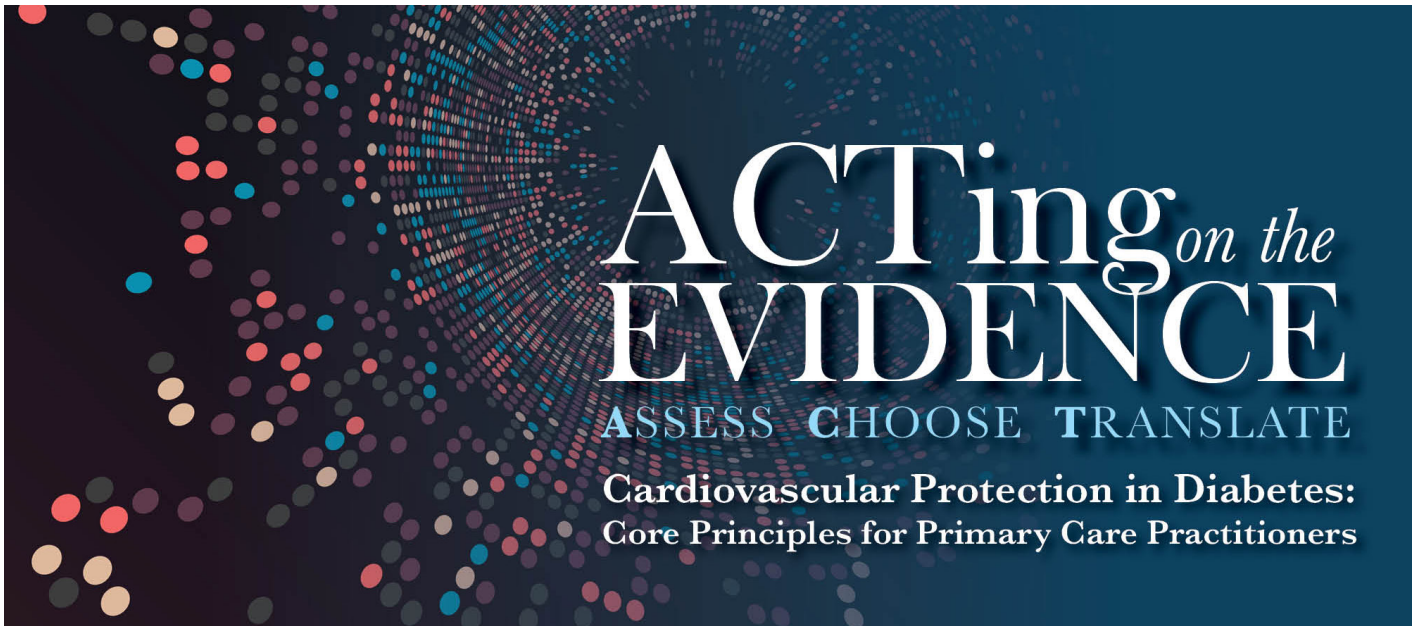

Cardiovascular and renal protection in diabetes

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Expert panel

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This report was made possible by an unrestricted educational grant from AstraZeneca. The content of the report is independent of the sponsor. The expert participated voluntarily.

Module 1: Cardiovascular prevention and heart failure in diabetes

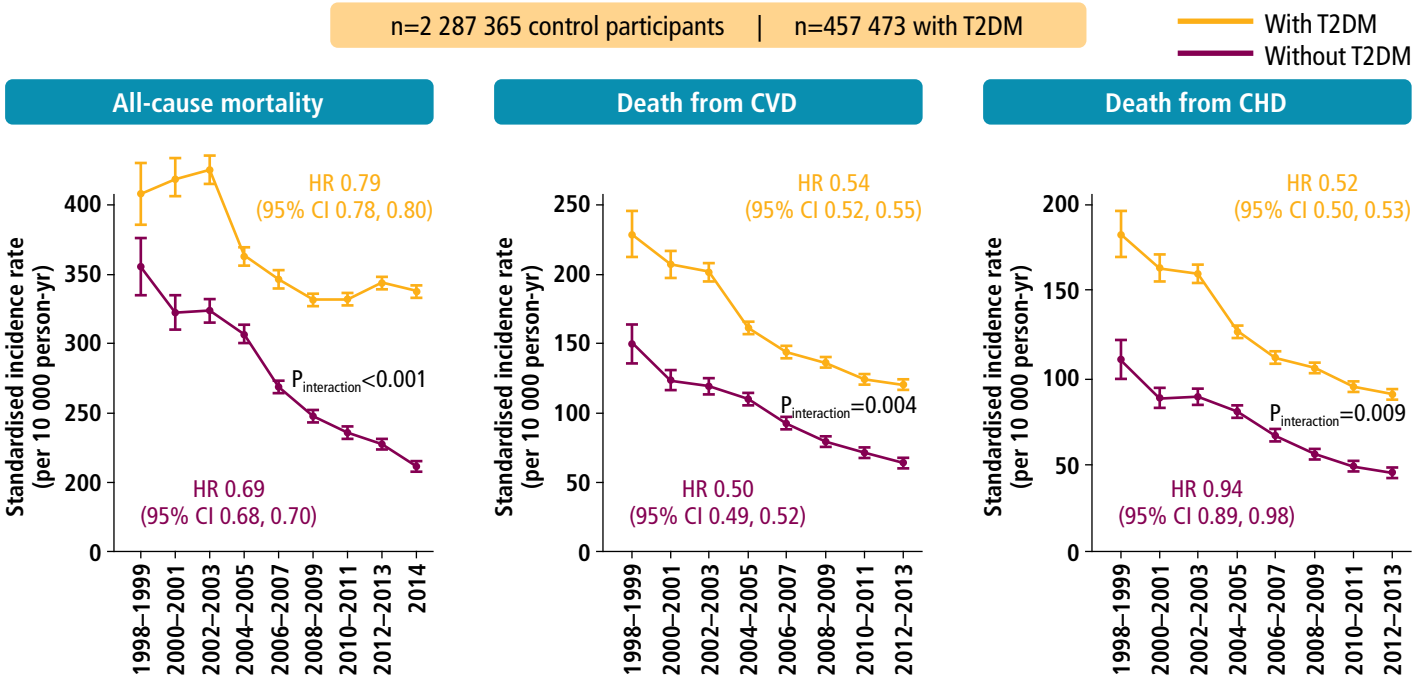
Introduction

Click here to watch the video

Diabetes is a large and growing global epidemic; it is currently estimated that globally, one in 11 adults has diabetes. Furthermore, it is estimated that there are currently 425 million people with diabetes worldwide, with a projected increase to 629 million by the year 2045. Of the global diabetes burden, 80% occurs in low- and middle-income countries, where some 30-80% of people with diabetes are undiagnosed.[1] It is well accepted that close on two-thirds of deaths in diabetes patients are attributable to cardiovascular disease (CVD).

Why is cardiovascular protection important in people with type 2 diabetes?

Swedish National Diabetes Register[2] data on almost half a million people with type 2 diabetes (T2DM) and more than two million control participants have shown, over the last 20 years, that the likelihood of dying from any cause, including CVD and coronary heart disease (CHD), has decreased in people both with and without T2DM. Importantly, however, people with diabetes continue to have about twice the risk for cardiovascular events as people without diabetes (Figure 1).



CVD: cardiovascular disease; CHD: coronary heart disease; T2DM: type 2 diabetes mellitus

Figure 1. Swedish National Diabetes Register: In patients with T2DM the gradient of increased mortality risk persists[2]

Other modules

Module 2
Cardiovascular outcome trials in diabetes

Module 3
Renal protection in type 2 diabetes

Module 4
Review of renal therapies prior to SGLT-2 inhibitors

Module 5
Renal benefits of SLGT-2 inhibitors in diabetes

Module 6
Safety of SGLT-2 inhibitors and side-effects

This register also examined the risk of acute myocardial infarction (MI) in relation to risk factor control. Evaluation of people with controlled risk factors such as glucose, blood pressure and lipids did not have an increased risk of acute MI, regardless of their age (Figure 2).

By contrast, the greater the number of uncontrolled risk factors, the greater the risk for acute MI.[3] This suggests that the risk for acute MI is not inevitable, being dramatically reduced if patients keep their cardiovascular risk factors well controlled.

The risk for acute MI is not inevitable, being dramatically reduced if patients keep their cardiovascular risk factors well controlled

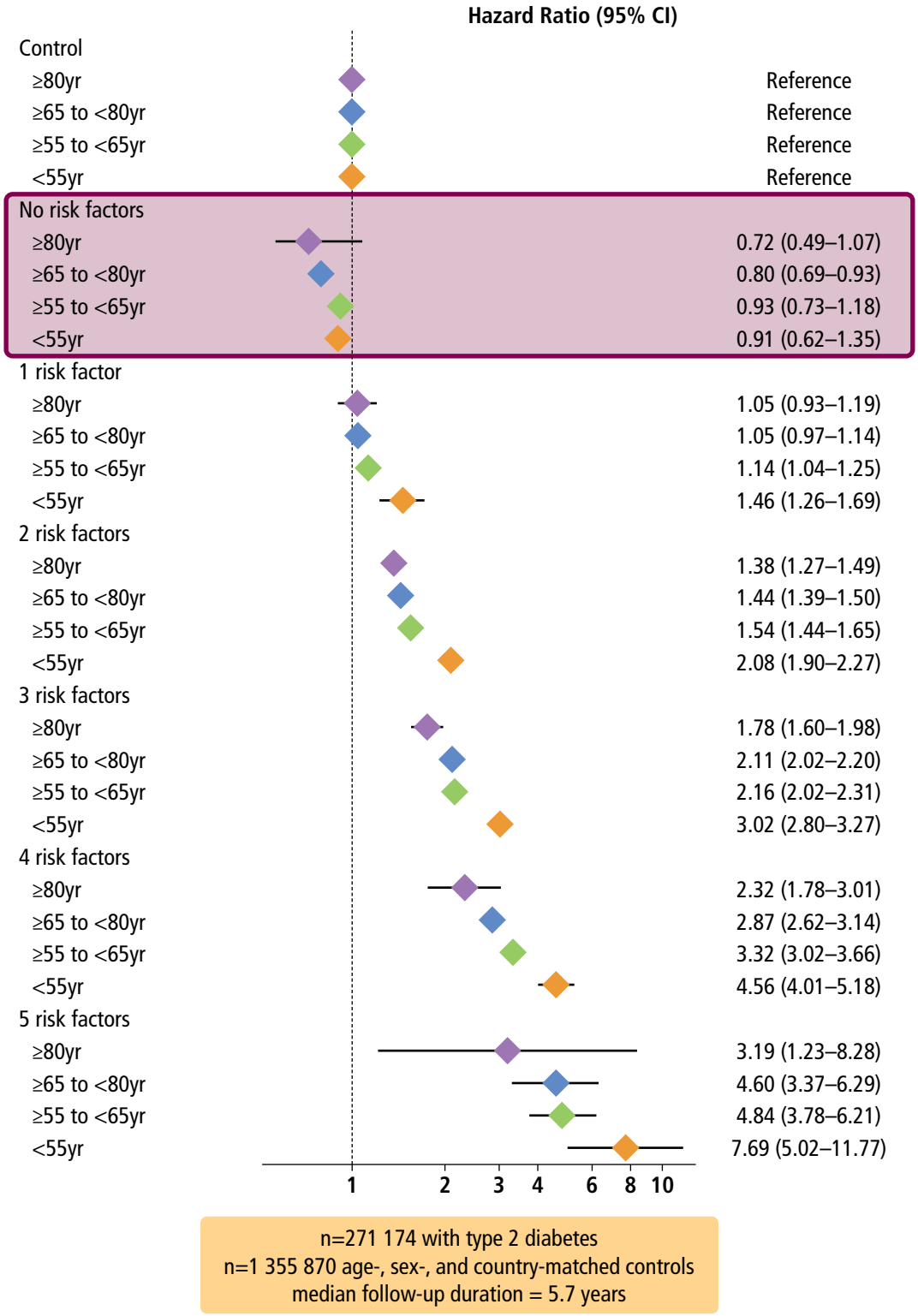
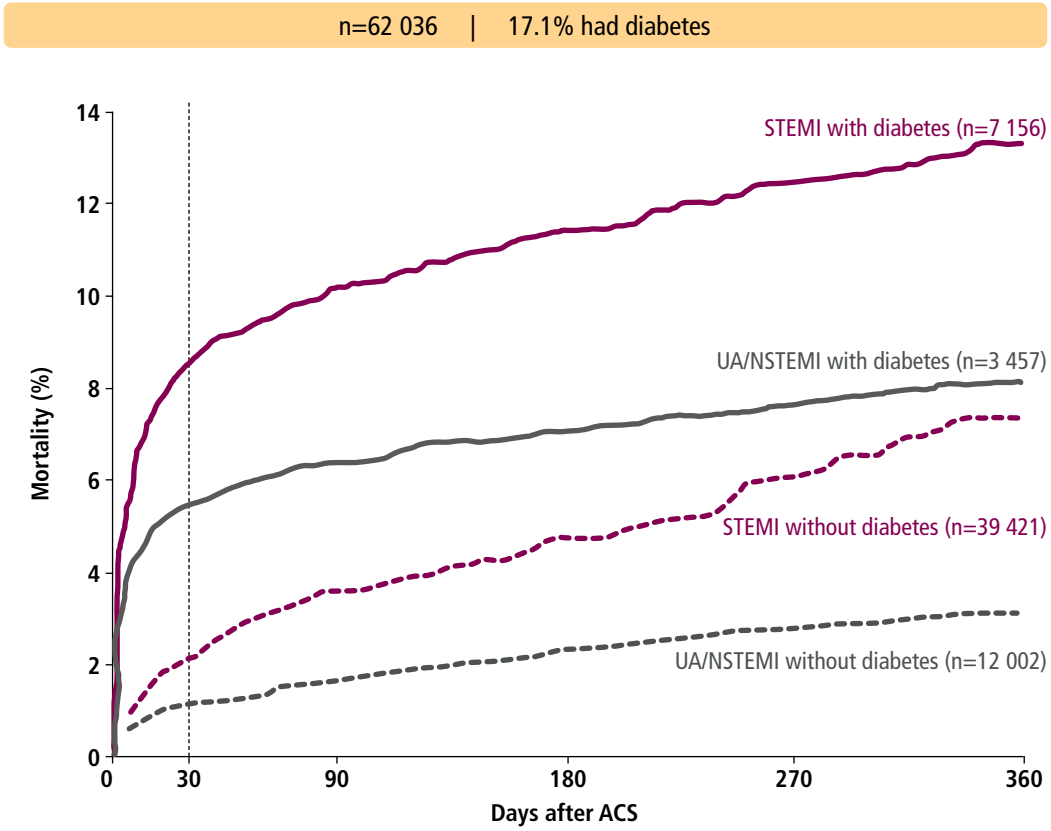


Figure 2. Swedish National Diabetes Register: Excess acute MI in relation to range of risk-factor control[3]

Data from 11 Thrombolysis in Myocardial Infarction (TIMI) studies indicate that once a person with diabetes has had an acute coronary syndrome (ACS), whether a STEMI or non-STEMI, they are twice as likely to die than if they did not have concomitant diabetes (Figure 3).[4] Prevention of the first event is therefore of paramount importance in those with diabetes.



UA/NSTEMI: unstable angina/non-STEMI; MI: myocardial infarction; STEMI: ST-segment elevation myocardial infaction; ACS: acute coronary syndrome

Figure 3. Post-MI mortality is higher in diabetes[4]

What is the pathophysiology of CVD in diabetes?

The pathophysiology of CVD in diabetes is multifactorial, with increases in oxidative stress, inflammation, insulin resistance and obesity. All of these factors contribute to an increased risk of major adverse cardiovascular events (MACE) and cardiovascular death. What is less well appreciated is that these same pathophysiological abnormalities also contribute to an increased risk of heart failure (HF) events, which in turn also contributes to an increased risk of cardiovascular death.

What is known about diabetes and HF?

Of diabetes-associated complications, macro- and microvascular complications are the most commonly considered; yet HF is a frequently forgotten and fatal complication. In the United States during the period 1998-2014, HF was the most common reason for people with T2DM being hospitalised. This situation has not improved since for both men and women (Figure 4).[5]

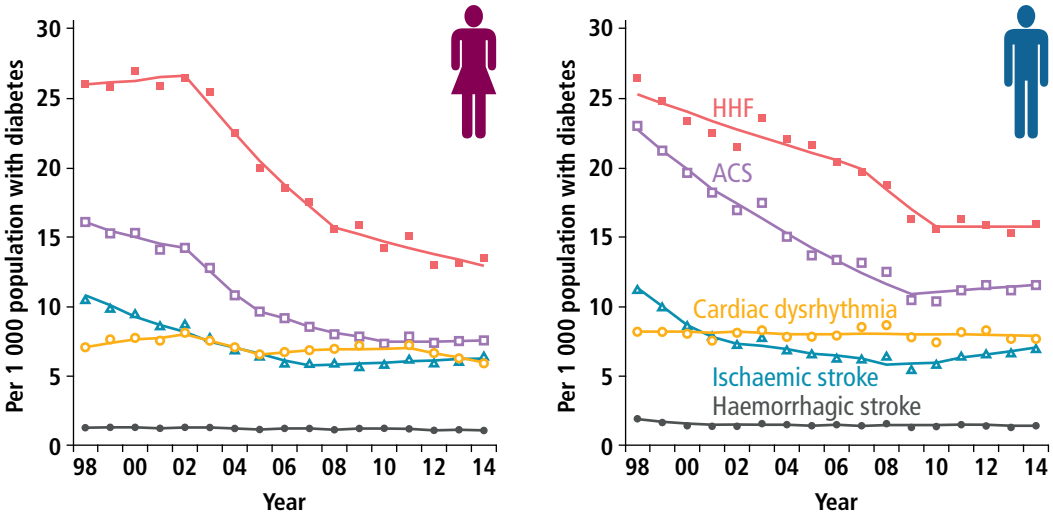


Figure 4. US national inpatient sample (1998-2014): hospitalisation for HF predominates[5]

Understanding the stages of HF

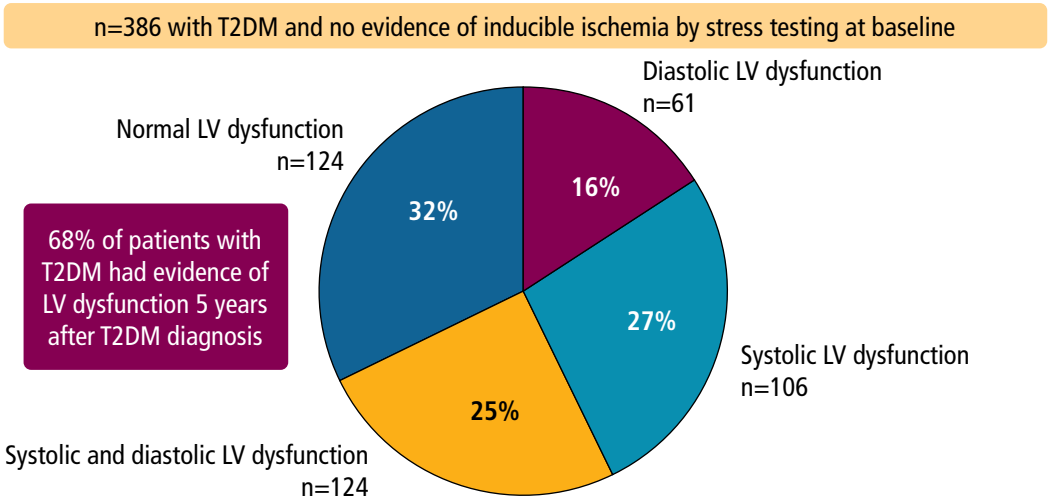
In understanding the American College of Cardiology (ACC) and American Heart Association (AHA) stages of HF (Table 1), the clinician is reminded that these guidelines emphasise stages A and B as being pre-HF stages - people at high risk of developing HF or who have sub-clinical HF, but have not yet developed overt HF.[6] It is these patients who were enrolled in the DECLARE primary prevention cohort, as it is clinically important to increasingly focus on preventing these patients from transitioning into HF stages C and D.

Treatment of diabetes, hypertension and obesity are all critically important in stage A and B, and the overall importance of diabetes as a HF risk factor must be remembered.

Table 1. ACC/AHA stages of HF

A	At **high risk** for HF but **without structural** heart disease or symptoms of HF
B	**Structural heart disease** but **without signs** or symptoms of HF
C	**Structural heart disease with** prior or current HF
D	**Refractory** HF requiring specialised interventions

The SHORTWAVE study[7] intensively assessed a cohort of 386 T2DM patients who had been diagnosed five years earlier and who showed no evidence of inducible ischaemia on stress testing. Among otherwise asymptomatic patients with no evidence of coronary disease, 68% showed evidence of left ventricular (LV) systolic or diastolic dysfunction without overt cardiac disease. It is evident that diabetes affects 'the pipes and the pump', but these effects may occur independently of each other (Figure 5).



LV: left ventricular; T2DM: type 2 diabetes mellitus

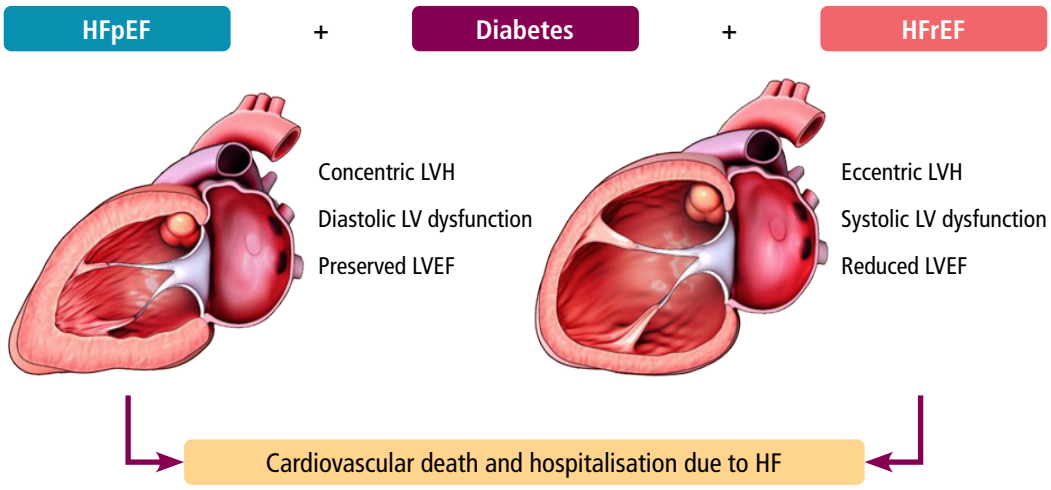
Figure 5. SHORTWAVE: Asymptomatic LV dysfunction is detectable in individuals without overt cardiac disease five years after a T2DM diagnosis[7]

Not only is HF one of the most common complications of T2DM, it is also the most disabling

Not only is HF one of the most common complications of T2DM, it is also the most disabling. There is a very high rate of sub-clinical HF and diastolic dysfunction in diabetes, and the cardiovascular effects of anti-hyperglycaemic agents have been an area of considerable discussion and debate.

HFpEF and HFrEF in diabetes

HF with preserved ejection fraction (HFpEF) is the more common phenotype encountered in T2DM; it leads to concentric LV hypertrophy and diastolic dysfunction with preserved LV ejection fraction. HF with reduced ejection fraction (HFrEF), usually presenting post-MI, leads to eccentric LV hypertrophy and systolic dysfunction with reduced ejection fraction. Both HFpEF and HFrEF are important causes of hospitalisation and cardiovascular death in people with diabetes (Figure 6).



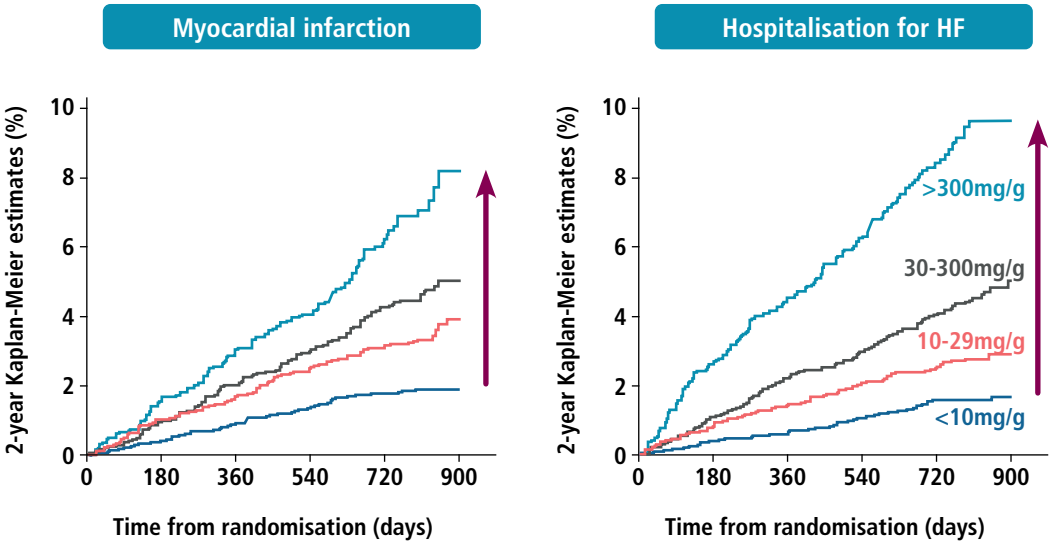
HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LV: left ventricular; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy

Figure 6. HFpEF and HFrEF in diabetes

After age and gender, diabetes is the third most important predictor of HF mortality in people with established HF, emphasising the important role of diabetes in adverse outcomes. Diabetes affects not only the heart, but also the circulation. Therefore, clinicians should consider HF and MACE as important manifestations and sequelae leading to mortality in patients with diabetes.

What is the relationship between kidney dysfunction and cardiovascular outcomes?

Cardiovascular outcomes according to baseline urinary albumin-to-creatinine ratio (UACR) were studied in the SAVOR-TIMI 53 trial. As kidney function declines, rates of coronary disease and HF increase considerably. Figure 7 illustrates that rates of MI increase significantly with worsening UACR, as does the rate of HF hospitalisations.[8] Reduced UACR is a biomarker for vascular and heart problems: in fact, HF-related risk may be even more profoundly affected than MI risk in people who are 'spilling protein'.[9]



UACR: urinary albumin to creatinine ratio

Figure 7. SAVOR-TIMI 53: Cardiovascular outcomes according to baseline UACR[8]

Key learnings

Diabetes leads to a malignant cardiovascular phenotype with macro- and microvascular events and HF events. Therefore, the prevention and treatment of MACE and HF-related events as a cause of cardiovascular death are crucial.

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