**Title:** Therapeutic Tightrope: Navigating Guideline Directed Medical Therapy for Heart Failure in Renal Dysfunction

## **Presenter:**

Andrew Teletnick, PharmD PGY2 Cardiology Resident UPMC Presbyterian

## Date: 10/02/2024

## Learning Objectives:

- 1. Describe the effect of heart failure guideline directed medication therapies on renal function
- 2. Define criteria for heart failure medication initiation and titration in chronic kidney disease
- 3. Explain considerations for heart failure medication management in impaired renal function

# Abstract:

Heart failure is a chronic cardiovascular condition with several different guidelinerecommended medication therapies (GDMT), including renin-angiotensin-aldosterone system inhibitors (RAASi), beta blockers (BB), mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter 2 inhibitors (SGLT2i). Initiation and titration of these agents may be limited in patients with renal dysfunction due to heightened risk of adverse effects. In chronic kidney disease patients, individual RAASi, SGLT2i, and MRA agents have manufacturing labeling thresholds for GDMT initiation, however balance of risks and benefits can be considered in initiation on a case-by-case basis. These agents also possess protective qualities that have evidence for reducing the rate of glomerular filtration rate decline in addition to cardiovascular benefit in heart failure. In patients with worsening renal function or decompensated heart failure, GDMT should be continued in mild acute renal impairment unless a related contraindication exists. As renal function approaches end-stage classification and risk of hyperkalemia increases, adjunctive therapies can be considered in addition to routine monitoring.

#### **References:**

- Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895-e1032.
- 2. Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. Circulation. 2005;111(21):2837-2849.
- 3. Fonarow GC, Abraham WT, Albert NM, et al. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZE-HF program. J Am Coll Cardiol. 2008;52(3):190-199.
- Gilstrap LG, Fonarow GC, Desai AS, et al. Initiation, Continuation, or Withdrawal of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers and Outcomes in Patients Hospitalized With Heart Failure With Reduced Ejection Fraction. J Am Heart Assoc. 2017;6(2):e004675.
- 5. Maisel A, Xue Y, van Veldhuisen DJ, et al. Effect of spironolactone on 30-day death and heart failure rehospitalization (from the COACH Study). Am J Cardiol. 2014;114(5):737-742.
- 6. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. N Engl J Med. 2019;380(6):539-548.
- Mebazaa A, Davison B, Chioncel O, et al. Safety, tolerability and efficacy of uptitration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. Lancet. 2022;400(10367):1938-1952.
- Maddox TM, Januzzi JL Jr, Allen LA, et al. 2024 ACC Expert Consensus Decision Pathway for Treatment of Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2024;83(15):1444-1488.
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024;105(4S):S117-S314.
- 10. (glomerulus picture, common domain) www.clipartkey.com/view/hThJww\_transparent-kidneys-png-glomerulus-vector
- 11. Schoolwerth AC, Sica DA, Ballermann BJ, Wilcox CS; Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. Circulation. 2001;104(16):1985-1991.

- 12. Weber MA, Drayer JI. Renal effects of beta-adrenoceptor blockade. Kidney Int. 1980;18(5):686-699.
- 13. Hubers SA, Brown NJ. Combined Angiotensin Receptor Antagonism and Neprilysin Inhibition. Circulation. 2016;133(11):1115-1124.
- 14. (nephron picture, common domain) https://smart.servier.com/smart\_image/smartnephron-ov/
- 15. Lother A. Mineralocorticoid Receptors: Master Regulators of Extracellular Matrix Remodeling. Circ Res. 2020;127(3):354-356.
- 16. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. Physiol Rev. 2011;91(2):733-794.
- 17. Bisoprolol fumarate [package insert]. DailyMed: Solco Heathcare; 2023.
- 18. Carvedilol [package insert]. DailyMed: Aurobindo; 2024.
- 19. Metoprolol succinate [package insert]. DailyMed: Ethex Corporation; 2010.
- 20. Entresto sacubitril and valsartan [package insert]. DailyMed: Novartis Pharmaceuticals; 2024.
- 21. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.
- 22. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2019;381(17):1609-1620.
- 23. Niu CY, Yang SF, Ou SM, et al. Sacubitril/Valsartan in Patients With Heart Failure and Concomitant End-Stage Kidney Disease. J Am Heart Assoc. 2022;11(18):e026407.
- 24. Haynes R, Judge PK, Staplin N, et al. Effects of Sacubitril/Valsartan Versus Irbesartan in Patients With Chronic Kidney Disease. Circulation.
  2018;138(15):1505-1514.
- 25. Butt JH, McMurray JJ, Claggett BL, et al. Therapeutic Effects of Heart Failure Medical Therapies on Standardized Kidney Outcomes: Comprehensive Individual Participant-Level Analysis of 6 Randomized Clinical Trials. Circulation. Published online September 1, 2024.
- 26. Aldactone spironolactone [package insert]. DailyMed: Pfizer Laboratories; 2023.
- 27. Inspra eplerenone [package insert]. DailyMed: Pfizer Laboratories; 2021.
- 28. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-717.
- 29. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364(1):11-21.

- 30. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370(15):1383-1392.
- 31. Oka T, Sakaguchi Y, Hattori K, et al. Mineralocorticoid Receptor Antagonist Use and Hard Renal Outcomes in Real-World Patients With Chronic Kidney Disease. Hypertension. 2022;79(3):679-689.
- 32. Yang CT, Kor CT, Hsieh YP. Long-Term Effects of Spironolactone on Kidney Function and Hyperkalemia-Associated Hospitalization in Patients with Chronic Kidney Disease. J Clin Med. 2018;7(11):459.
- 33. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. N Engl J Med. 2021;385(24):2252-2263.
- 34. Bakris GL, Agarwal R, Anker SD, et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. N Engl J Med. 2020;383(23):2219-2229.
- 35. Solomon SD, McMurray JJV, Vaduganathan M, et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. Published online September 1, 2024.
- Farxiga dapagliflozin [package insert]. DailyMed: AstraZeneca Pharmaceuticals; 2024.
- 37. Inpefa sotagliflozin [package insert]. DailyMed: Lexicon Pharmaceuticals; 2024.
- Jardiance empagliflozin [package insert]. DailyMed: Boehringer Ingelheim Pharmaceuticals; 2024.
- 39. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-1424.
- 40. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995-2008.
- 41. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021;384(2):117-128.
- 42. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383(15):1436-1446.
- 43. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017;377(7):644-657.
- 44. The EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, et al. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2023;388(2):117-127.
- 45. Chatur S, Vaduganathan M, Claggett BL, et al. Dapagliflozin in Patients With Heart Failure and Deterioration in Renal Function. J Am Coll Cardiol. 2023;82(19):1854-1863.

- 46. Ahmad T, Jackson K, Rao VS, et al. Worsening Renal Function in Patients With Acute Heart Failure Undergoing Aggressive Diuresis Is Not Associated With Tubular Injury. Circulation. 2018;137(19):2016-2028.
- 47. Jondeau G, Neuder Y, Eicher JC, et al. B-CONVINCED: Beta-blocker CONtinuation
   Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode. Eur Heart J. 2009;30(18):2186-2192.
- 48. Matsushita K, Delmas C, Marchandot B, et al. Optimal Heart Failure Medical Therapy and Mortality in Survivors of Cardiogenic Shock: Insights From the FRENSHOCK Registry. J Am Heart Assoc. 2024;13(5):e030975.
- 49. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med. 2022;28(3):568-574.
- 50. Tavares CAM, Azevedo LCP, Rea-Neto Á, et al. Dapagliflozin for Critically Ill Patients With Acute Organ Dysfunction: The DEFENDER Randomized Clinical Trial. JAMA. 2024;332(5):401-411.
- 51. Bhandari S, Mehta S, Khwaja A, et al. Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease. N Engl J Med. 2022;387(22):2021-2032.
- 52. Butler J, Anker SD, Lund LH, et al. Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: the DIAMOND trial. Eur Heart J. 2022;43(41):4362-4373.
- 53. Brunner-La Rocca HP, Knackstedt C, Eurlings L, et al. Impact of worsening renal function related to medication in heart failure. Eur J Heart Fail. 2015;17(2):159-168.

## Audience Response Questions:

- Which of the following GDMT classes does not possess a mechanism effecting electrolytes in the kidneys?
   A.ACEi's
   B.Beta Blockers
  - C.MRA's
  - D.SGLT2i's

 Which of the following agents has a guideline recommended restriction criteria for initiation to limit risk of adverse effects?
 A.Sacubitril-valsartan

**B.Carvedilol** 

C.Dapagliflozin

- D.Eplerenone
- 3. At which serum potassium threshold would intervention or adjunctive therapies become necessary?

A.K > 4.5 B.K > 5.0 C.K > 5.5 D.K > 6.0