Title: Analysing registries in heart failure: The case of angiotensin receptor blockers in Asians with heart failure with reduced ejection fraction

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Angiotensin converting enzyme (ACE) inhibitors remain the foundation of treatment for heart failure with reduced ejection fraction (HFREF) [1]. Angiotensin receptor blockers (ARB) are recommended as an alternative if the patient cannot tolerate an ACE inhibitor as a result of the CHARM-Alternative trial [2]. In many Asian countries ARBs are given as a first line drug, rather than ACE inhibitors, as many Asian patients fail to tolerate ACE inhibitors due to cough[3]. The reason for this racial disparity in the incidence of ACE inhibitor induced cough is not fully understood. However, many clinicians prescribe an ARB, before an ACE inhibitor, to Asian patients with HFREF. But does the benefit of an ARB persist in the real world, and, in a population that seem to react differently to ACE inhibitors? Answering this question is difficult. The best option would be to conduct a well-designed, and adequately powered, randomized clinical trial. However, clinical trials are costly and require a massive amount of effort on the part of investigators and patients alike. Can alternative data sources help answer specific questions (such as whether ARBs are effective in Asians) when there is already a solid foundation of evidence for their use from a large well conducted randomised trial? One option is to examine the Asian subgroup of a randomised trial. However, these are fraught with difficulty [4] and the subgroup may not exist or be large enough to assuage any apprehension. For these reasons many have turned to registries.

There has been a sharp increase in the use of registries to examine the association between treatments and outcomes. The difficulties surrounding such analyses have been widely discussed [5]. Randomisation overcomes the problems of registry based data but if used responsibly, registries can provide information on the use of a drug in real world populations outside the selected populations of clinical trials. Registries can answer specific questions that would never merit the cost and effort of a large randomised trial. More importantly they can reveal other avenues for research.

Choi and colleagues [6] used a registry to examine the use of ARBs in Asian patients with HFREF. Using a Korean registry of patients with decompensated heart failure they examined the association between ARB use and all-cause death and compared those who received an ARB to those who received an ACE inhibitor, and those who received neither. There were similarities to the patients enrolled in CHARM-Alternative (the mean age was 67 years and around two thirds were men) and differences (they were acutely decompensated, the prevalence of comorbidities was higher). The hazard of death was similar in the ACE inhibitor compared to the ARB group 0.91 (95%CI 0.76-1.09,p=0.32) after propensity adjustment. Compared to the group who did not receive any blockers of the renin angiotensin aldosterone system the hazard of death in the ARB group was 0.69 (95%CI 0.56-0.83,p<0.001). However, candesartan did not reduce all-cause mortality in CHARM-Alternative (HR=0.87,95%CI 0.74–1.03,p=0.11) yet Choi et al [6] report a 31% relative risk reduction. There is always the statistical possibility that this is true but it is more likely that this is due to unmeasured confounding [5]. Although propensity score weighting tries to overcome confounding by matching similar patients, it is not perfect and in this study matching was suboptimal. This highlights the need to exercise caution when interpreting the result of such analyses.

If registry data cannot ever establish the efficacy of ARBs, what can they do? Registries can provide information on treatment use and discontinuation rates. In a well-run clinical trial discontinuation rates are often low, in contrast to the multi-morbid patient with polypharmacy that heart failure specialists see in daily clinical practice. Discontinuation rates were high, 21% of those receiving an ARB and 34% of those receiving an ACE inhibitor discontinued it by 1 year. These numbers should worry heart failure specialists and remind us that our job does not stop after prescribing a drug, we must try and help our patients remain on the drug.

Registry based analyses can provide data on the treatment of conditions when randomised trials are not possible, such as in rare diseases or rare outcomes, and can allow exploration of groups not studied in randomised trials. Patients with heart failure with mid-range ejection fraction (HFMREF), an ejection fraction in the range of 40-49% [1,7], are such a group. Choi et al [6] found 839(16%) patients with HFMREF and 1309(25%) with heart failure with preserved ejection fraction (HFPEF), EF≥50%. They reported that the survival of patients with HFMREF receiving an ACE inhibitor or ARB was similar, and, better than those not receiving either, in HFPEF there was no difference. Could this simply be another statistical anomaly? A recent analysis of the beta-blocker trials reported that patients HFMREF may benefit from beta-blockers like those with HFREF [8]. Could renin angiotensin aldosterone system inhibition be similarly beneficial in HFMREF? In the TOPCAT trial there was a trend towards benefit in those with an EF of <50% compared to those with an EF >60% [9]. Another analysis of the CHARM trials also suggested that those with HFMREF demonstrated a similar response to candesartan as those with HFREF [10]. The data from Choi et al [6] therefore add to this growing body of evidence that patients with HFMREF may respond to drugs in a similar way to those with HFREF.

Registry based analyses are becoming more prevalent and their use looks set to continue to rise. With careful analysis, of the right question, with appropriate caution in the interpretation of the results and acknowledgment of the limitations, registry based analyses can help confirm the results of randomised controlled trials and answer specific questions about the real world use and tolerance of drugs in clinical practice. Registry based analyses are strongest when supported by a solid foundation of randomised trial evidence and interpretation should always be done with caution and with full consideration of the randomised evidence where it exists. If the reader keeps this in mind, new, and clinically important, insights can be gained.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, Meer P van der, Authors/Task Force Members, Document Reviewers. 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). Eur J Heart Fail. 2016;18:891–975.
2. Granger CB, McMurray JJ V, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K, CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet*. 2003;**362**:772–776.
3. Woo KS, Nicholls MG. High prevalence of persistent cough with angiotensin converting enzyme inhibitors in Chinese. Br J Clin Pharmacol. 1995; 40(2): 141–144.
4. Wedel H, Demets D, Deedwania P, Fagerberg B, Goldstein S, Gottlieb S, Hjalmarson A, Kjekshus J, Waagstein F, Wikstrand J, MERIT-HF Study Group. Challenges of subgroup analyses in multinational clinical trials: experiences from the MERIT-HF trial. *Am Heart J*. 2001;**142**:502–511.
5. Freemantle N, Marston L, Walters K, Wood J, Reynolds MR, Petersen I. Making inferences on treatment effects from real world data: propensity scores, confounding by indication, and other perils for the unwary in observational research. BMJ. 2013 Nov 11;347:f6409.
6. Choi et al. Effects of angiotensin receptor blocker at discharge in patients with heart failure with reduced ejection fraction:Korean Acute Heart Failure (KorAHF) registry.
7. Lam CS, Solomon SD. Fussing Over the Middle Child: Heart Failure With Mid-Range Ejection Fraction. Circulation. 2017 Apr 4;135(14):1279-1280.

8. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, Manzano L, McMurray JJV, Ruschitzka F, van Veldhuisen DJ, von Lueder TG, Böhm M, Andersson B, Kjekshus J, Packer M, Rigby AS, Rosano G, Wedel H, Hjalmarson Å, Wikstrand J, Kotecha D; Beta-blockers in Heart Failure Collaborative Group. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J. 2018 Jan 1;39(1):26-35
9. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, O'meara E, Shah SJ, McKinlay S, Fleg JL, Sopko G, Pitt B, Pfeffer MA. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J 2016;37:455–462
10. Lund LH. Heart failure with mid ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire EF spectrum. Heart Failure 2017. https://www.escardio.org/Congresses-&-Events/Heart-Failure/Congress-resources/candesartan-provides-similar-benefit-for-patients-with-mid-range-ejection-fracti (Last accessed 28 Dec 2017)