Addendum

Addendum. 10. Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes—2022*. Diabetes Care 2022;45(Suppl. 1):S144–S174

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*American Diabetes Association Professional Practice Committee**

Section 10, Cardiovascular Disease and Risk Management, of the *Standards of Medical Care in Diabetes—2022* has been annotated to include evidence from trials of medication effects in patients with type 2 diabetes on heart failure, cardiovascular, and chronic kidney disease outcomes including Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved), Effects of Dapagliflozin on Biomarkers, Symptoms and Functional Status in Patients With PRESERVED Ejection Fraction Heart Failure (PRESERVED-HF), Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease (FIDELIO-DKD), and Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease (FIGARO-DKD), and to remove information associated with the discontinued trial Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes (PROMINENT).

The online version of the article (https://doi.org/10.2337/dc22-S010) reflects the changes described below.

In the section "Statin Treatment," the subsection "Statin and Fibrate Combination Therapy" (p. S154) has been revised because of the discontinuation of trial referenced within.

The following sentence has been removed:

> "A prospective trial of a newer fibrate in this specific population of patients is ongoing (123)."

The associated reference below has also been removed:

> "Kowa Research Institute, Inc. Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes (PROMINENT). In: ClinicalTrials.gov. Bethesda, MD, National Library of Medicine. NLM Identifier: NCT03071692. Accessed 21 October 2021. Available from https://clinicaltrials.gov/ct2/show/NCT03071692"

References

Kowa Research Institute, Inc. KOWA to discontinue K-877 (pemafibrate) "PROMINENT" cardiovascular outcomes study. Cision PR Newswire. Published 8 April 2022. Accessed 25 May 2022. Available from https://www.prnewswire.com/news-releases/kowa-to-discontinue-k-877-pemafibrate-prominent-cardiovascular-outcomes-study-301520956.html

Kowa Research Institute, Inc. Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes (PROMINENT) In: ClinicalTrials.gov. Bethesda, MD, National Library of Medicine. NLM Identifier: NCT03071692. Accessed 21 October 2021. Available from https://clinicaltrials.gov/ct2/show/NCT03071692

In the section "Cardiovascular Disease," a new recommendation has been added and recommendation 10.43 has been revised to include the evidence from trials of medication effects in patients with type 2 diabetes on heart failure, cardiovascular, and chronic kidney disease outcomes.

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc22-SPPC.*

The following recommendation has been added as recommendation 10.44:

> "For patients with type 2 diabetes and chronic kidney disease treated with maximum tolerated doses of ACE inhibitors or angiotensin receptor blockers, addition of finerenone should be considered to improve cardiovascular outcomes and reduce the risk of chronic kidney disease progression. **A**"

Recommendation 10.43 (p. S158) has been revised to read as follows:

> "In patients with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, a sodium-glucose cotransporter 2 inhibitor with proven benefit in this patient population is recommended to reduce risk of worsening heart failure, hospitalizations for heart failure, and cardiovascular death. **A**"

References

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451–1461

Nassif ME, Windsor SL, Borlaug BA, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med 2021;27:1954–1960

Bakris GL, Agarwal R, Anker SD, et al.; FIDELIO-DKD Investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med 2020;383:2219–2229

Pitt B, Filippatos G, Agarwal R, et al.; FIGARO-DKD Investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med 2021;385:2252–2263

Filippatos G, Anker SD, Agarwal R, et al.; FIGARO-DKD Investigators. Finerenone reduces risk of incident heart failure in patients with chronic kidney disease and type 2 diabetes: analyses from the FIGARO-DKD trial. Circulation 2022;145:437–447

Agarwal R, Filippatos G, Pitt B, et al.; FIDELIO-DKD and FIGARO-DKD investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J 2022;43:474–484

In the section "Cardiovascular Disease," the subsection "Lifestyle and Pharmacologic Interventions" (p. S158) has been revised to include the evidence from trials of medication effects in patients with type 2 diabetes and chronic kidney disease on cardiovascular outcomes. The following sentence has been added:

> "Patients with type 2 diabetes and chronic kidney disease should be considered for treatment with finerenone to reduce cardiovascular outcomes and the risk of chronic kidney disease progression."

References

Bakris GL, Agarwal R, Anker SD, et al.; FIDELIO-DKD Investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med 2020;383:2219–2229

Pitt B, Filippatos G, Agarwal R, et al.; FIGARO-DKD Investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med 2021;385:2252–2263

Filippatos G, Anker SD, Agarwal R, et al.; FIGARO-DKD Investigators. Finerenone reduces risk of incident heart failure in patients with chronic kidney disease and type 2 diabetes: analyses from the FIGARO-DKD trial. Circulation 2022;145:437–447

Agarwal R, Filippatos G, Pitt B, et al.; FIDELIO-DKD and FIGARO-DKD investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J 2022;43:474–484

Table 10.3*C*, Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: SGLT2 inhibitors, (p. S162), has been revised to include the evidence from EMPEROR-Preserved.

The following column of data has been added:

	EMPEROR-Preserved (n = 5,988; 2,938 with diabetes)
Intervention	Empagliflozin/placebo
Main inclusion criteria	NYHA class II–IV heart failure and an ejection fraction of >40%
A1C inclusion criteria (%)	—
Age (years)†	71.8 .71.9
Race (% White)	76.3, 75.4
Sex (% male)	55.4, 55.3
Diabetes duration (years)†	
Median follow-up (years)	2.2
Statin use (%)	68.1, 68.8
Metformin use (%)	—
Prior CVD/CHF (%)	100% with CHF
Mean baseline A1C (%)	—
Mean difference in A1C between groups at end of treatment (%)	—
Year started/reported	2017/2020
Primary outcome§	CV death or HF hospitalization 0.79 (0.69–0.90)
Key secondary outcome§	All HF hospitalizations (first and recurrent) 0.73 (0.61–0.88) Rate of decline in eGFR (−1.25 vs. −2.62 mL/min/1.73 m^2; $P < 0.001$)
Cardiovascular death§	0.91 (0.76–1.09)
MI§	—
Stroke§	—
HF hospitalization§	0.73 (0.61–0.88)
Unstable angina hospitalization§	—
All-cause mortality§	1.00 (0.87–1.15)
Worsening nephropathy§‖	Composite renal outcome** 0.95 (0.73–1.24)

The following text has been added to the Table 10.3C legend:

> "**Composite outcome in EMPEROR-Preserved: time to first occurrence of chronic dialysis, renal transplantation; sustained reduction of ≥40% in eGFR, sustained eGFR <15 mL/min/1.73 m^2 for patients with baseline eGFR ≥30 mL/min/1.73 m^2."

Reference

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451–1461

In the section "Cardiovascular Disease," the subsections "SGLT2 Inhibitor Trials" and "Glucose-Lowering Therapies and Heart Failure" have been revised to include the evidence from trials of medication effects in patients with type 2 diabetes on heart failure outcomes.

In the subsection "SGLT2 Inhibitor Trials," the paragraph discussing the results of DAPA-HF and EMPEROR-Reduced (p. S164) has been revised to read as follows:

> "Results of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced), Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved), and Effects of Dapagliflozin on Biomarkers, Symptoms and Functional Status in Patients With PRESERVED Ejection Fraction Heart Failure (PRESERVED-HF), which assessed the effects of dapagliflozin and empagliflozin in patients with established heart failure (191), are described below in Glucose-Lowering Therapies and Heart Failure."

In the subsection "Glucose-Lowering Therapies and Heart Failure," the paragraph beginning "Therefore, in patients with type 2 diabetes and established HFrEF … " (p. S167) has been revised as follows:

"EMPEROR-Preserved, a randomized double-blinded placebo-controlled trial of 5,988 adults with NYHA functional class I–IV chronic heart failure with preserved ejection fraction (LVEF >40%), evaluated the efficacy of empagliflozin 10 mg daily versus placebo on top of standard of care on the primary outcome of composite cardiovascular death or hospitalization for heart failure. Approximately 50% had of subjects had type 2 diabetes at baseline. Over a median of 26.2 months, there was a 21% reduction (HR 0.79 [95% CI 0.69, 0.90]; $P < 0.001$) of the primary outcome. The effects of empagliflozin were consistent in patients with or without diabetes."

In the subsection "Glucose-Lowering Therapies and Heart Failure," the final paragraph (p. 167–168) has been divided into three paragraphs; the newly revised final two paragraphs read as follows:

"Furthermore, PRESERVED-HF, a multicenter study (26 sites in the U.S.) showed that dapagliflozin leads to significant improvement in both symptoms and physical limitation, as well as objective measures of exercise function in patients with chronic HFpEF, regardless of diabetes status.

Therefore, in patients with type 2 diabetes and established HF (with reduced or preserved ejection fraction), an SGLT2 inhibitor with proven benefit in this patient population is recommended to reduce the risk of worsening heart failure, heart failure hospitalization, and cardiovascular death. The benefits seen in this patient population likely represent a class effect, and they appear unrelated to glucose lowering given comparable outcomes in HF patients with and without diabetes."

References

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451–1461

Nassif ME, Windsor SL, Borlaug BA, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med 2021;27:1954–1960