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Atherosclerotic cardiovascular disease and heart failure: Determinants of risk and outcomes in patients with diabetes☆

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ABSTRACT

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality for patients with diabetes mellitus (DM). Although the burden of atherosclerotic CVD (ASCVD) is well documented, heart failure (HF) has been an under-appreciated CVD complication of DM. However, as more patients with DM live longer and survive acute ASCVD events, the distribution of CVD complications has evolved. This review summarizes the epidemiology of DM, the relative risk and prognosis of both ASCVD and HF following a diagnosis of DM, and the likelihood of cause-specific CVD mortality in patients with DM.

Contents

Those diagnosed with diabetes mellitus (DM) have a two out of three chance of developing some form of cardiovascular disease (CVD) over the course of their lifetime.[1] In fact, CVD – most commonly manifest by its key clinical entities of atherosclerotic CVD (ASCVD) and/or heart failure (HF) – represents the single largest cause of morbidity and mortality for these patients.[2] Although the causal link between diabetes and ASCVD is well established, the pathophysiological relationship to HF is more nebulous, and is a frequently neglected complication of DM. Additionally, as ASCVD risk factors, including smoking, blood pressure and hyperlipidemia are better managed, the incidence rates of ASCVD in those with DM has slowed and in some countries, actually decreased. In contrast, the incidence of HF appears to be accelerating.[3] Recognition of a patient's propensity for these outcomes – individually or combined – may facilitate earlier detection, personalize therapy and modify risk. The availability of newer pharmacotherapies that differentially impact CVD risk, as well as a renewed focus of modifiability of traditional risk is expanding the gluco-centric approach to treatment. This review summarizes the

Abbreviations and acronyms: AF, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL-C, low-density lipoprotein cholesterol; MALE, major atherosclerotic limb event; MI, myocardial infarction; PA, physical activity; PAD, peripheral arterial disease; SBP, systolic blood pressure; US, United States.

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epidemiology of diabetic complications, summarizes the burden of CVD in patients with DM, identifies high-risk features for the development of either ASCVD or HF and highlights the implications of these findings.

Diabetes epidemiology

The prevalence of DM has nearly quadrupled in the last 35 years with recent increases driven largely by low and middle income countries.[4] Diabetes currently affects 1 in 10 adults in the United States (US) and was associated with a $320 billion national economic burden in 2012.[5] Overall incidence rates slowed for the first time in the US between 2008 and 2014, however this was not the case for younger age strata, nor in non-white racial groups where the incidence continues to rise alongside disproportionate levels of obesity.[6] Extrapolation of the obesity-DM propensity suggests that with 85% of the US population currently overweight or obese, DM could affect as many as 1 in 3 Americans by 2050.[7] The situation is more alarming for low and middle-income countries where overall incidence continues to accelerate and global prevalence is now highest overall – somewhat, but not solely, explained by obesity and epigenetic changes surrounding dietary intake.[6]

First presentation of CVD in patients with DM

Similar to the unselected general population, coronary heart disease (CHD) is the most common initial presentation of CVD in patients with DM. The most contemporary and detailed evaluation of CVD incidence comes from a cohort of over 40,000 patients with DM (total sample 1.9 million) from the UK linked medical record CALIBER program.[8] Over a median follow up of 5.5 years, almost 1 in 5 participants with DM sustained a CVD event with over 40% related to CHD: stable angina (12%), non-fatal myocardial infarction (MI;11%), non-specified CHD (10%) unstable angina (4%), or unheralded CHD death (4%). Whilst peripheral artery disease (PAD) was reported in the manuscript as the most common 'single' diagnosis at 16%, presenting anywhere along the clinical spectrum of CHD was more than twice as likely. Furthermore, when adding the presentations of ischemic stroke to transient ischemic attack(TIA), the incidence of combined ischemic cerebrovascular disease (14%) was similar to heart failure (HF;14%). See Fig 1(A). Compared with matched controls, DM increased the risk of presenting with HF, CHD or stroke by 50% over the duration of follow up. In comparison, a new diagnosis of PAD was almost three times more common in participants with DM compared to matched controls (HR 2.98, 95%CI 2.76–3.22). The magnitude of this hazard may be exaggerated by a younger comparator group (mean age 45–48 vs. 61–65) and the modest rates of smoking – two key determinants of PAD in the general population. All CVD events occurred earlier in patients with DM (driving comparative cumulative incidence) and of those, stable angina and unstable angina occurred earliest at a median of 2.5 and 2.8 years respectively, followed by HF (2.8 years) and PAD (3.5 years). In patients <60 years of age with diabetes, females were more likely to sustain non-fatal MI, stable angina or PAD compared with males.

RISK of developing CVD in patients with DM

CHD

Elegant Framingham observations first revealed patients with DM were two to three times more likely to develop CHD than those without.[9] Numerous subsequent studies have confirmed the strength and direction of this association, however the magnitude of the relative risk remains of interest. Seminal work from Haffner et al. in the 'East-West' study in Finland showed that after modest adjustment (age, sex, smoking, hypertension and lipid profile) the hazard ratio for MI at 7-year follow up for participants with uncomplicated DM was the same for non-DM participants with established CHD.[10] These findings provided the basis for a recommendation in the 2001 US treatment guidelines[11] to ascribe 'CHD risk equivalent' status to patients with DM. This completely re-framed the approach to primary prevention in these patients, and was confirmed in other cohorts,[12,13] however subsequent more recent studies have weakened the 'risk equivalent' status.[14] Contemporary longitudinal data suggest diabetes confers a generic risk of between 1.5 and 2 times the general population however may reach near coronary-equivalence (>2.5 x) in the context of >10 years duration.[15] Whilst the varying risk ratios are impacted upon by myriad differences in study sample size, duration of follow up, inclusion criteria, era of treatment(both for DM and CHD) and degree of adjustment in analyses, there is greater recognition of the heterogeneity of risk that DM imparts.

Large participant-level collaborative meta-analyses involving patients with DM have shown women to be at greater relative risk of CHD than males. Data from the Emerging Risk Factors Collaboration, which evaluated 102 trials of ~50,000 patients with DM, showed females were 1/3 more likely to sustain fatal or non-fatal CHD than males over 10 year follow up (HR 2.59 (95%CI 2.29–3.93) vs. HR 1.89 (95%CI 1.73–2.06), $p < 0.0001$).[16] This relationship was numerically

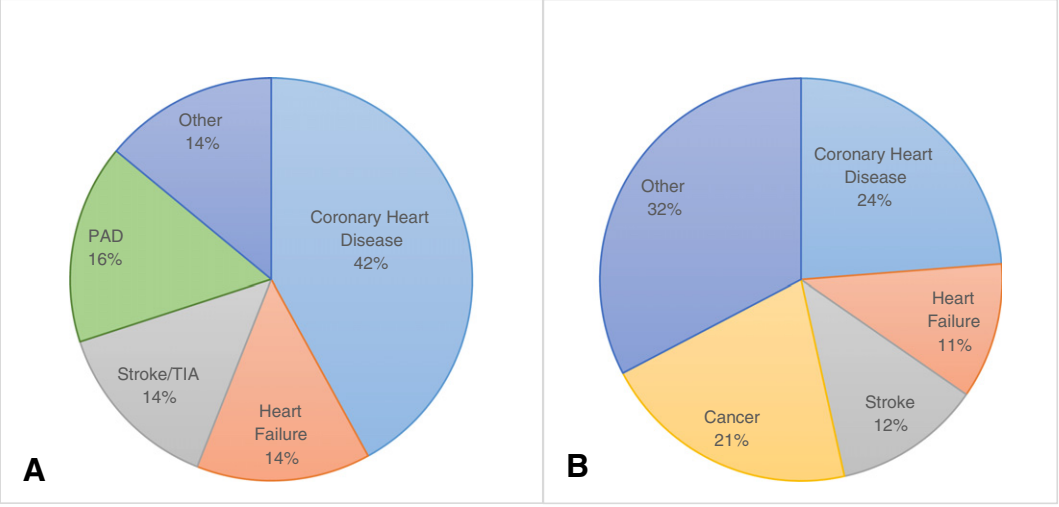

Fig 1. (A) Incident presentation of cardiovascular disease in patients with Type II diabetes. (Gregg Lancet 2018; Wang Circulation 2016; Baena-Diaz Diabetes Care 2016) and (B) cause-specific mortality in patients with Type II diabetes (Shah Lancet 2015).

consistent in a subsequent pooled analysis of close to 20,000 events confined to CHD death only (Female HR 3.00, (95%CI 2.68–3.36) vs. Male HR 2.1, (95%CI 1.96–2.25), $p < 0.0001$).[17] Given the higher absolute CHD risk observed in males, the increased relative risk conferred by DM in females (particularly in younger cohorts) approaches the event rates of males without DM. This, and a decreasing relative risk as a function of increasing age-strata, is evidence of erosion of the 'protection' usually afforded to younger females from premature CHD. Unifying explanations for the disparate sex outcomes remain to be elucidated however under-recognition and under-treatment of CVD risk in women may have a role.[18] This is supported by a cohort study in China where a screen-detected diagnosis of DM conferred no difference in relative risk for CHD (HR 1.83, (95%CI 1.70–1.98) vs. HR 1.71, (95%CI 1.58–1.84), $p = 0.2$) yet an established diagnosis on-treatment did (HR 2.67 (95%CI 2.35–3.03) vs. HR 2.15 (95%CI 1.88–2.45), $p = 0.02$ interaction).[19] Data from the National Diabetes Audit in the UK showed that even after adjustment, women were less likely to receive guideline directed care and/or reach treatment targets in the context of DM and CVD risk.[20] Whether this represents unconscious treatment bias, or a differential effect by sex on severity of DM remains unclear.

A large body of cohort and clinical trial evidence supports a causal association between dysglycemia and CHD.[21,22] In a contemporary longitudinal dataset from the UK EHR CALIBER program which included 34,000 participants with DM, increasing HbA1c conferred a consistent increase in risk for all CHD endpoints (stable and unstable angina, non-fatal MI, unheralded CHD death).[8] The additional hazard varied by type of coronary presentation but even modest elevations of HbA1c (>7.5%), after adjustment, were associated with an additional 60–90% relative risk compared to those achieving target control. Similar results were demonstrated in a large cohort of over 250,000 participants from the Swedish National Diabetes Register where HbA1c was linearly associated with increased risk of MI.[23] Notably this excess risk commenced from an A1c of 6.5% - a level of control that is rarely obtained in clinical practice and is not currently recommended in consensus guidelines given the competing risk of hypoglycemia. Impaired fasting glycemia is often viewed as a surrogate for peripheral insulin resistance but is also a coarse metric for glycemic exposure. In the Emerging Risk Factor Collaboration meta-analysis, after adjustment for traditional CHD risk factors, every additional 1 mmol/L over a fasting glucose of ~5.5 mmol/L was associated with an additional 12% risk of CHD (HR 1.12, 95%CI 1.08–1.15).[16]

Traditional risk factors for CHD, either untreated or not to target, remain a significant contributor to excess risk observed in DM. Data from the Swedish National Diabetes Register showed that beyond dysglycemia, elevated low-density lipoprotein cholesterol (LDL-C) and elevated systolic blood pressure (SBP) were the next most important contributors to risk and were linearly associated with MI.[23] Cigarette smoking and reduced physical activity (PA;<3 times/week) remained important relative contributors to propensity for MI. Whether these risk factors are additive to, or synergistic with DM remains contentious. Data from the Prospective Studies collaboration demonstrated separate linear relationships between occlusive vascular death and systolic blood pressure, body mass index (BMI) and LDL-C, in both diabetic and non-diabetic subgroups.[17] Particularly in the BMI and LDL-C regression plots, and in the SBP to a lesser extent, the diabetic data points were all displaced vertically toward higher relative risk despite a similar regression slope; the corollary being the presence of any of these risk factors is likely to convey similar relative risk but greater absolute relevance in the context of DM [see Fig 2].

PAD

Almost 1 in 5 patients with DM are impacted by PAD[24] and DM is implicated in up to 1/3 of the total PAD burden.[25] The relative risk of incident PAD ranges from two to four fold the general population although this varies depending on the definition of PAD as up to 50% of patients with PAD are asymptomatic by ankle-brachial index criteria.[26,27]

The impact of dysglycemia on propensity for ASCVD appears to be greatest for PAD than either stroke and MI. In the CALIBER program dataset of 34,000 participants with DM, increasing HbA1c strata conferred a consistent, monotonic increase in risk for all incident CHD, stroke and PAD presentations however the hazard imparted by an A1c >7.5% was greatest for PAD (HR 3.72, 95%CI 3.33–4.15) followed by stroke (HR 1.85, 95%CI 1.5–2.27) and non-fatal MI (HR 1.79, 95%CI 1.58–2.03).[8] Further insight into the PAD-dysglycemia relationship comes from the observation that patients with DM and PAD are more likely to have retinopathy or nephropathy than they are concomitant CHD; a stark contrast to the notion of 'coronary equivalence' conferred by a diagnosis of PAD in the general population.[28]

Whilst there is a consensus document from the American Heart Association suggesting a sex-difference in PAD risk for patients with DM,

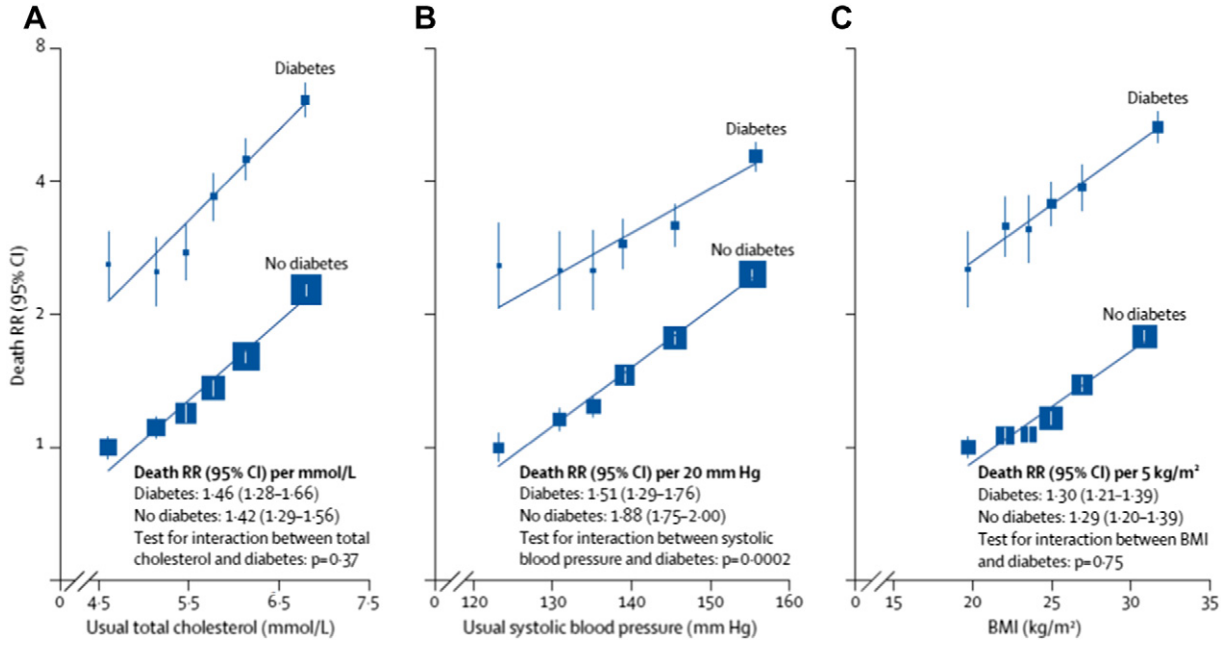

Fig 2. Amplified absolute risk of traditional risk factors for occlusive death (Gnatiuc Lancet 2018).

there is only modest data to support this assertion.[29] The earliest observations come from 30-year follow up of the original Framingham cohort where females were relatively more likely to develop intermittent claudication at 2 year follow up than age and risk factor adjusted males (HR 2.4, 95%CI 1.4–4.2).[30] Total events were <100 (consistent with the reported broad confidence intervals) and there was no adjustment for DM duration or treatment, and is of uncertain relevance given the era studied. More recently, a univariate analysis from the coronary revascularization trial, Bari 2D, showed females were more likely to sustain incident PAD during a median follow up of 4.6 years (HR 1.27, 95%CI 1.10–1.92) however this relationship weakened after adjustment for HbA1c.[31] Other linked registry data showed a female predisposition to a first presentation of PAD although this was only significant on sensitivity analysis for those <60 years of age (HR 5.11 (95%CI 4.05–6.44) vs. 3.77 (95%CI 3.21–4.44), $p < 0.001$). The significant impact of a major atherosclerotic limb event (MALE) on morbidity and mortality, and more recently its susceptibility to modification,[32] has generated renewed interest in PAD as a trial endpoint and in time, ought to clarify the magnitude of any sex-based differential risk in DM.

Stroke

Diabetes has consistently been linked to an increased risk of all-cause stroke however this is stronger for ischemic (HR 2.27, 95%CI 1.95–2.65) than hemorrhagic events (HR 1.56, 95%CI 1.19–2.05).[16] Although atherosclerosis, and thus DM, is fundamental to the pathophysiology of medium to large artery stroke, it has also been associated with lacunar infarcts,[33] as well as thromboembolic strokes[34] – the lattermost at least in part related to an excess of atrial fibrillation (AF) in patients with diabetes.[35]

Two large meta-analyses have been performed; one collaborative patient-level, and another a mixture of patient and trial-level analysis. Both provide some insight into differential risk of stroke among subgroups of patients with diabetes but suffer from the limitations around stroke event classification with up to 50% of stroke events listed as 'unclassified'.[16] Interaction testing revealed women were more likely to sustain an ischemic stroke (Female HR 2.83, (95%CI 2.35–3.4) vs. Male HR 2.16, (95%CI 1.84–2.52), $p = 0.0089$) as were younger subjects (40–59 yo HR 3.74, (95%CI 3.06–4.58) vs. >70 yo HR 1.8, (95%CI 1.42–2.27), $p = 0.0001$) and those with the highest tertile BMI (T3 HR 2.90, (2.49–3.37) vs. T1 HR 1.9, (95%CI 1.5–2.4)).[16] In a second meta-analysis of over 12,000 stroke events from 64 cohorts, females were again shown to have higher relative risk for stroke (HR 1.27 (95%CI 1.10–1.46)).[36] Sensitivity testing showed this to be consistent across stroke type, and although there was a similar trend for younger females to be at higher incremental risk, the interaction p value did not reach significance (<60 yo HR 1.44, (95%CI 1.11–1.87) vs. >60 yo HR 1.11, (95%CI 0.81–1.52), $p = 0.35$). As described for *CHD* above, the reasons for a sex discrepancy in ASCVD remain to be fully elucidated. It is worth noting in the unselected population that males are at least 1/3 more at risk of stroke than females but by the 7th decade, stroke is more common in women.[37] The reversal of this epidemiology reflects a key perturbation in the risk profile acquired by women with DM.

Traditionally considered a strong causal factor in the development of microvascular disease, dysglycemia has become increasingly implicated in stroke incidence. A recent meta-analysis of >500,000 participants showed after adjusting for traditional risk factors, for every 1% increase in A1c there was a 17% increase in ischemic stroke incidence (HR 1.17, 95%CI 1.09–1.25).[38] Of note the trend of this association persisted into a 'pre-diabetes' A1c level thereby strengthening glycemic exposure as a linear risk continuum and also providing rationale for a lower threshold to commence risk modification. Similar findings were reported from the Swedish Registry which also found a linear relationship between HbA1c and stroke. Cox hazard models suggested HbA1c imparted the greatest relative contribution of any risk factor, with similar magnitude exerted by SBP, duration of DM, PA and AF.[23] Ischemic stroke has multiple underlying etiologies and thus it remains unclear whether the dominant effect of glycemic exposure is mediated through increased atheroma at the carotids,[39] higher rates of atrial fibrillation[40] or through a prothrombotic tendency,[41] or all of the above.

HF

Certainly HF is a common, yet often neglected complication of DM. Despite the seminal associative description[42] in Framingham occurring prior to the same cohort's ASCVD publication,[43] HF has failed to capture the same attention. Over the last two decades, this has led many to call HF the 'forgotten' or 'ignored' diabetic complication.[44,45] Contemporary studies suggest DM is implicated in 1 in 4 HF presentations however, when one considers only hospitalized HF patients, this approaches 1 in 2.[46,47] The earliest cohort studies reported relative risk ratios of 4 and 5 for incident HF, however current epidemiological studies suggest this figure is between 1.7 (HR 1.73, 95%CI 1.66–1.81)[48] and 2.5 (HR 2.5, 95%CI 2.3–2.7)[49] depending on the degree of adjustment – a figure that is strikingly similar to ASCVD relative risk. Adding to a lack of patient awareness of the association,[44] HF has been hitherto undervalued in DM CVD outcomes trials: a large percentage failing to include HF as an endpoint, frequently reporting its incidence in a nonsystematic way, and when reported, rarely elevating it to primary endpoint status.[50]

The pathological basis linking HF and DM remains to be fully clarified however there appears to be a bidirectional relationship: insulin resistance is an independent predictor of HF prognosis irrespective of a DM diagnosis and yet HF patients have altered glucose metabolism and high rates of insulin resistance which increase the risk of developing DM.[51] There is undoubtedly a disproportionate clustering of CHD and hypertension in patients with DM; the presence of just the former doubling the likelihood of incident, symptomatic HF.[49] These are causally and often temporally related in the context of large (or recurrent) MI, however severe and diffuse CHD is commonly seen in patients with DM and is a cause of, at times asymptomatic, left ventricular dysfunction. However beyond these clear links, there is an appreciation for an independent, potentially synchronous 'diabetic cardiomyopathy' associated with interstitial fibrosis and linked to derangements in metabolic function.[52,53] Traditional understanding has been that 'diabetic cardiomyopathy' is exclusively diastolic however animal models have shown both HF with reduced ejection fraction(EF;HFrEF) and HF with preserved EF(HFpEF)[54]; the former more tightly associated with DM severity and duration.[55] Whether there is a temporal, sequential relationship, i.e. diastolic then systolic dysfunction, or separate disease phenotypes remains to be understood, however it is clear there is a spectrum of HF in DM.[56]

The differential effect of sex on diabetic propensity for CVD appears to be particularly amplified for HF. In Swedish registry data from over 200,000 individuals, diabetes conferred a greater relative risk of HF in women than in men over a median follow up of 4.6 years.[57] As described earlier for ASCVD, this was particularly pronounced in a premenopausal age-group and reduced in magnitude over increasing age strata (Age < 55yo, female HR 4.59 (95%CI 3.50–6.02) vs male HR 2.07 (95%CI 1.73–2.48), $p < 0.001$). See Fig 3. A similar trend for predilection in younger females was observed in the CALIBER dataset however the interaction p value did not reach significance (HR 3.37 (95%CI 2.41–4.73) vs. HR 2.32 (95%CI 1.79–3.01), $p = 0.076$).[8] The basis for a differential risk exerted by sex in DM-related HF incidence remains unclear. Some have suggested women are required to 'deteriorate' further metabolically and put on more weight to achieve a DM threshold,[58,59] both of which are independently associated with increased risk of HF in the general population. Disappointingly the seminal paper from Kannel which highlighted HF as a key complication of DM also showed a greater than two-fold relative risk for women[42] however almost half a century later little has been found to explain this disparity.

Glycemic exposure has been recognized as a key predictor of incident HF for over 20 years.[22] Contemporary data from the Swedish registry shows a steep linear relationship with HbA1c; a 20% increase in

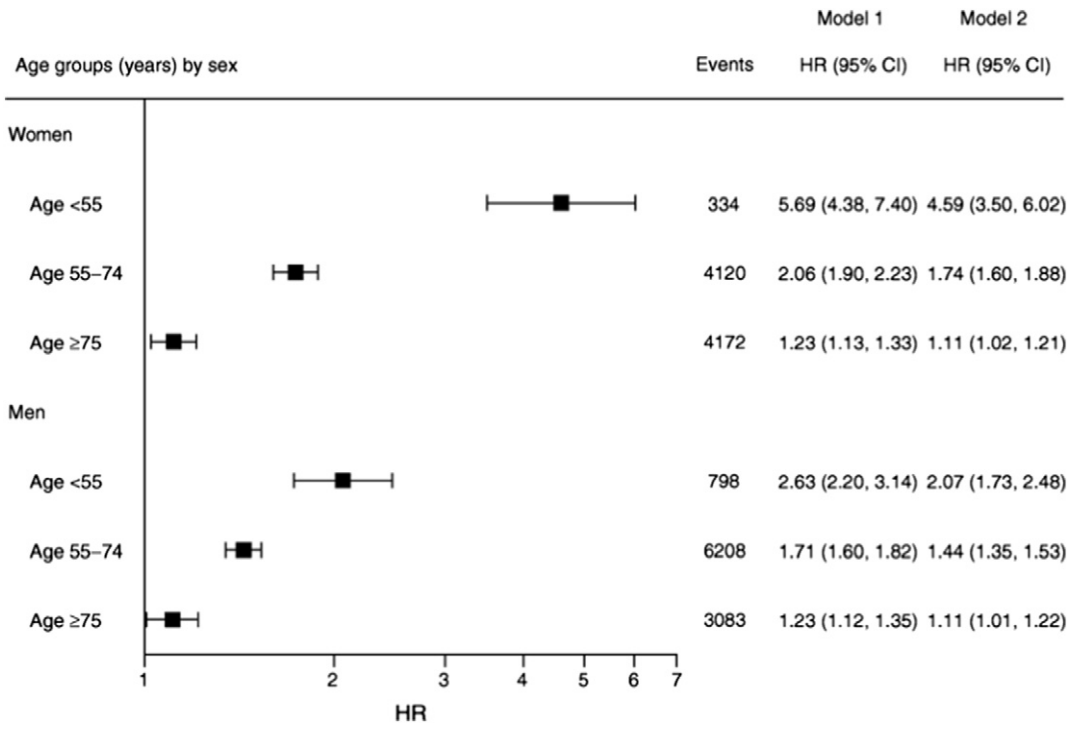

Fig 3. Risk of hospitalization among individuals with type 2 diabetes by sex and age group, compared with age- and sex-matched control individuals from the general population. Model 1 shows HRs adjusted for age and duration of diabetes. Model 2 shows HRs adjusted for age, duration of diabetes, income, education, marital status, immigration status, stroke, acute myocardial infarction, coronary heart disease, atrial fibrillation and renal dialysis or transplantation. Plots for Model 2 shown (Rosengren Diabetologia 2018).

relative risk of hospitalization for every 1% increment in HbA1c.[23] This figure was similar to both the 16% observed in the seminal UKPDS publication[22] and 15% reported in a large contemporary meta-analysis of over 14,000 incident DM-related HF events.[60] The biological relationship between glycemic exposure and HF remains incompletely understood and may be related to (or a marker of) a shift in free fatty acid myocardial metabolism[61] or the development of myocardial fibrosis, either directly or indirectly through production of reactive oxygen species.[62]

Other key risk factors identified from the Swedish registry were comorbid AF and renal disease, as well as increased BMI and reduced PA.[23] Of these, AF was twice as important as any other risk factor although the contribution from reverse causality is difficult to uncouple.

Prognosis of CVD in patients with DM

Patients with DM who develop CVD do worse on almost all metrics when compared to the general population. Certainly, MI in patients

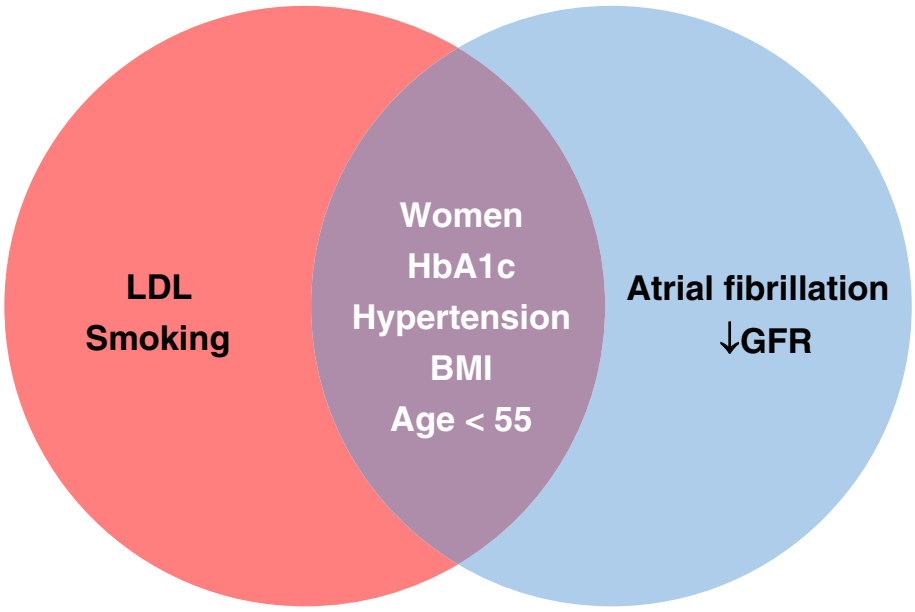

Fig 4. Risk factors for developing ASCVD (red), HF (blue) or both (purple). (Shah Lancet 2015; ERFC Lancet 2010; PSC Lancet 2018).

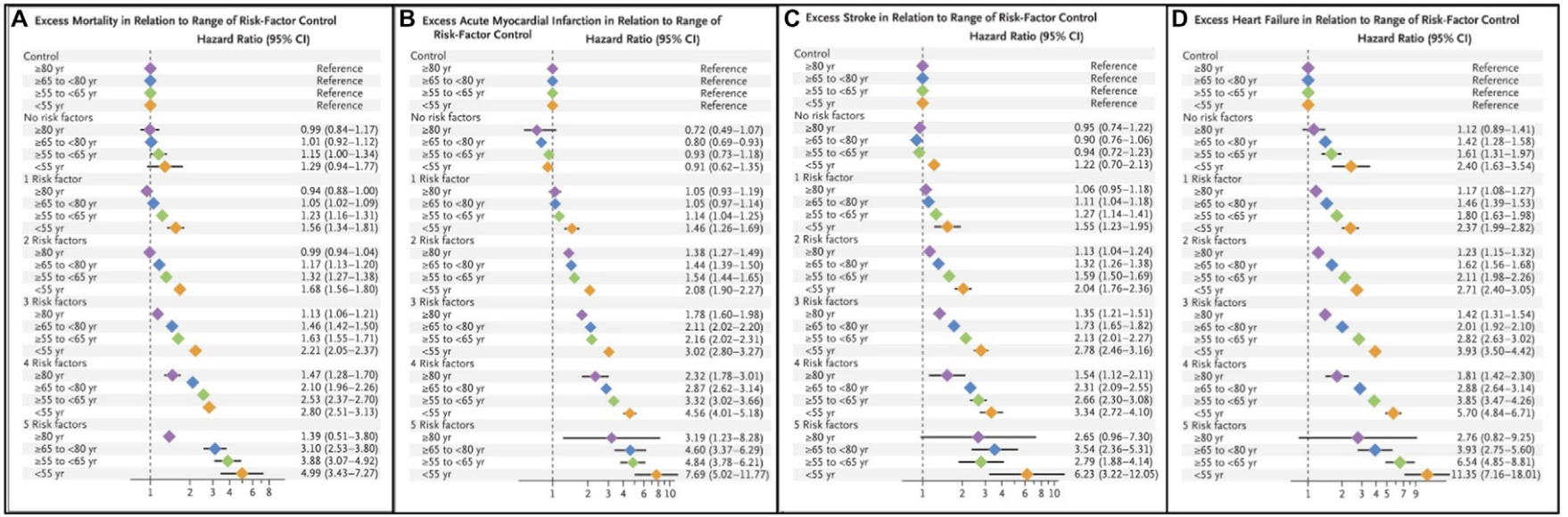

Fig 5. Adjusted hazard ratios for outcomes, according to age category and number of risk-factor variables outside target ranges, among patients with type 2 DIABETES, as compared with matched controls (Rawshani NEJM 2018).

with DM are associated with higher rates of re-infarction and almost twice the risk of mortality at 1 year.[63] At angiography their disease burden is higher,[64] their lesions more complex[65] and at follow up their atheroma is more likely to have progressed despite medical therapy.[66] Higher rates of stent thrombosis and re-stenosis following percutaneous intervention[67,68] may explain some of the comparative benefit derived from coronary artery bypass grafting, yet their overall outcomes remain inferior to the general population.[69] In those that develop stroke, DM is associated with increased disability, more frequent stroke recurrence, higher rates of readmission and greater all-cause mortality.[70,71] The outcomes are no better for PAD in part driven by a predilection for disease to occur in the smaller and more distal vessels; a key contributor to unsuccessful revascularization.[72] Concomitant neuropathy increases the probability of presenting later and with more advanced disease, and carries a greater likelihood of amputation - up to 12-fold the risk of the general population.[73]

The outcomes for HF patients with diabetes are sobering. Contemporary meta-analysis suggest that after adjustment, diabetes alone confers an additional 30% risk of all-cause mortality and an additional 35% increased risk of hospitalization over a median follow up of 3 years; findings that were consistent irrespective of ejection fraction.[74] Despite these marked differences in outcomes, prescription of guideline directed therapy appears similar to those without DM and there is no discernible heterogeneity in treatment effect from classical HF drugs such as beta blockers or angiotensin converting enzyme inhibitors/angiotensin receptor blockers.[75] Some of the disparity may come from ischemic-driven HF, which is associated with worse prognosis and is proportionally more common in patients with DM.[76] Underlying the grim prognosis of this subgroup was the finding that only half of the patients in the study with the combination of CHD, HF and DM were alive at 2 years.

CVD cause-specific mortality

Diabetes is associated with an approximate 75% increase in all-cause mortality with the average 60-year old person, regardless of sex, expected to lose 5 years of their life to the disease.[77] Current contemporary linked US data from the National Health Interview Survey of an unselected DM population, has consistently shown CVD to be the single largest contributor to cause-specific mortality. Of note, consistent across patients with and without DM, however, there has been an approximate 29% reduction in proportional mortality from CVD, a 16% reduction in cancer and equally sized proportional increase of 40% in non-vascular, non-cancer deaths (e.g. chronic lung disease, renal disease, accidents). In competing risk analysis of patients without pre-existing CVD, CHD remains the most likely specific mode of death for patients with DM.[78] Whilst this is similar to the general population, it was almost three times more likely to occur in patients with DM(HR 2.87, 95%CI 2.26–3.64) prematurely within a 10 year follow up of a pooled Spanish cohort of 55,292 patients (16% DM). The same directional trends, but of lesser magnitude, were present for premature stroke (HR 2.26, 95%CI 1.61–3.18) and HF deaths (HR 1.77, 95%CI 1.08–2.89). See Fig 1(B).

Implications

Despite cautious optimism in the overall slowing of DM incidence rates, reduced all-cause mortality and years of life lost for those with DM in high-income countries, we may yet be approaching the calm before the storm. In the US, growth in obesity and rising incidence of DM in the youngest age strata are key drivers of overall DM prevalence, but also represent additional, independent contributors to the risk of HF. Furthermore, diagnosis at an earlier age and generally reduced all-cause mortality are likely to increase time 'spent' with DM and drive complications most associated with glycemic exposure such as HF, microvascular disease and potentially PAD.[3] In low- and middle income countries where the incidence is accelerating and prevalence rapidly growing, without improvement in hitherto poor glycemic control, DM will remain a global problem of epidemic proportions.[3]

The differential CVD hazard of DM on younger people, and in particular on women, needs renewed attention. Whether the sex disparity is driven by unconscious treatment bias, a greater deterioration in risk factor or metabolic status, or a combination of these, needs clarification. An understanding of these differences may generate age and sex-specific prevention and treatment pathways, which may assist in mitigating incident CVD.

A swathe of new diabetes medication classes from successful outcome trials have provided renewed interest at moving beyond a gluco-centric algorithm for CVD risk reduction.[79] The prevention of HF and ASCVD are not mutually exclusive objectives (see Fig 4), however, it may be that an individualized approach to the prescription of these medications will evolve, e.g. an SGLT2 inhibitor in patients at greater relative risk of incident HF (obese, AF, females) or a GLP-1 receptor agonist in groups more at risk of ASCVD (dyslipidemia, cigarette smoking, hypertension). Despite the observed benefits of these agents occurring independent of glycemic control, the legacy lessons from the earliest intervention trials must provide an ongoing reminder for clinicians and patients to remain engaged with glycemic targets for long-term benefits. As the evidence above demonstrates, glycemic exposure remains the most potent risk factor for the development of both ASCVD and HF.

Although potentially expensive to setup and complex to maintain, multifaceted interventions have demonstrable long-term benefit in both heart failure and ASCVD. Elegant modelling from the Swedish diabetic registry, and others,[80] have shown that maintenance of LDL-C, SBP, HbA1c, smoking and BMI to 'normal' levels, either innately or through treatment, can ameliorate nearly all of the excess risk (ASCVD more than HF) associated with DM (see Fig 5).[23] Consistent with this finding has been the follow up analyses from Steno-2, a small but transformative study aimed at multifactorial risk factor control through individualized lifestyle intervention.[81] In this study, subjects who received an 8 year intensive intervention derived an additional 8.1 years of freedom from index CVD, a legacy CVD mortality benefit (driven by CHD) of 45% and reduction in the risk of HF hospitalization by 70% out to 21 years.[82]

Beyond trials of multifaceted intervention there is a critical need to address simple, traditional modifiable risk factors. Contemporary data from NHANES suggest this is difficult to achieve with <15% of patients with DM reaching target SBP, LDL-C, HbA1c and smoking cessation.[83] A systems approach is required: upstream public policy needs to facilitate intersectoral collaboration on primordial prevention; broader provider-level incentives for quality care targets need to be considered[84]; and a renewed and data-driven approach to understanding individual patient perceptions, propensity and motivation for behavior change. Patient-generated data and pragmatic trials in implementation science focused on Donabedian measures of quality[85] must usher in a new era of sustainable, scalable evidence-based approaches to stem the tide of DM-related CVD.

Statement of conflict of interest

None of the authors have any conflicts of interests with regard to this publication.

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