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Unit No. 2

HALTING CKD PROGRESSION IN PATIENTS WITH DIABETES MELLITUS

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ABSTRACT

Up to 16 percent of the world's population has chronic kidney disease, the leading causes of which are diabetes mellitus, hypertension, and ageing. Diabetic kidney disease (DKD) is classified by severity, like any CKD into five GFR categories (G1-G5) and three albuminuria categories (A1-A3).

This study unit covers:

1. **Chronic kidney disease (CKD) definition revisited, and pathophysiological pathways of DKD;**
2. **The prevalence of DKD and associated risk factors in Singapore, Asia, the United States, and worldwide;**
3. **The natural history of DKD and its diagnosis;**
4. **Delaying progression of DKD. Sodium-glucose transporter 2 inhibitors (SLGT2i) – a new weapon in our war against diabetic nephropathy. Results of early key cardiovascular outcome trials (CVOTs); and**
5. **Evidence-based decision-making in CKD management in diabetes.**

Lifestyle modification, treatment with metformin and ACEI/ARB to control hyperglycaemia, hypertension, and albuminuria are the first steps to halting DKD. SGLT2i and GLP-1 RA are both cardioprotective and renal protective. GLP-1 RA can be considered in patients with DKD who have not achieved glycaemic control despite the use of metformin and SGLT2i. Keeping the healthcare community, patients, and significant others updated on effective DKD care is a challenge.

Keywords: Chronic kidney disease, diabetic kidney disease, prevalence, Asia, cardiovascular outcome trials (CVOTs)

INTRODUCTION

Up to 16 percent of the world's population has chronic kidney disease (CKD).[1] The leading causes of CKD in Singapore are diabetes mellitus, hypertension, and ageing.[2] In its 2020 Annual Report, the Singapore Renal Registry[3] stated that "chronic kidney disease (CKD) is a worldwide epidemic, with diabetes as its leading cause". Halting CKD progression in patients with diabetes mellitus is thus a priority task for the healthcare community.

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THE DEFINITION OF CKD

CKD is defined by KDIGO as abnormalities of kidney structure or function for more than three months with implications for health. Two key criteria for CKD are presence of markers of kidney damage (e.g., Albuminuria with albumin excretion rate ≥30 mg/24 hours or urine albumin-to-creatinine ratio 30 mg/g) and reduced estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73m.[2,4,5]

DKD PATHOPHYSIOLOGICAL PATHWAYS

Diabetes causes kidney damage through two key complex inter-related mechanisms, namely:

- Chronic hyperglycaemia
- Activation of the renin-angiotensin system (RAS)[6,7]

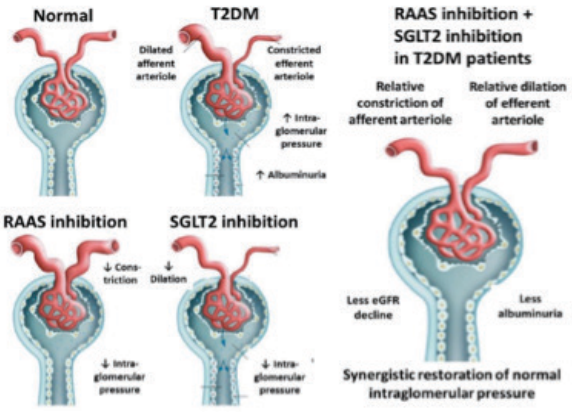


Figure 1-1. Regulation of single nephron glomerular filtration rate in T2DM patients treated with combined RAAS and SGLT2 inhibitors (adapted)[7]

Source: Delanaye P, Scheen AJ. Expert Opinion on Pharmacology (2019) 20:279.

CHRONIC HYPERGLYCAEMIA

Chronic hyperglycaemia results in advanced glycation end-products (AGE) formation and accumulation in the kidney. These end products cause kidney tissue inflammation, thickening of the glomerular basement membrane, and expansion of mesangial matrix.[6]

ACTIVATION OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)

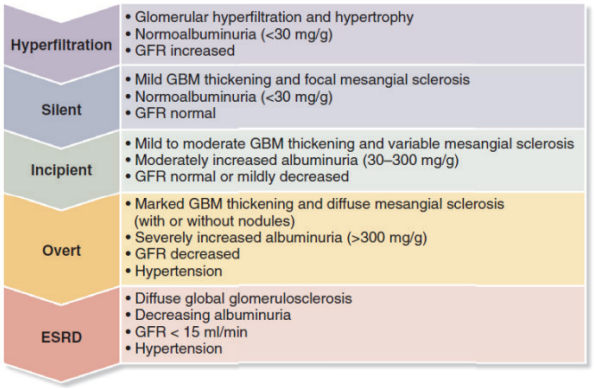
Hyperglycaemia also increases glucose filtered load to the glomerulus and this upregulates the sodium-glucose co-transporters (SGLT-1 and SGLT-2) to reabsorb the increase filtered glucose load. This upregulation of SGLT-1 and

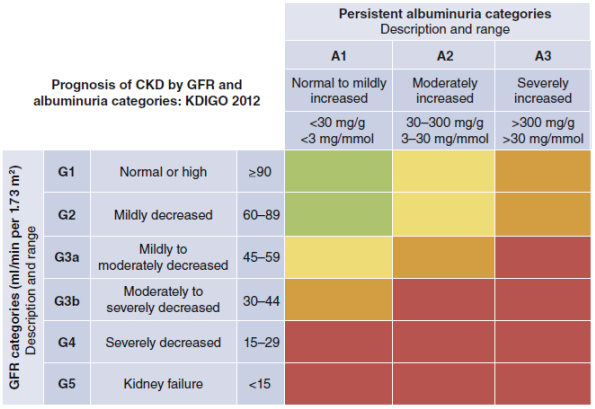
and SGLT-2 reduces delivery of sodium chloride to the distal tubule, which is sensed by the macula densa, and this in turn activates the RAAS, resulting in a relative vasodilatation of the afferent arteriole and a relative vasoconstriction of the efferent arteriole of the glomerulus. All these finally result in increased intraglomerular pressure.[6,7]

RAAS blockade, either with ACE inhibitor (ACEI) or angiotensin receptor blocker (ARB) – but not both, for safety reasons – results in relative efferent arteriole vasodilation. SGLT2i on the other hand, blocks both the glucose and sodium absorption at the proximal tubules and results in the constriction of the afferent arteriole. These agents summate to reduce the intraglomerular pressure back to normal. This results in a decrease in albuminuria, and in the long term, this benefits kidney function.[7] See **Figure 1-1**.

Five stages of diabetic nephropathy or DKD are recognised and these are shown in **Figure 1-2-1** (Samar H, Samh H, 2016).[8] **Figure 1-2-2**[4] shows the risk prediction for the outcome of DKD based on GFR and Albuminuria staging.

Figure 1-2. DKD stages and relationship to GFR and albuminuria





The five DKD stages[8] are:

1. **Hyperfiltration stage** – The GFR is increased beyond normal due to the activation of the RAAS, triggering increased renal plasma flow, resulting in glomerular hyperfiltration. There is normoalbuminuria (<30 mg/g).
2. **Silent nephropathy stage** – The GFR returns to normal. Normoalbuminuria (<30mg/g) is still maintained.
3. **Incipient nephropathy stage** – Moderately increased albuminuria (30-300 mg/g) is present, and GFR remains normal or is mildly decreased.
4. **Overt nephropathy stage** – Severely increased albuminuria (>300 mg/g) is present, and GFR is decreased. Hypertension makes its presence.
5. **End-stage kidney disease (ESKD)** – Decreasing albuminuria, GFR is <15 ml/min, and hypertension is present and may be challenging to control.

EXCLUSION OF OTHER CAUSES OF KIDNEY DISEASE

Diabetic nephropathy is the most prevalent cause of CKD in patients with diabetes. Nevertheless, we should not forget about the non-diabetic kidney disease causes as well. This is especially important when atypical features of CKD are present, namely:

- Sudden onset of a low eGFR or a rapidly decreasing eGFR;
- Sudden increase in albuminuria;
- Development of nephrotic or nephritic syndrome;
- Hypertension that is refractory;
- Appearance of symptoms or signs of another systemic disease; and
- eGFR decline >30 percent within 2-3 months of starting a renin-angiotensin aldosterone system inhibitor.[9]

PREVALENCE OF CKD AND ASSOCIATED RISK FACTORS

Factors Univariate Odds ratio (95 percent CI) for CKD	Univariate Odds ratio (95 percent CI) for CKD	Multivariable Odds ratio (95 percent CI) for CKD	p value
Demographic Factors			
Age (years)			
>65	2.74 (2.65-2.83)	2.54 (2.44-2.64)	**<0.001**
<65	1.00	1.00	
Gender			
Male	1.13 (1.09-1.16)	1.13 (1.09-1.18)	<0.001
Female	1.00	1.00	
Race			
Indian	1.02 (0.95-1.09)	0.77 (0.71-0.83)	<0.001
Malay	1.42 (1.36-1.48)	1.27 (1.20-1.33)	<0.001
Other	1.09 (1.09-1.18)	1.00 (0.91-1.10)	0.742
Chinese	1.00	1.00	-

Lifestyle Factors			
BMI (kg/m^2)			
<18	1.00 (0.88-1.13)	1.06 (0.92-1.22)	<0.531
18-<23	1.00	1.00	
23-<27.5	1.13 (1.08-1.18)	0.97 (0.92 -1.02)	0.402
>27.5	1.39 (1.33-1.18)	1.1 (1.04-1.16)	<0.001
Government-subsidised housing			
Yes	1.30 (1.23-1.37)	1.22 (1.15-1.31)	<0.001
No	1.00	1.00	–
Smoking Status			
Ever[§]	0.93 (0.89-0.98)	0.98 (0.92-1.04)	0.599
Never	1.00	1.00	–
Co-morbid Conditions			
Hypertension			
Yes	4.84 (4.56-5.15)	3.32 (3.09-3.56)	**0.001**
No	1.00	1.00	
Diabetes mellitus			
Yes	6.76 (6.53-7.00)	6.93 (6.67-7.20)	**<0.001**
No	1.00	1.00	
Cardiovascular disease			
Yes	2.05 (1.97-2.14)	1.84 (0.94-3.56)	0.062
No	1.00	1.00	
Stroke			
Yes	1.68 (1.60-1.77)	1.46 (1.36-1.56)	<0.001
No	1.00	1.00	

Figure 2-1. Factors associated with CKD[†] (n=23,015) among adults visiting polyclinics in Singapore
Source: Lew et al, 2018

[†]CKD is defined as (a) eGFR <60 mL/min/1.73 m^2 and/or (b) proteinuria with urine dipstick 1+ or evidence of microalbuminuria for three or more months.

[§]Ever smokers include both current and ex-smokers. Known co-morbidities as documented by physicians in the EHR.

Figure 2-2 shows the risk factors for CKD in 26 Asian countries, Singapore included, published in 2022 by Liyange T et al.[10] Note that out of the 26 countries studied, eight had a prevalence of 10 percent or more with diabetes; 17 had high BP (>140 mmHg); and five had obesity in 10 percent or more of its populations. The corresponding figures for Singapore in this study were: 7.9 percent prevalence for diabetes, 14.6 percent prevalence for BP greater than 140/90 mmHg, and 6.1 percent for BMI >30.

Country	Life expectancy at birth (years)	GNI per capita	Prevalence of diabetes (percent)	Prevalence of BP >140/90 mm (percent)	Prevalence of BMI >30 kg/m2 (percent)
Afghanistan	63.2	520	11.9	30.6	5.5
Bangladesh	74.3	1,750	9.8	24.7	3.6
Bhutan	73.1	2,970	11.8	28.1	6.4
Brunei	74.3	29,390	9.4	18.9	14.1
Cambodia	70.1	1,380	7.1	26.1	3.9
China	77.4	9,600	8.8	19.2	6.2
India	70.8	2,010	8.7	25.8	3.9
Indonesia	71.3	3,850	7.7	23.8	6.9
Iran	77.3	5,300	12.1	19.7	25.8
Japan	84.3	41,150	6.7	17.6	4.3
Laos	68.5	2,450	7.7	24.8	5.3
Malaysia	74.7	10,650	11.1	22.9	15.6
Maldives	79.6	9,210	10.9	24.4	8.6
Mongolia	68.1	3,630	11.7	29	20.6
Myanmar	69.1	1,370	7.4	24.6	5.8
Nepal	70.9	970	10.6	29.4	4.1
North Korea	72.6	No data	5.9	18.2	6.8
Pakistan	65.6	1,480	12.4	30.5	8.6
Philippines	70.4	3,710	7.2	22.6	6.4
Singapore	83.2	57,900	7.9	14.6	6.1
South Korea	83.3	32,730	8	11	4.7
Sri Lanka	76.9	4,040	7.4	22.4	5.2
Taiwan	80.9	26,594	6.6	24.1	8.2
Thailand	77.7	6,600	8.5	22.3	10
Timor-Leste	69.6	1,800	5.5	27.6	3.8
Vietnam	73.7	2,385	5.3	23.4	2.1

Figure 2-2. Country-level sociodemographic characteristics and risk factor prevalence in 26 Asian countries
Source: Liyanage T et al. BMJ Glob Health. 2022 Jan;[7.1] PMID:35078812.

CKD IN THE UNITED STATES

Among the risk factors for CKD in the United States, diabetes is second only to hypertension.[3] Diabetes is responsible for 35 percent of all cases of CKD, and 37 percent of adults with diabetes have CKD. Increasing years of diabetes increase CKD prevalence. Older age, male, ethnicity, family history, obesity, and smoking are risk factors for diabetes in the US. It is likely that these figures are similar with that of other countries worldwide.

With reference to the key statistics of NKF Singapore,[11] it was noted that in 2021, Singapore ranked first in the world for diabetes-induced kidney failure. Additionally , two in three cases of CKD in Singapore were due to diabetes, and one in three CKD patients with diabetes were not aware of their condition and were therefore not treated early.

NATURAL HISTORY OF DIABETIC KIDNEY DISEASE (DKD)

Conceptual model of the Natural History of DKD
Figure 3-1 shows a conceptual model of the natural history of DKD described by Alicic NZ et al.[9]

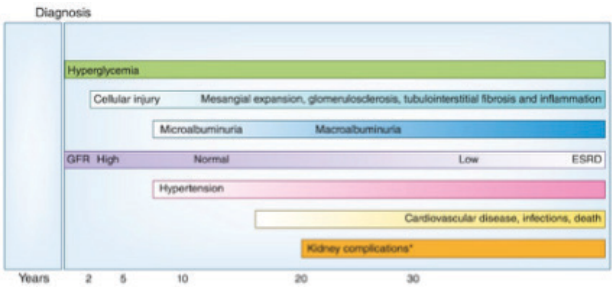


Figure 3-1. Conceptual model of natural history of DKD
Source: Alicic RZ, Rooney MT, Tuttle KR. CJASN 2017. PMID:29253844.[9]

Cellular injury to the kidney begins two years after the onset of diabetes mellitus. Microalbuminuria and hypertension set in between 5 to 10 years, and end-stage renal disease (ESRD) occurs some 20 years after that. As GFR declines further, deaths due to cardiovascular disease and infections start to climb and accompanies the progression to ESRD.[9] In poorly controlled diabetes, the progression of diabetic kidney disease will inevitably be hastened.

ROLE OF RAAS BLOCKADE AND CVOT TRIALS

RAAS blockade, through the use of Angiotensin Converting Enzyme Inhibitors (ACEI) or Angiotensin receptor blocker (ARB), is the cornerstone of CKD retardation strategy. However, that the concurrent use of both ACEI and ARB should be avoided for safety reasons of avoiding hyperkalaemia and acute kidney injury In T2DM.[7]

SGLT2 TUBULOGLOMERULAR FEEDBACK

In normal glucose-tolerant individuals, the afferent renal arteriole arborises into a diffuse capillary tuft that provides the surface area for glomerular filtration. The capillaries then coalesce to form the efferent arteriole. The glucose that is subsequently filtered is reabsorbed along with sodium by SGLT2 (~80-90 percent) and SGLT1 (~10-20 percent). As a result, no glucose reaches the juxtaglomerular apparatus (JGA) and normal tubuloglomerular feedback (TGF) is maintained.[12,13]

SGLT2 UPREGULATION IN POORLY CONTROLLED DIABETES MELLITUS

Figure 4-1[13] shows that in hyperglycaemic individuals with poorly controlled diabetes, the filtered glucose load is increased, and glucose – along with Na+ – reabsorption is increased in the proximal tubule by both SGLT2 and SGLT1. This reabsorption reduces Na+ delivery to the JGA, making the kidney seem under-perfused.

These effects result in local release of renin and angiotensin, resulting in constriction of the adjacent efferent arteriole, and dilation of the afferent arteriole secondary to undefined neurohormonal factors. The net result of these intrarenal haemodynamic changes is an increase in intraglomerular pressure and GFR, which on a long-term basis can cause glomerular damage. Treatment with an SGLT2 inhibitor increases the delivery of glucose, along with Na+, to the JGA, leading to afferent arteriole constriction, decreased intraglomerular pressure, and return of GFR to normal.

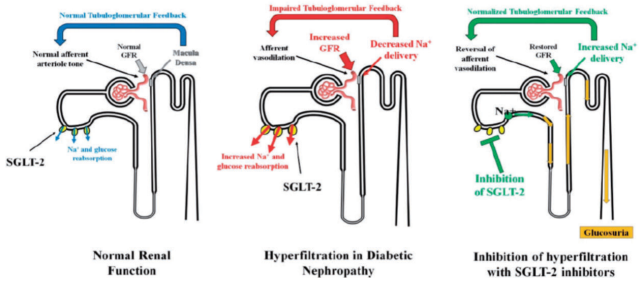


Figure 4-1. SGLT2 inhibitor effects in diabetic kidney disease
Source: Sarafidis et al. Nephrol Dial Transplant (2019):208-230. PMID:30753708.[13]

INITIAL CARDIOVASCULAR OUTCOME TRIALS (CVOTS) AND SURPRISES

CVOTs were initially focused on the reduction of major adverse cardiac events (MACE) and the results of key initial trials are shown in **Figure 4-2**.[14] incidentally, it was found that sodium-glucose co-transporter-2 inhibitors (SGLT2i), besides its cardioprotective benefits, were also effective in retardation of DKD progression. These findings in the CVOTs spurred the subsequent development of the SGLT2i renal outcome trials.

How does SGLT2i work to protect the kidneys? We know that SGLT2i blocks the reabsorption of glucose in the proximal tubule and this inhibits the hyperfiltration of the glomerulus and reduces the intraglomerular pressure to normal. Thus the early CVOT trials – Empagliflozin (EMPA-REG OUTCOME), 2015; Canagliflozin (CANVAS), 2017; and Dapagliflozine (DECLARE-TIMI), 2018 – had renal composite endpoints of HR (95 percent CI) of 0.54 (0.40-0.75), 0.60 (0.47-0.77), and 0.53 (0.43-0.66) provided the initial evidence of the reno-protective effects of SGLT2i.

SGLT2i Trial	Empagliflozin (EMPA-REG OUTCOME), 2015	Canagliflozin (CANVAS), 2017	Dapagliflozin (DECLARE-TIMI), 2018
N; percent male	7020; 71.5	10,142; 64.2	17,160; 62.6
Percentage with established atherosclerotic CV disease	99.2	65.6	40.6
Primary MACE endpoint; HR (95 percent CI)	0.86 (0.74-0.99)	0.86 (0.75-0.97)	0.93 (0.84-1.03)
CV death or hospitalisation for heart failure; HR (95 percent CI)	0.66 (0.55-0.79)	0.78 (0.67-0.91)	0.83 (0.73-0.95)
CV death; HR (95 percent CI)	0.62 (0.49-0.77)	0.87 (0.72-1.06)	0.98 (0.82-1.17)
Myocardial infarction; HR (95 percent CI)	0.87 (0.70 - 1.09)	0.85 (0.69-1.05)	0.89 (0.77-1.01)
Stroke; HR (95 percent CI)	1.24 (0.92-1.67)	0.90 (0.71-1.15)	1.01 (0.84-1.21)
Hospitalisation for heart failure; HR (95 percent CI)	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.73 (0.61-0.88)
Renal composite endpoint; HR (95 percent CI)	0.54 (0.40-0.75)	0.60 (0.47-0.77)	0.53 (0.43-0.66)

Figure 4-2. SGLT2i and efficacy outcomes in landmark Cardiovascular Outcome Trials[14]
Source: Mottl A. Journal of Family Practice 2021. 70:6. Page S61. PMID:34432626.

With the decline in eGFR as DKD progresses, what management strategies do we have? The concept of SGLT2i or Glucagon-like peptide-1 receptor agonists (GLP-1 RA) selection based on kidney failure stratification has been described by Li Jiahua et al.[15] The details are summarised in **Figure 4-3**. Note that with eGFR >60ml/min per 1.73 m^2 all the way down to 30 ml/min per 1.73 m2, SGLT2i or GLP1-RA can be used and SGLT2i is preferred over GLP-1 RA. Below eGFR of 30 ml/min per 1.73m^2, GLP1-RA is preferred.

eGFR	UACR <30 mg/g	UACR 30-299 mg/g	UACR >300 mg/g
>60 ml/min per 1.73m^2	SGLT2i or GLP1-RA	SGLT2i is preferred. GLP1-RA as an alternative if SGLT2i is contraindicated or not tolerated, and as an add-on for uncontrolled metabolic risk	SGLT2i should be initiated GLP1-RA as an add-on for controlled metabolic risk
30-60 ml/min per 1.73m^2	SGLT2i is preferred. GLP1-RA is an alternative if SGLT2i is contraindicated or not tolerated, and as an add-om for uncontrolled metabolic risk		SGLT2i should be initiated GLP1-RA as an add-on for controlled metabolic risk
15-29 ml/min per 1.73m^2	GLP1-RA (dulaglutide) is preferred.		

The more recent landmark DAPA-CKD trial further demonstrated the SGLT2i's (Dapagliflozin) potential to benefit patients with chronic kidney disease. It also showed the safety and tolerability of dapagliflozin, which was established in the earlier cardiovascular outcome trials. Even among non-diabetic trial participants, neither diabetic ketoacidosis nor severe hypoglycaemia was observed. Based on the trial findings, dapagliflozin can now be used in patients with an eGFR of 25 ml/min per 1.73m^2 and above.

In Singapore, just as in the US, based on the new evidence from the recent trials, dapagliflozin has been approved for use by HSA for the new indication of CKD treatment in patients with and without Type 2 diabetes mellitus. CKD treatment indication has not yet been approved by HSA for empagliflozin, pending results from EMPA-KIDNEY trial expected near the end of 2022. **Figure 4-4** is therefore useful in the interim.

SGLT2i	Dapagliflozin	Empagliflozin	Canagliflozin
eGFR cut-off (ml/min/1.73m^2) for initiation			
CKD treatment (Patients with T2DM)	≥25 (10 mg) continue until dialysis	Not HSA Approved	≥30 (100 mg) continue until dialysis
CKD treatment (Patients without T2DM)		Not HSA Approved	Not HSA Approved
HFrEF[#] treatment (Patients with/without T2DM)		≥20 (10 mg)	Not HSA Approved

Figure 4-4. Lower limits of SGLT2 inhibitors in DKD[16]
Source: Singhealth Renal Retardation Programme (SiRRP) Clinical Guide Mar 2022.

[#]HFrEF=Heart failure with reduced ejection fraction (LVEF <40 percent). The glucose-lowering efficacy of dapaglifozin is reduced in patients with eGFR <45 ml/min/1.73m^2. Additional glucose-lowering treatment may be considered to achieve glycaemic target.

DELAYING CKD PROGRESSION IN DIABETES

Glucose and blood pressure control are crucial in slowing the onset and progression of CKD in type 2 diabetes (see **Figure 5.1** (KDIGO, 2020)).[17] Note the six lifestyle management items for all patients. For most diabetic patients, RAAS inhibitors and SGLT2i will be prescribed as they develop persistent or worsening albuminuria.

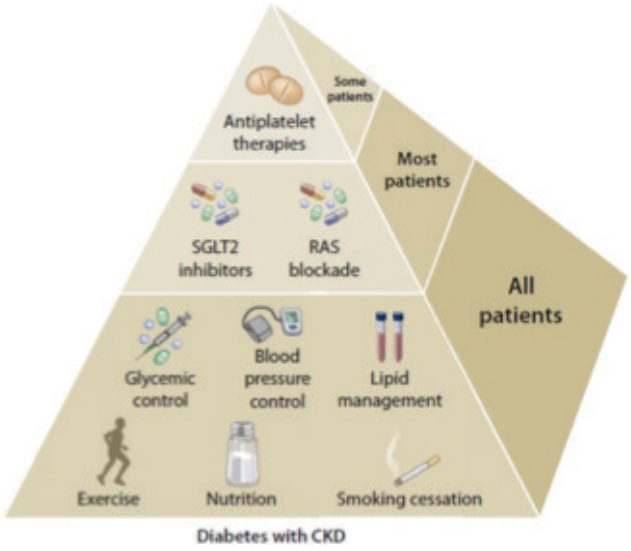


Figure 5-1. Evidence-based decision-making on management of T2DM and CKD – Lifestyle management and medications[17]
Source: KDIGO, 2020. Source: KDIGO 2020 CPG for DM Mgt in CKD. PMID:32998798 PMID:32998798.

At the early stages of diabetic kidney disease, lifestyle strategies of exercise, smoking cessation, and avoidance of excessive intake of carbohydrates and salt are important in complementing the pharmacological measures in retarding CKD progression. In addition, they will also allow patients to achieve better glycaemic, blood pressure, and lipid control, which provides significant cardiovascular benefits. Metformin can be used to promote insulin sensitivity in patients with eGFR greater than 30 ml/min per 1.73 m^2 to improve their glycaemic control. It is recommended as a first-line treatment together with an SGLT2i in most patients with Type 2 DM and CKD.

As DKD advances, a combination therapy of RAAS Blockade, SGLT2i, and GLP-1 RA may be progressively added. The choice of alternative glucose-lowering drugs (other than SGLT2i & metformin) can be decided based on patient preference categories (KDIGO, 2020 CPG for DM Management in CKD.[18] See **Figure 5-2**). As an example, in an obese patient in whom weight loss is desired, GLP-1 RA may be a more suitable choice, as opposed to a sulphonylurea (SU) or insulin therapy.

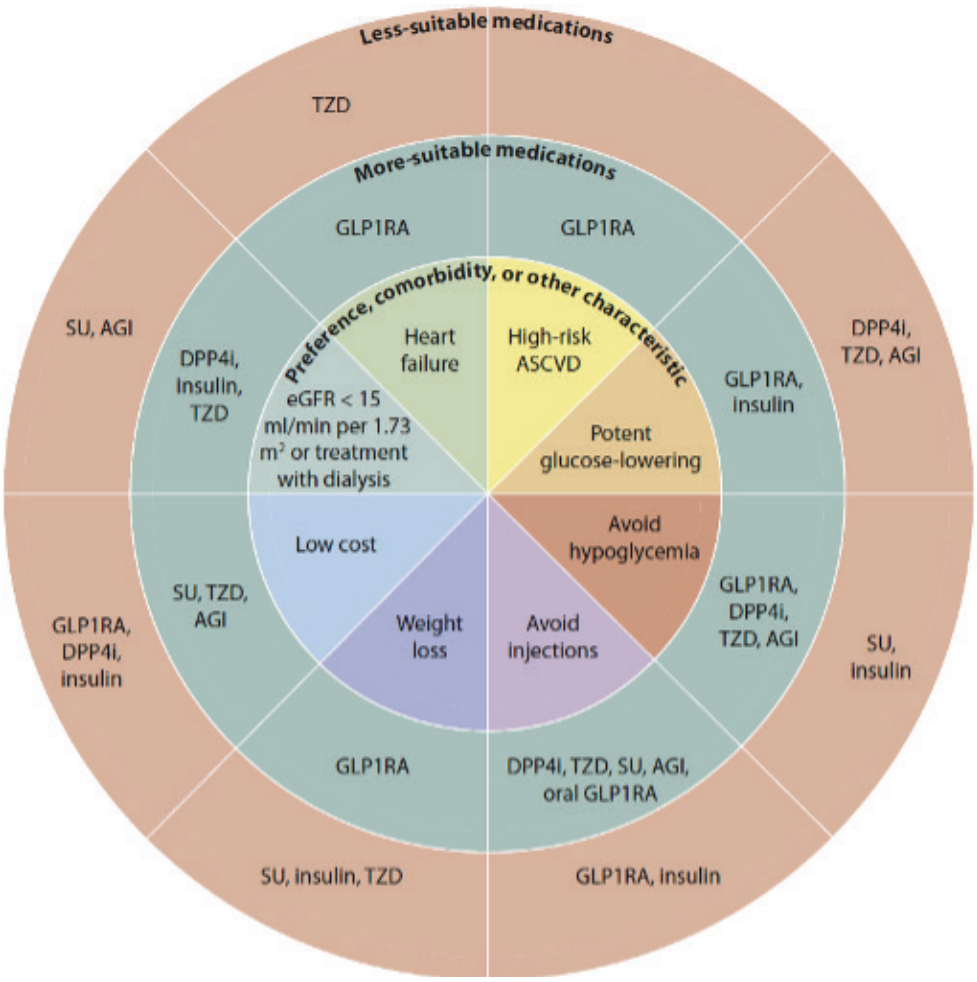


Figure 5-2. Choice of glucose lowering drugs (other than SGLT2i & Metformin) based on patient preference categories[17]

Source: KDIGO 2020 CPG for DM Mgt in CKD. PMID:32998798.

CONCLUSION

DKD is the leading cause of chronic kidney disease in Singapore, Asia, the US, and worldwide. Patients with diabetes and CKD should be treated with a comprehensive strategy incorporating multidisciplinary team-based care, patient education, lifestyle modification, and evidenced-based pharmacological therapies described in the sections above to "HALT" the progression of CKD as well as to reduce the risks of cardiovascular adverse events.

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LEARNING POINTS

- **What is known?**
- **The "traditional" Halt-CKD strategies are:**
  - **Lifestyle modifications: dietary sodium intake restriction, weight management, and smoking cessation**
  - **Optimising glycaemic control**
  - **Optimising BP control**
  - **Instituting pharmacological agents with reno-protective effects e.g. RAAS blockers**
- **What is new?[15,18]**
- **SGLT2i and GLP1-RA reduce cardiovascular events. SGLT2i is preferred in patients with heart failure and CKD**
- **In patients with T2DM who are unable to achieve glycaemic targets with lifestyle therapy, metformin and SGLT2i, GLP-1 RA is preferred among patients with established ASCVD and CKD.**
- **SGLT2i can now be initiated in both T2DM and non-T2DM patients with CKD, and eGFR ≥ 25ml/min/1.73m^2**
- **GLP-1 RA should not be initiated in T1DM patients and in T2DM patients whose eGFR is less than 15ml/min/1.73m^2 (eGFR Cut-offs vary among the various agents, e.g., Liraglutide >15ml/min/1.73m^2, Semaglutide >30ml/min/1.73m^2, Semaglutide >30ml/min/1.73m^2**
- **Future research**
- **The efficacy of combined use of SGLT2i and GLP-1 RA is not fully known[15]**