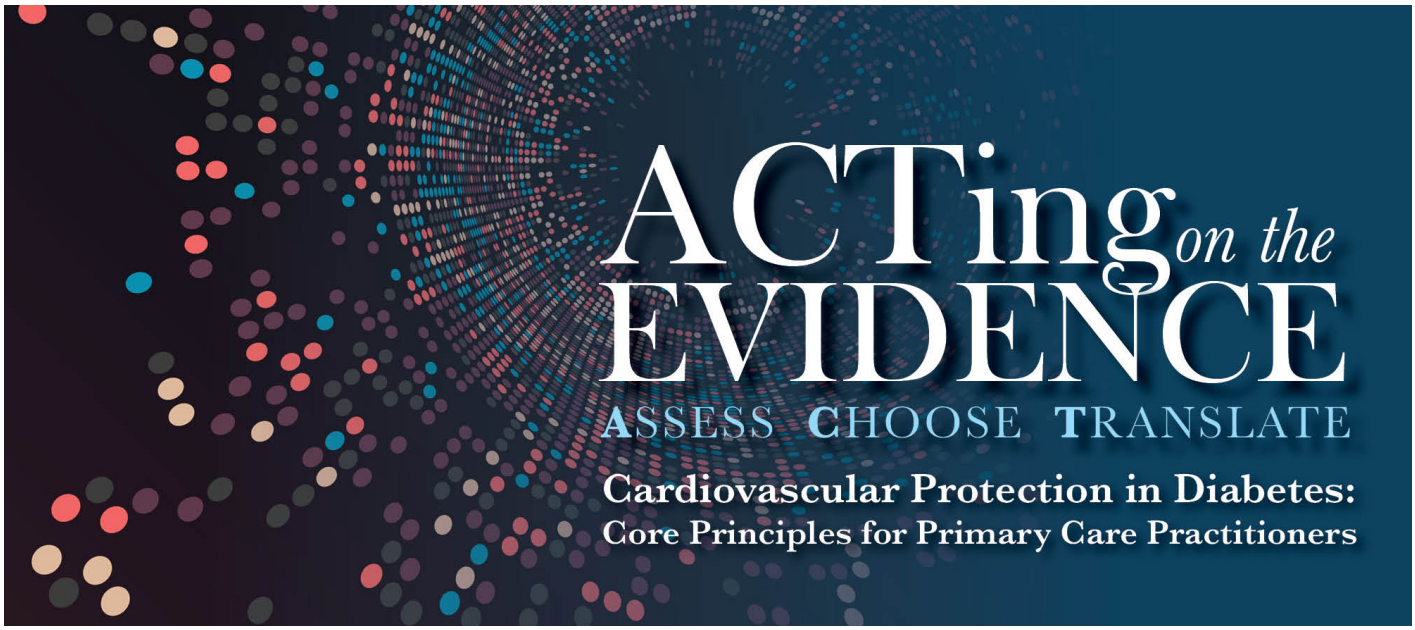

Review of renal therapies prior to SGLT-2 inhibitors

An educational programme for general practice developed by international experts.

What you will gain…

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

- An understanding of the therapies available to protect kidneys prior to SGLT-2 inhibitor therapy
- The ability to introduce renoprotective therapies, including multifactorial risk management strategies in type 2 diabetes
- Perspective on the contribution of important earlier clinical trials in renal protection.

Expert

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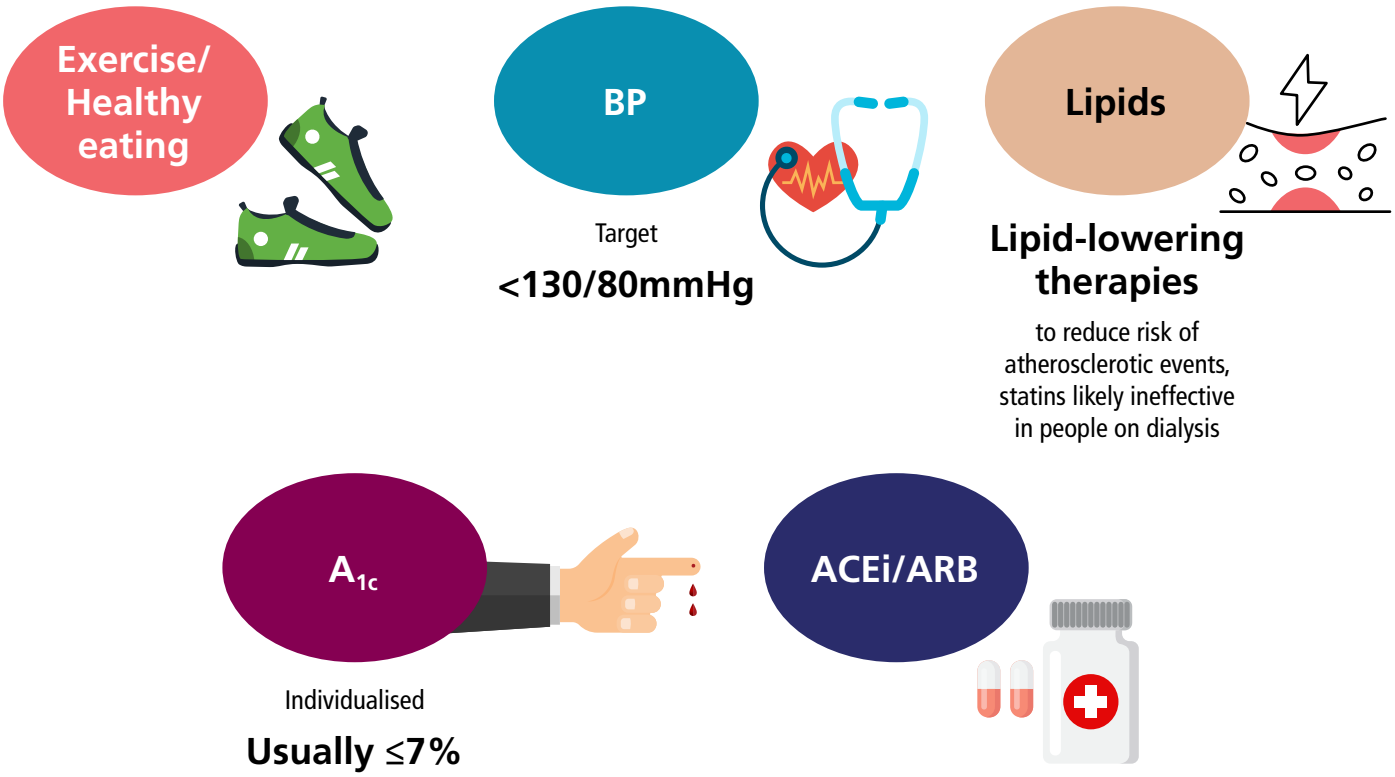
Module 4: Review of renal therapies prior to SGLT-2 inhibitor therapy

Introduction

Click here to watch the video

It is commonly accepted and understood that to achieve cardiovascular and renal protection in diabetes, a multifactorial management strategy is necessary. Exercise and healthy eating, blood pressure control and treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), lipid control and HbA_{1C} control are the cornerstones of management of diabetic kidney disease (DKD) (Figure 1).[1-5]

The purpose of this module is to review proven renal therapies in type 2 diabetes (T2DM) prior to the sodium-glucose co-transporter-2 (SGLT-2) inhibitor trials.



ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BP: blood pressure

Figure 1. Cardiovascular and renal protection in diabetes requires a multifactorial risk management strategy

Other modules

Module 1
Cardiovascular prevention and heart failure in diabetes

Module 2
Cardiovascular outcome trials in diabetes

Module 3
Renal protection in type 2 diabetes

Module 5
Renal benefits of SGLT-2 inhibitors in diabetes

Module 6
Safety of SGLT-2 inhibitors and side effects

How does risk factor management affect the outcome of DKD?

Intensive glucose control reduces the risk of albuminuria

Meta-analysis of cumulative studies shows that intensive HbA_{1c} control offers a consistent benefit over standard HbA_{1c} control (Figure 2). Intensive glucose control shows less microalbuminuria with a relative risk reduction (RRR) of 14%, as well as less macroalbuminuria (RRR 26%).[3]

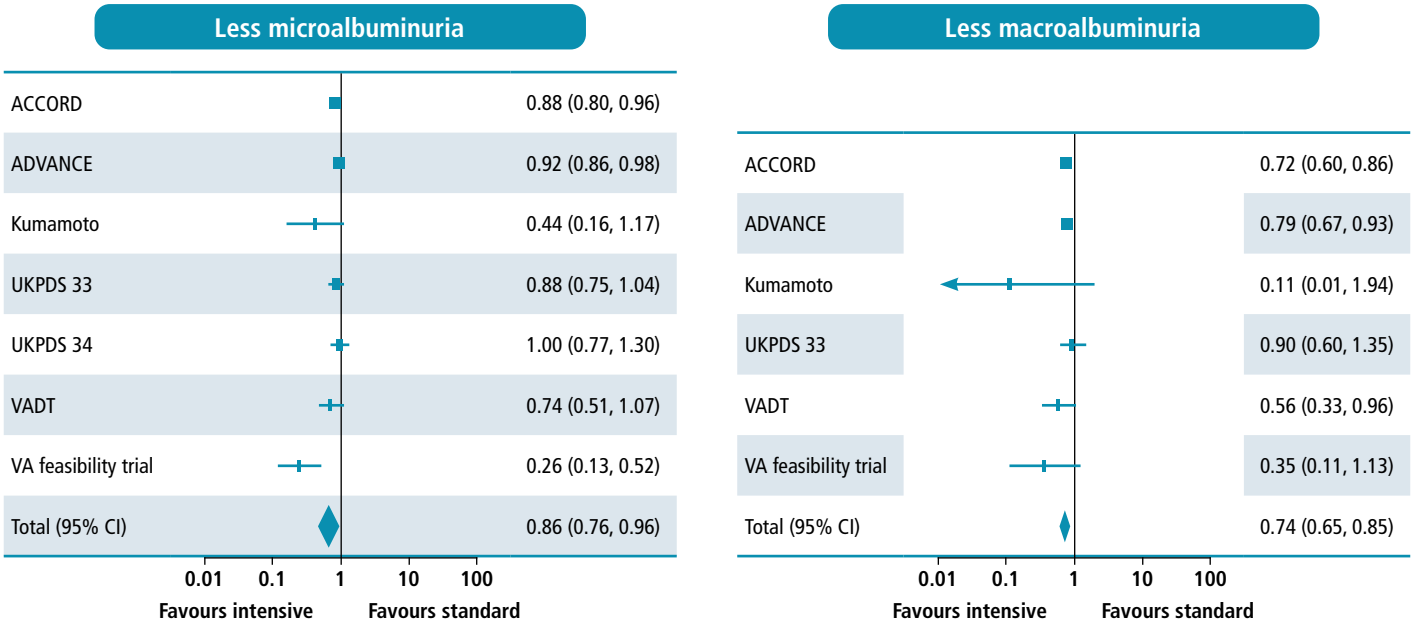


Figure 2. Intensive glucose control reduces the risk of albuminuria

Intensive glucose control reduces the risk for ESRD

A management approach of intensive glucose control reduces the risk of end-stage renal disease (ESRD). For the outcome of ESRD in the ADVANCE-ON trial, an RRR of 46% (p=0.007) was observed with intensive glucose control, compared to standard glucose control (Figure 3).[4]

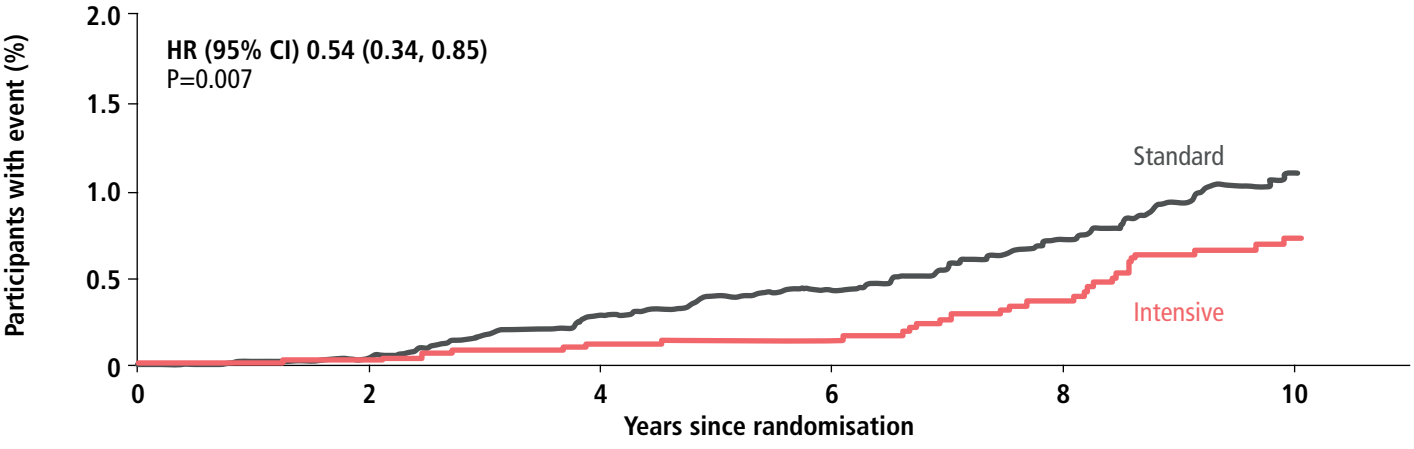


Figure 3. ADVANCE-ON: Intensive glucose control reduces the risk for ESRD

Blood pressure lowering confers renal protection

The ADVANCE study also evaluated the effect of blood pressure lowering in relation to renal events.[5] Figure 4 depicts the renal event rate correlated relative to achieved systolic blood pressure lowering from 170mmHg down to 110mmHg. There is an inverse relationship between reducing blood pressure and improving overall renal protection; the lower the blood pressure, the greater the overall renal protection observed.

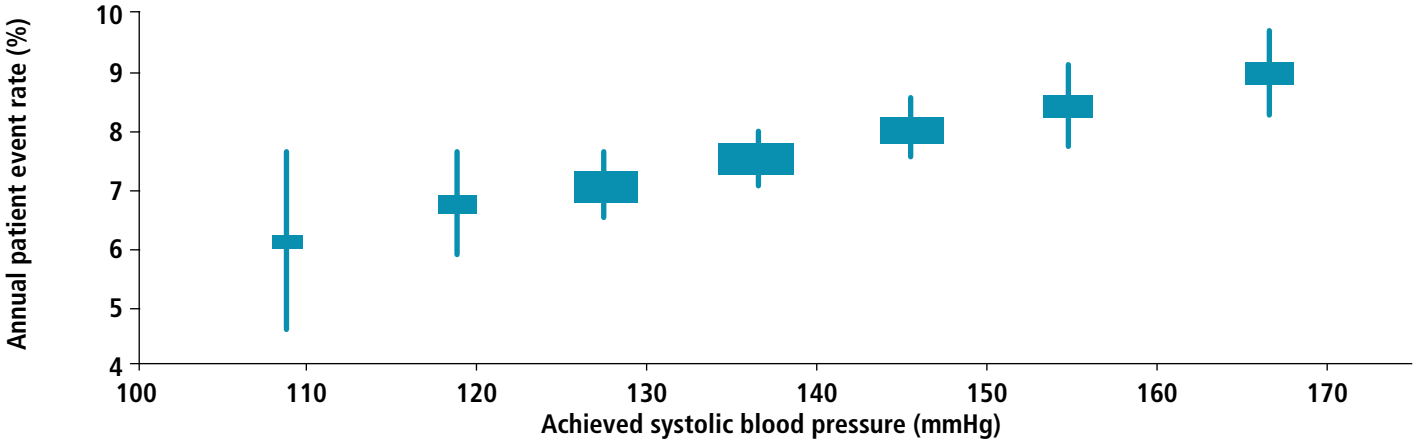
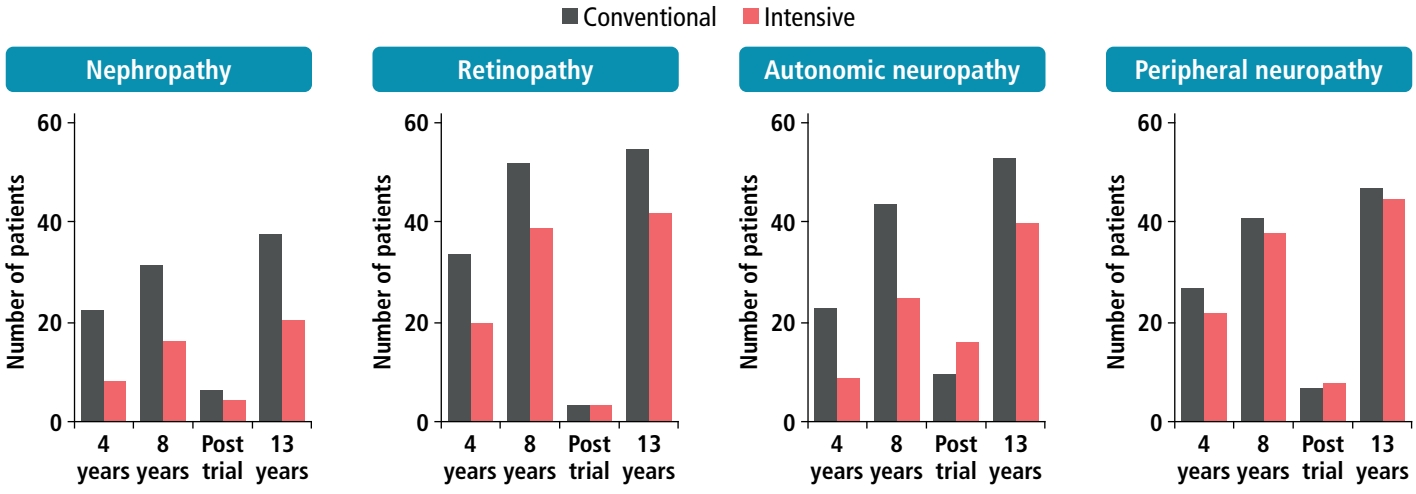


Figure 4. ADVANCE study: Blood pressure lowering reduces the risk of renal events

Multifactorial risk factor intervention in T2DM

In T2DM, multifactorial risk factor interventions lower cardiovascular complications, risk of nephropathy and all-cause mortality. The Steno-2 trial results indicated that cardiovascular events and all-cause mortality were significantly reduced when intensive multifactorial risk factor control was instituted in people with T2DM and, importantly, a very significant reduction in nephropathy was observed at four years, eight years and even 13 years following the trial (Figure 5). Nephropathy and other microvascular complications are affected to the same degree by intensive multifactorial risk factor control, as are cardiovascular complications.[6]



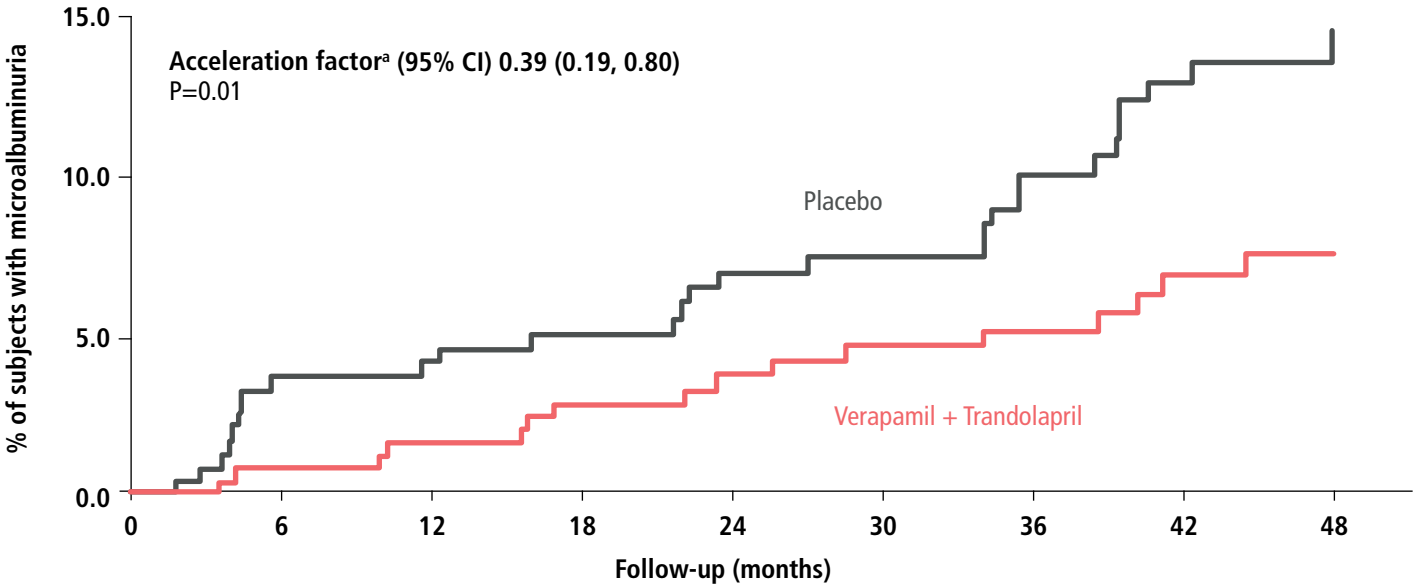
CVD: cardiovascular disease; CHD: coronary heart disease; T2DM: type 2 diabetes mellitus

Figure 5. Steno-2 trial: A multifactorial intervention strategy reduces the risk for nephropathy and other microvascular complications in T2DM

Primary prevention in T2DM

The BENEDICT trial set out to evaluate primary prevention of renal events in T2DM. It was evident that the combination strategy of trandolapril and verapamil, compared to placebo, substantially reduced the percentage of subjects with new microalbuminuria. The curves separated early, suggesting that the ACE inhibitor and calcium channel blocker (CCB)-based regimen had a profound effect with regard to preventing the development of new microalbuminuria (Figure 6).[7]

More recently the ROADMAP study of olmesartan, an ARB, addressed the question of primary prevention of renal events in T2DM. With regard to the cumulative proportion of patients with microalbuminuria, olmesartan achieved statistical significance with a 23% reduction (Figure 7).[8]



a. quantifies the effect of one treatment relative to another in accelerating or slowing disease progression

Figure 6. BENEDICT trial: Reduction in new microalbuminuria using an ACE inhibitor + CCB[7]

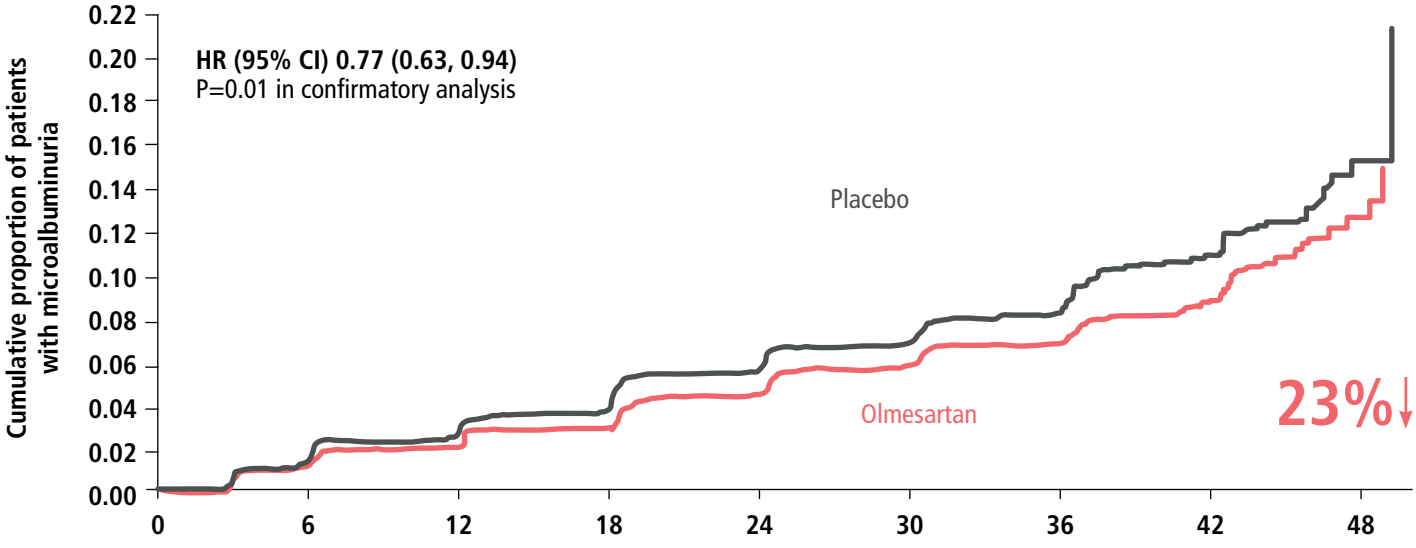
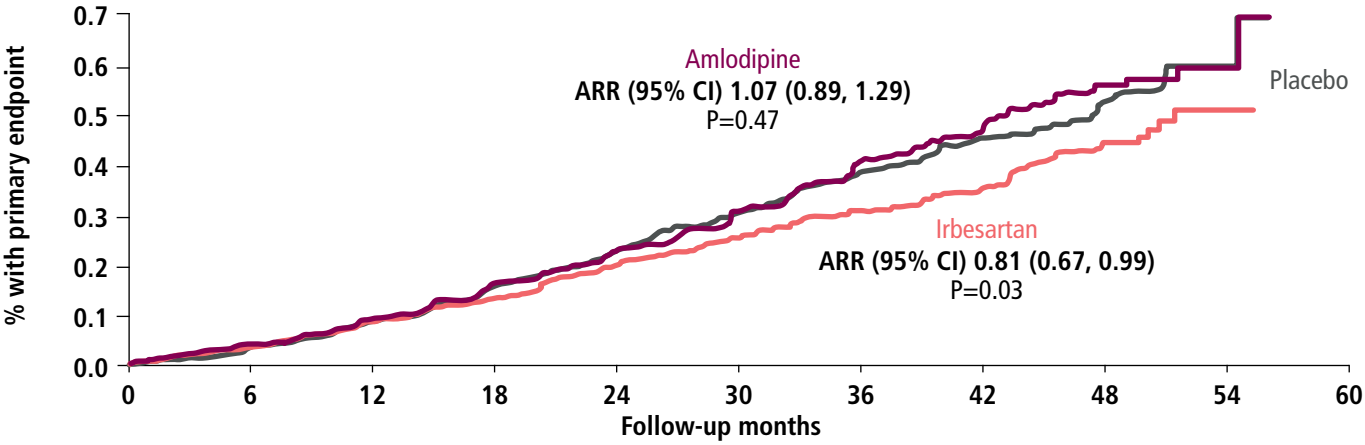


Figure 7. ROADMAP trial: Reduction of microalbuminuria risk using an ARB[8]

Secondary prevention in T2DM with established nephropathy

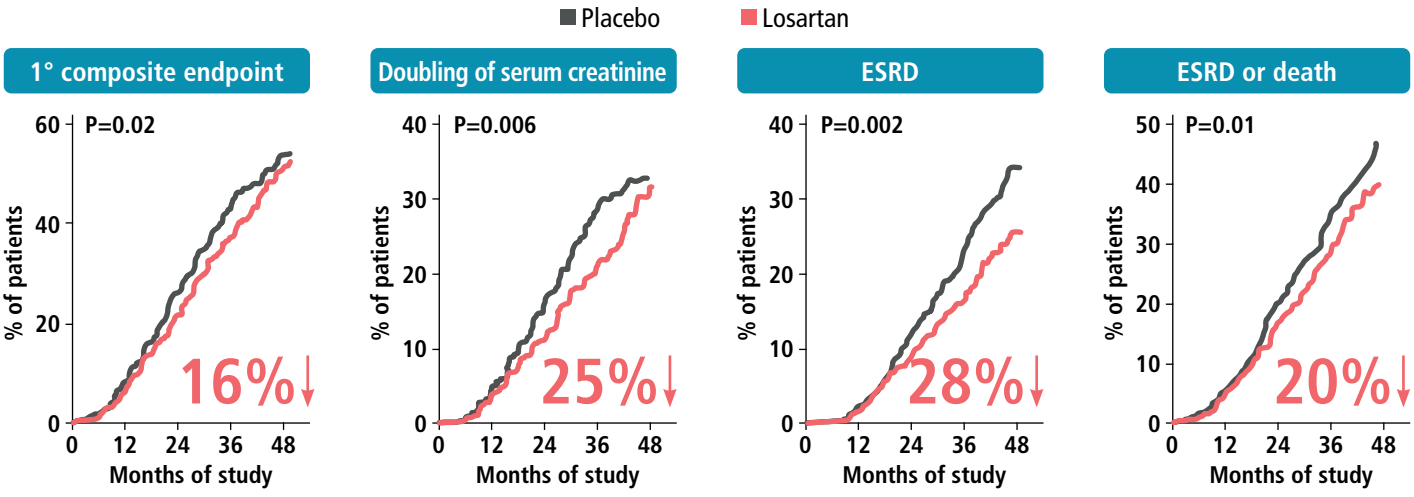
In T2DM patients who have established nephropathy, does secondary prevention improve renal mortality outcomes? Older data from the Irbesartan Diabetic Nephropathy Trial (IDNT) demonstrated the superiority of irbesartan, compared to placebo and the CCB amlodipine, in respect of renal mortality outcomes in patients with both T2DM and nephropathy (Figure 8).[9]



ARR: adjusted relative risk (vs. placebo)

Figure 8. IDNT: Irbesartan improves renal mortality outcomes in T2DM with established nephropathy[9]

The RENAAL study, also of patients with both T2DM and nephropathy, evaluated several outcomes using losartan versus placebo (Figure 9).[10] The primary composite outcome of a doubling of the baseline serum creatinine concentration, ESRD or death was reduced by 16%. Specifically, doubling of serum creatinine was reduced by 25% and ESRD was reduced by 28%; both outcomes were statistically highly significant with p-values of 0.006 and 0.002, respectively. The composite of ESRD or death was reduced by 20% with a p-value of 0.01.



ESRD: end-stage renal disease

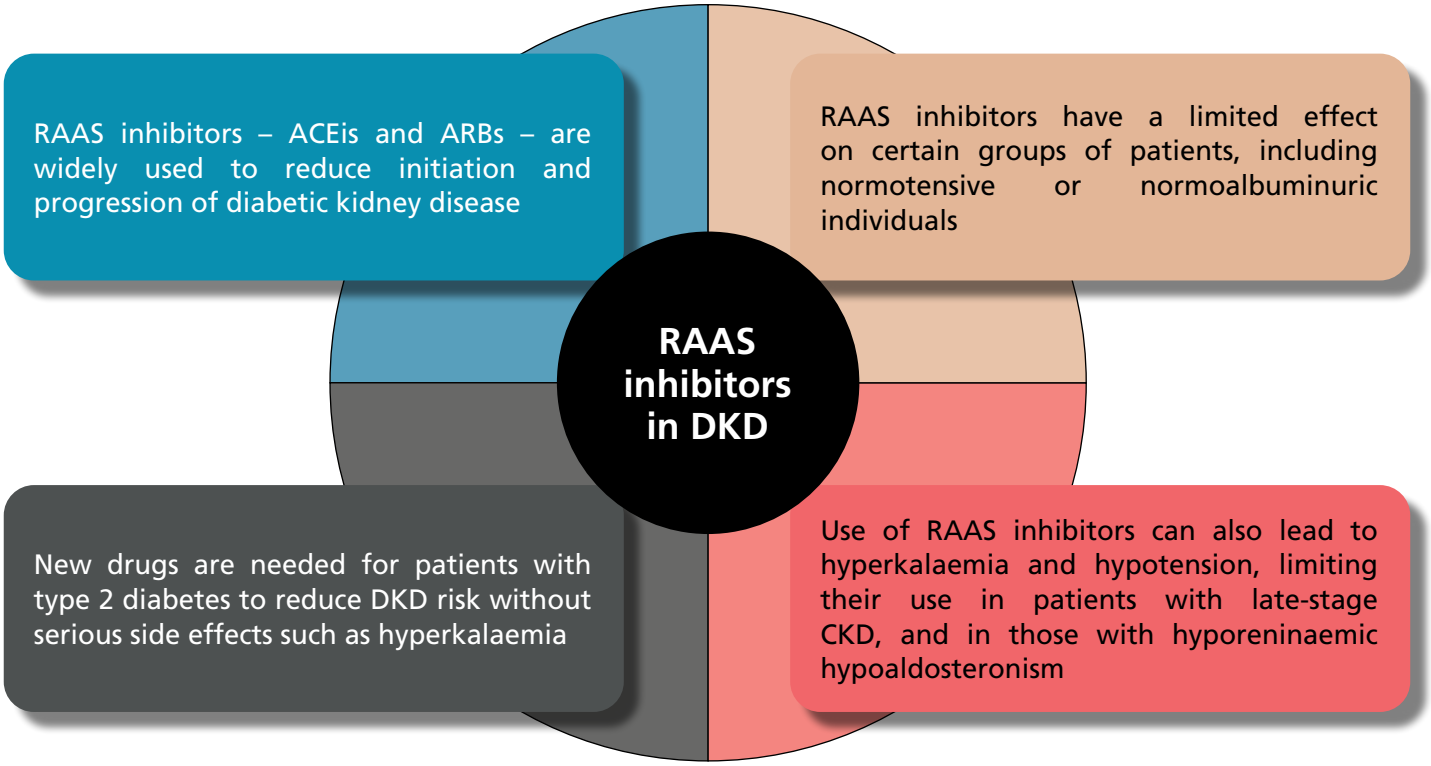
Figure 9. RENAAL STUDY: Losartan improves renal mortality outcomes in T2DM with established nephropathy

Has RAAS blockade reached its limits in the treatment of DKD?

New drugs that reduce incidence and severity of DKD, without serious side effects such as hyperkalaemia, are needed for T2DM patients

What are the limitations of renin-angiotensin-aldosterone system (RAAS) blockers with regard to treatment of DKD? Arguments, as presented in Figure 10, are that although ACE inhibitors and ARBs are widely used as foundational therapies to reduce both the initial development and the progression of DKD, they have a limited effect on certain groups of patients, particularly those that are normotensive or normoalbuminuric.

In addition, the use of RAAS inhibitors can also lead to hyperkalaemia and hypotension, which limits their use in patients with late-stage chronic kidney disease and those with hyporeninaemic hypoaldosteronism. [11] New drugs that reduce incidence and severity of DKD, without serious side effects such as hyperkalaemia, are needed for T2DM patients.



ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blocker; CKD: chronic kidney disease; DKD: diabetic kidney disease; RAAS: renin–angiotensin–aldosterone system

Figure 10. Has RAAS blockade reached its limits in the treatment of DKD?

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