deNOVO Medica

Leader in digital CPD for Southern African healthcare professionals

The kidney – the heart of the matter in diabetes

Professor Brian Rayner
Division of Nephrology and Hypertension
University of Cape Town

Professor Ikechi Okpechi
Director
Division of Nephrology and Hypertension, and Kidney and Hypertension Research Unit University of Cape Town

Introduction

Type 2 diabetes mellitus (T2DM) is associated with an increased risk of cardiovascular and renal disease. Chronic kidney disease (CKD) develops in 42% of patients with diabetes, and is also associated with high cardiovascular morbidity and mortality. Nearly half of patients entering dialysis programmes in the South African private sector have T2DM, with a minimum estimated cost of R600 million per year.

At the Connecting the Experts in CVRM (Cardiovascular, Renal, Metabolic) meeting hosted by AstraZeneca in Cape Town on 9-10 February 2019, Professor Brian Rayner considered the pivotal role of hypertension in T2DM and Professor Ikechi Okpechi provided guidance on prescribing medicines in kidney disease.

KEY MESSAGES

- The prevalence of hypertension increases with impaired glucose tolerance and T2DM
- Intensive blood pressure control in T2DM hypertensives achieves significant reductions in diabetes-related endpoints, death related to diabetes, stroke, microvascular disease, retinal photocoagulation and heart failure
- Automated office blood pressure measurement (AOBPM) is the preferred in-office method
- A diagnosis of masked hypertension is suggested by the presence of extensive target organ damage in a patient with normal office blood pressure, and is more common in the diabetic
- Blood pressures that are too high or too low are both associated with adverse cardiovascular outcomes
- The ADA recommends a blood pressure target of <140/90mmHg, or <130/80mmHg if tolerated, in T2DM
- Renal impairment can alter the pharmacokinetic and pharmacodynamic properties of drugs
- The greater the degree of renal impairment, the greater the need for drug dose modification
- Many commonly prescribed drugs are nephrotoxic
- Many commonly prescribed drugs are significantly cleared by haemodialysis
- SGLT inhibition with empagliflozin improves both cardiovascular and renal outcomes in patients with T2DM and established cardiovascular disease.

In collaboration with the Southern African Hypertension Society.

Southern African Hypertension Society
SAHS
Know your blood pressure by

Hypertension in T2DM

The prevalence of hypertension increases with impaired glucose tolerance (60.2%) and diabetes (79.4%), compared with the normoglycaemic population (43.1%).[1] A steady rise in blood pressure and pulse pressure is suggestive of premature vascular ageing in the diabetic, which further compounds the problem of hypertension.

The UK Prospective Diabetes Study Group (UKPDS) shows that intensive blood pressure control (systolic blood pressure (SBP) 154mmHg vs 144mmHg) in patients with hypertension and T2DM achieves significant reductions in any diabetes-related endpoints, death related to diabetes, stroke, microvascular disease, retinal photocoagulation and heart failure.[2] In terms of protecting against cardiovascular complications in T2DM, management of hypertension is of greater benefit than both LDL-cholesterol- and HbA1c-lowering (Figure 1).[3]

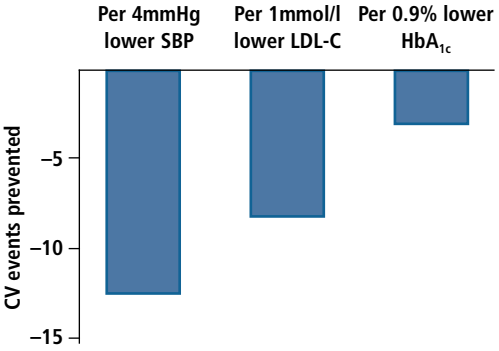

Figure 1. Cardiovascular outcomes in T2DM[3]

Measuring blood pressure correctly

Professor Rayner emphasises that it is critical to measure blood pressure correctly - accuracy is essential for diagnosis and blood pressure control if targets are low. Meta-analysis of routine measurement of resting blood pressure in the clinical setting shows significant variation in SBP, -23.6mmHg to +33.0mmHg, and diastolic blood pressure (DBP), -14.0mmHg to +23.0mmHg, readings being inaccurate in over one-third of patients.[4]

Automated office blood pressure measurement (AOBPM) is the preferred in-office method, as it closely approximates ambulatory blood pressure monitoring (ABPM); it mitigates the white coat effect and is more predictive of end organ damage. The difference between routine OBPM and AOBPM is -15.0mmHg, reflecting the inaccuracy of measurement and the white coat effect.[5] Meta-analysis shows a mean difference of 10.0/5.0mmHg when comparing AOBPM with OBPM, but no significant difference between AOBPM and 24-hour daytime ABPM.[6]

Diabetics are a high-risk group of patients that are prone to elevated blood pressure at night; this is one of the most powerful markers of cardiovascular outcome in any hypertensive patient and 24-hour ABPM is useful for assessing diurnal variation in blood pressure.

The use of both ABPM and OBPM methods together can enable the clinician to identify white coat hypertension (hypertensive by OBPM, normotensive by ABPM), which has low relative risk of cardiovascular morbidity; and masked hypertension (normotensive by OBPM and hypertensive by ABPM), common in the diabetic. More extensive target organ damage is observed with masked hypertension than in true normotensives.[7]

Depending on the method of blood pressure measurement used, definitions of hypertension vary (Table 1).

Table 1. Definitions of hypertension by different methods of blood pressure measurement

	Office	Automated office	Self	Ambulatory
Predicts outcome	+	++	++	+++
Initial diagnosis	Yes	Yes	Yes	Yes
Cut-off (mmHg)	140/90	Mean 135/85	135/85	Mean day 135/85 Mean night 120/70
Evaluation of treatment	Yes	Yes	Yes	Limited, but valuable
Assess diurnal variation	No	No	No	Yes

EARN FREE CPD POINTS

Join our CPD community at www.denovomedica.com and start to earn today!

Optimal blood pressure targets?

Discrepancies in definitions of hypertension between international guidelines (Table 2), most notably the recent ACC/AHA recommendation to target <130/80mmHg, have further fuelled controversy as to optimal blood pressure targets in the treatment of hypertension. The 2018 ESC/ESH hypertension guidelines'[8] recommendations for blood pressure management in diabetes is a target SBP <130mmHg, but not <120mmHg; and DBP <80mmHg, but not <70mmHg.

While it has been established that cardiovascular mortality risk doubles with each 20/10mmHg increment in blood pressure,[9] targets that are too low are also of concern. Data from patients with stable coronary artery disease being treated for hypertension indicate that SBP <120mmHg and DBP <70mmHg are both associated with adverse cardiovascular outcomes, including mortality.[10] Blood pressure that is too high is associated with stroke, congestive cardiac failure, chronic kidney disease, ischaemic heart disease and peripheral vascular disease; whereas if too low, there is an increased risk of dizziness and falls, acute kidney injury and cardiovascular events.

The HOT study[11] is the only trial targeting DBP that suggests cardiovascular risk reduction in diabetes patients with DBP ≤80mmHg. From the ACCORD study,[12] in which intensive blood pressure-lowering in high-risk T2DM patients targeted SBP <120mmHg, no reduction in fatal and nonfatal major cardiovascular events was evident, although there was stroke reduction. Of note, there was no increase in major cardiovascular events with intensive blood pressure- lowering; however, there were increased adverse events in respect of hypotension, bradycardia or arrhythmia, hyperkalaemia and reduction in glomerular filtration rate (GFR). Another meta-analysis of blood pressure-lowering treatment in hypertensive patients with and without diabetes has shown that in diabetes, there is no further cardiovascular risk reduction benefit with SBP <130mmHg and DBP <80mmHg.[13] Professor Rayner considers the ADA recommendation of <140/90mmHg, or <130/80mmHg if tolerated, to be an appropriate blood pressure target in diabetes.

Table 2. Blood pressure target guidelines (mmHg)

Guideline	All target	If tolerated	Lower limit SBP	Lower limit DBP
ACC/AHA	<130/80	–	–	–
ESC/ESH	<140/90	<130/80	120	70
ADA	<140/90	<130/80	–	–
SAHS	<140/90	–	–	–
SEMDSA	<140/90	130-140/80-90	<130 except for stroke and CKD	80

ACC: American College of Cardiology; AHA: American Heart Association; ESC: European Society of Cardiology; ESH: European Society of Hypertension; ADA: American Diabetes Association; SAHS: South African Hypertension Society; SEMDSA: Society for Endocrinology, Metabolism and Diabetes of South Africa

Approach to drug treatment

An approach to drug treatment for all hypertensives is outlined in Figure 2.[8] ACE inhibitors have shown better cardiovascular benefit than ARBs in diabetes,[13] although there are other meta-analyses that do not show this discrepancy.

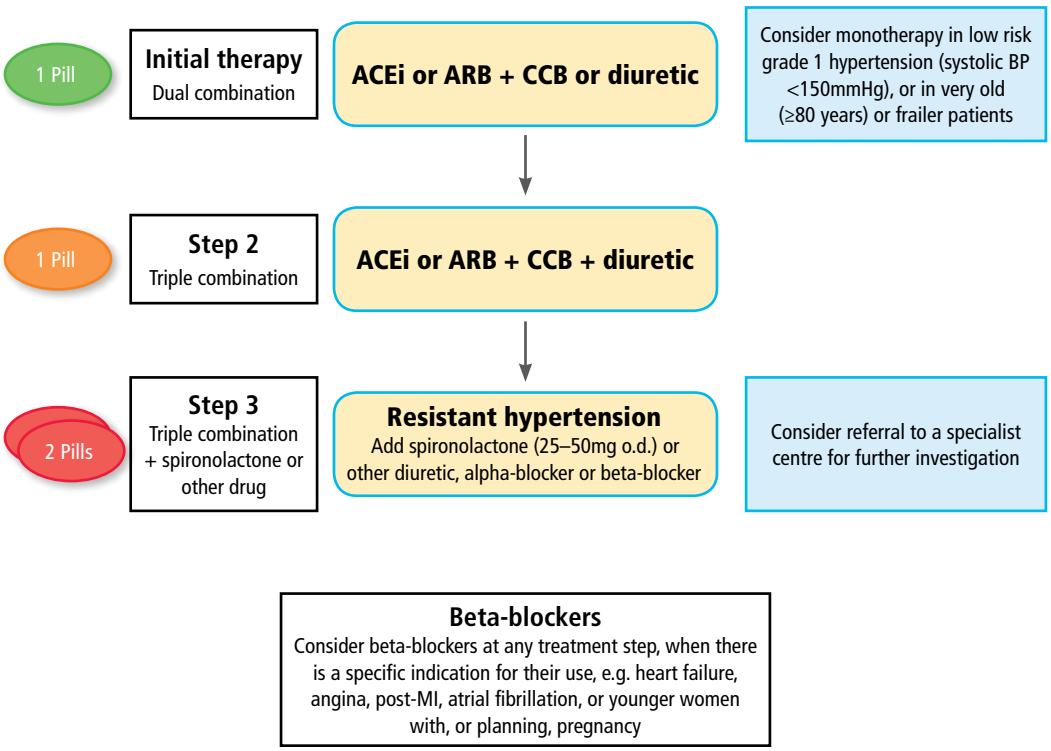

Figure 2. Approach to hypertension drug treatment[8]

Drugs in kidney disease

Renal impairment can alter the pharmacokinetic and pharmacodynamic properties of drugs, thereby increasing the risk of adverse events. Patients with CKD often receive several medications that require dose adjustment and may also have potential for interactions. Professor Okpechi emphasises that safe and effective prescribing requires familiarity with the pharmacokinetic behaviour of drugs in varying stages of renal impairment, and there are many resources available for information on drugs, dosing in renal impairment, nephrotoxicity and dialysis drug removal (e.g. the South African Medicines Formulary, Medscape).

Renal clearance

$$= \frac{\textit{amount of drug in urine}}{\textit{plasma concentration of drug}}$$

Principles of drug therapy, dosing and prescribing in renal impairment

After hepatic metabolism of oral medication, some becomes systemically available in the form of protein-bound or free drug, with the kidney playing a major role in drug elimination (Figure 3). Renal drug clearance is determined by GFR, renal tubular secretion and tubular reabsorption of the drug.

As GFR decreases, drugs dependent on tubular secretion are excreted more slowly. Professor Okpechi reminds us, however, that when GFR is low, drugs that are not tubularly secreted are still affected. A drug with a low molecular weight will be filtered, or a lipid-soluble drug will be reabsorbed; but as GFR decreases, the active transport of the drug is compromised, leading to systemic accumulation.

EARN FREE CPD POINTS
Join our CPD community at www.denovomedica.com and start to earn today!

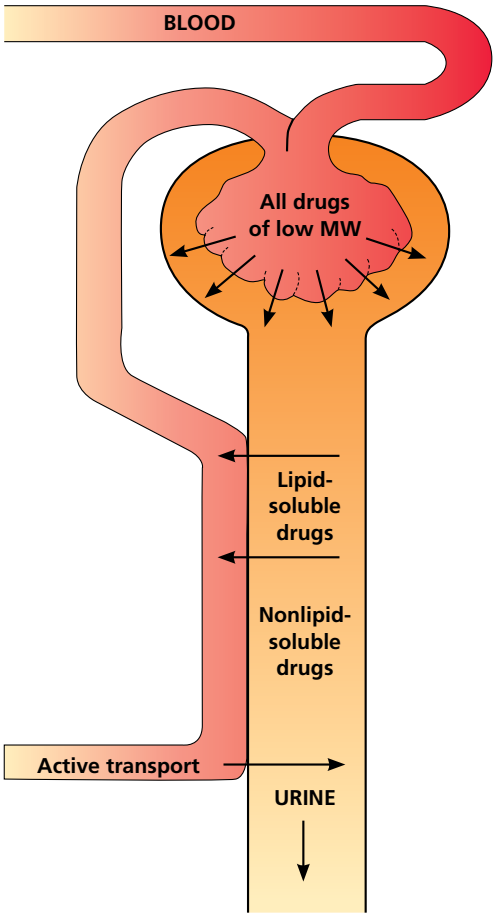

Figure 3. Renal elimination of drugs
https://clinicalgate.com/pharmacokinetics-pharmacodynamics-and-drug-interactions/

Principles of prescribing in CKD and renal replacement therapy

The greater the degree of renal impairment, the greater the need for drug dose modification. Dose modification is usually not clinically necessary until GFR is <30ml/min, where adequately estimating renal function is essential for assessing drug dose (Table 3). Professor Okpechi cautions that the Cockroft-Gault method often underestimates the GFR of the patient; the modification of diet in renal disease (MDRD) equation may overestimate GFR but provides adequate assessment.

Table 3. Methods of assessing GFR

MDRD	GFR = 186 x (serum creatinine: mg/dl)$^{-1.154}$ × (age: years)$^{-0.203}$
Cockroft-Gault	GFR = [(140 – age: years) x weight (kg)]/serum creatinine × 72
CKD-EPI	If serum creatinine ≤0.9mg/dl: GFR = 141 × (Scr/0.9)$^{-0.411}$ × (0.993)$^{\text{age: years}}$ If serum creatinine >0.9mg/dl: GFR = 141 × (Scr/0.9)$^{-1.209}$ × (0.993)$^{\text{age: years}}$

Dose reduction in renal impairment can be carried out using the interval method whereby the same dose is administered less frequently, or the dose method where a smaller dose (usually ~50% of normal dose) is administered at the usual interval schedule. It is also important to know the fraction of the active drug and inactive metabolite that is excreted by the kidney. When 25-50% of the drug is excreted as active metabolite, dose adjustment will be necessary.

Commonly used nephrotoxic drugs are considered in Table 4. It is important that patients with acute kidney injury (AKI) are not initiated on ACE-inhibitor or

ARB therapy, which will reduce intraglomerular pressure and worsen AKI.

Drugs known to be significantly cleared by haemodialysis (Table 5) should be dosed after dialysis where possible. For drugs given as multiple doses, at least one should be given soon after the completion of dialysis. Continuous ambulatory peritoneal dialysis (CAPD) is less efficient than haemodialysis in removing drugs; therefore for patients on CAPD, the need for further dose adjustment because of drug removal is minimal.

Table 4. Commonly prescribed nephrotoxic drugs

Examples	Mechanism	Prevention/management
ACE-i/ARB	Impairment of Ang II–mediated afferent arteriole dilation during renal hypoperfusion	• Withdraw in renal hypoperfusion
Aminoglycosides	In proximal tubules, are taken up into the cell, accumulate, and cause direct toxicity	• Alternative, if possible • Monitor drug concentrations • Avoid multiple daily dosing • Withdraw if creatinine rises
Antivirals	Deposition of drug crystals, intratubular obstruction and foci of interstitial inflammation	• Avoid bolus dose • Reduce dose in renal impairment • Hydrate during therapy
NSAIDs	AKI due to vasoconstriction via ↓ PG production Recruitment and activation of lymphocytes AIN and CIN	• Avoid use • Withdraw during hypoperfusion
Lithium	Impairment of collecting duct concentrating ability → diabetes insipidus CIN (tubular atrophy and interstitial fibrosis)	• Measure plasma concentrations • Prevent dehydration • Avoid thiazides
Proton pump inhibitors	Interstitial nephritis	• Withdraw (±add corticosteroids)
Radiocontrast media	High osmolarity Medullary vasoconstriction ↑active transport in thick ascending loop of Henle → ↑O_2 demand	• Hydration pre- and post-procedure • N-acetylcysteine

AKI: acute kidney injury; PG: prostaglandin; AIN: acute interstitial nephritis; CIN: contrast-induced nephropathy

Table 5. Commonly prescribed drugs significantly cleared by haemodialysis

Antibiotics	Aminoglycosides · amikacin · gentamicin · tobramycin · cephalosporins · cefotaxime · cefazolin · ceftazidime · carbapenems · imipenem · meropenem · metronidazole · penicillins · amoxicillin · ticarcillin · piperacillin · fluoroquinolones · ciprofloxacin · glycopeptides · vancomycin (high-flux dialysers) · teicoplanin · miscellaneous antibiotics · ethambutol · cotrimoxazole
Antifungals	Fluconazole
Antivirals	Acyclovir · cidofovir · famciclovir · foscarnet · ganciclovir · ribavirin · valganciclovir · zidovudine
Antineoplastics	Cyclophosphamide · methotrexate
Antiepileptics	Gabapentin · pregabalin · levetiracetam
Psychotropics	Lithium
Cardiovascular	Sotalol
Antidiabetic	Metformin (in overdose)

EARN FREE CPD POINTS

Join our CPD community at www.denovomedica.com and start to earn today!

SGLT2 inhibition in the diabetic kidney

In T2DM, maladaptive upregulation of sodium-glucose cotransporter type 2 (SGLT2) contributes to hyperglycaemia. Inhibition of SGLT2 effectively improves glycaemic control through inducing glycosuria and also favourably affects body weight, blood pressure, serum uric acid and glomerular hyperfiltration (Figure 4).[14]

The SGLT2 inhibitor, empagliflozin, has been shown to improve both cardiovascular and renal outcomes in patients with T2DM and established cardiovascular disease. In the EMPA-REG OUTCOME trial, those receiving empagliflozin (vs placebo) added to standard care had a lower rate of the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke. The empagliflozin group also had significantly lower risks for hospitalisation for heart failure. There was no significant difference in hospitalisation for unstable angina.[15] Empagliflozin was also associated with slower progression of kidney disease (as defined by incident or worsening nephropathy), a significantly lower risk of progression to macroalbuminuria or clinically relevant renal events such as doubling of serum creatinine level accompanied by GFR ≤45ml/min or initiation of renal replacement therapy.[16] The most common side effects of empagliflozin are urinary tract infection and genital infection.

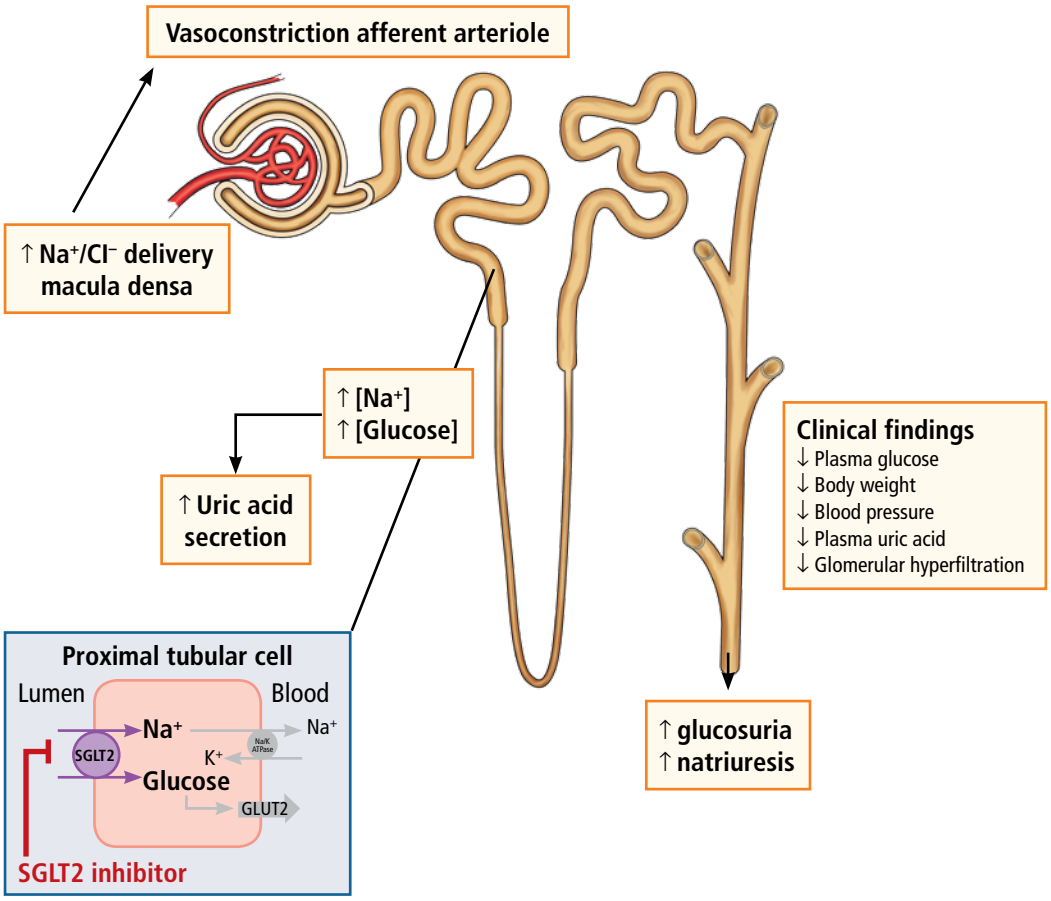

Figure 4. SGLT2 inhibition affects multiple sites in the diabetic kidney[14]

Conclusions

Substantial improvements of cardiovascular and renal outcomes can be expected in T2DM when multiple risk factors are simultaneously targeted.

References

1. De Pablos-Velasco P, Martinez-Martin FJ, Perez FR, *et al*. Prevalence, awareness, treatment and control of hypertension in a Canarian population. Relationship with glucose tolerance categories. The Guía Study. *J Hypertension* 2002; **20**(10): 1965-1971.
2. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; **317**: 703-713.
3. Sattar N. Revisiting the links between glycaemia, diabetes and cardiovascular disease. *Diabetologia* 2013; **56**: 686–695. DOI: 10.1007/s00125-012-2817-5.
4. Kallioinen N, Hill A, Horswill MS, *et al*. Sources of inaccuracy in the measurement of adult patients' resting blood pressure in clinical settings: a systematic review. *J Hypertens* 2017; **35**: 421–441.
5. Myers MG, Godwin M, Dawes M, *et al*. Measurement of blood pressure in the office: recognizing the problem and proposing the solution. *Hypertension* 2010; **55**(2): 195-200. DOI: 10.1161/HYPERTENSIONAHA.109.141879.
6. Pappaccogli M, Di Monaco S, Perlo E, *et al*. Comparison of automated office blood pressure with office and out-of-office measurement techniques. *Hypertension* 2019; **73**(2): 481-490. DOI: 10.1161/HYPERTENSIONAHA.118.12079
7. Pickering TG, Davidson K, Gerin W, *et al*. Masked hypertension. *Hypertension* 2002; **40**: 795-796.
8. Williams B, Mancia G, Spiering W, *et al*. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *J Hypertens* 2018; **36**: 1953–2041.
9. Lewington S, Clarke R, Qizilbash N, *et al*. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903-1913.
10. Vidal-Petiot E, Ford I, Greenlaw N, *et al*. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. *Lancet* 2016; **388**: 2142-2152. DOI: 10.1016/S0140-6736(16)31326-5.
11. Hansson L, Zanchetti A, Carruthers SG, *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998; **351**: 1755-1762.
12. The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; **362**: 1575-1585.
13. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 - Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. *J Hypertens* 2017; **35**(5): 922-944. DOI: 10.1097/HJH.0000000000001276.
14. Van Bommel EJ, Muskiet MH, Tonneijck L, *et al*. SGLT2 inhibition in the diabetic kidney - from mechanisms to clinical outcome. *Clin J Am Soc Nephrol* 2017; **12**(4): 700-710. DOI: 10.2215/CJN.06080616.
15. Zinman B, Wanner C, Lachin JM, *et al*. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; **373**(22): 2117-2128. DOI: 10.1056/NEJMoa1504720.
16. Wanner C, Inzucchi SE, Lachin JM, *et al*. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016; **375**: 323-334. DOI: 10.1056/NEJMoa1515920.

EARN FREE CPD POINTS

Are you a member of Southern Africa's leading digital Continuing Professional Development website earning FREE CPD points with access to best practice content?

Only a few clicks and you can register to start earning today

Visit

www.denovomedica.com

For all Southern African healthcare professionals

This CPD accredited report was compiled by Glenda Hardy on behalf of deNovo Medica.

Find us at

DeNovo Medica

@deNovoMedica

Disclaimer

The views and opinions expressed in the article are those of the presenters and do not necessarily reflect those of the publisher or its sponsor. In all clinical instances, medical practitioners are referred to the product insert documentation as approved by relevant control authorities.

Published by

deNovo Medica

Reg: 2012/216456/07

70 Arlington Street, Everglen, Cape Town, 7550

Tel: (021) 976 0485 | info@denovomedica.com