EDITORIAL

Pharmacological Treatment Following Myocardial Infarction: How Large Is the Gap Between Guideline Recommendations and Routine Clinical Care?

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By now, more than one decade has passed since publication of guideline-relevant landmark studies investigating the prognostic role of important pharmacotherapies (ie, beta blockers, inhibitors of the renin angiotensin aldosterone system, and mineralocorticoid receptor antagonists [MRA]) for primary prevention of sudden cardiac death.[1] However, because of improvement of the nationwide healthcare supply, revascularization strategies of coronary artery disease, and increasing supply of invasive cardiac devices (such as an implantable cardioverter defibrillator or cardiac resynchronization therapy), mortality rates following acute myocardial infarction (AMI) have significantly decreased.[1] As a consequence, characteristics and comorbidities of patients admitted to hospital have changed, leading to a higher number of older patients with increasing rates of progressive heart failure, complex coronary artery disease, atrial fibrillation, diabetes mellitus, and chronic kidney disease. Curiously, whether one of these established pharmacotherapies may still affect prognosis in patients with current complex heart failure syndromes has not yet been reevaluated within further randomized controlled trials. Therefore, European guidelines demand registry data to reassess the prognostic impact of established pharmacotherapies nowadays.[1] To further close this gap in literature, Goldberger et al and Wong et al investigated the prognostic impact of beta blockers and their appropriate dose, as well as the current use and guideline adherence of MRA treatment in patients with AMI within this issue of the *Journal of the American Heart Association* (*JAHA*).[2,3] Goldberger et al analyzed retrospectively more than 3,000 patients originally enrolled in the OBTAIN (Outcomes of Beta-blocker Therapy After Myocardial Infarction) registry (2007–2011) using propensity score matched cohorts.[2] They demonstrated lowest mortality rates in the presence of beta blocker intake of at least 12.5% to 25% of recommended target dosages at a median follow-up of one year. Their findings are in line with results from the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry (2006–2015) demonstrating target dosages at more than 50% than recommended were not associated with improved freedom from re-infarction or all-cause mortality.[4] Despite the utmost importance of the

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See Articles by Goldberger et al. and Wong et al.

findings by Goldberger and colleagues further studies will be necessary to provide robust data on the best duration of beta blocker therapy, especially in patients with heart failure with preserved ejection fraction.[5] The common indications for heart failure pharmacotherapies are based on the assessment of left ventricular ejection fraction and patients' symptoms.[6] However, one may wonder whether this still appropriate in the complex heart failure patient with different underlying aetiologies and multi-modal treatments.

A recently published study by Cohen et al identified different phenotypes of heart failure (ie, younger patients with mild symptoms, older patients with stiff arteries and obese diabetics with advanced symptoms) associated with different long-term mortality, risk of heart failure readmission, biomarker courses, but also response to pharmacotherapies (ie, especially MRA).[7] Accordingly, again guidelines demand the importance to investigate different phenotypes and targeted therapies in heart failure following AMI. The evaluation of the prognostic impact of beta blockers and their appropriate dosage stratified by etiology, comorbidities, severity of symptoms and concomitant multi-pharmacological treatments is of major interest.[5]

Furthermore, MRA treatment is recommended in patients with AMI with systolic heart failure defined as left ventricular ejection fraction ≤40%.[6] This recommendation is mainly based on the results of the EPHESUS (Eplerenone Post-AMI Heart Failure Efficacy and Survival) trial (published in 2003) demonstrating improved mortality at 30-days already in patients treated with eplerenone as compared to placebo.[8] Especially an early initiation of MRA was demonstrated to improve patient's outcomes, which may be related to the decrease of ischemia-driven cardiac fibrosis in the initial period of AMI already. However, a clear gap between these findings and real-life supply with MRA was demonstrated within the ACTION-GWTG (Acute Coronary Treatment and Intervention Outcomes Network-Get With The Guidelines) study (2007–2011), where only less than a fifth of eligible patients were discharged on MRA treatment.[9] To reassess this gap between guideline recommendations and real-world data, 317 patients from the "Vancouver Coastal Health Authority STEMI [ST-segment–elevation myocardial infarction] database" (enrollment period 2007–2018) were analysed by Wong et al in the current issue of the *JAHA*.[3] Only 22% of patients eligible for MRA were finally treated by MRA at discharge. Only 10% of patients without MRA at discharge were subsequently treated at 3 months of follow-up. The authors were able to provide a time trend suggesting increasing supply with MRA over time (ie, more than half of patients eligible for MRA in 2017–2018). The low prescription rate of MRA observed in their study is in line with previous heart failure studies. Our working group recently found a

treatment rate by MRA of only 20% in a real-life cohort of consecutive implantable cardioverter defibrillator recipients and a history of ventricular tachyarrhythmias (left ventricular ejection fraction <35: 70%).[10] The prospective BioSTAT-CHF (A Systems Biology Study to Tailored Treatment in Chronic Heart Failure) study revealed a MRA treatment rate of only 56% of 1,049 eligible patients suffering from systolic heart failure (ie, left ventricular ejection fraction <35%) and formal indication for MRA treatment (ie, estimated glomerular filtration rate ≥30 mL/min per 1.73 m^2 and potassium level ≤5.0 mmol/L).[11] Even the discontinuation of MRA therapy was reported in 16% of patients at 9 months, whereas a new initiation of MRA therapy was observed in only 36%. The frequent change of MRA treatment raises the question whether it is appropriate to investigate the prognostic impact of MRA treatment on prognostic end points within a dichotomized analytical approach. Therefore, the lack of end point-related data in the study by Wong and colleagues should not be considered as a major limitation. In contrast, it underlines the lack of optimal supply and guideline-adaption in daily clinical practice as well as in the setting of a clinical study.

Although there is a clear class IA guideline recommendation the definite reasons for the rather low prescription rates or withholding from so many patients need to be investigated urgently. The most common reasons to withhold MRA treatment from patients with advanced systolic heart failure are potential hyperkalemia, chronic kidney disease, and arterial hypotension, which may further provoke the development of the cardiorenal syndrome.[8] In particular, the risk of hyperkalemia-related death due to MRA therapy reflects the major concern why many clinicians withheld MRA from patients with heart failure. In contrast, it has to be outlined, that hyperkalemia-related death in patients treated with MRA is more common in nonrandomized registries, which also include patients with contraindications for MRA treatment as well as those with inappropriate MRA dosages.[12,13] Albert et al reported a high variability regarding treatment with MRA in the United States ranging from 0% to 100% (median 28%, interquartile range 18%–40%), which may be related to poor pharmaceutical company-sponsored drug marketing and education to physicians.[14] Poor adherence to guidelines may be increased by the large amount of randomized studies in the field of beta blockers and angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) and a contrastively smaller number of MRA studies.[1] MRA are usually initiated after up-titration of beta blockers and ACEI/ARB, which is also outlined in the current European guidelines for acute and chronic heart failure, although MRA are recommended in symptomatic patients treated with beta blockers plus ACEI/ARB.[6] However, the fear

of severe hypotension with consecutive low output and acute renal failure is often overestimated. A substudy of the EPHESUS trial reported hypotension in only 2.6% of patients with early eplerenone therapy.[15] The subordinate role of MRA in comparison to beta blockers and ACEI/ARB is supported by the European Society of Cardiology Heart Failure Long-Term Registry (ie, at least 92% with chronic heart failure treated with beta blockers and ACEI/ARB versus 67% with MRA).[16] The present study by Wong et al therefore underlines the necessity to further improve the clinical education of medical staff regarding indications and optimal use of MRA alongside with continuous and appropriate monitoring of renal function and serum potassium levels. Especially important subgroups of patients (ie, obese diabetics with advanced symptoms as identified by Cohen et al) may benefit from routine MRA administration.[3,7] Further studies in the field of MRA to prove the impact of an early MRA initiation in patients with heart failure nowadays are necessary to improve poor guideline adherence. Although specific heart failure units have been more frequently established in maximum care hospitals in developed countries, the optimal pharmacotherapies of all necessary heart failure drugs including MRA should at last be a standard for all physicians worldwide even more than 10 years after publication of the EPHESUS trial.

ARTICLE INFORMATION

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Disclosures

None.

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