Yes, hyperglycaemia is indeed a modifiable cardiac risk factor: so says Mendel

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This editorial refers to ‘Mendelian randomization analysis supports the causal role of dysglycaemia and diabetes in the risk of coronary artery disease’, by S. Ross et al., on page 1454.

The presence of diabetes is clearly associated with excess cardiovascular risk. However, much controversy exists over whether current glucose-lowering strategies in type 2 diabetes mellitus in fact reduce cardiovascular event rates. Older data had suggested that lowering blood glucose reduced ischaemic events, but contemporary trials were largely of European ancestry, so similar analyses in other racial and ethnic groups would be of added value.

Ross et al. have now published what will become a classic paper in the field of diabetes and cardiovascular risk. Using the powerful technique of Mendelian randomization, these authors show that a lifetime of lower glucose levels is indeed associated with a lower risk of adverse cardiovascular outcomes. Particular genetic variants—known as single nucleotide polymorphisms (SNPs)—which have been associated with diabetes, HbA1c levels, and fasting glucose were examined. The causal effect of diabetes on the risk of coronary artery disease (CAD) was estimated at an odds ratio (OR) of 1.57 (P = 0.008) and, importantly, per 1% increase, the HbA1c was associated with an OR of 1.53 (P = 0.023) in the risk of CAD. Somewhat surprisingly, SNPs associated with fasting glucose levels were not significantly associated with CAD risk (though the analysis had very limited statistical power for this particular variable, so this null finding should be interpreted with caution).

The authors carefully adjusted for genetic effects of the diabetes-associated SNPs under study on other cardiovascular risk factors such as hypercholesterolaemia, hypertension, and obesity; without this step, a direct independent effect of diabetes on cardiac risk could not be assumed. With adjustment for lipids and body mass index, which previous studies of diabetes had not done as elegantly, the SNPs associated with diabetes remained significantly associated with CAD (OR 1.63, P = 0.002), though the association with HbA1c was no longer statistically significant (but was still directionally consistent). Not all potential confounders were available for adjustment. For example, smoking and waist-to-hip ratio were not incorporated, as the authors acknowledge among the limitations of this analysis. Also, it is worth mentioning that the patients included were largely of European ancestry, so similar analyses in other racial and ethnic groups would be of added value.

It is noteworthy that in the current study the degree of risk associated with diabetes is similar to what has been noted in prior observational analyses and meta-analyses, though with different populations and statistical techniques. It is comforting and reassuring to see so many different lines of evidence converging in support of diabetes and elevated levels of glycaemia being causally associated with CAD. Several other points about this analysis deserve mention. The use of Mendelian randomization essentially replicates a randomized double-blind clinical trial, with nature serving as the ultimate randomizer. These types of studies also allow the follow-up period to be essentially life-long, far surpassing what can be practically done in most randomized clinical trials. The genetic biobank data utilized in this study were freely available, thus allowing a very cost-effective and efficient method to address a hypothesis.

Whether specific lifestyle, medical, or surgical approaches to improving glycaemic control provide similar benefit to genetically influenced glucose levels would need to be proved, but this supposition appears likely if hypoglycaemia or other potential side effects do not create counterbalancing effects. Interestingly, in the analysis by Ross et al., there were no significant differences according to whether the effect of the genetic loci was on beta-cell function or insulin resistance. This finding provides strong indirect evidence...
Mendelian Randomization Results

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Figure 1  Mendelian randomization studies have demonstrated which putative cardiovascular risk factors really do appear to be causal and which appear to be merely associative, at least to the extent that these factors have been demonstrated to be modifiable in randomized clinical trials, with resultant reductions in cardiovascular event rates; shown in green are factors that remain unproven in clinical trials at this point in time, although there are studies ongoing in some cases; shown in red are factors which have been shown in clinical outcome trials not to be modifiable cardiovascular risk factors. CRP, C-reactive protein; Lp(a), lipoprotein(a); Lp-PLA<sub>2</sub>, lipoprotein-associated phospholipase A<sub>2</sub>; sPLA<sub>2</sub>, secretory phospholipase A<sub>2</sub>

that the exact mechanism of glucose lowering may not matter, again assuming it can be accomplished safely.

Questions that the current study design could not answer include whether the relationship between HbA<sub>1c</sub> and cardiovascular risk is linear or non-linear. That is, would the excess risk conferred by moving from an HbA<sub>1c</sub> of 7% to 8% be similar to moving from 8% to 9%? That knowledge would be important from a therapeutic standpoint in terms of thresholds at which to initiate treatment and also to determine HbA<sub>1c</sub> targets. However, since these authors lacked individual level data, they could not perform that type of analysis, but potentially it could be done in the future.

The study by Ross and colleagues further reinforces the value of Mendelian randomization studies to elucidate what risk factors are truly causal as opposed to being merely associative. Mendelian randomization is a powerful example of instrumental variable analysis that, when done properly, largely circumvents the confounding and reverse causation that often plagues observational analyses. Prior Mendelian randomization work has shown that LDL-cholesterol is on the causal pathway towards development of CAD. More recently, inactivating mutations of Niemann–Pick C1-like 1 (NPC1L1) protein have been associated with lower cardiovascular risk. The value of this genetic study was confirmed in a large randomized clinical trial that subsequently demonstrated the ability of ezetimibe (which inhibits the activity of NPC1L1 protein) to reduce the risk of ischaemic events. Mendelian randomization studies showed that triglycerides (or more specifically their associated apolipoproteins) are also on the causal pathway for CAD, and large cardiovascular outcome studies are underway. In contradistinction, the HDL-associated SNPs studied to date do not support a causal role for HDL-cholesterol in CAD. The negative clinical trials of HDL-raising drugs confirm that lack of causality.

Now, the present study by Ross and colleagues extends these previous observations regarding other putative cardiac risk factors and the relationship to CAD risk to diabetes and HbA<sub>1c</sub>, demonstrating that better glycaemic control (when achieved naturally through genetic determinants) does correlate with lower cardiovascular risk (Figure 1). As such, this paper by Ross et al. is a major contribution to the field of diabetes and cardiovascular prevention and strongly supports ongoing efforts to lower HbA<sub>1c</sub> through lifestyle, pharmacological, and surgical means while awaiting randomized clinical trials that validate specific approaches to reduce cardiovascular event rates.

Conflict of interest: D.L.B. has reported the following relationships: Advisory Boards: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences. Boards of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care. Chair: American Heart Association Get With The Guidelines Steering Committee. Data Monitoring Committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute. Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Associate Editor; Section Editor, Pharmacology), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today’s Intervention), WebMD (CME steering committees); other: Clinical Cardiology (Deputy Editor). Research funding: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi Aventis, St. John Medical, The Medicines Company. Unfunded Research: FlowCo, PLx Pharma, and Takeda.

References


Large protruding thrombus over left atrial appendage occlusion device successfully treated with apixaban

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This was a 61-year-old male patient with permanent non-valvular atrial fibrillation (NVAF) and CHA2DS2VASc of 5 with a relative contraindication to oral anti-coagulation (OAC) for previous intracranial haemorrhage. Left atrial appendage occlusion (LAAO) was successfully conducted with implantation of a 25-mm Amplatzer Amulet. Patient was discharged with aspirin and clopidogrel. At 3 months, trans-oesophageal echocardiography (TEE) did not show device thrombosis and clopidogrel was therefore discontinued. At 9 months, a control TEE exhibited a 25 × 23 × 1.3 mm protruding and mobile device thrombus (Panels A and B). In our opinion, the two most plausible explanations for the thrombus formation were the doubtful treatment compliance of the patient and the presence of spontaneous echo-contrast in the left atrium. The patient was treated with apixaban 5 mg/12 h for 6 months with progressive thrombus resolution and no clinical events (Panels C and D). Considering the risk of intracranial bleeding, apixaban was stopped and aspirin was restarted again without further complications. To the best of our knowledge, this is the first report of an LAAO device thrombosis successfully treated with apixaban. Since apixaban has shown a good balance among efficacy for stroke prevention and safety for bleeding events in previous reports, this alternative might be a very valid temporary option to prevent or manage device thrombosis in patients with contraindication to conventional OAC.

2D (Panel A) and 3D (Panel B; Supplementary material online, Video S1) TEE image of the protruding thrombus attached to the LAA occlusion device. Two-dimensional TEE image of the partially and completely thrombus resolution after 3 months (Panel C) and 6 months (Panel D) therapy with apixaban, respectively.

Supplementary material is available at European Heart Journal online.

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