and revascularization procedures as well as treatment were collected annually.

Data were entered into electronic case report forms. Completeness, consistency and correctness were verified, managed and analyzed centrally by an independent academic statistics centre (Robertson Centre for Biostatistics, University of Glasgow, United Kingdom). Approximately 5% of the sites were randomly selected for audit and quality control. In those, site visits were conducted and 100% of data were source documents verified for all records. Baseline characteristics were obtained from the patient history and examination. Diabetes was defined as history of diabetes, or current diabetes, diagnosed by two fasting blood glucose measures >7 mmol/L or >126 mg/dL, or by an abnormal oral glucose tolerance test, independently of whether the subject received drug treatment for diabetes. Ethnicity was provided by the participant, and categorised as Caucasian, South Asians (those from the Indian subcontinent), East Asians (China or Korea/Japan), Hispanics, Black/Africans. In France and

Portugal, recording of ethnicity was not permitted by ethics committees and accounted for the majority of "unknown ethnicity". To ascertain if there was geographical variation of outcomes of patients with diabetes, subjects were categorized into 6 geographical regions, Europe; Gulf countries; India; East and South-East Asia; Central and South America; and the United Kingdom, Canada, Australia and South Africa. The last four regions were grouped together based on the similarities of healthcare systems, and referred to as "commonwealth countries outside of Asia".

Outcomes

For the purpose of this analysis, we defined the composite of cardiovascular death, myocardial infarction and stroke as the primary outcome of interest. Secondary outcomes were each component of the primary outcome, total death, and hospitalization for heart failure. The rate of coronary revascularization, either by percutaneous coronary intervention or coronary artery bypass grafting, was also studied in the analyses conducted in the total population. 32,703 patients were enrolled in the CLARIFY registry, but information on diabetes was lacking in 9 patients, leaving 32,694 patients for the present analysis.

Statistical Analysis

Continuous variables are summarized as mean with standard deviation or median with interquartile range, as appropriate. Categorical variables are presented as numbers and percentages. Comparison of patients with and without diabetes were performed using chi-squared tests or unadjusted analysis of variance, as appropriate. Confidence intervals for prevalence of diabetes per region, ethnicity, or country were calculated using binomial tests.

Cox proportional hazards models were used to assess the association between diabetes status and outcomes. In addition to crude hazard ratios (HRs), adjusted HRs were estimated after adjustment for potential confounding factors, selected a priori as potential confounders, namely age, sex, geographical region, smoking status, body-mass index, treated hypertension, baseline systolic blood pressure, estimated glomerular filtration rate (eGFR, calculated from the creatinine-derived chronic kidney disease Epidemiology Collaboration [CKD-EPI] equation[20]), previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting, number of diseased coronary vessels at baseline, peripheral artery disease at baseline, previous stroke or transient ischemic attack, previous hospital admission for (or symptoms of) heart failure, left ventricular ejection fraction, atrial fibrillation or flutter, and baseline drugs (any antiplatelet, statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers and diuretics). Interactions between diabetes and geographical regions were tested by introduction of product terms. Subgroup analyses, both crude and adjusted, were performed by geographical region and by ethnicity (for which the adjusted model did not include geography).

Data were analyzed as recorded without imputation for missing data. Adjustment variables with a high number of missing data (eGFR, number of diseased coronary vessels and left ventricular ejection fraction) were analysed including a category for missing data to minimize the loss of data in the analysis.

Statistical analyses were performed using R (3.4.1).

RESULTS

Prevalence of diabetes

Among 32,694 participants, 9502 (29%) were found to have diabetes. There were marked disparities in the prevalence of diabetes across the 45 participating countries, ranging from 14% in Ireland (n=190) to 67% in Saudi Arabia (n=758) (Table S1). Across the various broad geographical regions, there was substantial heterogeneity in the prevalence of diabetes (P< 0.0001), which was highest in the Gulf Countries, with approximately 3 of 5 of participants affected, and lowest in Europe and Commonwealth countries outside of Asia (Canada, South Africa, United Kingdom and Australia), with approximately 1 of 4 participants affected (Figure 1). Likewise, there was heterogeneity in the prevalence of diabetes according to self-reported ethnicity (P< 0.0001), although more modest, with a prevalence of nearly 40% in South Asians and Black/Africans and a prevalence 27 to 30% in Caucasian and East Asian patients.

Baseline characteristics

Baseline characteristics of the patients are reported in Table 1. Compared with patients without diabetes, patients with diabetes were older, and more often female. They were more likely to be obese and to have hypertension, performed less physical activity and had a lower education level, but were less likely to be current smokers and more likely to have LDL-cholesterol level below 70 mg/dL. Compared with patients without diabetes, patients with diabetes were more likely to have peripheral artery disease, cerebrovascular disease, and a previous hospitalization for heart failure. Patients with diabetes were slightly less likely to have a history of percutaneous coronary intervention but markedly more likely to have undergone a coronary artery bypass grafting. Even though patients with diabetes were more likely to receive beta-blockers, their resting heart rate was higher. Thienopyridines, lipid lowering drugs, renin-

angiotensin system blockers, calcium antagonists, and diuretics were more frequently prescribed to patients with diabetes.

Clinical Outcomes

After a median follow up of 5 years, 2807 patients met the primary outcome, and 2544 patients died (1619 of cardiovascular cause). Stroke and myocardial infarction, occurred in 686 and 1106 patients, respectively, 1647 patients were hospitalised for heart failure, and 2526 underwent coronary revascularization.

All adverse clinical outcomes occurred more frequently among patients with diabetes (Table 2). After statistical adjustment, the risk for the primary outcome (adjusted HR 1.28, 95% CI 1.18-1.39), as well as the risks of all secondary outcomes remained higher for patients with diabetes (adjusted HR 1.38 [95% CI 1.27-1.50] for all-cause death, 1.39 [95% CI 1.25-1.54] for cardiovascular death, 1.26 [95% CI 1.10-1.43] for myocardial infarction, 1.29 [95% CI 1.09-1.52] for stroke, 1.15 [95% CI 1.03-1.28] for hospital admission for heart failure, and 1.14 [95% CI 1.04-1.25] for coronary revascularization)

The rates of 5-year clinical outcomes in patients with and without diabetes across geographical regions are shown in Table 3. Despite the marked geographical disparities in the prevalence of diabetes, the prognostic value of diabetes after adjustment for potential confounders was similar across geographical regions, and interaction between diabetes and geography was non-significant for all outcomes (Table 3).

The rates of 5-year clinical outcomes in patients with and without diabetes across ethnic groups are shown in Table S2. The highest crude and adjusted risk associated with diabetes for

the primary outcome and for cardiovascular and all-cause death was observed for South Asians, the majority of whom were of Indian origin.

Of note, the higher rate of hospitalization for heart failure in patients with versus without diabetes was observed consistently across the geographical regions and ethnic groups, except for subgroups in whom the number of events was too low for a reliable estimate of the risk, as shown by wide confidence intervals (Table 3 and Table S2).

DISCUSSION

In this large contemporary international registry of patients with chronic coronary syndromes, the prevalence of diabetes was 29%, much higher than in the general population in which the estimated prevalence is approximately 8-10%.[1,2]

Data on the prevalence of diabetes in the population of patients with chronic coronary syndrome across multiple regions are scarce, especially from "real-life" international registries. In the Diabetes and Heart survey, a multi-centre European prospective observational study conducted in 25 countries (enrolment 2003-2004), the prevalence of diabetes was 31%, and was similar in patients recruited after acute admissions or elective consultations.[21] In the large-scale Swedish registry of patients with a primary myocardial infarction recruited from 2006 to 2011,[22] the prevalence of diabetes was 23% both in the total population and in the stable population who survived for 12 months without a subsequent myocardial infarction or stroke, reflecting the relatively lower prevalence of diabetes in Europe (especially northern Europe) than in other regions of the world. In the subgroup of patients with coronary artery disease (n=26389) from the Reduction of Atherothrombosis for Continued Health (REACH) registry, which recruited patients 6 years earlier that CLARIFY, 38% had diabetes.[9] The majority of contemporary data on

the prevalence of diabetes in chronic coronary syndromes arise from randomized trials. In the Study Assessing the Morbidity–Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY) trial,[23] which recruited patients with stable coronary artery disease of at least 55 years of age, during the same time period as CLARIFY, the prevalence of diabetes was 43%. In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial (recruitment 2013-2016), the prevalence of diabetes in the 24824 patients with coronary artery disease at baseline was 37%.[24] Interestingly, in one of the most recent reported population with stable coronary artery syndromes, the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial, in which patients were randomly assigned to revascularization or optimal medical therapy, the prevalence of diabetes was 41%.[25] Overall, although the prevalence of diabetes may vary depending on the recruitment period, proportion of women, mean age and geographical origins of study participants, the prevalence of this comorbidity is extremely high in patients with coronary artery disease. Noteworthy, in all these studies as well as ours, since oral glucose tolerance tests were not systematically performed to screen for diabetes, the true prevalence of diabetes was very likely underestimated, as shown by studies from the Euro Heart Survey [21] and from the European Society of Cardiology surveys European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) IV[26] and V.[27]

In our study, there were considerable disparities in the prevalence of diabetes across different geographical regions. There were also disparities among ethnic groups, with a high prevalence observed in South Asians. While the prevalence of diabetes is rising worldwide, the rate of increase varies considerably across geographical regions. The increase in the prevalence

of diabetes is higher in low and middle-income countries, and especially high among developing Asian countries in which prevalence may nowadays exceed by far that observed in some developed countries.[1,28] Accordingly, we found that the prevalence of diabetes was highest in Asian regions, particularly in the Middle East and India. Our data which showed a prevalence of 60% in the Gulf Countries confirms reports of the World Health Organization warning that the Eastern Mediterranean Region has been experiencing the greatest rise in diabetes prevalence in the past decade and is now the region with the highest prevalence of diabetes.[1]. Such high rates of diabetes in those regions considered as the epicentre of the epidemic may be attributed to the rising affluence, urbanization and the associated changes in lifestyle.[28] Increasing and westernization of food intake together with reduction in physical activity could explain part of this adverse trend.[29,30] This is best illustrated by the substantial increase of childhood obesity.[28] Genetic variants may also predispose to the increasing prevalence of diabetes in the Middle East and Asia,[31] with a higher proportion of body fat and abdominal obesity in Asian people compared to people of European origin for similar body mass index.[32,33] Conversely, we observed the lowest prevalence in Northern Europe and Commonwealth countries outside of Asia. Through comprehensive and integrated public health approach including well-targeted education programs, other countries have been made more aware of the benefits of healthy living and modified their lifestyle to promote better health.

The definition of ethnicity is challenging, particularly when the number of inter-ethnic and inter-national marriages is increasing, so that geographical regions may provide a more stable cross-sectional assessment. Therefore, geographical region, rather than ethnicity, was included in the multivariable adjusted model. Geographical regional approach is however confronted with its unique set of challenges in today's world of global migration, with

individuals of the same regions having markedly different customs, practices, and beliefs. Prevalence of diabetes differed to a larger extent across geographical regions than ethnicities. Independently of their ethnicity, patients tend to be exposed to the norms and customs of their host countries and to adopt the practices of the country they live in. Accordingly, it has been shown that with increasing duration of residence, migrants in the United States were more likely to display a higher prevalence of cardiometabolic risk factors.[34]

Overall, as underscored by the World Health Organization, the particularly high prevalence of diabetes measured in some regions highlight the need for strong public action and implementation of programs targeting groups of people at high-risk to oppose the rising trend of diabetes. Research on the epidemiology of diabetes needs to be combined with efforts in primary prevention of diabetes – weight control and exercise being the first steps –, early detection of the disorder, and improved management of patients with established diabetes, both at the individual level and through health system interventions.[28,35]

Our study provides important data on the magnitude of associations of diabetes with adverse outcomes in a contemporary registry of patients with chronic coronary syndromes. After adjustment for multiple potential confounders, patients with diabetes and with stable coronary artery disease had a significantly increased risk for all adverse events. The adjusted HR for patients with diabetes versus those without diabetes for the composite outcome of cardiovascular death, myocardial infarction or stroke was 1.28 (95% CI 1.18, 1.39). Of note, the total mortality rates were10.5% and 6.8%in patients with and without diabetes, respectively. Interestingly, as previously observed in the REACH registry,[9] our results showed that the rate of hospitalization for heart failure was significantly higher in patients with diabetes, even after adjusting for

baseline heart failure symptoms and left ventricular ejection fraction. In the SIGNIFY trial, the incidence of the primary endpoint (cardiovascular death or non-fatal myocardial infarction) was 1.27 times higher (in the placebo arm) in those with diabetes after a median follow up of 28 months.[23] Patients with diabetes had a 1.40 to 1.50 increased risk for the composite of cardiovascular death, myocardial infarction, or stroke, depending on treatment arm, in the COMPASS trial, and this was true in the total population[36] as well as in patients with coronary artery disease.[24] Interestingly, in the recent ISCHEMIA trial, those with diabetes had one of the highest estimated 5-year cardiovascular event rate (primary outcome, defined as of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest), which was 1.30 to 1.38 times higher than in those without diabetes.[37] These contemporary data from randomized trials corroborate our results obtained in a registry. These large complementary sets of data provide an accurate picture of the increased risk associated with diabetes nowadays.

Overall, patients with diabetes remain at high risk of adverse cardiovascular events. This is true worldwide, across geographic regions and ethnicities, although the challenge is even greater in some regions where the prevalence of diabetes is extremely high such as the Middle East. In parallel with worldwide efforts to reduce overweight, obesity, physical inactivity and unhealthy diets responsible for the rising prevalence of diabetes, new and improved therapies to address the cardiovascular consequences of diabetes are direly needed. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors[38] and glucagon-like peptide-1 receptor agonist[39] appear to impact adverse cardiovascular outcomes in this group of patients.[40] Notably, SGLT-2 inhibitors have been shown to reduce cardiovascular death and hospitalization for heart failure among patients with or without cardiovascular disease and with or without a history of heart failure.[38,41]

Recently, SGLT-2 inhibitors have even been shown to reduce cardiovascular mortality and hospitalization for heart failure when initiated soon after an episode of decompensated heart failure.[42] These improvements are particularly relevant in the context of our finding that patients with diabetes were more likely to be hospitalized for heart failure. In addition, SGLT-2 inhibitors have been shown to have a marked benefit for kidney disease progression in patients with diabetes.[41,43] Of note, disparities in access to these lifesaving therapies will likely further drive regional differences over time until generic access is widely available.

Beyond glycaemic control, other secondary prevention therapies need to be optimized. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, such as evolocumab[44] and alirocumab,[45] reduce low-density lipoprotein cholesterol level more than statins alone, and have the potential to improve outcomes of patients with dyslipidaemia, with and without diabetes, particularly in very high-risk patients. Likewise, newer evidence-based potent antiplatelet agents may also lower cardiovascular event rates in diabetic patients with chronic coronary syndromes.[46] In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, it has been recently shown that the concomitant use of low-dose oral direct thrombin inhibitors in addition to antiplatelet agents further improves outcome among patients with diabetes[36,47].

Although the rates of evidence-based secondary prevention medicines were very high in our registry of patients with coronary disease, risk factor management could be further improved, has shown by data on physical activity, by the high rate of patients with uncontrolled blood pressure, and levels of LDL-cholesterol above target. Likewise, it was recently shown in the large European Survey EUROASPIRE V that management of diabetes in patients with coronary artery disease was far from optimal.[27,48] In addition, many of the above-mentioned newer

improved therapies – in particular SGLT-2 inhibitors – were not available during the conduct of this study, and may contribute to improve cardiovascular outcomes in diabetes in the coming years. In our study, patients with diabetes were more likely to undergo coronary revascularization. This finding suggested that they were treated aggressively. However, our data were unable to ascertain to what extent these procedures followed a higher rate of ischemic events or prevented an otherwise higher rate of ischemic events. Information on the use of drug-eluting stents was not collected in the registry.

Although CLARIFY was a large global prospective study, participants were enrolled from clinics which were not randomly allocated. Therefore, our findings may not accurately reflect the epidemiology of each country. Furthermore, ethnicity was self-reported, which may have affected the accuracy of the data, and it was unknown in about 10% of the population, mainly due to statutory regulations, specifically in France and Portugal. In addition, we did not separate type 1 and type 2 diabetes, although the prevalence of the latter was likely most common, and our study was not designed to analyse the effect of diabetic medication, which were not extensively collected beyond insulin versus oral agents. Finally, endpoints were not adjudicated by an independent blinded committee; however they were reported by physicians according to the detailed requirement of case report forms and onsite monitoring visits were conducted in randomly selected centres with source verification of events. Therefore, we believe that despite these limitations, our results provided valuable insight into the prevalence and outcomes of patients with diabetes and chronic coronary syndromes.

CONCLUSION

In conclusion, in this global registry of patients with chronic coronary syndromes, overall prevalence of diabetes was 29%, with marked disparities across geographical regions which reflect those reported by the Word Health Organization in the general population. Patients with diabetes and coronary artery disease have a markedly increased risk of cardiovascular events, independently of multiple confounding factors, and this is true across all geographical regions and ethnicities. Improved strategies to slow the progression of diabetes and more effective intervention to prevent its adverse consequences through lifestyle modification, revascularisation procedures and pharmacological therapies, are direly needed.

Funding

The CLARIFY registry was supported by Servier. The sponsor had no role in the study design or in data analysis, and interpretation; or in the decision to submit the manuscript for publication, but assisted with the set-up, data collection and management of the study in each country. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of Interest

K.H.M. has nothing to disclose. E.V.P. reports non-financial support and personal fees from Servier, outside the submitted work. R.Y. has nothing to disclose. E.S. reports personal fees and non-financial support from Servier, during the conduct of the study; personal fees and non-financial support from Astra Zeneca, Bayer, Bristol Meyers Squibb, Merck Sharpe & Dhome,

and Novartis, outside the submitted work. N.G. reports grants from Servier, during the conduct of the study. I.F. reports grants and personal fees from Servier, during the conduct of the study. M.T. reports personal fees from Servier, during the conduct of the study; and personal fees from Bayer, Cadila Pharmaceuticals, Janssen-Cilag, Kowa, OncoArendi, PERFUSE Group, Servier, and UCB Pharmaceuticals, outside the submitted work. R.F. discloses grants and personal fees from Servier International and Novartis, and personal fees from Merck Serono, Bayer, and Boehringer Ingelheim outside the submitted work. J.C.T. reports grants from Servier, during the conduct of the study, and grants from Amarin, Esperion, Ionis, RegenXBio, grants and personal fees from Astra Zeneca, Sanofi, Servier, grants, personal fees and other support from Dalcor, outside the submitted work. In addition, J.C.T. has a patent Genetic markers for predicting responsiveness to therapy with hdl-raising or hdl mimicking agent pending, a patent Methods for using low dose colchicine after myocardial infarction pending to Invention assigned to the Montreal Heart Institute, and a patent Methods of treating a coronavirus infection using Colchicine pending.

J.A.U. discloses he received consulting or speaker honoraria from Amgen, AstraZeneca, Boehringer-Ingelheim, Janssen, Novartis and Sanofi; and received grants to his institution for clinical trial research from AstraZeneca, Boehringer-Ingelheim, Janssen, Novartis and Sanofi outside the submitted work. J.E. has nothing to disclose.

K.M.F. reports personal fees and other support from Servier, during the conduct of the study, personal fees and other support from Celixir, UCH, Broadview Ventures, and other support from AstraZeneca, outside the submitted work. In addition, he is Director of Vesalius Trials.

P.G.S. reports grants and personal fees from Servier, during the conduct of the study; grants and personal fees from Bayer/Janssen, Merck, Sanofi, and Amarin, and personal fees from Amgen, Bristol Myers Squibb, Boehringer-Ingelheim, Pfizer, Novartis, Regeneron, AstraZeneca, Servier, Novo Nordisk, Idorsia, and Mylan, outside the submitted work.

Authors' contributions

KHM and EVP designed the study, interpreted the data, designed tables and figures, and wrote the first draft and subsequent iterations of the manuscript. RY, NG and IF did the statistical analysis, designed tables and figures, and reviewed and provided critical comments on drafts. MT, RF, JCT, JAU, and JE conceived and initiated the CLARIFY registry, coordinated the study and collected data in their respective countries, and reviewed and provided critical comments on the manuscript. ES provided critical comments on the manuscript. KMF and PGS initiated and coordinated the CLARIFY registry, designed the study, interpreted the data, and provided critical comments on the manuscript. All authors gave final approval for submission of the manuscript.

References

1. Roglic G, World Health Organization (eds). *Global report on diabetes*. Geneva, Switzerland: World Health Organization, 2016.

2. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. *The Lancet* 2011; 378: 31–40.

3. Selvin E, Parrinello CM, Sacks DB, et al. Trends in Prevalence and Control of Diabetes in the United States, 1988–1994 and 1999–2010. *Ann Intern Med* 2014; 160: 517.

4. Geneva, World Health Organization. Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016.

5. Emerging Risk Factors Collaboration, Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *The Lancet* 2010; 375: 2215–2222.

6. Dal Canto E, Ceriello A, Rydén L, et al. Diabetes as a cardiovascular risk factor: An overview of global trends of macro and micro vascular complications. *Eur J Prev Cardiol* 2019; 26: 25–32.

7. 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.

8. Krempf M, Parhofer KG, Steg PG, et al. Cardiovascular event rates in diabetic and nondiabetic individuals with and without established atherothrombosis (from the REduction of Atherothrombosis for Continued Health [REACH] Registry). *Am J Cardiol* 2010; 105: 667–671.

9. Cavender MA, Steg PhG, Smith SC, et al. Impact of Diabetes Mellitus on Hospitalization for Heart Failure, Cardiovascular Events, and Death: Outcomes at 4 Years From the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Circulation* 2015; 132: 923–931.

10. Mak KH, Moliterno DJ, Granger CB, et al. Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. *J Am Coll Cardiol* 1997; 30: 171–179.

11. Gustafsson I. Long-term prognosis of diabetic patients with myocardial infarction: relation to antidiabetic treatment regimen. *Eur Heart J* 2000; 21: 1937–1943.

12. Gurm HS, Lincoff AM, Lee D, et al. Outcome of acute ST-segment elevation myocardial infarction in diabetics treated with fibrinolytic or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition. *J Am Coll Cardiol* 2004; 43: 542–548.

13. Hsu LF. Clinical outcomes of patients with diabetes mellitus and acute myocardial infarction treated with primary angioplasty or fibrinolysis. *Heart* 2002; 88: 260–265.

14. Timmer J. Long-term, cause-specific mortality after myocardial infarction in diabetes. *Eur Heart J* 2004; 25: 926–931.

15. Gregg EW, Cheng YJ, Srinivasan M, et al. Trends in cause-specific mortality among adults with and without diagnosed diabetes in the USA: an epidemiological analysis of linked national survey and vital statistics data. *The Lancet* 2018; 391: 2430–2440.

16. 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.

17. 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.

18. Vidal-Petiot E, Ford I, Greenlaw N, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. *The Lancet* 2016; 388: 2142–2152.

19. 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.

20. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612.

21. Bartnik M. The prevalence of abnormal glucose regulation in patients with coronary artery disease across EuropeThe Euro Heart Survey on diabetes and the heart. *Eur Heart J* 2004; 25: 1880–1890.

22. Jernberg T, Hasvold P, Henriksson M, et al. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *Eur Heart J* 2015; 36: 1163–1170.

23. Fox K, Ford I, Steg PG, et al. Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure. *N Engl J Med* 2014; 371: 1091–1099.

24. Connolly SJ, Eikelboom JW, Bosch J, et al. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. *The Lancet* 2018; 391: 205–218.

25. Hochman JS, Reynolds HR, Bangalore S, et al. Baseline Characteristics and Risk Profiles of Participants in the ISCHEMIA Randomized Clinical Trial. *JAMA Cardiol* 2019; 4: 273–286.

26. Gyberg V, De Bacquer D, Kotseva K, et al. Screening for dysglycaemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test, and HbA1c: a report from EUROASPIRE IV--a survey from the European Society of Cardiology. *Eur Heart J* 2015; 36: 1171–1177.

27. Ferrannini G, De Bacquer D, De Backer G, et al. Screening for Glucose Perturbations and Risk Factor Management in Dysglycemic Patients With Coronary Artery Disease-A Persistent Challenge in Need of Substantial Improvement: A Report From ESC EORP EUROASPIRE V. *Diabetes Care* 2020; 43: 726–733.

28. Yoon K-H, Lee J-H, Kim J-W, et al. Epidemic obesity and type 2 diabetes in Asia. *The Lancet* 2006; 368: 1681–1688.

29. Badran M, Laher I. Type II Diabetes Mellitus in Arabic-Speaking Countries. *Int J Endocrinol* 2012; 2012: 1–11.

30. Majeed A, El-Sayed AA, Khoja T, et al. Diabetes in the Middle-East and North Africa: An update. *Diabetes Res Clin Pract* 2014; 103: 218–222.

31. Zabetian A, Keli HM, Echouffo-Tcheugui JB, et al. Diabetes in the Middle East and North Africa. *Diabetes Res Clin Pract* 2013; 101: 106–122.

32. Park YW, Allison DB, Heymsfield SB, et al. Larger amounts of visceral adipose tissue in Asian Americans. *Obes Res* 2001; 9: 381–387.

33. He Q, Horlick M, Thornton J, et al. Sex and Race Differences in Fat Distribution among Asian, African-American, and Caucasian Prepubertal Children. *J Clin Endocrinol Metab* 2002; 87: 2164–2170.

34. Commodore-Mensah Y, Ukonu N, Obisesan O, et al. Length of Residence in the United States is Associated With a Higher Prevalence of Cardiometabolic Risk Factors in Immigrants: A Contemporary Analysis of the National Health Interview Survey. *J Am Heart Assoc*; 5(11):e004059..

35. Flood D, Hane J, Dunn M, et al. Health system interventions for adults with type 2 diabetes in low- and middle-income countries: A systematic review and meta-analysis. *PLoS Med* 2020; 17: e1003434.

36. Bhatt DL, Eikelboom JW, Connolly SJ, et al. Role of Combination Antiplatelet and Anticoagulation Therapy in Diabetes Mellitus and Cardiovascular Disease: Insights From the COMPASS Trial. *Circulation* 2020; 141: 1841–1854.

37. Maron DJ, Hochman JS, Reynolds HR, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. *N Engl J Med* 2020; 382: 1395–1407.

38. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *The Lancet* 2019; 393: 31–39.

39. Bethel MA, Patel RA, Merrill P, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes Endocrinol* 2018; 6: 105–113.

40. Ghosh-Swaby OR, Goodman SG, Leiter LA, et al. Glucose-lowering drugs or strategies, atherosclerotic cardiovascular events, and heart failure in people with or at risk of type 2 diabetes: an updated systematic review and meta-analysis of randomised cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2020; 8: 418–435.

41. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. *JAMA Cardiol*. Epub ahead of print 7 October 2020. DOI: 10.1001/jamacardio.2020.4511.

42. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med*. Epub ahead of print 16 November 2020. DOI: 10.1056/NEJMoa2030183.

43. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. *N Engl J Med*. Epub ahead of print 16 November 2020. DOI: 10.1056/NEJMoa2030186.

44. Sabatine MS, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. *Lancet Diabetes Endocrinol* 2017; 5: 941–950.

45. Leiter LA, Zamorano JL, Bujas-Bobanovic M, et al. Lipid-lowering efficacy and safety of alirocumab in patients with or without diabetes: A sub-analysis of ODYSSEY COMBO II: LEITER et al. *Diabetes Obes Metab* 2017; 19: 989–996.

46. Steg PG, Bhatt DL, Simon T, et al. Ticagrelor in Patients with Stable Coronary Disease and Diabetes. *N Engl J Med* 2019; 381: 1309–1320.

47. Vanassche T, Verhamme P, Anand SS, et al. Risk factors and clinical outcomes in chronic coronary and peripheral artery disease: An analysis of the randomized, double-blind COMPASS trial. *Eur J Prev Cardiol* 2020; 27: 296–307.

48. Kotseva K, De Backer G, De Bacquer D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. *Eur J Prev Cardiol* 2019; 26: 824–835.

FIGURES AND TABLES

Figure 1

Prevalence of diabetes across various geographic regions and ethnic groups

Error bars indicate 95% confidence intervals.

Table 1: Demographic and baseline characteristics of the patients by diabetes status

Parameter	Available data	Diabetes (n = 9502)	No diabetes (n = 23192)	p-value
Age (years)	32679	65.0 (9.7)	63.8 (10.7)	<0.0001
Men	32684	7099 (74.8 %)	18259 (78.7 %)	<0.0001
Body mass index (kg/m²)	32651	28.9 (4.9)	27.4 (4.3)	<0.0001
Obesity (Body mass index ≥ 30 kg/m²)	32651	3443 (36.3%)	5510 (23.8%)	<0.0001
Smoking status	32693			<0.0001
Current	-	997 (10.5%)	3080 (13.3%)	-
Former	-	4205 (44.3%)	10902 (47.0%)	-
Never	-	4299 (45.2%)	9210 (39.7%)	-
Treated hypertension	32689	7756 (81.7%)	15450 (66.6%)	<0.0001
Systolic blood pressure (mm Hg)	32667	132.7 (17.1)	130.4 (16.4)	<0.0001
Diastolic blood pressure (mm Hg)	32667	76.8 (10.1)	77.4 (9.9)	<0.0001
Blood pressure ≥ 140/90 mmHg	32667	3651 (38.5%)	7857 (33.9%)	<0.0001
Heart rate (beats/minute)	32665	70.2 (10.9)	67.4 (10.4)	<0.0001
Geographical region	32694			<0.0001
Europe		4809 (50.6%)	13513 (58.3)	
Gulf countries		902 (9.4%)	606 (2.6%)	
India		304 (3.2%)	405 (1.7%)	
East and South-East Asia		1464 (15.4%)	3515 (15.2%)	
Central and South America		811 (8.5%)	1418 (6.1%)	
Commonwealth (outside of Asia)*		1212 (12.7%)	3735 (16.1%)	
Education	32687			<0.0001
Primary school (or less)		3100 (32.6%)	5546 (23.9%)	
Secondary school		4229 (44.5%)	10,972 (47.3%)	
College/University		2170 (22.8%)	6670 (28.8%)	
Weekly Physical Activity	32684			<0.0001
None		2061 (21.7%)	3226 (13.9%)	
Only light		4999 (52.6%)	11808 (50.9%)	
Vigorous at least once or twice		1260 (13.3%)	4209 (18.2%)	
Vigorous 3 or more times		1176 (12.4%)	3945 (17.0%)	
Myocardial Infarction	32689	5601 (59.0%)	13988 (60.3%)	0.0266
Percutaneous coronary intervention	32688	5471 (57.6%)	13686 (59.0%)	0.0197
Coronary artery bypass graft surgery	32688	2608 (27.5%)	5092 (22.0%)	<0.0001
Peripheral artery disease	32694	1360(14.3)	1879 (8.1)	<0.0001
Transient Ischemic Attack	32691	339 (3.6%)	662 (2.9%)	0.0008
Stroke	32692	516 (5.4%)	798 (3.4%)	<0.0001
Atrial fibrillation/flutter	32693	635 (6.7%)	1677 (7.2%)	0.0837
Hospitalization for heart failure	32693	640 (6.7%)	890 (3.8%)	<0.0001
Symptoms of heart failure	32686	1414 (14.9%)	3511 (15.1%)	0.5783
Left ventricular ejection fraction (%)	22514	54.7 (11.5)	56.7 (10.8)	<0.0001

HbA1C in patients with diabetes (%)	5121	7.3 (1.8)	-	-
eGFR (mL/min/1.73m²)	22166	73.1 (20.9)	76.1 (18.7)	<0.0001
Total cholesterol (mmol/L)	26297	4.3 (1.1)	4.4 (1.1)	<0.0001
HDL-cholesterol (mmol/L)	23267	1.1 (0.3)	1.2 (0.3)	<0.0001
LDL-cholesterol (mmol/L)	22131	2.4 (0.9)	2.5 (0.9)	<0.0001
LDL-cholesterol ≥ 1.8 mmmol/L (70 mg/dL)	22131	4828 (73.8%)	12684 (81.3%)	<0.0001
Fasting triglycerides (mmol/L)	24141	1.8 (1.0)	1.5 (0.8)	<0.0001
Baseline medication				
Insulin in patients with diabetes	9497	2048 (21.6%)	-	-
Aspirin	32681	8350 (87.9%)	20329 (87.7%)	0.5435
Thienopyridine	32546	2806 (29.6%)	6073 (26.2%)	<0.0001
Other antiplatelet agent	32652	924 (9.7%)	2098 (9.1%)	0.0554
Lipid-lowering drugs	32684	8889 (93.6%)	21,294 (91.8%)	<0.0001
Beta-blockers	32685	7349 (77.4%)	17256 (74.4%)	<0.0001
Calcium antagonists	32680	3149 (33.2%)	5757 (24.8%)	<0.0001
Angiotensin-converting enzyme inhibitors	32683	4995 (52.6%)	11895 (51.3%)	0.0347
Angiotensin II receptor antagonists	32677	3098 (32.6%)	5574 (24.0%)	<0.0001
Diuretics	34681	3683 (38.8%)	5902 (25.5%)	<0.0001

Data are mean (SD) or number (%). Some percentages do not add up to 100 because of rounding. eGFR=Glomerular Filtration Rate estimated from the CKD-EPI equation; NYHA=New York Heart Association (NYHA) Functional Classification; HDL cholesterol=high-density lipoprotein cholesterol; LDL cholesterol=low-density lipoprotein cholesterol.

*Canada, South Africa, Australia and United Kingdom

Table 2: Five-year event rates and crude and adjusted hazard ratios (95% CI) by diabetes status

	Diabetes	No diabetes	p-value
Cardiovascular death, myocardial infarction or stroke			
event rate (n/N, %)	1035/9393 (11.0%)	1772/22985 (7.7%)	
unadjusted HR	1.48 (1.37, 1.60)	1.00 (-)	<0.0001
adjusted HR	1.28 (1.18, 1.39)	1.00 (-)	<0.0001
All-cause death			
event rate (n/N, %)	990/9393 (10.5%)	1554/22985 (6.8%)	
unadjusted HR	1.61 (1.48, 1.74)	1.00 (-)	<0.0001
adjusted HR	1.38 (1.27, 1.50)	1.00 (-)	<0.0001
Cardiovascular death			
event rate (n/N, %)	650/9393 (6.9%)	969/22985 (4.2%)	
unadjusted HR	1.69 (1.53, 1.87)	1.00 (-)	<0.0001
adjusted HR	1.39 (1.25, 1.54)	1.00 (-)	<0.0001
Myocardial infarction (fatal or not)			
event rate (n/N, %)	390/9393 (4.2%)	716/22985 (3.1%)	
unadjusted HR	1.37 (1.21, 1.55)	1.00 (-)	<0.0001
adjusted HR	1.26 (1.10, 1.43)	1.00 (-)	0.0007
Stroke (fatal or not)			
event rate (n/N, %)	252/9393 (2.7%)	434/22985 (1.9%)	
unadjusted HR	1.47 (1.26, 1.71)	1.00 (-)	<0.0001
adjusted HR	1.29 (1.09, 1.52)	1.00 (-)	0.0024
Hospital admission for heart failure			
event rate (n/N, %)	608/9064 (6.7%)	1039/22280 (4.7%)	
unadjusted HR	1.49 (1.35, 1.65)	1.00 (-)	<0.0001
adjusted HR	1.15 (1.03, 1.28)	1.00 (-)	0.0110
Coronary revascularisation			
event rate (n/N, %)	804/9070 (8.9%)	1722/22282 (7.7%)	
unadjusted HR	1.18 (1.09, 1.28)	1.00 (-)	<0.0001
adjusted HR	1.14 (1.04, 1.25)	1.00 (-)	0.0035

HR= hazard ratio; 95% CI=95% confidence interval
n/N=number of events/number of patients
Covariates for the adjusted model: age, sex, geographical region, smoking status, body-mass index, treated hypertension, baseline systolic blood pressure, eGFR, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting, number of diseased coronary vessels at baseline, peripheral artery disease at baseline, previous stroke or transient ischemic attack, previous hospital admission for (or symptoms of) heart failure, left ventricular ejection fraction, atrial fibrillation or flutter, and baseline drugs (any antiplatelet, statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers and diuretics).

Table 3. Five-year outcomes by diabetic status within geographical subgroups

	n/N (event rates, %)		HR (95% CI)	
	Diabetes	No diabetes	(Diabetes vs no diabetes)	p-value
Cardiovascular death, myocardial infarction or stroke				0.7964[$]
Europe	559/4776 (11.7%)	1019/13426 (7.6%)	1.29 (1.15, 1.44)	<0.0001
Gulf countries	81/890 (9.1%)	41/603 (6.8%)	1.40 (0.93, 2.11)	0.1061
India	28/303 (9.2%)	21/403 (5.2%)	1.51 (0.80, 2.84)	0.2010
East Asia	122/1462 (8.3%)	211/3498 (6.0%)	1.32 (1.05, 1.66)	0.0194
Central and South America	98/788 (12.4%)	125/1382 (9.0%)	1.34 (1.01, 1.78)	0.0415
Commonwealth (outside of Asia)	147/1174 (12.5%)	355/3673 (9.7%)	1.18 (0.96, 1.45)	0.1222
Cardiovascular death				0.5342[$]
Europe	355/4776 (7.4%)	549/13426 (4.1%)	1.42 (1.23, 1.63)	<0.0001
Gulf countries	55/890 (6.2%)	27/603 (4.5%)	1.31 (0.79, 2.19)	0.2929
India	23/303 (7.6%)	16/403 (4.0%)	1.58 (0.75, 3.31)	0.2263
East Asia	65/1462 (4.4%)	96/3498 (2.7%)	1.59 (1.15, 2.21)	0.0055
Central and South America	67/788 (8.5%)	90/1382 (6.5%)	1.21 (0.86, 1.71)	0.2726
Commonwealth (outside of Asia)	85/1174 (7.2%)	191/3673 (5.2%)	1.22 (0.92, 1.60)	0.1646
All-cause death				0.0887[$]
Europe	547/4776 (11.5%)	893/13426 (6.7%)	1.41 (1.26, 1.58)	<0.0001
Gulf countries	85/890 (9.6%)	34/603 (5.6%)	1.65 (1.07, 2.55)	0.0246
India	34/303 (11.2%)	22/403 (5.5%)	1.83 (1.00, 3.35)	0.0495
East Asia	101/1462 (6.9%)	153/3498 (4.4%)	1.55 (1.19, 2.01)	0.0010
Central and South America	87/788 (11.0%)	127/1382 (9.2%)	1.05 (0.79, 1.41)	0.7289
Commonwealth (outside of Asia)	136/1174 (11.6%)	325/3673 (8.8%)	1.20 (0.97, 1.49)	0.0955
Myocardial infarction (fatal or not)				0.9537[$]
Europe	187/4776 (3.9%)	388/13426 (2.9%)	1.24 (1.03, 1.49)	0.0213
Gulf countries	32/890 (3.6%)	13/603 (2.2%)	1.41 (0.71, 2.81)	0.3228
India	10/303 (3.3%)	10/403 (2.5%)	1.08 (0.38, 3.06)	0.8825
East Asia	41/1462 (2.8%)	82/3498 (2.3%)	1.13 (0.77, 1.67)	0.5376
Central and South America	49/788 (6.2%)	57/1382 (4.1%)	1.58 (1.05, 2.37)	0.0270
Commonwealth (outside of Asia)	71/1174 (6.0%)	166/3673 (4.5%)	1.26 (0.93, 1.69)	0.1341
Stroke (fatal or not)				0.9180[$]
Europe	141/4776 (3.0%)	256/13426 (1.9%)	1.26 (1.01, 1.56)	0.0385
Gulf countries	13/890 (1.5%)	5/603 (0.8%)	2.88 (0.88, 9.39)	0.0803
India	4/303 (1.3%)	2/403 (0.5%)	-	-
East Asia	43/1462 (2.9%)	78/3498 (2.2%)	1.30 (0.88, 1.90)	0.1889
Central and South America	22/788 (2.8%)	22/1382 (1.6%)	1.45 (0.77, 2.72)	0.2471
Commonwealth (outside of Asia)	29/1174 (2.5%)	71/3673 (1.9%)	1.20 (0.75, 1.90)	0.4496
Hospital admission for heart failure				0.7817[$]
Europe	402/4632 (8.7%)	765/13057 (5.9%)	1.14 (1.00, 1.30)	0.0453
Gulf countries	42/868 (4.8%)	20/586 (3.4%)	1.45 (0.80, 2.61)	0.2194
India	11/299 (3.7%)	11/393 (2.8%)	0.82 (0.31, 2.17)	0.6916
East Asia	63/1409 (4.5%)	93/3391 (2.7%)	1.57 (1.12, 2.18)	0.0082
Central and South America	38/746 (5.1%)	47/1324 (3.5%)	1.10 (0.69, 1.77)	0.6902
Commonwealth (outside of Asia)	52/1110 (4.7%)	103/3529 (2.9%)	1.16 (0.81, 1.68)	0.4193

HR= hazard ratio; 95% CI=95% confidence interval
Commonwealth countries in CLARIFY are Canada, South Africa, Australia and United Kingdom

Covariates the adjusted subgroup models: age, sex, smoking status, body-mass index, treated hypertension, baseline systolic blood pressure, eGFR, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting, number of diseased coronary vessels at baseline, peripheral artery disease at baseline, previous stroke or transient ischemic attack, previous hospital admission for (or symptoms of) heart failure, left ventricular ejection fraction, atrial fibrillation or flutter, and baseline drugs (any antiplatelet, statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers and diuretics).
[$] p-value for interaction between geographical region and diabetes (adjusted model)