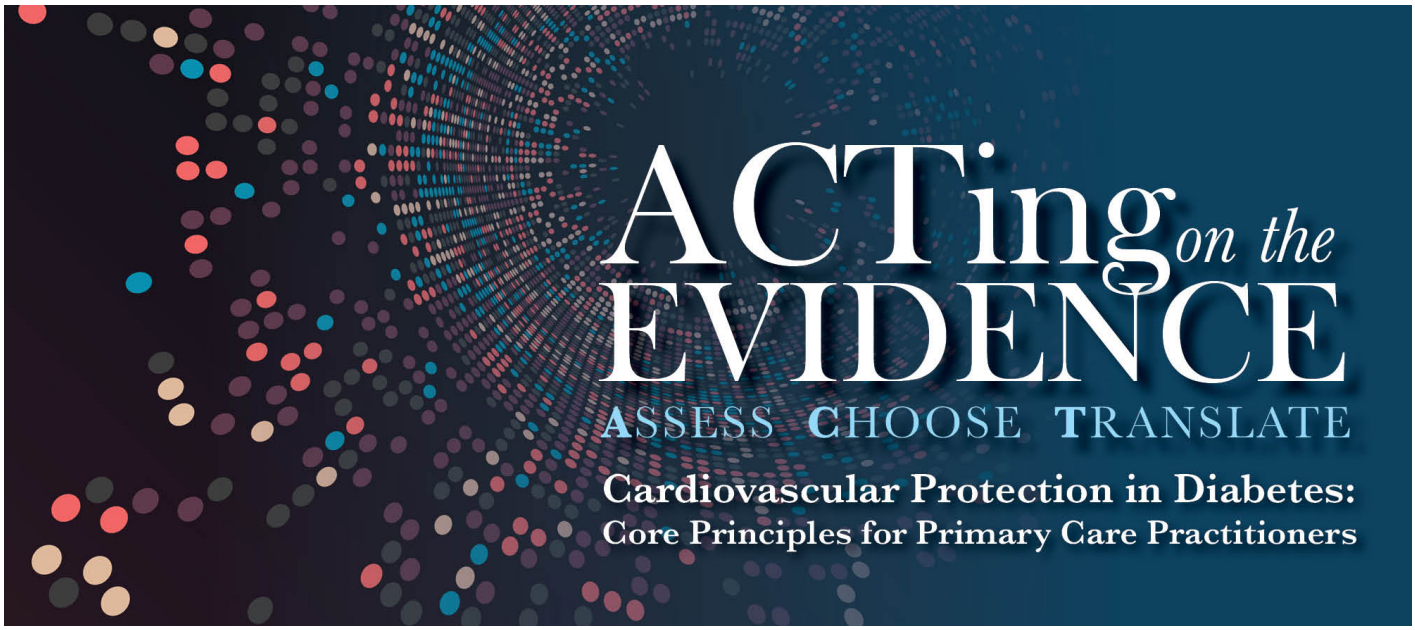

Renal protection in type 2 diabetes

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Participation in this fully accredited CPD programme gives you the opportunity to learn:

- Understanding of the renal complications of type 2 diabetes
- Insight into the consequences of diabetic kidney disease
- Perspective on the relationship between kidney disease and cardiovascular events
- Understanding of the clinical imperative to protect kidney function in your diabetic patients

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Expert panel

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Division of Endocrinology and Metabolism
St Michael's Hospital

Professor of Medicine and Nutritional Sciences,
University of Toronto, Toronto, ON, Canada

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Division of Cardiac Surgery
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Module 3: Renal protection in diabetes

Introduction

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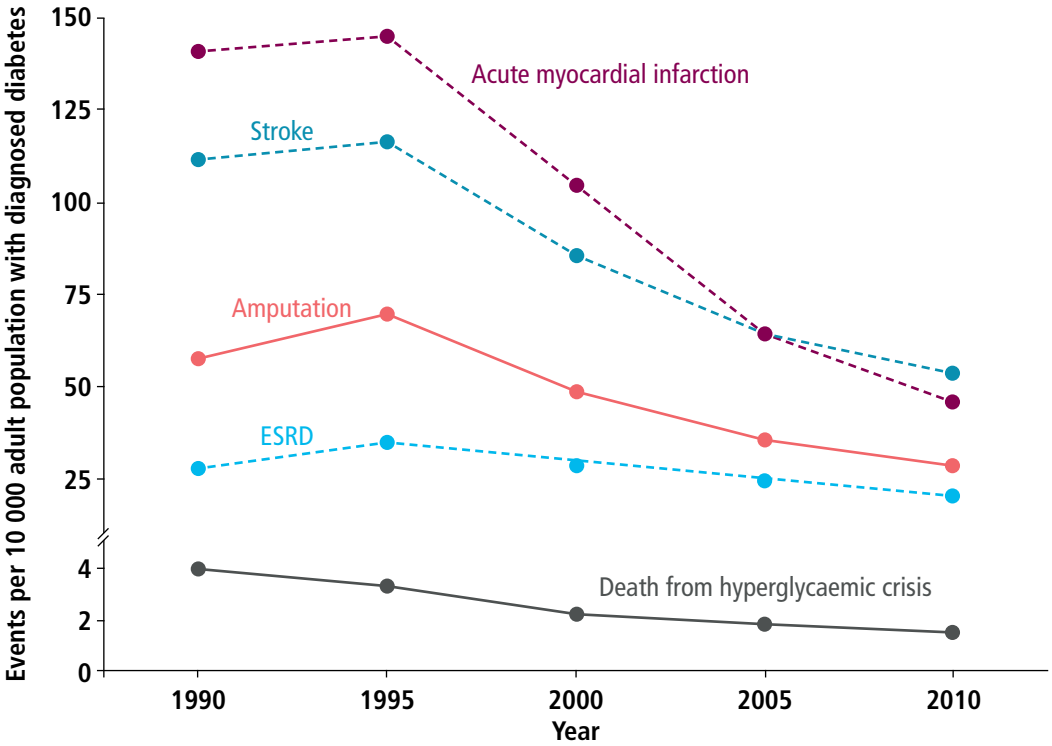
The importance of renal protection in diabetes is evident in the data from the Canadian Chronic Disease Surveillance System - people with diabetes are six times more likely to be hospitalised for chronic kidney disease (CKD) and 12 times more likely to be hospitalised for end-stage renal disease (ESRD).[1] While the rates of cardiovascular events in diabetes have been declining, those related to ESRD have not.

A review of two decades of diabetes complications in the United States from 1990 to 2010 indicates that many diabetes complications such as acute myocardial infarction, stroke and amputation, have been declining in diabetes. However, the incidence of ESRD has not shown substantial or appreciable changes.[2] Data from the Public Health Agency of Canada and other global data show that diabetes was the commonest cause of new ESRD in the period 2000-2009 and that this trajectory seems to be on the rise. This emphasises the need for clinicians to do better with regard to the treatment of ESRD in people with diabetes (Figure 1).

Global data show that diabetes was the commonest cause of new ESRD in the period 2000-2009 and that this trajectory seems to be on the rise



ESRD: end-stage renal disease

Figure 1. Diabetes complication events in the United States: 1990-2010[2]

Other modules

Module 1
Cardiovascular prevention and heart failure in diabetes

Module 2
Cardiovascular outcome trials in diabetes

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

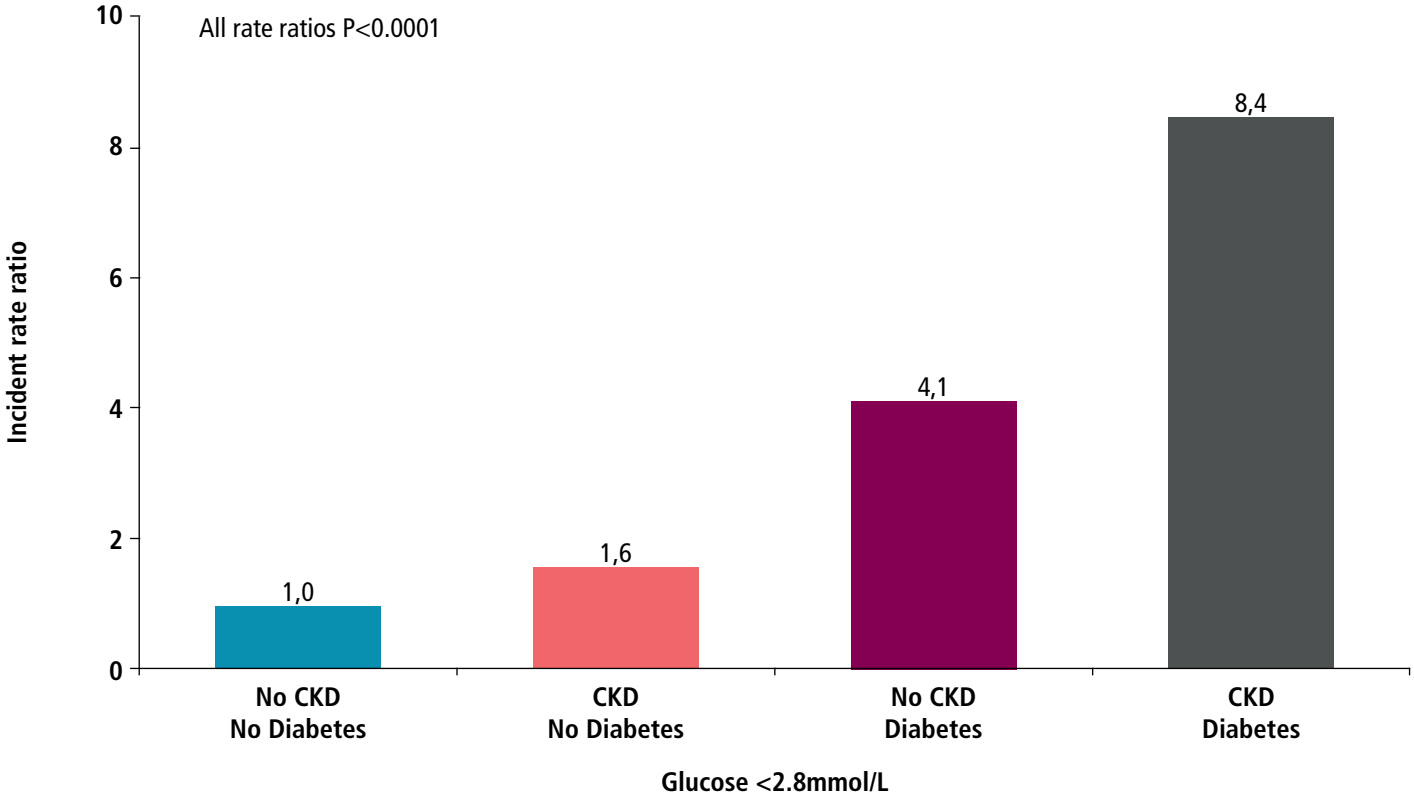
Module 5
Renal benefits of SGLT-2 inhibitors in diabetes

Module 6
Safety of SGLT-2 inhibitors and side effects

Risks of renal impairment in the diabetic patient

Does renal impairment increase the risk of hypoglycaemia?

Renal impairment increases the risk of many complications, but specifically also increases that of hypoglycaemia. Compared to a reference group of people with no CKD or no diabetes, a substantially higher incidence of hypoglycaemia occurs as CKD develops and progresses in the patient with diabetes (Figure 2).[3,4] Among individuals who are older than 70 years of age with CKD stages 3-5, for example, hypoglycaemia occurs more frequently: in excess of 60% of these patients.



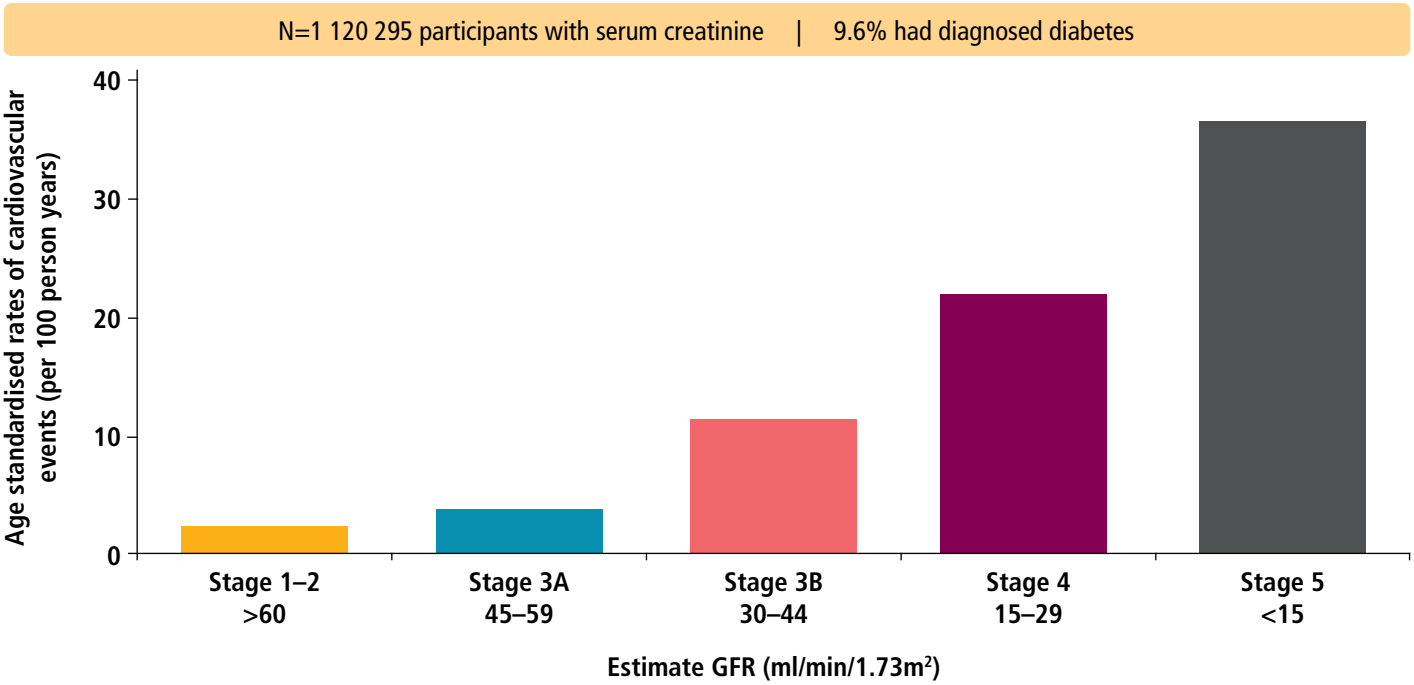
Groups adjusted for race, gender, age, cancer, diabetes and CVD
CKD: chronic kidney disease; CVD: cardiovascular disease

Figure 2. Renal impairment increases hypoglycaemia risk in people with diabetes[3,4]

What are the risks of declining GFR on cardiovascular events?

It is evident that diabetic kidney disease predisposes to cardiovascular and renal events, as well as to cardiovascular death and all-cause mortality

It is well established that declining glomerular filtration rate (GFR) is a significant risk factor for cardiovascular events. Data from more than one million participants with serum creatinine, of whom 9.6% had diagnosed diabetes, have shown that declining eGFR from stage 1-2 (≥60ml/min/1.73m^2) to stage 5 (<15ml/min/1.73m^2) is accompanied by a very steep increase in cardiovascular events (Figure 3).[5] It is evident that diabetic kidney disease predisposes to cardiovascular and renal events, as well as to cardiovascular death and all-cause mortality. Diabetic kidney disease is also associated with other comorbidities and morbid conditions, such as impaired cognition, depression and reduced quality of life.



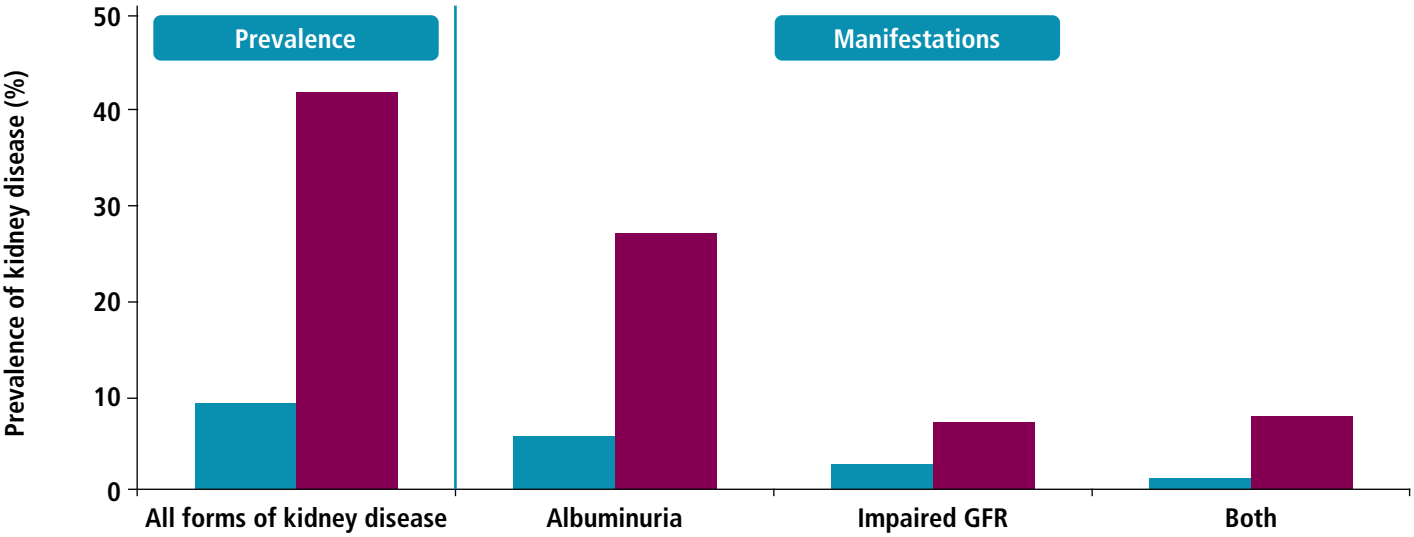
CV: cardiovascular; eGFR: estimated glomerular filtration rate

Figure 3. Risk of cardiovascular events increases as eGFR declines

Identify those patients who have the worst prognosis and are at very high risk - those who have the greatest amount of albumin excretion as well as the lowest GFR category

Manifestations of kidney disease in diabetes

People with diabetes have a substantially higher prevalence of kidney disease of any form, with manifestations of albuminuria and/or impaired GFR, compared to people with no diabetes (Figure 4).[6] This contextualises the importance of evaluating CKD using both GFR and albuminuria measurements to identify those patients who have the worst prognosis and are at very high risk - those who have the greatest amount of albumin excretion as well as the lowest GFR category. Individuals with combinations of less severe albuminuria or less severe GFR have a better prognosis (Figure 5).[7]



GFR: glomerular filtration rate

Figure 4. Prevalence and manifestations of kidney disease[6]

low CKD risk (if no other markers of kidney disease, no CKD)
moderately increased risk
high risk
very high risk

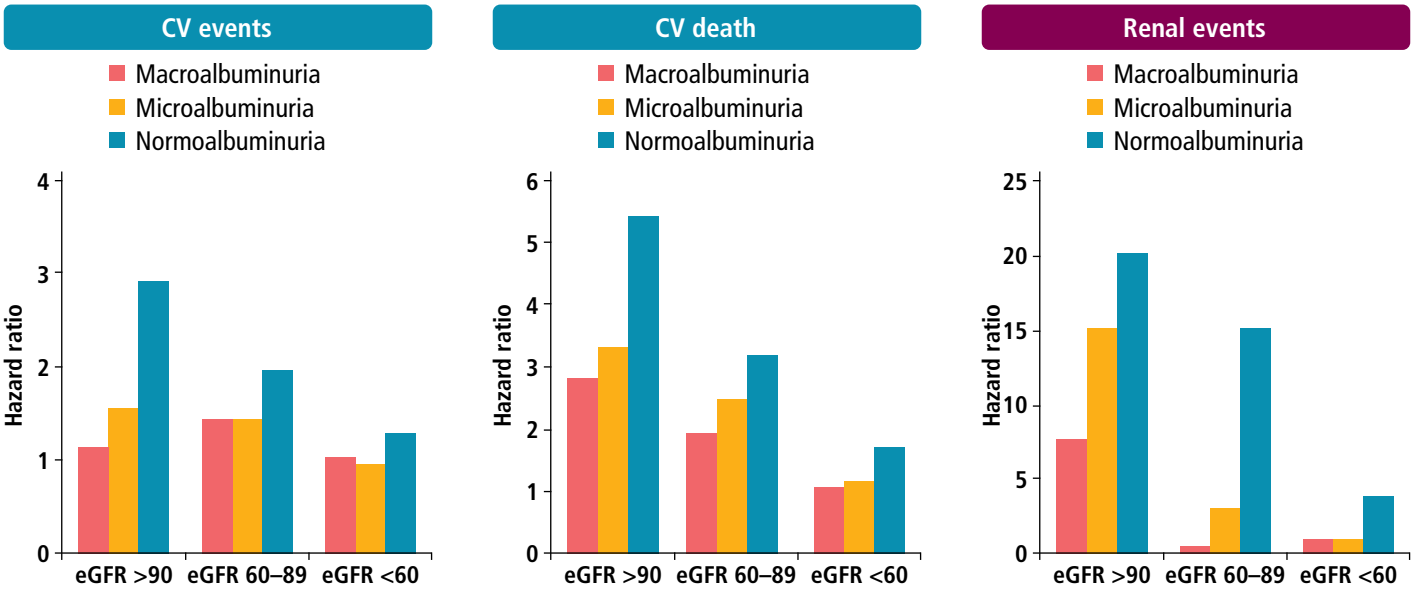
GFR categories, description and range (mL/min/1.73m²)				Albuminuria stages, description and range (mg/mmol)		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<3.4	3.4 to 34	>34
	G1	Normal or high	>90			
	G2	Mild decrease	60 to 89			
	G3a	Mild to moderate decrease	45 to 59			
	G3b	Moderate to severe decrease	30 to 44			
	G4	Severe decrease	15 to 29			
	G5	Kidney failure	<15			

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate

Figure 5. Prognosis of CKD by GFR and albuminuria[7]

What is the impact of GFR and albuminuria on cardiovascular and renal events?

The interaction between reduced GFR and albumin excretion in respect of the adverse outcomes of cardiovascular events, cardiovascular deaths and renal events is represented in Figure 6. The worst outcomes are observed in those who are 'spilling the most protein' and those with greater impairment of GFR.[8] In people with diabetes, GFR and albuminuria should both be evaluated carefully. There is also a prognostic implication when both occur independently, but the outcome is significantly worsened when impaired GFR and albuminuria co-exist.



The estimates were adjusted for baseline covariates, including age, gender, duration of diabetes, systolic blood pressure, history of currently treated hypertension, history of macrovascular disease, A_{1c}, LDL cholesterol, HDL cholesterol, log-transformed triglycerides, body mass index, electrocardiogram abnormalities, current smoking, and current drinking
CV: cardiovascular; eGFR: estimated glomerular filtration rate

Figure 6. Impact of eGFR and albuminuria on cardiovascular and renal events

What is the impact of diabetes and kidney disease on risk of mortality?

Diabetes increases the risk of all-cause and cardiovascular mortality in people with CKD (Table 1). Analysis of 10-year data from the Third National Health and Nutrition Examination Survey (NHANES III) indicated that for the first outcome of all-cause mortality, the standardised cumulative incidence was 19.1% in people with diabetes compared to 8.6% in people without diabetes, and a similar step-up was seen with regard to cardiovascular and non-cardiovascular mortality.[6]

Table 1. Diabetes increases the risk of all-cause and cardiovascular mortality[6]

	Standardised cumulative incidence, % (95% CI)
All-cause mortality	
No diabetes	8.6 (7.9-9.3)
Diabetes	19.1 (15.5-22.7)
Cardiovascular mortality	
No diabetes	4.0 (3.7-4.4)
Diabetes	11.2 (8.7-13.7)
Non-cardiovascular mortality	
No diabetes	6.3 (5.7-6.9)
Diabetes	13.1 (9.8-16.4)

Kidney disease itself increases the risk of all-cause mortality in people with type 2 diabetes. Recent data comparing people with no kidney disease, albuminuria, impaired GFR and the combination of albuminuria and impaired GFR, suggest that people with diabetes who are spilling protein and have a reduced GFR show a higher 10-year incidence of mortality (>40%) compared to those who have no kidney disease (Figure 7).[8]

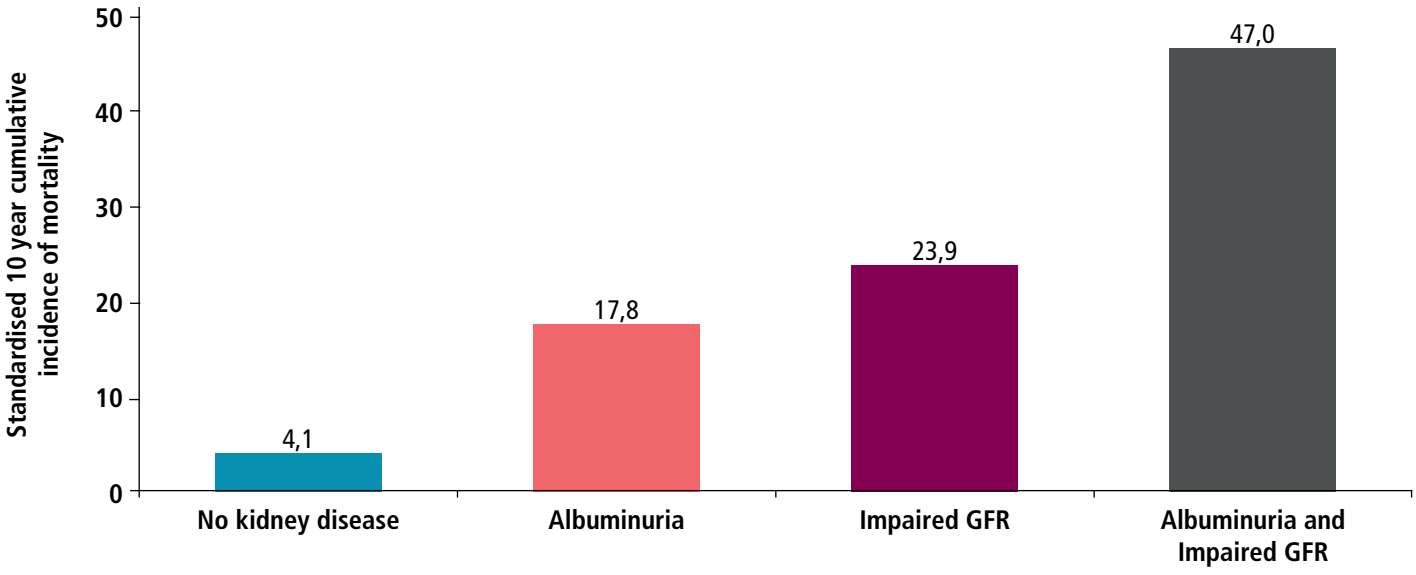


Figure 7. Kidney disease increases the risk of mortality in type 2 diabetes[6]

Cardiorenal syndrome

The concept of the cardiorenal syndrome relates to effects of diabetes on the heart, specifically heart failure and renal insufficiency (Figure 8).[9] Systemic risk factors such as diabetes, obesity, metabolic syndrome, hypertension and others lead to four important biological changes: primarily sympathetic and neurohormonal activation, inflammation, endothelial dysfunction and oxidative stress. In turn, these changes trigger heart failure and renal insufficiency, referred to as the cardiorenal syndrome in people with diabetes.

The primary supporting author of this module was Professor David Cherney, a nephrologist from the University of Toronto.

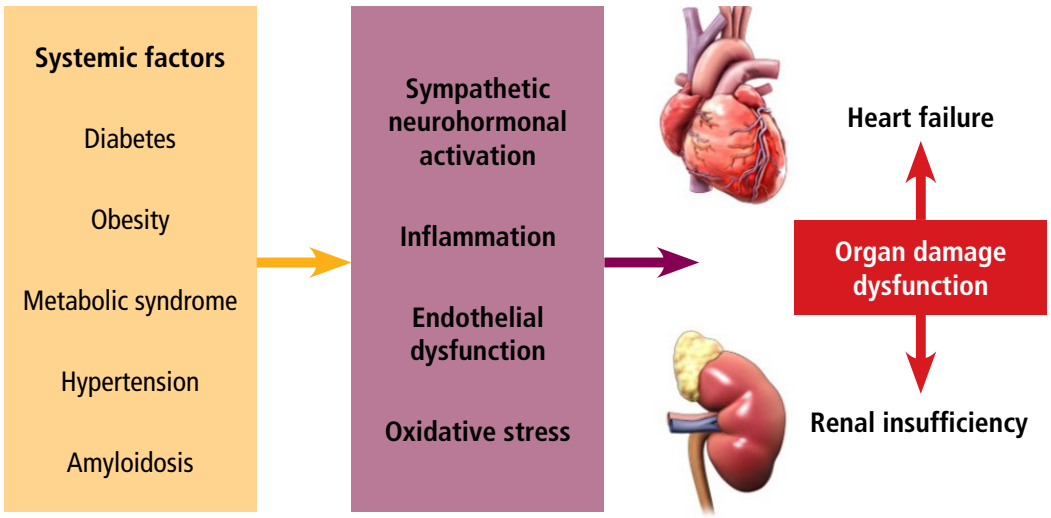


Figure 8. Cardiorenal syndrome[9]

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