

## Mineralocorticoid Receptor Antagonists in High-Risk Heart Failure Patients With Diabetes Mellitus and/or Chronic Kidney Disease

Bertram Pitt, MD; Patrick Rossignol, MD, PhD

The steroidal mineralocorticoid receptor antagonists (MRAs) spironolactone and eplerenone have been shown in large-scale prospective double-blind trials to reduce cardiovascular mortality and hospitalizations for heart failure in patients with a reduced left ventricular ejection fraction (HFrEF).<sup>1</sup> Their use in patients with midrange and preserved left ventricular function (HFpEF) remains controversial. Despite designation as a class 1 indication in current US<sup>2</sup> and European<sup>3</sup> guidelines for patients with HFrEF, their use remains suboptimal in comparison to  $\beta$ -adrenergic blocking agents, angiotensin-converting enzyme inhibitors, or angiotensin receptor blocking agents.<sup>4</sup> The relative underuse of MRAs in guideline-eligible patients with HFrEF<sup>5</sup> has in large part been attributed to the fear of inducing hyperkalemia and/or renal insufficiency (RI), especially in patients with diabetes mellitus (DM) and/or chronic kidney disease.<sup>6</sup> In part these fears have been amplified by questions raised as to their effectiveness and safety in “real world” settings based upon retrospective analysis of data in various registries.<sup>7,8</sup> While large-scale prospective randomized trials are recognized as the criterion standard for evaluating the safety and efficacy of new therapies for approval, the application and relevance to clinical practice obtained from these studies to the “real world” has been questioned because of various restrictions on inclusion into the large-scale randomized trials and the intensity of patient monitoring and follow-up in comparison to clinical practice in “real world” settings. “Real world” data

regarding the safety and efficacy of a given intervention based upon retrospective analysis of registry data have, however, been criticized as suffering from bias by intent to treat. In an observational study, observations are collected without assignment, and no adjustment, however elaborate it may be, can protect against the “unavoidable risk of selection bias and of systematic differences in outcomes that are not due to the treatment itself.”<sup>9</sup> Nevertheless, registry-based analysis of safety and efficacy of a given therapeutic intervention is valuable in pointing out areas for further investigation.

In this issue of *JAHA*, Cooper et al,<sup>10</sup> using the Get With The Guidelines registry linked to Medicare outcome data, have evaluated the first-time use of MRAs in high-risk patients with either a history of DM or RI at hospital discharge after an episode of HF. In contrast to some previous registry studies, they included both patients with a left ventricular ejection fraction <35% (HFrEF) as well as those with borderline (midrange: heart failure with midrange left ventricular ejection fraction-HFmrEF) or preserved ejection fractions (HFpEF). They evaluated the factors favoring or not favoring the use of a MRA at hospital discharge as well as the 30-day, 1-year, and 3-year incidence of mortality, hospitalizations for heart failure, and hospitalization for hyperkalemia and RI. Of 16 848 eligible patients, 2067 (12.3%) were prescribed a MRA for the first time at hospital discharge, of whom 60.5% had HFrEF. In the overall population after inverse probability weighting, the use of a MRA in these relatively high-risk patients with a history of either DM and/or RI was not associated with a significant reduction in 30-day, 1-, or 3-year mortality. MRA use was, however, associated with a 1- and 3-year lower risk of hospital readmissions. This benefit of MRA use was associated with a greater risk of readmissions for hyperkalemia and RI at 1 and 3 years. The increased rate of readmissions for RI was, however, restricted to those with borderline and preserved ejection fractions.<sup>10</sup> In the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) study of patients with HFpEF randomized to spironolactone, there was a significant increase in the incidence of doubling of serum creatinine but no increase in the need for renal dialysis.<sup>11</sup> It should also be pointed out that the absolute increase in the incidence of hospitalizations for hyperkalemia over 3 years in the analysis

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the University of Michigan School of Medicine, Ann Arbor, MI (B.P.); Inserm, Centre d'Investigations Cliniques-Plurithématique 14-33, Inserm U1116, CHRU Nancy, Université de Lorraine, Nancy, France (P.R.); F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France (P.R.).

**Correspondence to:** Bertram Pitt, MD, School of Medicine, University of Michigan, 1500 East Medical Center Dr, Ann Arbor, MI 48109. E-mail: bpitt@med.umich.edu

*J Am Heart Assoc.* 2017;6:e008054. DOI: 10.1161/JAHA.117.008054.

© 2017 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

by Cooper et al<sup>10</sup> was relatively low and that previous studies have suggested that the use of a MRA is associated with a reduction in mortality in comparison to placebo in patients with hyperkalemia, at least up to a serum K<sup>+</sup> value of 5.5 mmol/L.<sup>12</sup>

### What Are the Implications of the Findings by Cooper et al From This “Real World” Analysis?

An analysis of “real world” data such as that by Cooper et al<sup>10</sup> cannot provide a definitive answer as to the efficacy or safety of MRAs in high-risk patients with HF, as pointed out above. It can, however, suggest the need for further prospective study in these high-risk HF patients with DM and/or RI. The evidence available from the prospective randomized trials of MRAs in patients with HFrEF would support the use of a MRA in these high-risk guideline-eligible patients<sup>13</sup> (inclusion if serum K<sup>+</sup> <5.0 mmol/L and estimated glomerular filtration rate >30 mL/min per 1.73 m<sup>2</sup>). Cooper et al<sup>10</sup> also point out that “the benefits of therapy may outweigh the risks in this high-risk population” since there was an overall decrease in the risk of readmissions in patients treated with a MRA. One should, however, closely monitor these high-risk patients. Current evidence suggests that many patients prescribed a MRA for HF do not undergo recommended serial monitoring of serum potassium (K<sup>+</sup>) and renal function.<sup>14</sup> Monitoring of serum K<sup>+</sup> and renal function would allow appropriate dose adjustment and/or discontinuation of a MRA as well as discontinuation of other medications that might affect renal function and thus serum K<sup>+</sup>. Those who do undergo appropriate serial monitoring often discontinue their MRA because of an increase in serum K<sup>+</sup> and/or creatinine. While clearly one would like to avoid the increased risk of ventricular arrhythmias and sudden cardiac death associated with the occurrence of hyperkalemia, discontinuing a MRA could potentially expose the patient to an even greater risk since the steroidal MRA eplerenone has been shown to reduce all-cause mortality and all-cause hospitalizations in patients with HFrEF<sup>1</sup> including those patients with DM and/or chronic kidney disease.<sup>13</sup> The situation in regard to the use of a MRA in those patients with borderline and/or preserved ejection fractions (HFmrEF or HFpEF), especially those with DM and/or RI, is less certain. Although spironolactone appeared to reduce cardiovascular mortality and HFHs (Heart Failure Hospitalizations) in the Americas region in TOPCAT, the overall results including patients from Russia and the Republic of Georgia, who have been found not to have had the mortality rate we expect in patients with HFpEF and in whom there is evidence that many patients randomized to spironolactone and claiming to have taken it did not take it,<sup>15</sup> were not significant. Until further strategies are identified that clearly reduce cardiovascular mortality and hospitalizations for heart failure in patients with HFmrEF and HFpEF, one should consider the use of

spironolactone in these patients as suggested by the class II indication in current US guidelines.<sup>2</sup> Further information in regard to the efficacy and safety of spironolactone in patients with midrange left ventricular function and HFpEF should be forthcoming from the prospectively randomized open label SPIRRIT-HFpEF (Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction) (n=3200) in which the primary outcome is cardiovascular mortality.<sup>16</sup> In those patients with DM and/or RI, one might consider it prudent to await further data from the SPIRRIT trial<sup>16</sup> before considering a MRA in view of the increased risk of RI noted by Cooper et al in these patients.<sup>10</sup> However, even in these high-risk patients there was a decrease in the incidence of readmissions without any increase in mortality, which would favor the use of a MRA. While the decision as to whether or not to administer a MRA to these high-risk patients with borderline and/or preserved ventricular function remains uncertain, the data by Cooper et al<sup>10</sup> are of value in focusing our attention on the need to consider new strategies to reduce the risk of hyperkalemia and RI in these high-risk patients who are at great risk of dying of HF. The availability of new safe and well-tolerated potassium-lowering agents such as patiromer should avoid the risks of hyperkalemia associated with MRA use and potentially could allow the long-term use of a MRA in these high-risk patients despite the occurrence of hyperkalemia. The long-term risks and benefits of such a strategy will, however, require further prospective evaluation.<sup>17</sup> The use of new nonsteroidal MRAs such as Finerenone, which in early studies has been shown to be as effective as spironolactone in reducing brain natriuretic peptide and N-terminal pro-brain natriuretic peptide in HF patients but associated with a lower incidence of hyperkalemia,<sup>18</sup> also holds promise for the high-risk patients with HF complicated by DM and/or chronic kidney disease identified by Cooper et al.<sup>10</sup> Whether Finerenone improves cardiovascular and renal outcomes in patients with diabetic nephropathy (Figaro n=6400, clinicaltrials.gov NCT02540993), (Fidelio n=4800, NCT02545049) is currently being evaluated.

Finally, the trend toward the design of more pragmatic prospective randomized trials with fewer exclusions should hopefully in the future reduce the differences between “real world” data obtained retrospectively from registries such as that by Cooper et al<sup>10</sup> and the prospective randomized trials used for drug approval. Until then, both the large-scale prospective randomized trials and the retrospective analysis of registries to provide “real world” data such as that by Cooper et al<sup>10</sup> have a role in informing clinical practice—but in a different manner.

### Disclosures

Dr Pitt reports personal fees (consulting) from Bayer, KBP Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Merck,

Takeda, Relypsa, Sanofi, sc Pharmaceuticals, Sarfez Pharmaceuticals, Stealth Peptides, Vifor, and Tricida; stock options from KBP Pharmaceuticals, scPharmaceuticals, Sarfez Pharmaceuticals, Relypsa, and Tricida; patent pending for site-specific delivery of eplerenone to the myocardium. Dr Rossignol reports personal fees (consulting) from Novartis, Relypsa, AstraZeneca, Grünenthal, Stealth Peptides, Fresenius, Vifor Fresenius Medical Care Renal Pharma, Vifor, and CTMA; lecture fees from Bayer and CVRx, and is a cofounder of CardioRenal.

## References

- Zannad F, Gattis Stough W, Rossignol P, Bauersachs J, McMurray JJ, Swedberg K, Struthers AD, Voors AA, Ruilope LM, Bakris GL, O'Connor CM, Gheorghiadu M, Mentz RJ, Cohen-Solal A, Maggioni AP, Beygui F, Filippatos GS, Massy ZA, Pathak A, Pina IL, Sabbah HN, Sica DA, Tavazzi L, Pitt B. Mineralocorticoid receptor antagonists for heart failure with reduced ejection fraction: integrating evidence into clinical practice. *Eur Heart J*. 2012;33:2782–2795.
- Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–e161.
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129–2200.
- Maggioni AP, Anker SD, Dahlstrom U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozdz J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavaliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2013;15:1173–1184.
- Rao KK, Enriquez JR, de Lemos JA, Alexander KP, Chen AY, McGuire DK, Fonarow GC, Das SR. Use of aldosterone antagonists at discharge after myocardial infarction: results from the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry-Get With the Guidelines (GWTG). *Am Heart J*. 2013;166:709–715.
- Pitt B, Rossignol P. Impact of hyperkalemia and worsening renal function on the use of renin angiotensin aldosterone system inhibitors in chronic heart failure with reduced ejection fraction. *Clin Pharmacol Ther*. 2017;102:389–391.
- Wang TY, Vora AN, Peng SA, Fonarow GC, Das S, de Lemos JA, Peterson ED. Effectiveness and safety of aldosterone antagonist therapy use among older patients with reduced ejection fraction after acute myocardial infarction. *J Am Heart Assoc*. 2016;5:e002612. DOI: 10.1161/JAHA.115.002612.
- Lund LH, Svennblad B, Melhus H, Hallberg P, Dahlstrom U, Edner M. Association of spironolactone use with all-cause mortality in heart failure: a propensity scored cohort study. *Circ Heart Fail*. 2013;6:174–183.
- Pocock SJ, Elbourne DR. Randomized trials or observational tribulations? *N Engl J Med*. 2000;342:1907–1909.
- Cooper LB, Lippmann SJ, Greiner MA, Sharma A, Kelly JP, Fonarow GC, Yancy CW, Heidenreich PA, Hernandez AF. Use of mineralocorticoid receptor antagonists in patients with heart failure and comorbid diabetes mellitus or chronic kidney disease. *J Am Heart Assoc*. 2017;6:e006540. DOI: 10.1161/JAHA.117.006540.
- Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383–1392.
- Rossignol P, Dobre D, McMurray JJ, Swedberg K, Krum H, van Veldhuisen DJ, Shi H, Messig M, Vincent J, Giererd N, Bakris G, Pitt B, Zannad F. Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Circ Heart Fail*. 2014;7:51–58.
- Eschaliel R, McMurray JJ, Swedberg K, van Veldhuisen DJ, Krum H, Pocock SJ, Shi H, Vincent J, Rossignol P, Zannad F, Pitt B. Safety and efficacy of eplerenone in patients at high-risk for hyperkalemia and/or worsening renal function: analyses of EMPHASIS-HF study subgroups. *J Am Coll Cardiol*. 2013;62:1585–1593.
- Cooper LB, Hammill BG, Peterson ED, Pitt B, Maciejewski ML, Curtis LH, Hernandez AF. Consistency of laboratory monitoring during initiation of mineralocorticoid receptor antagonist therapy in patients with heart failure. *JAMA*. 2015;314:1973–1975.
- de Denus S, O'Meara E, Desai AS, Claggett B, Lewis EF, Leclair G, Jutras M, Lavoie J, Solomon SD, Pitt B, Pfeffer MA, Rouleau JL. Spironolactone metabolites in TOPCAT—new insights into regional variation. *N Engl J Med*. 2017;376:1690–1692.
- Lund LH, Oldgren J, James S. Registry-based pragmatic trials in heart failure: current experience and future directions. *Curr Heart Fail Rep*. 2017;14:59–70.
- Pitt B, Rossignol P. Potassium lowering agents: recommendations for physician and patient education, treatment reappraisal, and serial monitoring of potassium in patients with chronic hyperkalemia. *Pharmacol Res*. 2017;118:2–4.
- Pitt B, Rossignol P. The safety of mineralocorticoid receptor antagonists (MRAs) in patients with heart failure. *Expert Opin Drug Saf*. 2016;15:659–665.

**Key Words:** Editorials • chronic kidney disease • diabetes mellitus • heart failure • hyperkalemia • outcomes research



**Mineralocorticoid Receptor Antagonists in High-Risk Heart Failure Patients With Diabetes Mellitus and/or Chronic Kidney Disease**

Bertram Pitt and Patrick Rossignol

*J Am Heart Assoc.* 2017;6:e008054; originally published December 23, 2017;  
doi: 10.1161/JAHA.117.008054

The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
Online ISSN: 2047-9980

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://jaha.ahajournals.org/content/6/12/e008054>