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EDITORIAL

Angiotensin inhibition in patients with acute kidney injury: Dr. Jekyll or Mr. Hyde?

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Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are among the most frequently applied antihypertensive drugs. Their beneficial pleiotropic effects go far beyond blood pressure reduction. Remodeling of myocardium enhances the effects of afterload reduction for the heart and makes ACEIs/ARBs a key drug in treatment of chronic heart failure as well as for secondary prevention after acute myocardial infarction. With regard to the kidney, ACEIs/ARBs have demonstrated to reduce proteinuria and slow progression of CKD [1].

By inhibiting angiotensin II (ANG II), either by reducing its conversion from angiotensin I (ACEI) or by blocking it on the receptor levels (ARBs), ACEIs/ARBs reduce the generation of reactive oxygen species and increase the synthesis and bioactivity of NO, thereby augmenting renal cortical microvascular oxygenation [2] and restoring endothelial function [3]. In the kidney, on the other hand, inhibition of ANG II leads to dilation of the efferent arteriole of the glomerulus resulting in a drop of intraglomerular pressure and hence of glomerular filtration (GFR). In patients with decreased renal reserve, this may manifest in a moderate increase in serum creatinine, which can be observed when patients are started on ACE/ARBs but the beneficial effects of a reduced filtration and reduced tubular protein load in a chronically damaged kidney are clearly dominating.

These effects of ACEIs/ARBs, however, may become highly unwanted in the situation of acute kidney injury (AKI) where GFR has dropped because of a renal insult and a further reduction of GFR is clearly something treating physicians may want to avoid. This is even more relevant in a situation where a patient is hemodynamically unstable and ANG II inhibition hampers postglomerular vasoconstriction which is key to preserving impaired GFR. This effect is even more pronounced in patients who are treated with non-steroidal anti-inflammatory drugs (NSAIDs), since these block prostaglandin generation who are key for dilation of the afferent glomerular arteriole.

ACEIs/ARBs have been identified as the major predisposing factors for AKI in the setting of hypovolemia [4], and increased use of ACEI/ARBs was associated with an significant increase in hospital admissions with AKI in the UK [5]. A recent pilot study in high-risk patients who underwent cardiac surgery demonstrated that the use of an AKI care bundle which included withholding ACEI/ARBs decreased incidence of AKI [6]. Consequently, most recommendations suggest stopping administration of ACEI/ARBS in the setting of AKI [7, 8]. On the other hand, some studies showed that not re-starting ACEIs/ARBs after surgery was associated with increased mortality, presumably caused by inadequate hypertension

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control and consequent cardiac decompensation. Also, some smaller studies showed beneficial effects of ACEI in patients undergoing cardiac surgery [9, 10], making the question whether or not to use ACEIs/ARBs in patients with AKI still controversial.

In a recent article in *Intensive Care Medicine*, Gayat and co-workers investigate the long-term outcome effects of ACEIs/ARBs in patients who had suffered from AKI [11]. By retrospective analysis of the large FROG-ICU database, including 1551 ICU survivors, of which 611 had AKI during their ICU stay, the authors could demonstrate reduced 1-year mortality in the cohort who had AKI and who were prescribed ACEIs/ARBs. This observation was further sustained after adjustment for covariates, subgroup analyses, and propensity matching for patients receiving ACEIs/ARBs. Variables that were included in the multivariate analysis and propensity score comprised clinically relevant factors such as hypertension, ACEI/ARB pre-treatment, chronic kidney disease (CKD), severity of AKI, non-recovery of AKI, here defined as acute kidney disease (AKD), cardiogenic shock, and NT proBNP levels. Interestingly the beneficial effects of ACEIs/ARBs on 1-year survival could not be reproduced in the patient cohort without AKI after adjustment and propensity matching. The data suggest that ACEIs/ARBs may improve renal recovery or reduce fibrotic processes leading to impaired renal function after AKI or AKD [12]. Furthermore, it is well known that patients who have survived AKI show increased long-term cardiovascular and even neurological morbidity and mortality [13]. It may be presumed that ACEIs/ARBs antagonize pathophysiological mechanisms which are similar for the development of CKD and chronic heart failure [14, 15].

Acknowledging the authors' efforts for solid data analysis, the study by Gayat et al. [11] still remains a retrospective cohort analysis with all the inherent caveats. First, there is always the issue of unmeasured confounders that may explain the findings. Second, ACEIs/ARBS were prescribed in a selected number of patients. Only 17.8% of ICU survivors who had AKI had a prescription of ACEI/ARBs, and in only 5.7% of these patients was this a new prescription. In the end, the matched cohort analysis was based on just 82 matched pairs of AKI patients (i.e., 27% of all AKI patients) with and without ACEIs/ARBs. Propensity score matching is a technique that comes with concerns: correct matching depends on the covariates used for inclusion, and these may not include the reason for prescribing ACEIs/ARBs, also, it requires a large sample size. Therefore, this analysis leaves some uncertainty about the power of the obtained results. Furthermore, the study does not reveal why it was decided to initiate these drugs in this risk group. Obviously, the treating physicians had already made a risk assessment and decided that the benefits of ACEIs/ARBs outweighed the potential nephrotoxicity. In addition, effects on kidney function had already been assessed while in the ICU. In patients who had an increase in serum creatinine after initiation, these drugs were most probably stopped. Finally, co-morbidities were much more frequent in the patients who had suffered from AKI compared to those without AKI. For instance the AKI group showed rates for chronic heart failure, hypertension, CKD and diabetes which were 2- to 10-fold higher than the non-AKI group. These conditions

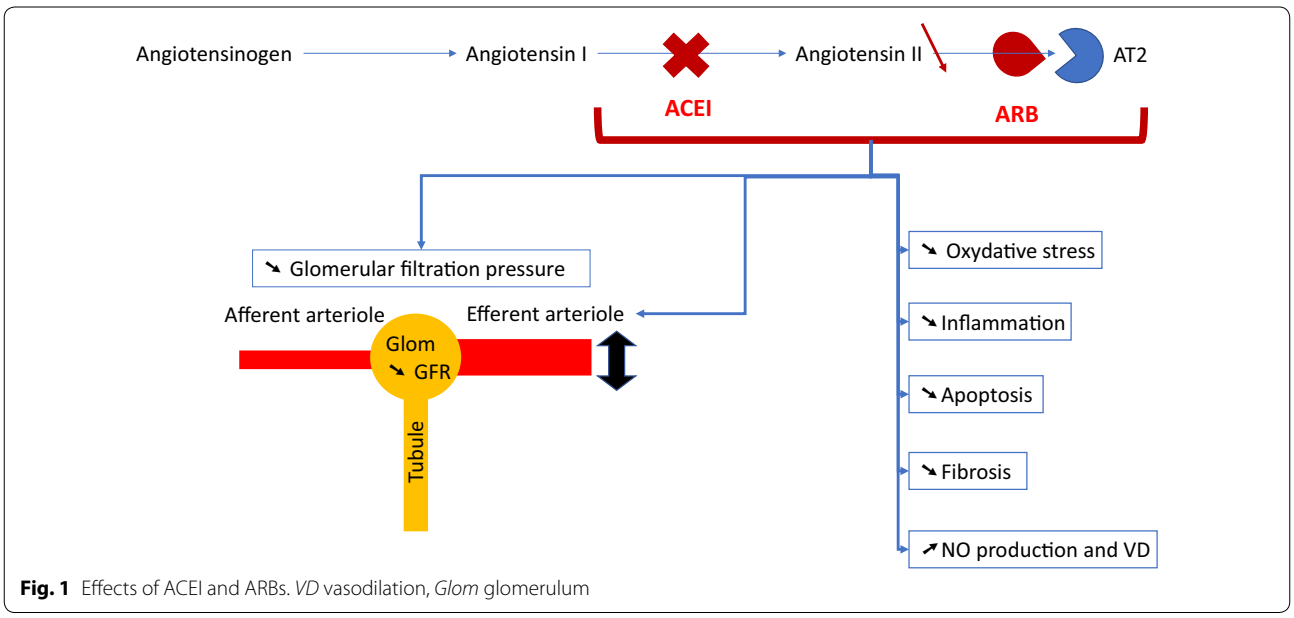

Fig. 1 Effects of ACEI and ARBs. *VD* vasodilation, *Glom* glomerulum

may definitely benefit from treatment with ACEIs/ARBs, which might explain why no effect on 1-year survival could be found in patients without AKI (Fig. 1).

Overall, Gayat et al. have to be commended on having performed this elegant study which created an interesting working hypothesis and a silver lining on the horizon of improving currently unfavourable long-term outcome in AKI patients. However, the proof lies in eating the pudding and, as such, a randomized controlled trial would absolutely be necessary to answer the question whether ACEI/ARB are good or bad for patients with AKI. Questions such as when to re-install ACEI/ARB therapy after AKI, the optimal dose and the duration of therapy are still waiting to be answered.

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Compliance with ethical standards

Conflicts of interest
MJ and EH report no COI.

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