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Second-line Glucose-Lowering Therapy in Type 2 Diabetes Mellitus

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Abstract

Purpose of Review There is consensus that metformin should be the first-line pharmacological therapy for type 2 diabetes. Although new evidence on effective treatments for type 2 diabetes is rapidly evolving, there is uncertainty regarding the optimal choice of second-line therapy. Our aim was to review the current major guidelines for second-line therapy in type 2 diabetes, along with findings from the recent cardiovascular outcome trials, focusing on two particularly promising classes of glucose-lowering drugs, sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP1 RAs).

Recent Findings In the recent randomized controlled trials, two SGLT2 inhibitors (i.e., empagliflozin and canagliflozin) and two GLP1 RAs (i.e., liraglutide and albiglutide) reduced cardiovascular events in patients with type 2 diabetes, of whom most had established atherosclerotic cardiovascular disease. Some clinical guidelines have changed their recommendations for second-line therapy based on these findings. The first choice for a second-line therapy by the new American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) guidelines is SGLT2 inhibitors or GLP1 RAs for patients with atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease. For patients without these conditions, the ADA/EASD lists five options of noninsulin second-line therapy without a suggested hierarchy of use. On the other hand, the 2019 consensus statement from the American Association of Clinical Endocrinologists/American College of Endocrinology lists nine hierarchical options, with GLP1 RAs as the first recommended therapy, followed by SGLT2 inhibitors and dipeptidyl peptidase 4 (DPP4) inhibitors, and sulfonylurea as the last option. The American College of Physicians recommends four oral treatment options, which do not include GLP1 RAs. The International Diabetes Federation recommends sulfonylureas, DPP4 inhibitors, or SGLT2 inhibitors as preferred second-line drugs with GLP1 RAs as an alternative in obese patients. The World Health Organization strongly recommends sulfonylureas in low-resource settings. The National Institute for Health and Care Excellence in the UK recommends DPP4 inhibitors, thiazolidinediones, or sulfonylureas, with use of SGLT2 inhibitors only under special circumstances.

Summary Clinical guidelines for the choice of second-line therapy in type 2 diabetes are inconsistent. A comprehensive assessment of the risks and benefits of second-line therapy is needed to address knowledge gaps that underlie core clinical practice.

Keywords Second-line glucose-lowering therapy · Type 2 diabetes mellitus · Clinical guidelines · Cardiovascular outcome trials

Introduction

More than 450 million people worldwide, including more than 30 million Americans, have diabetes [1, 2]. The vast majority (90 to 95%) has type 2 diabetes. Type 2 diabetes causes macrovascular and microvascular complications and carries at least 2 times the risk of cardiovascular disease (CVD) and chronic kidney disease (CKD) compared with the general population [3–6]. In the USA, the total estimated cost of diagnosed diabetes in 2017 was $327 billion, a 26% increase from 2012 [7]. Along with lifestyle modification, glucose-lowering drug treatment is the mainstay of therapy to prevent and delay diabetes-related complications and maintain quality of life. In the USA, there are eleven classes of noninsulin medications currently approved to treat hyperglycemia in type 2 diabetes [8]. The median cost (i.e., median of the average wholesale price) of different noninsulin therapies ranges from $50 to $2547 per month [8].

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Given the many therapeutic options with a wide range of costs, a challenge for clinicians in diabetes care is deciding on optimal therapy for the individual patient. Metformin is recommended by most as the first-line drug for type 2 diabetes given long-standing evidence for its efficacy and safety and its low cost [8–12]. When metformin alone fails to achieve or maintain glycemic goals—which may happen in over 50% of patients—another agent should be added. However, there is no consensus across guidelines for the choice of second-line therapy in large part because of insufficient evidence supporting the use of one second-line therapy over another. In this paper, we will review evidence from the recent cardiovascular outcome trials of sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP1 RAs) and specific recommendations of second-line therapy for type 2 diabetes in major clinical guidelines, as well as key knowledge gaps to improve clinical care in type 2 diabetes.

Cardiovascular Outcome Trials of SGLT2 Inhibitors and GLP1 RAs

SGLT2 Inhibitors

SGLT2 inhibitors act on the proximal tubule of the nephron to block approximately 90% of urinary glucose reabsorption and increase urinary glucose excretion, lowering blood glucose levels. SGLT2 inhibitors have benefits beyond glycemic control such as diuresis, natriuresis, and reduction in weight, systolic blood pressure, and albuminuria [13]. There are four SGLT2 inhibitors currently approved by the US Food and Drug Administration (FDA) for hyperglycemia management in type 2 diabetes.

In large, randomized, placebo-controlled, clinical trials in patients with type 2 diabetes, of whom most had established atherosclerotic cardiovascular disease (ASCVD), empagliflozin and canagliflozin reduced major adverse cardiovascular events (MACE: cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and hospitalization for heart failure (Table 1) [14, 15••]. Empagliflozin also significantly decreased the risk of cardiovascular and all-cause mortality [14]. In a trial of a broad population of patients with type 2 diabetes (i.e., 40% with established ASCVD and 60% with multiple risk factors for ASCVD), dapagliflozin did not reduce MACE but reduced hospitalization for heart failure [16]. A recent meta-analysis of these three cardiovascular outcome trials of SGLT2 inhibitors suggests that benefits on MACE in SGLT2 inhibitors seem to be limited to patients with established ASCVD, but benefits on reducing hospitalization for heart failure were robust regardless of existing ASCVD or heart failure [18]. Ongoing dedicated heart failure outcome trials in both patients with and without type 2 diabetes, such as DAPA-HF (the effect of DAPAgliflozin on the incidence of worsening Heart Failure or cardiovascular death in patients with chronic heart failure) [19], EMPEROR-PRESERVED (EMPagliflozin outcomE tRial in patients with chrOnic heaRt failure with preserved ejection fraction) [20], and EMPEROR-REDUCED (EMPagliflozin outcomE tRial in patients with chrOnic heaRt failure with reduced ejection fraction) [21], will shed further light on benefits of SGLT2 inhibitors on heart failure, including whether these benefits can be extended for chronic heart failure patients without type 2 diabetes.

Although the cardiovascular outcome trials of SGLT2 inhibitors (i.e., EMPA-REG OUTCOME [empagliflozin], CANVAS/CANVAS-R [canagliflozin], and DECLARE-TIMI-58 [dapagliflozin]) were not primarily designed for kidney outcomes, all of the three SGLT2 inhibitors slowed the progression of kidney disease [16, 22, 23]. A meta-analysis of three trials of SGLT2 inhibitors suggests that there were robust benefits on reducing the progression of kidney disease, regardless of ASCVD, heart failure, or baseline kidney function [18]. In July 2018, the CREDENCE (Canagliflozin and Renal Endpoint in Diabetes with Established Nephropathy Clinical Evaluation) trial was stopped early because prespecified renal efficacy criteria had been achieved at a planned interim data analysis [24]. The results of this study were published in April 2019, reporting canagliflozin reduced the risk of the primary outcome (i.e., a composite of end-stage kidney disease, a doubling of the serum creatinine level, or death due to kidney or cardiovascular disease) by 30%, the risk of kidney-specific composite outcome by 34%, and the risk of end-stage kidney disease by 32% [25••]. However, it is still unknown whether there exist renoprotective effects of SGLT2 inhibitors among patients with severe CKD because individuals with estimated glomerular filtration (eGFR) less than 30 ml/min/1.73 m^2 were excluded from these trials [16, 22, 23, 24, 25••]. Other forthcoming clinical trials with primary kidney outcomes in both patients with and without type 2 diabetes, such as EMPA-KIDNEY (the study of heart and KIDNEY protection with EMPAgliflozin) [26] and DAPA-CKD (the effect of DAPAgliflozin on renal outcomes and cardiovascular mortality in patients with Chronic Kidney Disease) [27], will provide important information on the renal effects of SGLT2 inhibitors in both diabetic and non-diabetic populations. These trials will also increase understanding of the renal effects of these medications in severe CKD as two of the trials include participants with severe CKD (i.e., eligibility criteria: eGFR ≥ 20 ml/min/1.73 m^2 and eGFR ≥ 25 ml/min/1.73 m^2 for EMPA-KIDNEY and DAPA-CKD, respectively).

GLP1 RAs

GLP1 is an incretin hormone secreted from the distal ileum and colon after food consumption [28]. GLP1 RAs reduce blood glucose level by stimulating glucose-dependent insulin

Table 1 Summary of the published cardiovascular outcome trials of SGLT2 inhibitors

	EMPA-REG OUTCOME [14]	CANVAS/CANVAS-R [15••]	DECLARE-TIMI-58 [16]
Baseline characteristics			
Patient enrolled	*n* = 7020	*n* = 10,142	*N* = 17,610
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Median duration of follow-up (years)	3.1	2.4	4.2
Mean baseline HbA1c (%)	8.1	8.2	8.3
ASCVD (%)	100	72	41
Heart failure (%)	11	14	10
Kidney disease (%)	26	18	7
Outcomes (HR [95% CI])			
Primary outcome†	0.86 (0.74–0.99)	0.86 (0.75–0.97)	0.93 (0.84–1.03)
Cardiovascular death	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.98 (0.82–1.17)
Fatal or nonfatal myocardial infarction	0.87 (0.70–1.09)	0.89 (0.73–1.09)	0.89 (0.77–1.01)
Fatal or nonfatal stroke	1.18 (0.89–1.56)	0.87 (0.74–1.01)	1.01 (0.84–1.21)
All-cause mortality	0.68 (0.57–0.82)	0.87 (0.74–1.01)	0.93 (0.82–1.04)
Heart failure hospitalization	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.73 (0.61–0.88)
Renal composite outcome	0.54 (0.40–0.75)ǂ	0.60 (0.47–0.77)§	0.76 (0.67–0.87)¶

† Primary outcome was three-point major cardiovascular adverse events (MACE), a composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death

ǂ A doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease

§ 40% reduction in eGFR, renal-replacement therapy, or death from renal disease

¶ ≥ 40% decrease in estimated glomerular filtration rate to < 60 ml per minute per 1.73 m^2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes

SGLT2 sodium-glucose cotransporter 2, *HbA1c* hemoglobin A1c, *ASCVD* atherosclerotic cardiovascular disease, *HR* hazard ratio, *CI* confidence interval, *EMPA-REG OUTCOME* empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients-remove excess glucose outcome, *CANVAS/CANVAS-R* canagliflozin cardiovascular assessment study, *DECLARE-TIMI-58* dapagliflozin effect on cardiovascular events

Table adapted from Das et al. [17], with permission from Elsevier, and updated by including the most recent studies

secretion and inhibiting glucagon secretion, and by delaying gastric emptying, which results in decreasing food intake [28].

Of the six approved GLP1 RAs by the FDA, liraglutide and albiglutide have been definitively shown to reduce MACE, although albiglutide was pulled from the market in 2017 due to poor sales (Table 2) [29••, 33]. While all components of MACE contributed to the cardiovascular benefit of liraglutide [29••], the overall reduction in MACE with albiglutide was mainly driven by a benefit on myocardial infarction [33]. A similar benefit on MACE was observed in semaglutide, but this was driven by nonfatal stroke rather than cardiovascular mortality [30]. The reduction in MACE with oral semaglutide (new drug application submitted to the FDA on March 21, 2019) was not statistically significant [34, 35]. The full detailed results of cardiovascular outcome trials with oral semaglutide (the PIONEER 6 study) will be announced at the 2019 American Diabetes Association Scientific Sessions. Exenatide showed results in a direction that was protective for MACE without statistical significance [31]. Lixisenatide did not reduce MACE after acute coronary syndrome [32]. Taken together, these results suggest the potential heterogeneous effects on cardiovascular risk within the class of GLP1 RAs among patients with established CVD. Some of this heterogeneity may be due to the dosages of study drugs, specific drug properties, or differences in study design and population.

Trials of GLP1 RAs did not demonstrate significant improvement on hospitalization for heart failure [29••, 30, 31, 33]. Two small phase 2 clinical trials of liraglutide in chronic heart failure patients with reduced ejection fraction suggested a lack of benefit in this clinical setting [36, 37]. The LIVE (effect of LIraglutide on left VEntricular function in chronic heart failure patients with and without type 2 diabetes, *n* = 243) trial reported that serious cardiac events occurred more frequently in the liraglutide group (12 events) than in the placebo group (3 events) ($p = 0.04$) [36]. The full results of the cardiovascular outcome trials of dulaglutide (the REWIND study) and oral semaglutide (the PIONEER 6 study) [34, 38], expected to be available this year, may shed further light on whether this class of medications is safe and effective in patients with heart failure.

With respect to kidney outcomes, most GLP1 RAs reduced progression of kidney disease, albeit as secondary outcomes [30, 39–41]. It is important to keep in mind that progression of albuminuria was the most common element of the composite

Table 2 Summary of the published cardiovascular outcome trials of GLP1 RAs

	LEADER [29••]	SUSTAIN-6 [30]	EXSCEL [31]	ELIXA [32]	HARMONY [33]
Baseline characteristics					
Patients enrolled	9340	3297	14,752	6068	9463
Drug	Liraglutide	Semaglutide	Exenatide QW	Lixisenatide	Albiglutide
Median duration of follow-up (years)	3.8	2.1	3.2	2.1	1.6
Mean baseline HbA1c (%)	8.7	8.7	8.0	7.7	8.7
ASCVD (%)	81	72	73	100	100
HF (%)	18	24	16	22	20
Kidney disease (%)	23	28	22	23	23
Outcomes (HR [95% CI])					
Primary outcome[†]	0.87 (0.78–0.97)	0.74 (0.58–0.95)*	0.91 (0.83–1.00)	1.02 (0.89–1.17)	0.78 (0.68–0.90)
Cardiovascular death	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.98 (0.78–1.22)	0.93 (0.73–1.19)
Fatal or nonfatal MI	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	1.03 (0.87–1.22)	0.75 (0.61–0.90)
Fatal or nonfatal stroke	0.86 (0.71–1.06)	0.61 (0.38–0.99)	0.85 (0.70–1.03)	1.12 (0.79–1.58)	0.86 (0.66–1.14)
All-cause mortality	0.85 (0.74–0.97)	1.05 (0.74–1.50)	0.86 (0.77–0.97)	0.94 (0.78–1.13)	0.95 (0.79–1.16)
HF hospitalization	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.94 (0.78–1.13)	0.96 (0.75–1.23)	0.85 (0.70–1.04)[ǂ]
Renal outcome	0.78 (0.67–0.92)[§]	0.64 (0.46–0.88)[¶]	0.85 (0.73–0.98)[Δ]	0.81 (0.66–0.99)[•]	N/A

[†] In LEADER, SUSTAIN-6, and EXSCEL trials, the primary outcome was three-point major cardiovascular adverse events (MACE), a composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death. In ELIXA trial, the primary outcome was four-point MACE, a composite of nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, and hospitalization for unstable angina

*SUSTAIN-6 was designed and powered as a noninferiority trial. Test for superiority for the primary CV outcomes was not prespecified

[ǂ] In Harmony trial, it was a composite of cardiovascular death or HF hospitalization

[§] Composite of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level and an eGFR ≤ 45 ml/min/1.73 m^2, end-stage renal disease, or death due to renal disease. This result was driven primarily by the new onset of persistent macroalbuminuria

[¶] Composite of persistent macroalbuminuria, persistent doubling of the serum creatinine level and eGFR < 45 ml/min/1.73 m^2, and end-stage renal disease

[Δ] Composite of 40% eGFR decline, renal-replacement therapy, renal death, and new-onset macroalbuminuria. Adjusted for age, sex, ethnicity, race, region, duration of diabetes, prior history of CV event, insulin use, baseline HbA1c, eGFR, and body mass index. This result was driven by the new-onset macroalbuminuria

[•] New-onset macroalbuminuria after adjustment for baseline and one-trial HbA1c and other traditional renal risk factors

QW once weekly, *ASCVD* atherosclerotic cardiovascular disease, *HF* heart failure, *MI* myocardial infarction, *LEADER* the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results, *SUSTAIN-6* semaglutide and cardiovascular outcomes in patients with type 2 diabetes, *EXSCEL* exenatide study of cardiovascular event lowering, *ELIXA* lixisenatide in patients with type 2 diabetes and acute coronary syndrome, *Harmony* albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease

Table adapted from Das et al. [17], with permission from Elsevier, and updated by including the most recent studies

kidney outcome in these trials, whereas the other elements (e.g., doubling of serum creatinine, end-stage kidney disease, or death due to kidney disease) did not contribute significantly to the benefit on kidney outcomes. Unfortunately, there are no dedicated kidney outcome trials with GLP1 RAs ongoing or planned. We may not have a clear answer for the benefits of GLP1 RAs on kidney outcomes for many years, particularly for hard kidney endpoints.

Limitations of Cardiovascular Outcome Trials

Despite that studies with an active control comparator are most relevant for clinical practice, only one trial (the RECORD study with rosiglitazone [42]) used active comparator among 15 recent major cardiovascular outcome trials between 2005 and 2019 [14, 16, 22, 29••, 30–33, 42–48]. In the remaining trials, patients in the placebo arm were expected to receive standard of care recommended by the FDA Advisory Committee: achieving comparable control of glycemia and cardiovascular risk factors in both treatment arms [49–52]. However, the study design did not make sure that patients in the placebo arm achieved comparable control of hemoglobin A1c (HbA1c) or other cardiovascular risk factors [52]. For example, mean HbA1c levels in placebo groups during most of the study period remained around 8% in trials of empagliflozin, canagliflozin, liraglutide, and exenatide [14, 22, 31, 39]. Thus, an important question remains unanswered regarding whether any benefit of treatment on cardiorenal outcomes is due to the

improvement in glycemic control or a true beneficial effect of the drug class itself.

The Ongoing Glycemic Reduction Approaches in Diabetes: a Comparative Effectiveness Study

To address the question of comparative effectiveness of drug classes, rather than the efficacy of one class compared with placebo, the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) funded the glycemic reduction approaches in diabetes: a comparative effectiveness (GRADE) study, a pragmatic, unmasked clinical trial which began the recruitment in 2014, to make head-to-head comparisons of four drug classes (sulfonylureas, DPP4 inhibitors, GLP1 RAs, and basal insulin) as an add-on therapy to metformin [53]. Although this study has certain limitations (e.g., exclusion of SGLT2 inhibitors), the results of this trial, expected in 2021, may provide better guidance to clinicians in the choice of second-line therapy.

Recommendations of Second-line Glucose-Lowering Therapy for Type 2 Diabetes

American Diabetes Association/European Association for the Study of Diabetes [10]

Based on new evidence from cardiovascular outcome trials with SGLT2 inhibitors and GLP1 RAs, the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) updated their consensus report regarding the management of hyperglycemia in type 2 diabetes in 2018. For second-line therapies after metformin, the ADA/EASD recommends SGLT2 inhibitors or GLP1 RAs with proven cardiovascular benefits for patients with type 2 diabetes who have established ASCVD (Table 3). SGLT2 inhibitors are preferred after metformin for patients with heart failure or CKD. For patients without these conditions, the ADA/EASD does not explicitly recommend one drug class over another when additional therapy is needed after metformin. Rather, they suggest taking into account side effects, cost, and patient preferences: GLP1 RAs or SGLT2 inhibitors if there exists a compelling need to minimize weight gain or promote weight loss; DPP4 inhibitors, GLP1 RAs, SGLT2 inhibitors, or thiazolidinediones (TZDs) if there exists a compelling need to minimize hypoglycemia; sulfonylureas, or TZDs if cost is a major issue. These recommendations are consistent with the 2019 ADA guidelines [8], which was endorsed by the American College of Cardiology.

American Association of Clinical Endocrinologists/American College of Endocrinology [9]

The 2019 American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) guidelines kept nine suggested hierarchical options for second-line therapy in their glycemic control algorithm for type 2 diabetes, with GLP1 RAs as the first recommended therapy, followed by SGLT2 inhibitors and DPP4 inhibitors, and sulfonylureas as the last option, regardless of ASCVD, CKD, or heart failure status. Although the suggested hierarchy of usage for second-line therapy itself has not been changed since the 2018 consensus statement, the AACE/ACE incorporated new evidence from cardiovascular outcome trials into the 2019 new consensus statement, stating (1) "certain GLP1 RAs and SGLT2 inhibitors have shown CVD and CKD benefits—preferred in patients with those complications" and (2) "include SGLT2 inhibitors or GLP1 RAs if coronary heart disease is present" [9].

American College of Physicians [11]

The 2017 American College of Physicians (ACP) updated guideline did not incorporate the results from the recent cardiovascular outcome trials because placebo-controlled trials were excluded from the evidence synthesis. This guideline stated, "Insufficient evidence exists for clinical outcomes, including mortality, cardiovascular morbidity, and microvascular outcomes, for most drugs and drug comparisons" [11]. As a result, the ACP guideline recommends four oral treatment options (i.e., sulfonylureas, TZDs, SGLT2 inhibitors, or DPP4 inhibitors) without preference and does not include GLP1 RAs. This guideline was endorsed by the American Academy of Family Physicians.

International Diabetes Federation [12]

According to the 2017 International Diabetes Federation (IDF) guidelines, the best choices of the second-line drug are sulfonylureas (except glibenclamide/glyburide), DPP4 inhibitors, or SGLT2 inhibitors. GLP1 RAs are alternative choices if there is a concern for weight gain. Of note, results of the cardiovascular outcome trials of two SGLT2 inhibitors (i.e., empagliflozin and canagliflozin) and two GLP1 RAs (i.e., liraglutide and semaglutide) came out after the completion of the review used to develop these IDF guidelines. The IDF guidelines acknowledge that new evidence may be taken into consideration when selecting a second-line drug in patients with established ASCVD.

Table 3 Recommendations for second-line therapy for type 2 diabetes across guidelines

Organization/year of publication	Recommendations for a second-line noninsulin agent				
American Diabetes Association/European Association for the Study of Diabetes/2018–2019	ASCVD (+)		ASCVD (−)		
	ASCVD predominant	HF or CKD predominant	To minimize hypoglycemia	To minimize weight gain or promote weight loss	Cost is a major issue
	• GLP1 RAs • SGLT2 inhibitors with proven cardiovascular benefit	• SGLT2 inhibitors with proven cardiovascular benefit	• DPP4 inhibitors • GLP1 RAs • SGLT2 inhibitors • TZDs	• GLP1 RAs • SGLT2 inhibitors	• Sulfonylureas • TZDs
American Association of Clinical Endocrinology/ American College of Endocrinology/2019	9 hierarchical options • GLP1 RAs (1st) • SGLT2 inhibitors (2nd) • DPP4 inhibitors (3rd) • TZDs (4th) • Sulfonylureas (9th)		Note: • Certain GLP1 RAs and SGLT2 inhibitors have shown CVD and CKD benefits—preferred in patients with those complications • Include SGLT2 inhibitors or GLP1 RAs if coronary heart disease is present		
American College of Physicians/2017	4 oral treatment options • Sulfonylureas • TZDs • SGLT2 inhibitors • DPP4 inhibitors				
International Diabetes Federation/2017	3 best choices • Sulfonylureas • DPP4 inhibitors • SGLT2 inhibitors GLP1 RAs can be used if weight loss is a priority				
World Health Organization/2018	• Sulfonylureas (strong recommendation) in low-resource settings				
National Institute for Health and Care Excellence in the UK/2019	3 suggested options + 1 additional option • DPP4 inhibitors • TZDs • Sulfonylureas • SGLT2 inhibitors only if ✓ a sulfonylurea is contraindicated or not tolerated or ✓ the person is at significant risk of hypoglycemia or its consequences				

ASCVD atherosclerotic cardiovascular disease, *HF* heart failure, *CKD* chronic kidney disease, *GLP1 RAs* glucagon-like peptide 1 receptor agonists, *SGLT2* sodium-glucose cotransporter 2, *DPP4* dipeptidyl peptidase 4, *TZDs* thiazolidinediones

World Health Organization [54]

The 2018 World Health Organization (WHO) guideline strongly recommends sulfonylureas as second-line therapy in low-resource settings after balancing the risks and benefits of medications. GLP1 RAs were not considered because they are seldom available in low-income countries. The WHO guideline group concluded that the evaluated medications (i.e., sulfonylureas, DPP4 inhibitors, SGLT2 inhibitors, and TZDs) generally had similar glucose-lowering effects, but sulfonylureas had a higher risk of hypoglycemia compared with DPP4 inhibitors and SGLT2 inhibitors. Relying on limited data [55, 56], they considered the absolute risk for hypoglycemia with sulfonylureas (from 0.2 to 1.8 events per 100 person-years) acceptable. While the WHO guideline group acknowledged that SGLT2 inhibitors look promising, they pointed out this evidence derived from placebo-controlled clinical trials. In addition, the WHO recognized the need for studies including randomized control trials comparing each new drug class with all others, particularly new drugs compared with old drugs.

National Institute for Health and Care Excellence in the UK [57]

According to the 2019 updated National Institute for Health and Care Excellence (NICE) guidelines, DPP4 inhibitors,

TZDs (i.e., pioglitazone), or sulfonylureas are suggested second-line therapies. SGLT2 inhibitors are recommended as an option, only if (1) a sulfonylurea is contraindicated or not tolerated or (2) the person is at significant risk of hypoglycemia or its consequences. GLP1-RAs are not considered as an option.

The new NICE guidelines, published on March 26, 2019, have not yet incorporated the results of the recent cardiovascular outcome trials. At the time that evidence reviews for SGLT2 inhibitors and GLP1 RAs were done (March 2018), the NICE guideline group concluded that there was insufficient evidence to make further specific recommendations on SGLT2 inhibitors or GLP1 RAs at the drug class level because there were only two trials with SGLT2 inhibitors (i.e., empagliflozin and canagliflozin) and two trials with GLP1 RAs (i.e., liraglutide and lixisenatide) in a population with ASCVD or with high cardiovascular risk for evidence synthesis, with other trials still ongoing [58]. A lack of cost-effectiveness studies, particularly for SGLT2 inhibitors, was another consideration for decision by the NICE guideline group [58]. The NICE will consider incorporating new evidence from more trials with these two classes of medication into the next update of this guideline [58].

Conclusions

The choice of a second-line medication after metformin in type 2 diabetes has become extraordinarily complex with the expanding number of glucose-lowering drugs. Some guidelines have changed their recommendations for second-line therapy based on emerging evidence for specific classes of medication such as SGLT2 inhibitors and GLP1 RAs from the cardiovascular outcome trials, but not all of the major guidelines have incorporated new evidence into their recommendations. More evidence is needed to determine whether there is a true class effect rather than a more general benefit to glucose-lowering in the cardiorenal protective effect in patients with type 2 diabetes. This could take the form of a randomized study with drug-drug comparisons (i.e., study with an active rather than placebo comparator), including studies for comparing new drugs (e.g., SGLT2 inhibitors) with old drugs. Furthermore, more safety data in the real-world settings, particularly for new classes of drugs such as SGLT2 inhibitors, is warranted. Ongoing cardiovascular outcome trials, along with post-marketing observational studies using real-world data, will help to guide clinicians in the choice of second-line therapy for patients with type 2 diabetes by providing information on benefits and risks of different classes of medication.

Compliance with Ethical Standards

Conflict of Interest The author declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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