The SGLT-2 Inhibitor: Its Indication in Glycemic, Cardiovascular, and Renal Disease

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## Disclosures:

• I have no relevant relationships with ineligible companies to disclose within the past 24 months.

## Learning objectives:

- Review the key results from cardiovascular outcome trials (CVOTs) focusing on cardiovascular and renal protection in T2DM.
- Discuss clinical indications for SGLT-2 inhibitors from CVOTs and additional recent SLGT-2i trials
- Discuss how to design treatment approaches based on the newest guidelines that incorporate the results of recent trials
- Prevalence of T2DM and complications
- History of CVOT
- Role and Indications for SLGT-2 inhibitor use in T2DM
- Potential adverse reactions with SGLT-2 inhibitor use
- CVOT: EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, VERTIS-CV
- Potential MOAs in cardio-renal risk reduction
- Indication for use in management of T2DM
- CHF trials: DAPA-HF/EMPORER-REDUCED/EMPORER-PRESERVED/DELIVER
- Role of SGLT-2i use in HFrEF and HFpEF
- HFrEF case study
- SGLT-2 inhibitor CHF inpatient use SOLIST WHF, TRANSLATE-HF
- Renal trials: CREDENCE/DAPA-CKD/EMPA KIDNEY
- Indication for SGLT-2i use in CKD
- T2DM/DKD case study

## SGLT-2 inhibitor conclusions:

- The paradigm of treatment for T2DM has shifted dramatically from a focus on normoglycemia as the principal goal of treatment due to the new CVOT data
- Revise SOC and use appropriate therapies earlier and often for risk reduction, especially since CVOT results have been achieved on top of implementation of SOC
- AVOID INERTIA and pursue earlier intensification of treatment, including combination therapy
- Identify and apply use of SGLT-2i in clinical practice in both patients with and without T2DM

- Decrease risk of HHF -- greatest benefit likely HFrEF, however evidence of benefit in HFpEF following EMPORER-PRESERVED; additional trials ongoing
- Decrease risk of progression of kidney disease across range of baseline kidney function
- Reduce risk of CV death in high risk groups
- Reduce risk of MACE
- Primarily CV death and MI
- Over time frame studied, appears confined to pts with established ASCVD

## **REFERENCES**

- Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2020. Raghavan, Sridharan, et al. "Diabetes Mellitus–Related All-Cause and Cardiovascular
  - Mortality in a National Cohort of Adults." Journal of the American Heart Association, vol. 8, no. 4, 2019. Crossref, doi:10.1161/jaha.118.011295.
- 2. The Journal of the American Medical Association 294(20):2581-6 · December 2005DOI:10.1001/jama.294.20.joc50147 https://www.nejm.org/doi/full/10.1056/NEJMoa072761
- 3. Cefalu, William T., et al. "Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From ADiabetes CareEditors' Expert Forum." Diabetes Care, vol. 41, no. 1, 2017, pp. 14–31. Crossref, doi:10.2337/dci17-0057.
- 4. Moses, R., Colagiuri, S., & Dellock, C. (2014). SGLT2 inhibitors: New medicines for addressing unmet needs in type 2 diabetes. Australasian Medical Journal, 405-415. doi:10.4066/amj.2014.2181
- 5. Bommel, Erik J. M. van, et al. "SGLT2 Inhibition in the Diabetic Kidney—From Mechanisms to Clinical Outcome." Clinical Journal of the American Society of Nephrology, vol. 12, no. 4, 2017, pp. 700–10. Crossref, doi:10.2215/cjn.06080616.
- 6. Zinman, Bernard, et al. "Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes." New England Journal of Medicine, vol. 373, no. 22, 2015, pp. 2117–28. Crossref, doi:10.1056/nejmoa1504720.
- 7. Neal, Bruce, et al. "Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes." New England Journal of Medicine, vol. 377, no. 7, 2017, pp. 644–57. Crossref, doi:10.1056/nejmoa1611925.
- 8. Wiviott, Stephen D., et al. "Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes." New England Journal of Medicine, vol. 380, no. 4, 2019, pp. 347–57. Crossref, doi:10.1056/nejmoa1812389.
- 9. Cannon, C., Pratley, R., Dagogo-Jack, S., Mancuso, J., Huyck, S., Masiukiewicz, U., . . . Gantz, I. (2020). Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. The New England Journal of Medicine, 1425-1435. doi:DOI: 10.1056/NEJMoa2004967
- 10. Bommel, Erik J. M. van, et al. "SGLT2 Inhibition in the Diabetic Kidney—From Mechanisms to Clinical Outcome." Clinical Journal of the American Society of Nephrology, vol. 12, no. 4, 2017, pp. 700–10. Crossref, doi:10.2215/cjn.06080616.
- 11. American Diabetes Association Professional Practice Committee; 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2022.

- Diabetes Care 1 January 2022; 45 (Supplement\_1): S125–S143. https://doi.org/10.2337/dc22-S009
- 12. McMurray, John J. V., et al. "Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction." New England Journal of Medicine, vol. 381, no. 21, 2019, pp. 1995–2008. Crossref, doi:10.1056/nejmoa1911303.
- 13. Williams, D., & Dapagliflozin for Heart Failure with Preserved Ejection Fraction: Will the DELIVER Study Deliver? [Abstract]. Diabetes Therapy: Research, Treatment, and Education of Diabetes Related Disorders, 2207-2219. doi:10.1007/s13300-020-00911-0
- 14. CHIEF-HF: Fully Remote Clinical Trial Shows Canagliflozin Improved HF Symptoms in Patients With/Without Diabetes. American College of Cardiology. Accessed March 1, 2022. https://www.acc.org/latest-in-cardiology/articles/2021/11/08/12/02/sun-415pm-chief-hf-aha-2021
- 15. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. New England Journal of Medicine. Published online November 16, 2020. doi:10.1056/nejmoa2030183
- 16. TRANSLATE-HF: More than 80% of Heart Failure Patients Eligible for Dapagliflozin. Practical Cardiology. Accessed March 1, 2022. https://www.practicalcardiology.com/view/translate-hf-more-than-80-of-heart-failure-patients-eligible-for-dapagliflozin
- 17. Rao VN, Murray E, Butler J, et al. In-Hospital Initiation of Sodium-Glucose Cotransporter-2 Inhibitors for Heart Failure With Reduced Ejection Fraction. Journal of the American College of Cardiology. 2021;78(20):2004-2012. doi:10.1016/j.jacc.2021.08.064
- 18. Packer, M., Anker, S. D., Butler, J., Filippatos, G., Pocock, S. J., Carson, P., Januzzi, J., Verma, S., Tsutsui, H., Brueckmann, M., Jamal, W., Kimura, K., Schnee, J., Zeller, C., Cotton, D., Bocchi, E., Bohm, M., Choi, D. J., Chopra, V., ... Zannad, F. (2020). Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure, 383(15), 1413–1424. https://doi.org/10.1056/NEJMoa2022190
- 19. Anker, S., Butler, J., Filippatos, G., Jamal, W., Salsali, A., Schnee, J., . . . Packer, M. (2019). Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: Rationale for and design of the EMPEROR-Preserved Trial [Abstract]. European Journal of Heart Failure, 1279-1287. doi:10.1002/ejhf.1596
- 20. Perkovic, Vlado, et al. "Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy." New England Journal of Medicine, vol. 380, no. 24, 2019, pp. 2295–306. Crossref, doi:10.1056/nejmoa1811744.