American Heart Association | American Stroke Association

# Hyperkalemia in Heart Failure: Probably Not O"K"

Marat Fudim, MD; Justin L. Grodin, MD, MPH; Robert J. Mentz, MD

Hyperkalemia is routinely defined as a serum potassium level >5 mmol/L and is a common occurrence in patients with acute and chronic heart failure (HF). For example, prior work has demonstrated that hyperkalemia is present in ≈9% of patients admitted for acute HF,[1] and the total annual charges for Medicare admissions related to a primary diagnosis of hyperkalemia are substantial, with estimates as high as $697 million in 2011.[2] Elevated potassium levels may affect the activity of myocardial potassium channels, leading to more rapid membrane depolarization. The downstream effects of this may translate into slower myocardial electrical conduction, resulting in malignant tachyarrhythmias or bradyarrhythmias. Hyperkalemia, especially with potassium levels >5.5 mmol/L, has been consistently linked to poor clinical outcomes in patients with HF.[3,4] Recent estimates from the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial suggest the incidence of hyperkalemia in a trial population receiving treatment with renin-angiotensin system inhibition (RASi) was ≈16% over a median follow-up time of 27 months, despite a highly selected and carefully monitored clinical trial population.[5] Similarly, in a large cohort from the United Kingdom of 19 194 patients with new-onset HF, 11% developed hyperkalemia during a 4-year follow-up.[6] Multiple prior analyses of clinical trials and population-based studies identify renal dysfunction, type 2 diabetes mellitus, and the use of mineralocorticoid antagonists (MRAs) and RASi as major risk factors for hyperkalemia. Given that 5.7 million people in the United States alone have HF and this number is increasing, there is an overwhelming number of patients at risk for hyperkalemia and associated adverse events.[7] Patients with HF are at a particularly high risk for hyperkalemia, which is likely reflective of their medical comorbidity, including renal dysfunction. In addition, several of the current medical therapies for the management of HF with reduced ejection fraction (EF) add to this risk. These include cornerstone therapies, such as the following: (1) RASi, including angiotensin-converting enzyme inhibitors and angiotensin receptor inhibitors with or without neprilysin inhibition; and (2) MRAs, such as spironolactone and eplerenone. Whether a consequence of a real or perceived risk of hyperkalemia, evidence supports that these therapies are underused, and when used there is suboptimal dose titration.[8,9] Although there are data to support that mild hyperkalemia (potassium level, 5–5.5 mmol/L) in the setting of RASi and MRA therapy might not be associated with poor clinical outcomes, hyperkalemia in HF remains a major clinical dilemma.[3,10]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Thomsen et al performed an analysis to determine the incidence and predictors of hyperkalemia as well as the outcomes attributed to various levels of hyperkalemia in a large population-based cohort (N=31 649).[11] The study included patients with a new diagnosis of hospitalized HF in northern Denmark between 2000 and 2012. Risk factors and clinical outcomes were compared in patients with HF with versus without hyperkalemia. The main finding of the study was that over a mean follow-up of 2.2 years, hyperkalemia (potassium level, >5.0 mmol/L) occurred in 39% of patients. Repeated hyperkalemia episodes were even more common, with 43%, 54%, and 60% for each subsequent event in the patients with an index hyperkalemia event. The 3 main predictors of hyperkalemia were chronic kidney disease, diabetes mellitus, and MRA use. Finally, patients with hyperkalemia were at an increased risk of rehospitalization (6-month hazard ratio, 2.75; 95% confidence interval, 2.65–2.85) and death (hazard ratio, 3.39; 95% confidence interval, 3.19–3.61) when compared with 12 151 matched counterparts with HF without incident hyperkalemia.

Indeed, there are several notable findings from this large-scale analysis. In this population-based sample of patients with HF, there was a high incidence of hyperkalemia (4 in 10),

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

*From the Division of Cardiology, Duke Clinical Research Institute, Durham, NC (M.F., R.J.M.); Duke Clinical Research Institute, Durham, NC (M.F., R.J.M.); and Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX (J.L.G.).*

**Correspondence to:** Marat Fudim, MD, 2301 Erwin Rd, Durham, NC 27710. E-mail: marat.fudim@duke.edu

*J Am Heart Assoc.* 2018;7:e009429. DOI: 10.1161/JAHA.118.009429.

which is substantially higher than prior reports from clinical trials or population-based cohorts. Potential explanation for this observation could be the following:

1. First, the higher incidence of hyperkalemia may be attributable to the lower potassium cutoff value (>5 mmol/L) used in the analysis than it was used in other comparable analyses (>5.5 mmol/L).[1,5] Interestingly, 50% of the initial hyperkalemia events were in the range of 5.1 to 5.5 mmol/L in the present study, and the rate of initial hyperkalemia events with >5.5 mmol/L amounted to a smaller proportion at ≈20% of the entire population, which is still higher, but closer to prior hyperkalemia rates in the literature.
2. Second, the higher incidence of hyperkalemia may be secondary to the older age of this cohort. The median age of 79 years (interquartile range, 69–85 years) was high. As a comparison, the average age in a cohort with acute HF in the United States (OPTIMIZE (Organized Program to Initiate Life-saving Treatment In Hospitalized Patients With Heart Failure)) was 73 years,[12] and older age is a well-described risk factor for developing hyperkalemia.[13]
3. Third, one of the main risk factors of hyperkalemia, renal dysfunction, was present in 41% of this cohort. In comparison, the incidence of chronic kidney disease in a younger US-wide population from the Get With The Guidelines—Heart Failure Registry is 22%.[14] In the northern Danish cohort, the presence of chronic kidney disease (estimated glomerular filtration rate, <60 mL/min per 1.73 $m^2$) alone was associated with a hazard ratio of 1.46 (95% confidence interval, 1.43–1.49), and estimated glomerular filtration rate <30 mL/min per 1.73 $m^2$ was the strongest predictor of hyperkalemia in the present analysis (hazard ratio, 2.05; 95% confidence interval, 1.94–2.17).

Fortunately, the high incidence of hyperkalemia was only infrequently associated with a discontinuation or a dose reduction of guideline-directed medical therapy RASi or MRA (Figure 3 in the aforementioned article), as has been seen in a prior MRA-specific analysis in the Swedish heart registry.[15] This is an important and reassuring finding given the concern for the overall underuse of RASi and MRA in HF with reduced EF.[8,9] Deferring the use of guideline-directed medical therapies poses a major risk to patients' life expectancy and morbidity and, therefore, requires a careful consideration of the benefit/risk ratio associated with the use of RASi/MRA. Historically, fears for the risk of hyperkalemia were particularly high with MRA after an initial uptake in spironolactone use in HF with reduced EF was linked to a parallel increase in hyperkalemia-related hospitalizations and hyperkalemia-associated mortality.[16] On the other hand, because MRA and angiotensin receptor inhibitors are some of the few guideline-recommended medical therapies for HF with preserved EF (both level IIB), there is a particular urgency to understand the real-world incidence of hyperkalemia and the relationship of hyperkalemia with HF outcomes and to address concerns associated with its use.[17]

When evaluating the risks associated with hyperkalemia, one should consider the cause of the potassium elevation. Data consistently support that hyperkalemia attributable to underlying cardiovascular and noncardiovascular causes (chronic kidney disease and diabetes mellitus) is associated with a poor prognosis. On the other hand, episodes or even chronic states of hyperkalemia associated with a medical treatment, such as RASi/MRA, are not necessarily markers of a poor prognosis but might be more reflective of drug effect as opposed to evolving maladaptive cardiorenal interactions. Current HF treatment guidelines do not recommend MRA use in patients with estimated glomerular filtration rate <30 mL/min per 1.73 $m^2$ or serum potassium levels >5.0 mmol/L,[17] which, for safety concerns, may translate to the exclusion of a large portion of the population with HF from receiving MRA. However, evidence from landmark MRA trials in the HF space indicate that the beneficial effects of MRA may be preserved despite hyperkalemia. Support for this was found in the RALES (Randomized Aldactone Evaluation Study), where patients randomized to spironolactone experienced a potassium level increase within 1 month of randomization, with persistent elevation for the duration of the trial (from 4.29±0.5 to 4.54±0.49 mmol/L). Although hyperkalemia was associated with higher mortality, patients randomized to spironolactone had a sustained mortality benefit, with potassium levels <5.0 to 5.5 mmol/L.[3] Similar findings were reported from the EMPHASIS (Eplerenone in Mild Patients Hospitalization and Survival Study), where favorable effects of eplerenone on all-cause death were seen irrespective of the incidence of hyperkalemia or worsening renal function.[4] These findings have been replicated in other data sets. Results from a recent, large, network-wide analysis suggested there was no difference in outcomes between patients with normal or mildly elevated potassium levels (<5.5 mmol/L).[10] There are at least 2 concepts that could explain the apparent lack of association between low levels of hyperkalemia and poor clinical outcomes, seen in the studies previously cited. First, elevated potassium level (<5.5 mmol/L) could be a surrogate of successfully implemented RASi/MRA therapy, which could balance the benefit (RASi/MRA therapy) to risk (hyperkalemia) ratio. Second, it has been suggested that some of the benefit of MRA therapy might derive from a prevention of hypokalemia, which, like hyperkalemia, is strongly linked to poor clinical outcomes in patients with HF.[3,10]

Notably, preserved drug efficacy at higher potassium levels remained true even in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone

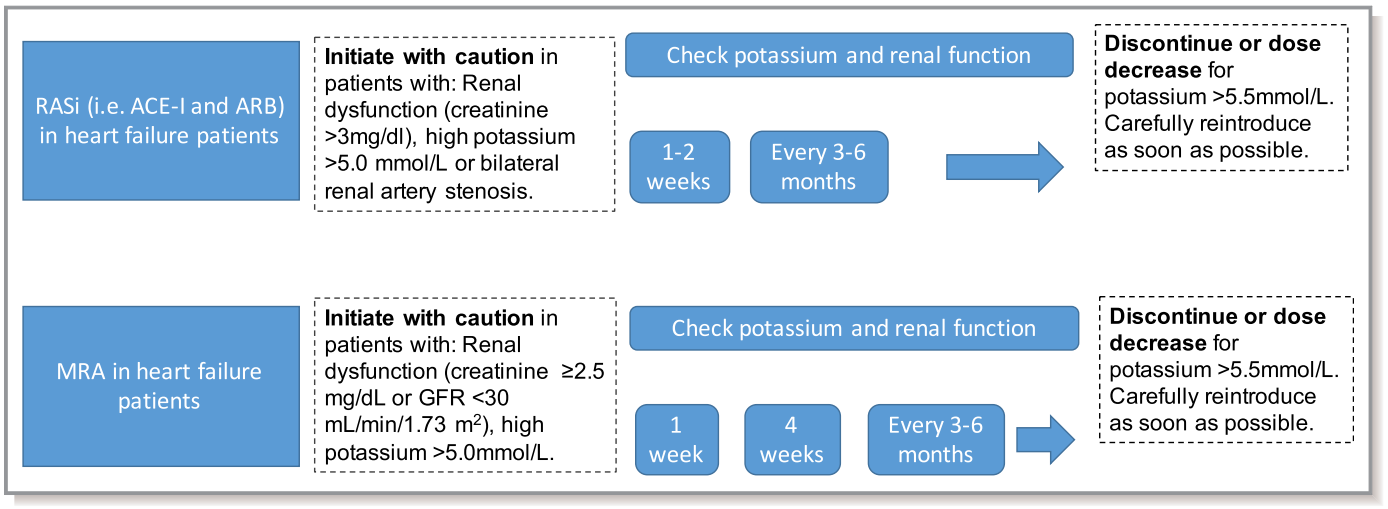


**Figure.** Summary of currently recommended potassium/renal function monitoring after initiation of renin-angiotensin system inhibition (RASi) and mineralocorticoid antagonists (MRAs). ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate.

Antagonist) trial, which studied the safety and efficacy of spironolactone versus placebo in HF with preserved EF. Once again, incident hypokalemia (using a potassium level of either <3.5 or <4.0 mmol/L as cutoff) and hyperkalemia (using a cutoff ≥5.5 or ≥6.0 mmol/L) were associated with increased risk for cardiovascular and all-cause mortality. Although there was no effect of MRA use on the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for HF in the whole study population, the reduction in cardiovascular mortality seen in subjects in the Americas randomized to spironolactone endured after accounting for postrandomization variations in serum potassium.[18]

Given the evidence that hyperkalemia in HF is not always an ominous sign, the analysis of the northern Danish cohort needs to be approached with some caution. Despite careful analytical methods that attempted to mitigate sources of bias, findings from this analysis remain limited by residual confounding. Individuals with incident hyperkalemia were more burdened by comorbidities, such as more prevalent ischemic heart disease, chronic kidney disease, diabetes mellitus, and peripheral arterial disease. Thus, we have to be careful to assert a general causal relationship between hyperkalemia and clinical outcomes across the entire spectrum of hyperkalemia.

Furthermore, there are new treatment options either approved or in the pipeline for patients with a history of hyperkalemia, such as the potassium binders (patiromer and ZS-9).[2] Future studies will need to prove safety and efficacy of these agents, especially in their use as a preventative strategy in patients at risk for hyperkalemia. Specifically, we need to understand whether potassium binder use in the population with HF will do the following: (1) allow added RASi or MRA; (2) permit increasing doses of RASi or MRA to maximize tolerated dosing; and (3) sustain the long-term benefits of RASi or MRA use. Given the risks associated with hyperkalemia, unmonitored use of RASi/MRA can be dangerous, as was seen with the introduction of spironolactone for the treatment of HF with reduced EF.[16] More contemporary reports have confirmed the suboptimal laboratory monitoring after RASi/MRA initiation, even in patients at highest risk.[18,19] Suboptimal monitoring puts patients at increased risk for adverse effects related to hyperkalemia, particularly in the "high-risk zone" of potassium level >5.5 mmol/L. Efforts to encourage guideline-directed laboratory monitoring appear logical, but we also need to understand whether greater monitoring efforts and what monitoring strategies would improve safety of patients with HF and particular the ones at high risk for hyperkalemia in the real world. A summary of currently recommended potassium/renal function monitoring[20,21] after initiation of RASi and MRA is presented in the Figure. In conclusion, because hyperkalemia in HF is highly prevalent, efforts to understand its associated risk, predict and monitor its onset, and develop effective treatment strategies that do not impede the use of guideline-directed medical therapy should be of highest priority.

## Disclosures

Fudim is supported by American Heart Association grant 17MCPRP33460225 and the National Heart, Lung, and Blood Institute T32 postdoctoral training grant 5T32HL007101-42, and reports consulting for Coridea, AxonTherapies, and Galvani. Mentz receives research support from the National Institutes of Health (U01HL125511-01A1, U10HL110312, and R01AG045551-01A1), Amgen, AstraZeneca, Bayer, GlaxoSmithKline, Gilead, Luitpold, Medtronic, Merck, Novartis, Otsuka, and ResMed; reports honoraria from Abbott, Bayer,

Janssen, Luitpold Pharmaceuticals, Merck, Novartis, and ResMed; and has served on an advisory board for Amgen, Luitpold, Merck, and Boehringer Ingelheim. Grodin has no disclosures to report.

## References


1. Tromp J, Ter Maaten JM, Damman K, O'Connor CM, Metra M, Dittrich HC, Ponikowski P, Teerlink JR, Cotter G, Davison B, Cleland JG, Givertz MM, Bloomfield DM, van der Wal MH, Jaarsma T, van Veldhuisen DJ, Hillege HL, Voors AA, van der Meer P. Serum potassium levels and outcome in acute heart failure (data from the PROTECT and COACH Trials). *Am J Cardiol*. 2017;119:290–296.
2. Sarwar CM, Papadimitriou L, Pitt B, Pina I, Zannad F, Anker SD, Gheorghiade M, Butler J. Hyperkalemia in heart failure. *J Am Coll Cardiol*. 2016;68:1575–1589.
3. Vardeny O, Claggett B, Anand I, Rossignol P, Desai AS, Zannad F, Pitt B, Solomon SD; Randomized Aldactone Evaluation Study Investigators. Incidence, predictors, and outcomes related to hypo- and hyperkalemia in patients with severe heart failure treated with a mineralocorticoid receptor antagonist. *Circ Heart Fail*. 2014;7:573–579.
4. Rossignol P, Dobre D, McMurray JJ, Swedberg K, Krum H, van Veldhuisen DJ, Shi H, Messig M, Vincent J, Girerd 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.
5. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.
6. Michel A, Martin-Perez M, Ruigomez A, Garcia Rodriguez LA. Risk factors for hyperkalaemia in a cohort of patients with newly diagnosed heart failure: a nested case-control study in UK general practice. *Eur J Heart Fail*. 2015;17:205–213.
7. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER III, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation*. 2016;133:447–454.
8. Roth GA, Poole JE, Zaha R, Zhou W, Skinner J, Morden NE. Use of guideline-directed medications for heart failure before cardioverter-defibrillator implantation. *J Am Coll Cardiol*. 2016;67:1062–1069.
9. 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, Kavoliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L; Heart Failure Association of the ESC. 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.
10. Hoss S, Elizur Y, Luria D, Keren A, Lotan C, Gotsman I. Serum potassium levels and outcome in patients with chronic heart failure. *Am J Cardiol*. 2016;118:1868–1874.
11. Thomsen RW, Nicolaisen SK, Hasvold P, Garcia-Sanchez R, Pedersen L, Adelborg K, Egfjord M, Egstrup K, Sørensen HT. Elevated potassium levels in patients with congestive heart failure: occurrence, risk factors, and clinical outcomes: a Danish population-based cohort study. *J Am Heart Assoc*. 2018;7:e008912. DOI: 10.1161/JAHA.118.008912.
12. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB; OPTIMIZE-HF Investigators and Hospitals. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol*. 2007;50:768–777.
13. Muzzarelli S, Maeder MT, Toggweiler S, Rickli H, Nietlispach F, Julius B, Burkard T, Pfisterer ME, Brunner-La Rocca HP; TIME-CHF Investigators. Frequency and predictors of hyperkalemia in patients >/=60 years of age with heart failure undergoing intense medical therapy. *Am J Cardiol*. 2012;109:693–698.
14. Pandey A, Golwala H, DeVore AD, Lu D, Madden G, Bhatt DL, Schulte PJ, Heidenreich PA, Yancy CW, Hernandez AF, Fonarow GC. Trends in the use of guideline-directed therapies among dialysis patients hospitalized with systolic heart failure: findings from the American Heart Association Get With The Guidelines-Heart Failure Program. *JACC Heart Fail*. 2016;4:649–661.
15. Savarese G, Carrero JJ, Pitt B, Anker SD, Rosano GMC, Dahlstrom U, Lund LH. Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. *Eur J Heart Fail*. 2018. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/ejhf.1182. Accessed May 19, 2018.
16. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;351:543–551.
17. 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, Levine GN, O'Gara PT, Halperin JL, Al-Khatib SM, Birtcher KK, Brindis RG, Cigarroa JE, Curtis LH, Fleisher LA, Gentile F, Gidding S, Hlatky MA, Ikonomidis J, Joglar J, Pressler SJ, Wijeysundera DN. 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. *J Cardiac Fail*. 2017;23:628–651.
18. Desai AS, Liu J, Pfeffer MA, Claggett B, Fleg J, Lewis EF, McKinlay S, O'Meara E, Shah SJ, Sweitzer NK, Solomon S, Pitt B. Incident hyperkalemia, hypokalemia, and clinical outcomes during spironolactone treatment of heart failure with preserved ejection fraction: analysis of the TOPCAT Trial. *J Cardiac Fail*. 2018;24:313–320.
19. Shah KB, Rao K, Sawyer R, Gottlieb SS. The adequacy of laboratory monitoring in patients treated with spironolactone for congestive heart failure. *J Am Coll Cardiol*. 2005;46:845–849.
20. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62:e147–e239.
21. National Clinical Guideline Centre. Chronic heart failure: the management of chronic heart failure in adults in primary and secondary care. London: National Clinical Guideline Centre. 2010. Available at: https://www.nice.org.uk/guidance/cg108/evidence/full-guideline-pdf-136060525. Accessed May 3, 2018.


**Key Words:** Editorials • cardiovascular outcomes • heart failure • hyperkalemia