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REVIEW ARTICLE

Second revolution in cardiovascular prevention

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Abstract Type 2 diabetes has become a major disease burden in twenty-first century. Both incidence and prevalence of type 2 diabetes have quadrupled between 1980 and 2004 in the whole world. Atherosclerotic cardiovascular disease (ASCVD) is the major complication of type 2 diabetes. The introduction of statins in clinical settings is the first revolution in our battle against ASCVD. Most ASCVDs could be prevented or treated with statins. However, statin failed to reduce chronic kidney diseases (CKD) and heart failure (HF). Owing to a mandate from US Food and Drug Administration in 2008 that every new antidiabetic drug should be tested in clinical trials to demonstrate its safety, we now have a good opportunity to look for better antidiabetic drugs not only to decrease blood sugar but also to decrease CVD or renal disease. Among them, glucagon-like peptide-1 receptor agonists and sodium-glucose transport protein 2 inhibitors (SGLT-2 i) are two most extensively studied ones. SGLT-2 i, in particular, prevent CKD and end-stage renal disease, and prevent HF. In the recent CREDENCE trial, canagliflozin reduced renal endpoints by 34% and end-stage renal disease by 32%. Furthermore, in the recent DAPA-HF trial, dapagliflozin decreased hospitalization for HF/cardiovascular death by 26%, and total death by 17%, in patients with HF with reduced ejection fraction, irrespective of diabetes or nondiabetes. The beneficial effects of SGLT-2 i in CKD and HF are complementary to the effects of statins. The introduction of SGLT-2 i in clinical practice is the second revolution in cardiovascular prevention.

Keywords: Cardiovascular disease; Chronic; Diabetes mellitus, Type 2; Heart failure; Renal insufficiency; Sodium-glucose transporter 2 inhibitors

1. INTRODUCTION

Cardiovascular disease (CVD) remains the number 1 killer in the world.[1] Controlling major risk factors can reduce atherosclerotic cardiovascular disease (ASCVD).[2] Among all these risk factors, type 2 diabetes is becoming more important. Type 2 diabetes has become a major disease burden in twenty-first century. Both the incidence and prevalence of type 2 diabetes have quadrupled between 1980 and 2004 in the whole world.[3] The total diabetic population will increase from 415 million in 2015 to 642 million by 2040,[4] much higher than those of hypertension and hyperlipidemia. Patients with type 2 diabetes generally die from ASCVD.[5] Furthermore, ASCVD may occur 10 to 15 years before the clinical diagnosis of diabetes.[6]

The introduction of statins in clinical settings is the first revolution in our battle against ASCVD.[7] Most ASCVDs could be prevented or treated with statins. However, statins had some limitations that they failed to reduce chronic kidney diseases (CKD)[8,9] and heart failure (HF).[10,11] Therefore, we need a second revolution in dealing with ASCVD.

2. FIRST REVOLUTION IN CARDIOVASCULAR PREVENTION

An extensive body of evidence demonstrates that statin therapy effectively prevents and treats coronary heart disease (CHD), myocardial infarction (MI), ischemic stroke, and peripheral artery diseases.[7] Therefore, the discovery and use of statins can be regarded as the first revolution in CV prevention (Table 1). However, statins have important limitations. Statins could not prevent CKD,[12] nor improve renal function in patients with established CKD.[13,14] Statins might decrease CV events in patients with CKD,[14] but not in patients with end-stage renal disease (ESRD).[8,9] Furthermore, statins could not prevent HF,[15] nor treat patients with established HF.[11] These drawbacks of statins limit more extensive use, given that CKD and HF have becoming the final common events of many CV diseases and diabetes.[16–18]

3. PREVIOUS "LOWER IS BETTER" TRIALS FOR TYPE 2 DIABETES

Although plenty of evidence suggested an association of hyperglycemia and increased risk of ASCVD, intensive glucose reduction did not reduce ASCVD in four major randomized controlled trials (RCTs) (Table 2).[19–22] Why decreases in blood sugar could not be translated to a reduction in ASCVD was still unknown. One

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Table 1

First revolution in cardiovascular prevention with the use of statins

	Prevention	Treatment
Coronary heart disease	V	V
Myocardial infarction	V	V
Stroke	V	V
Peripheral artery disease	V	V
Chronic kidney disease (1-4)	X	V
End-stage renal disease	X	X
Heart failure	X	X

possible reason was that durations of these RCTs were too short, as more extended follow-up studies of these trials did show some positive findings (Table 2). It is generally believed that with traditional antidiabetic drugs, it might take 10 years to show their benefits in reducing macro-vascular diseases. Interestingly, a meta-analysis comprising five RCTs[19–22,27] did show a benefit of lowering glucose in reducing nonfatal MI and CHD.[28] A more recent meta-analysis also showed a benefit of using safer antidiabetic agents (dipeptidyl peptidase-4 inhibitors [DPP-4 i], glucagon-like peptide-1 receptor agonist [GLP-1 RA], and sodium/glucose transporter 2 inhibitors [SGLT-2 i]) in reducing macro-vascular diseases.[29]

4. WHAT HAPPENED IN 2007-2008?

In 2007, a provocative meta-analysis claimed that rosiglitazone was associated with significant increases in the risk of MI and CV death.[30] As a consequence, the US Food and Drug Administration (FDA) issued a mandate in December 17, 2008 that rigorous assessment of the CV safety was needed for all new antidiabetic drugs. Only noninferiority, instead of superiority, trials were required. The European Medicines Agency also followed the same regulatory requirement since 2012. Since then, >250 000 patients were enrolled in several CV outcome trials, and more than half of these RCTs have been completed and published.[31] These RCTs enrolled all or some patients with preexisting ASCVD, and the CV outcomes correlated with the severity of underlying CV risk levels (Fig. 1). In spite that these trials had been designed to show noninferiority vs. placebo, it was very surprising that some of these trials showed superiority versus placebo. Without these large-scaled outcome trials, we never would be able to know their broad and substantial benefits. From this view point, the issuing of the mandate by FDA in 2008 was a wonderful mistake.

5. RCTS OF DPP-4 INHIBITORS

DPP-4 inhibitors have modest glucose-lowering effects. Four DPP-4 inhibitors have been tested in CV outcome trials.[32–35] The only exception is vildagliptin. Results of these RCTs are shown in Table 3. None of these drugs could decrease major adverse cardiovascular events (MACE), CKD, and HF. There was an increase in the risk of HF by saxagliptin in the SAVOR trial.[32] The advantage of using DPP-4 inhibitors lies in their good safety profiles, including a very low risk of hypoglycemia.

6. RCTS OF GLP-1 RECEPTOR AGONISTS

GLP-1 RAs have more potent glucose-lowering effects than DPP-4 inhibitors. GLP-1 RAs can be classified into two groups based on their structure: those containing exentin-4 backbone and human GLP-1 backbone. Two exentin-4 backbone GLP-1 RAs (lixisenatide and exenatide) have been tested and failed to decrease MACE (Table 4).[36,37] On the other hand, human GLP-1 backbone GLP-1 RAs, except oral semaglutide, successfully decreased MACE and decreased all-cause mortality in some trials (Table 4).[38–42] ASCVDs, including MI and stroke, were generally decreased by GLP-1 RAs, suggesting an antiatherosclerotic effect. Some of them decreased renal events, but none of them was able to decrease hospitalization for HF (HHF).[43]

7. RCTS OF SGLT-2 INHIBITORS

SGLT-2 i inhibit sodium glucose transporter in the proximal tubule in the kidney,[44] resulting in glucosuria, a decrease in blood glucose, and body weight loss about 3 to 4 kg.[45] SGLT-2 i also cause osmotic diuresis and natriuresis.[46] The hemodynamic effects include a decrease in blood pressure,[47] and tissue sodium[48] and tissue water.[49,50] The preload and afterload decrease in the CV system. It has been shown that SGLT-2 i decreased left ventricular (LV) mass and improved LV diastolic function in diabetic patients.[51] Another important effect of SGLT-2 i is on the Na^+/hydrogen exchanger.[52,53] SGLT-2 i directly inhibited Na^+/hydrogen exchanger 1 in the myocardium, and reduced cytoplasmic NA^+ and Ca^{++},[49,54] resulting in a reduction in intracellular calcium overload and cardiac protection.[55]

Type 2 diabetes, CKD, and HF have interconnected pathways and share several metabolic and signaling cascades.[56] Two most important effects of SGLT-2 i are their renal protective effect and their potential benefits in decreasing HF. After the use of SGLT-2 i, there is an increase in sodium output into distal tubule, stimulating the juxtaglomerular apparatus, and causing vasoconstriction of afferent arteriole.[57,58] The decrease in the intraglomerular pressure protects glomerulus.[57,58] In older diabetic patients who did not have HF, SGLT-2 i ameliorated the increase in N-terminal pro B-type natriuretic peptide.[59] SGLT-2 i also increased ketone body in the blood and might enhance myocardial energetics.[60] Interestingly, CKD and HF can now be managed with SGLT-2 i, which could not be solved by statins.

Table 2

"Lower is better" trials

	UKPDS[19]	ACCORD[20]	ADVANCE[21]	VADT[22]
Age	53	62	66	60
Duration of diabetes (y)	0	10	8	12
Prior CVD (%)	0	35	32	40
FU (y)	10	3.7	5	5.6
MI (HR)	0.84 (p = 0.052)	0.80 (p = 0.015)	1.01 (p = NS)	0.88 (p = NS)
Total death (HR)	0.94 (p = NS)	1.22 (p = 0.04)	0.93 (p = NS)	1.07 (p = NS)
Extended FU (y)	20[23]	4.8[24]	11[25]	12[26]
MI (HR)	0.85 (p = 0.01)	0.84 (p = 0.02)	1.02 (p = NS)	0.83 (p = 0.04)
Total death (HR)	0.87 (p = 0.007)	NR	1.00 (p = NS)	1.05 (p = NS)

CVD = cardiovascular disease; FU = follow up; HR = hazard ratio; MI = myocardial infarction; NS = nonsignificant; RRR = relative risk reduction.

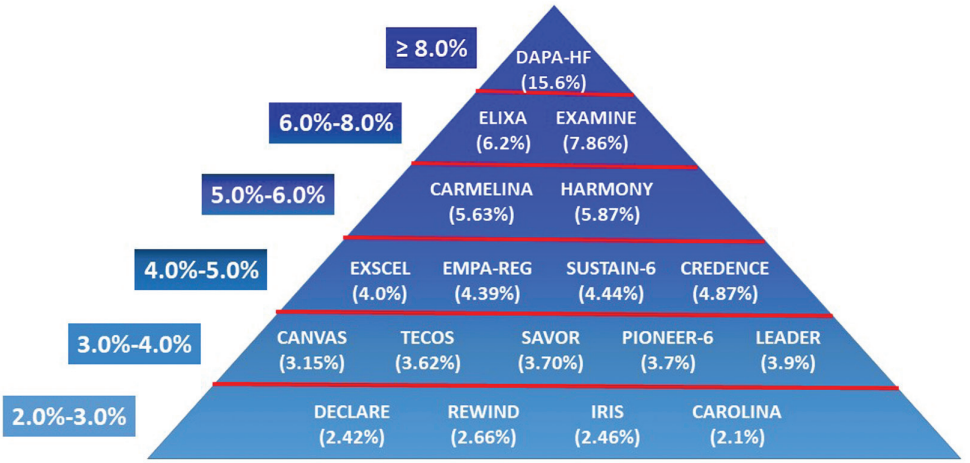

Fig. 1 Cardiovascular outcome trials of new antidiabetic drugs. The hierarchy was on the basis of the underlying cardiovascular risk levels. The percentages on the left hand side were the event rates of the placebo groups in individual trials.

There are four CV outcome trials of SGLT-2 i (Table 5).[61–64] Three of them successfully demonstrated a marginal effect in reducing MACE, except the DECLARE trial which enrolled more low-risk patients.[63] There were no significant antiatherosclerotic effects, given that MI and stroke were no decreased. Two most striking findings were significant decreases in renal events and HHF.

8. EFFECTS OF SGLT-2 INHIBITORS ON RENAL EVENTS

Type 2 diabetes is one of the major causes of CKD and ESRD.[65] The number of people who receive renal replacement therapy for ESRD worldwide is projected to increase from 2.6 million in 2010, to >5 million in 2030.[65]

8.1. Prevention

The efficacy in prevention of renal events has been shown in three RCTs of SGLT-2 i.[61,62,66] In general, SGLT-2 i decreased 30% to 50% composite renal endpoints and 50% to 70% ESRD.[61,62,66] The renal protective effect is about two-fold that of ARBs.[67,68] After 15 years of the discovery of ARBs' renal protective effects, we now have a second renoprotective drug. Their potential use in nondiabetic patients will be answered by the ongoing EMPA-KIDNEY (NCT03594110) and DAPA-CKD (NCT03036150) trials.

Table 3

Cardiovascular outcome trials of DPP-4 inhibitors

Trial name	SAVOR[32]	EXAMINE[33]	TECOS[34]	CARMELINA[35]
Drug name	Saxagliptin	Alogliptin	Sitagliptin	Linagliptin
CVD history (%)	78.7%	100%	74.5%	57%
MACE (HR)	1.00	0.96	0.99	1.02
MI (HR)	0.95	1.08	0.95	1.12
Stroke (HR)	1.11	0.91	0.97	0.91
CV death (HR)	1.03	0.85	1.03	0.96
HHF (HR)	1.27[a]	1.07	1.00	0.90
Renal events (HR)	1.08	NR	NR	1.04
All-cause death (HR)	1.11	0.88	1.01	0.98

CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; HHF = hospitalization for heart failure; HR = hazard ratio; MACE = major adverse cardiovascular events; MI = myocardial infarction; NR = not reported.

[a]Saxagliptin increased hospitalization for heart failure in the SAVOR trial ($p = 0.007$). Other statistics were negative.

8.2. Treatment

The CREDENCE trial enrolled patients with type 2 diabetes and albuminuric CKD.[64] All the patients had an estimated glomerular filtration rate (eGFR) of 30 to 90 mL/min and albuminuria, and were treated with renin–angiotensin system (RAS) blockade.[64] Canagliflozin decreased composite renal events by 34% and ESRD by 32%. MACE and HHF were also decreased significantly (20% and 39%, respectively).[64] This trial established the role of SGLT-2 i in the treatment of diabetic kidney disease (DKD).[69]

8.3. Earlier is better

The DECLARE trial enrolled low-risk patients, and about 60% of patients were devoid of any history of CVD.[63] The average eGFR was 86 mL/min. The CREDENCE trial enrolled patients with preexisting DKD and the average eGFR was 56 mL/min.[64] The risk of developing renal endpoints in the placebo group was 1.41%/y in the DECLARE trial, about a quarter of that in the CREDENCE trial (6.12%/y) (Fig. 2A). Likewise, the risk of MACE in placebo group in the DECLARE trial is only 2.42%/y, about a half of that in the CREDENCE trial (4.87%/y) (Fig. 2B) It is very clear that "earlier is better" for the management of CKD in type 2 diabetes.

9. EFFECTS OF SGLT-2 INHIBITORS ON HF

9.1. A deadly duo

Patients with type 2 diabetes have a two-fold increase in the risk of developing HF.[70] HF has becoming an important complication for patients with type 2 diabetes. In a recent study from the United States, HF was more common than acute coronary syndrome for adult diabetic patients.[71] In a recent Swedish registry, controlling five major risk factors, including blood sugar, cannot prevent HF.[2] None of antidiabetic drugs, except SGLT-2 i, could reduce the risk of HF.

The prevalence of the Stage C HF, that is, symptomatic ones, in diabetic patients is around 12%.[72,73] However, >70% of asymptomatic diabetic patients have Stage B HF.[16] Diabetic patients who have symptomatic HF have a 2.5-fold increased risk of death and a five-fold increased risk of HHF.[74] Elderly patients who have incident HF have a 10-fold increased risk of death.[75]

The prevalence of diabetes in HF patients was around 20% from most of the Western studies.[17] In a recent ASIAN-HF

Table 4

Cardiovascular outcome trials of GLP-1 receptor agonists

Trial name	ELIXA[36]	EXSCEL[37]	LEADER[38]	SUSTAIN-6[39]	PIONEER-6[40]	HARMONY[41]	REWIND[42]
Drug name	Lixisenatide	Exenatide-ER	Liraglutide	Semaglutide	Oral semaglutide	Albiglutide	Dulaglutide
CVD history (%)	100	70	81	83	85	100	31
MACE (HR)	1.02[a]	0.91	0.87* ($p = 0.01$)	0.74* ($p = 0.02$)	0.79	0.78* ($p < 0.001$)	0.88* ($p = 0.026$)
MI (HR)	1.03	0.97	0.88	0.74	1.18	0.75* ($p = 0.003$)	0.96
Stroke (HR)	1.12	0.85	0.89	0.61* ($p = 0.04$)	0.74	0.86	0.76* ($p = 0.01$)
CV death (HR)	0.98	0.88	0.78* ($p = 0.007$)	0.98	0.49* ($p < 0.05$)	0.93	0.91
HHF (HR)	0.96	0.94	0.87	1.11	0.86	0.85	0.93
Renal events (HR)	1.16	0.88	0.78* ($p = 0.003$)	0.64* ($p = 0.005$)	NR	NR	0.85* ($p < 0.001$)
All-cause death (HR)	0.94	0.86* ($p < 0.05$)	0.85* ($p = 0.02$)	1.05	0.51* ($p < 0.05$)	0.95	0.90

CVD = cardiovascular disease; GLP-1 = glucagon-like peptide-1; HHF = hospitalization for heart failure; HR = hazard ratio; MACE = major adverse cardiovascular disease; MI = myocardial infarction; NR = not reported.

[a]Four-point MACE (CVD, MI, stroke, and hospitalization for unstable angina).

*p value < 0.05.

registry, the prevalence of diabetes was around 40% in 11 Asian countries,[18] much higher than that from the Western countries.[17]

9.2. Prevention

In the four RCTs of SGLT-2 i, only a few patients had prior HF (10.5% in the EMPA-REG trial,[61] 14.4% in the CANVAS trial,[62] 10.2% in the DECLARE trial,[63] and 14.8% in the CREDENCE trial[64]) (Table 5). HHF was significantly reduced in all four trials. The DECLARE trial is the only one to put HHF/CV death as primary endpoints, and the use of dapagliflozin clearly reduced 17% of HHF/CV death ($p = 0.005$).[63] SGLT-2 i is the first antidiabetic drug capable of preventing HHF/CV death.

A useful clinical scoring system (TIMI Risk Score for Heart Failure in Diabetes [TRS-HF_{DM}]) has recently been proposed to predict the risk of developing HF in diabetic patients who do not have prior HF.[76] It was derived from the SAVOR trial[32] and validated in the DECLARE trial.[63] There were five risk indicators: prior HF (two points), atrial fibrillation (one point), CHD (one point), eGFR <60 mL/min (one point), and urine albumin to creatinine ratio (>300 mg/g, two points and 30-300 mg/g, one point).[76] Those with a total score ≥2 have a relatively high risk of developing HF, and targeting preventive medications such as SGLT-2 i in these patients may have a high cost-effectiveness (number to treat [NNT] 36 for score ≥3, and NNT 65 for score = 2).[76]

9.3. Treatment

In a subanalysis of 671 patients with HF reduced ejection fraction (HFrEF) in the DECLARE trial, dapagliflozin reduced HHF/CV death by 38% ($p = 0.046$), and all-cause death by 41% ($p = 0.016$).[77] These data suggested a potential use of SGLT-2 i in patients with HFrEF. Can an antidiabetic drug be re-purposed to treat HF? Many will argue about their effects in nondiabetics. Throughout the medical history, in fact, there are many successful examples to re-purpose drugs to extend their use (Table 6).

There are five large-scaled RCTs dedicated to study the effect of SGLT-2 i in patient with HF. Three of them were performed in patients with HFrEF: (EMPEROR-REDUCED [NCT03057977], DAPA-HF [NCT03036124],[78] and SOLOIST-WHF [NCT03521934]). Two of them were performed in patients with HF with preserved EF (EMPEROR-PRESERVED [NCT03057951], and DELIVER [NCT03619213]). SOLOIST-WHF enrolled only diabetic patients, while other four trials enrolled both diabetic and nondiabetic patients. DAPA-HF is the first completed one.[78] The other four trials will be finished before the end of 2021.

9.4. DAPA-HF trial

DAPA-HF trial is the only one that has been completed among these five trials.[78] Actually it has been prematurely stopped at 18 months due to an early demonstration of its efficacy. Among the 4744 patients with HFrEF, dapagliflozin 10 mg significantly decreased HHF/CV death (hazard ratio [HR], 0.74; 95% CI, 0.65-0.85; $p < 0.001$), and all-cause death (HR, 0.83; 95% CI, 0.71-0.97; $p = 0.022$).[78] There were 20 countries participated and Taiwan randomized 141 patients. Two most important subgroup analyses showed dapagliflozin reduced HHF/CV death in both diabetic and nondiabetic patients (HR, 0.75; 95% CI, 0.63-0.90, and HR, 0.73; 95% CI, 0.60-0.88, respectively;

Table 5

Cardiovascular outcome trials of SGLT-2 inhibitors

Trial name	EMPA-REG[61]	CANVAS[62]	DECLARE[63]	CREDENCE[64]
Drug name	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin
CVD history (%)	100%	65.6%	40.6%	50.4%
MACE (HR)	0.86* ($p = 0.04$)	0.86* ($p = 0.02$)	0.93	0.80* ($p = 0.01$)
MI (HR)	0.87	0.89	0.89	0.70
Stroke (HR)	1.18	0.87	1.01	0.60
CV death (HR)	0.62* ($p < 0.001$)	0.87	0.98	0.78
HHF (HR)	0.65* ($p = 0.002$)	0.67* ($p = 0.002$)	0.73* ($p < 0.001$)	0.61* ($p < 0.001$)
Renal events (HR)	0.54* ($p < 0.001$)	0.60* ($p < 0.001$)	0.53* ($p < 0.001$)	0.70* ($p < 0.001$)
All-cause death (HR)	0.68* ($p < 0.001$)	0.87	0.93	0.83

CVD = cardiovascular disease; HHF = hospitalization for heart failure; HR = hazard ratio; MACE = major adverse cardiovascular events; MI = myocardial infarction; NR = not reported; SGLT-2 = sodium-glucose transport protein 2.

*p value < 0.05.

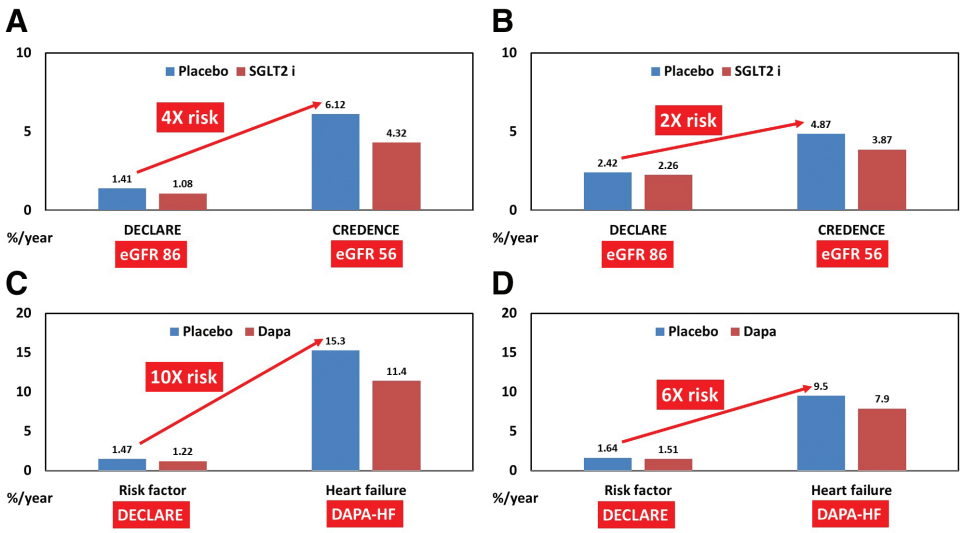

Fig. 2 "Earlier is better" in the renal protection and heart failure protection. A, Renal endpoints in the DECLARE trial and the CREDENCE trial. The baseline eGFR was 86 mL/min in the DECLARE trial[63] versus 56 mL/min in the CREDENCE trial.[64] The baseline risk levels in the CREDENCE trial was four-fold than those in the DECLARE trial. B, The major adverse cardiovascular event rates in the DECLARE trial and the CREDENCE trial. The baseline risk levels in the CREDENCE trial was two-fold than those in the DECLARE trial. C, Hospitalization for heart failure/CV death in the DECLARE trial and the DAPA-HF trial. Only 10% in the DECLARE trial had prior heart failure, whereas 100% patients in the DAPA-HF trial had heart failure. The baseline risk levels in the DAPA-HF trial were about 10-fold than those in the DECLARE trial. D, Total death in the DECLARE trial and the DAPA-HF trial. The baseline risk levels in the DAPA-HF trial were about six-fold than those in the DECLARE trial. eGFR = estimated glomerular filtration rate; CV = cardiovascular.

interaction p = 0.80), and in both angiotensin receptor-neprilysin inhibitor (ARNI) users and ARNI nonusers (HR, 0.75; 95% CI, 0.50-1.13, and HR, 0.74; 95% CI, 0.65-0.86, respectively; interaction p = nonsignificant). The effect of dapagliflozin on the primary outcome was generally consistent across other prespecified subgroups, including elderly patients.[79] Furthermore, dapagliflozin reduced composite renal endpoints (HR, 0.71; 95% CI, 0.44-1.16; p = 0.17).[78]

Symptoms and life quality were both significantly improved by dapagliflozin.[78] The increase in the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) (indicating fewer symptoms) was greater in the dapagliflozin group than in the placebo group from baseline to month 8 (+6.1 vs +3.3, p < 0.001).[80] Adverse events rarely led to a discontinuation of the drug. There was no notable excess of any serious adverse event in the dapagliflozin group.[78]

9.5. Earlier is better

Only about 10% of patients in the DECLARE trial had prior HF.[63] When comparing with the DAPA-HF trial,[78] the DECLARE trial is like a prevention trial.[63] The risk of developing HHF/CV death in the placebo group was 1.47%/y in the DECLARE trial, about one tenth of that in the DAPA-HF trial (15.3%/y) (Fig. 2C). Likewise, the risk of all-cause death in placebo group in the DECLARE trial was only 1.64%/y, about one sixth of that in the DAPA-HF trial (9.5%/y) (Fig. 2D). Consistent with the prevention of CKD, "earlier is better" for the prevention of HF in type 2 diabetes.

Table 6

Examples of repurposing drugs

	Original indications	Repurposed indications
Aspirin	Analgesia	Coronary artery disease
Minoxidil	Hypertension	Hair loss
Sildenafil	Angina	Erectile dysfunction
Rituximab	Cancer	Rheumatoid arthritis
Colchicine	Gout	Acute myocardial infarction
Dapagliflozin	Diabetes	Heart failure

10. SGLT-2 INHIBITORS VERSUS ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR

ARNI has been recommended in most recent HF guidelines,[81,82] based on the findings from the PARADIGM-HF trial.[83] In the DAPA-HF trial, guideline-directed medical therapy (GDMT) was recommended in both arms by the protocol, which include ARNI. However, only about 11% received ARNI (20% in Taiwan) in the trial.[78] In a post hoc analysis, the efficacy of dapagliflozin was independent of the use of ARNI.[78] We would not have head-to-head comparison of ARNI versus SGLT-2 i. Table 7 shows the magnitude of risk reduction and NNT for each endpoint and KCCQ of these two drugs in the trials. Both drugs were very effective and SGLT-2 i should be recommended in the future HF guidelines.

Table 7

Efficacy of sacubitril/valsartan in the PARADIGM trial[83] and dapagliflozin in the DAPA-HF trial[78]

	RRR	ARR/y	NNT/y
HHF/CVD			
PARADIGM	20%	2.1%	48
DAPA-HF	25%	3.9%	26
HHF			
PARADIGM	21%	1.2%	84
DAPA-HF	30%	2.9%	35
CVD			
PARADIGM	20%	1.4%	72
DAPA-HF	18%	1.4%	72
All-cause death			
PARADIGM	16%	1.2%	84
DAPA-HF	17%	1.6%	63
KCCQ			
PARADIGM	+1.64	...	...
DAPA-HF	+2.8	...	...

ARR = absolute risk reduction; CVD = cardiovascular death; HHF = hospitalization for heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; NNT = number to treat; RRR = relative risk reduction.

Table 8

Comparison of effects of GLP-1 RA versus SGLT-2 i

	GLP-1 RA	SGLT-2 i	p_{int}
MACE			
Primary prevention	1.03 (0.87-1.23) ($p = 0.71$)	(0.87-1.16) (p: NR)	0.11
Secondary prevention	0.87 (0.82-0.92) ($p < 0.001$)	0.86 (0.80-0.93) (p: NR)	0.99
HHF	0.93 (0.83-1.04) ($p = 0.20$)	0.69 (0.61-0.79) ($p < 0.001$)	0.003
Broad kidney endpoints[a]	0.82 (0.75-0.89) ($p < 0.001$)	0.62 (0.58-0.67) ($p < 0.001$)	0.01
Hard kidney endpoints[b]	0.92 (0.80-1.06) ($p = 0.24$)	0.55 (0.48-0.64) ($p < 0.001$)	<0.001

GLP-1 RA = glucagon-like peptide-1 receptor agonist; HHF = hospitalization for heart failure; MACE = major adverse cardiovascular events; p_{int} = p value for interaction; RA = receptor agonist; SGLT-2 i = sodium-glucose transport protein 2 inhibitors.

[a]Proteinuria, doubling of creatinine or a 40% decline in estimated glomerular filtration rate, end-stage renal disease, and renal death.

[b]Doubling of creatinine or a 40% decline in estimated glomerular filtration rate, end-stage renal disease, renal death.

11. SGLT-2 INHIBITORS VERSUS GLP-1 RECEPTOR AGONISTS

In a recent meta-analysis of eight trials of 77 242 patients, both GLP-1 RAs and SGLT-2 i were effective in reducing MACE, HHF, and renal endpoints (Table 8).[84] MACE was reduced only in the secondary prevention group, not in the primary prevention group, by both drugs. SGLT-2 i, not GLP-1 RAs, decreased HHF. Both drugs decreased broad kidney endpoints which included the reduction in proteinuria. But only SGLT-2 i decreased hard kidney endpoints. Overall, SGLT-2 i were the treatment of choice for HF and CKD.[84]

12. EXTENDED USE OF SGLT-2 INHIBITORS

SGLT-2 i should have more extended use in different clinical settings in diabetic patients (Table 9). For primary prevention purpose, that is, in patients who have HT, or hypercholesterolemia, or smoking, SGLT-2 i decrease HHF/CVD and renal endpoints.[63,85] For secondary prevention purpose, that is, in patients with prior ASCVD, SGLT-2 i decrease MACE, HHF/CV death, and renal endpoints. For diabetic and nondiabetic patients who have HFrEF, SGLT-2 i decrease HHF/CV death, renal events, and all-cause death.[85] For medical doctors of different disciplines, SGLT-2 i can now be more widely used than before (Fig. 3).

13. REEXAMINATION OF THE ROLE OF METFORMIN IN TYPE 2 DIABETES

The only randomized RCT testing metformin's CV effects was the UKPDS trial.[86] In 753 mildly obese diabetic patients, MI was reduced by 39% ($p = 0.01$), and all-cause death by 36% ($p = 0.011$).[86] All previous international guidelines recommended metformin as the first-line antidiabetic drug, based on this small trial. Theoretically, it is impossible to do another RCT to test the efficacy of metformin versus placebo. Only one ongoing trial is testing the efficacy of metformin in patients with prediabetes and established ASCVD (VA-IMPACT, NCT02915198). But we have to wait until 2024. Several registries or observational studies supported the efficacy of

Table 9

Spectrum of beneficial effects of SGLT-2 inhibitors

Patient types	MACE	HHF/CVD	Renal events	All-cause death
Primary prevention (DM + risk factors)				
Hypertension	...	V	V	...
Hypercholesterolemia	...	V	V	...
Smoking	...	V	V	...
Secondary prevention (DM + ASCVD)				
Myocardial infarction	V	V	V	...
CHD	V	V	V	...
Stroke	V	V	V	...
PAD	V	V	V	...
HFrEF (DM + non-DM)	...	V	V	V

ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; DM = diabetes mellitus; HFrEF = heart failure with reduced ejection fraction; HHF/CVD = hospitalization for heart failure and cardiovascular death; MACE = major adverse cardiovascular events; PAD = peripheral artery disease; SGLT-2 = sodium-glucose transport protein 2.

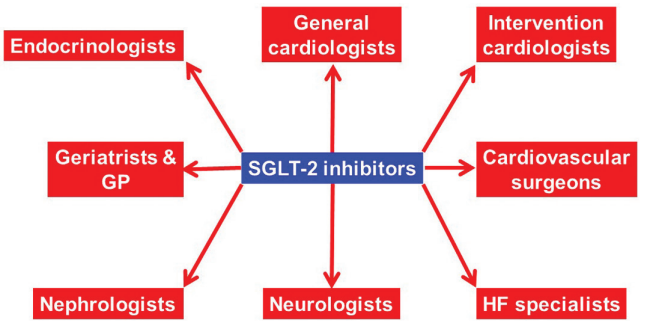

Fig. 3 Extended use of sodium-glucose transport protein 2 (SGLT-2) inhibitors. Doctors from at least eight different disciplines could be potential prescribers. GP = general practitioner; HF = heart failure.

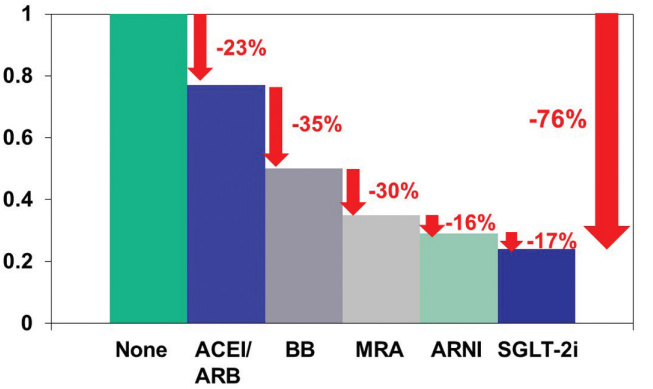

Fig. 4 The cumulative reduction in total mortality by previous guideline-directed medical therapy, plus sodium-glucose transport protein 2 (SGLT-2) inhibitors, in recent 30 years. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor blocker-neprilysin inhibitor; BB = beta-blocker; MRA = mineralocorticoid receptor antagonist.

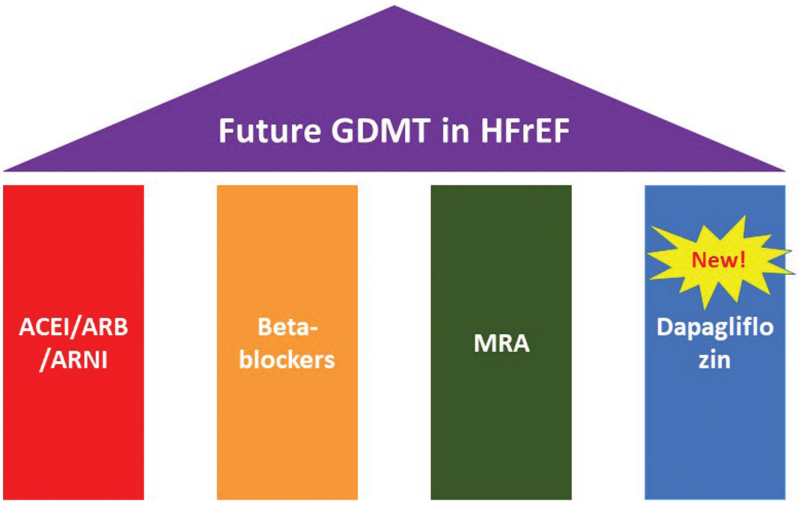

Fig. 5 Future guideline-directed medical therapy (GDMT) in HFrEF. Dapagliflozin represents the new fourth pillar. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor blocker-neprilysin inhibitor; GDMT = guideline-directed medical therapy; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist.

Table 10

Second revolution in cardiovascular prevention with the use of SGLT-2 inhibitors

	Prevention		Treatment	
	Statins	SGLT-2 i	Statins	SGLT-2 i
Coronary heart disease	V	X	V	V
Myocardial infarction	V	X	V	V
Stroke	V	X	V	V
Peripheral artery disease	V	X	V	V
Chronic kidney disease (1-4)	X	V	V	V
End-stage renal disease	X	V	X	X
Heart failure	X	V	X	V

SGLT-2 i = sodium-glucose transport protein 2 inhibitors.

metformin in reducing all-cause death in high-risk patients or HF patients.[87–89]

In a more recent subanalysis from the SAVOR trial, metformin use reduced all-cause death by about 25%.[90] In the same article, an additional meta-analysis of 815 639 patients also demonstrated a 26% reduction in all-cause death by metformin.[90] A further analysis disclosed that in patients with prior HF or moderate to severe CKD metformin could not reduce all-cause death.[90] This is a strong evidence to suggest that in patients with prior HF or moderate-to-severe CKD metformin should be moved to second-line therapy, and SGLT-2 i should step up as the first choice. Indeed, in the recent European guidelines, SGLT-2 i or GLP-1 RAs, but not metformin, were recommended in drug naïve patients who have ASCVD or high/very high CV risk.[91]

14. FUTURE GUIDELINES

In the three decades from 1980s to 2010s, we were very successful in the management of HFrEF. Putting together of RAS blockers, beta-blockers, mineralocorticoids antagonists, ARNI, and SGLT-2 i, we were able to decrease the total death by 76% (Fig. 4). SGLT-2 i will be included in the future HF guidelines and represent the fourth pillar in the management of HFrEF (Fig. 5).

There will be some important changes in the recommendations in future diabetic guidelines as well. For patients with ASCVD, CKD, and HFrEF, SGLT-2 i and GLP-1 RAs will be ranked first place. SGLT-2 i, in particular, will be the treatment of choice for patients with CKD and HFrEF.

15. SECOND REVOLUTION IN CARDIOVASCULAR PREVENTION

Although initially considered to be only glucose-lowering drugs, the effects of SGLT-2 i expanded far beyond that. The most exciting ones are the protective effects on CKD and HF. SGLT-2 i are now complementary to the effects of statins. We have witnessed this historical moment. We can now call the application of SGLT-2 i is the second revolution in cardiovascular prevention (Table 10).

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