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EDITORIAL

Adverse events in HEAAL: when to hold and when to fold

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This editorial refers to 'Predicting adverse events during angiotensin receptor blocker treatment in heart failure: results from the HEAAL trial', by M.S. Kiernan *et al.*, published in this issue on pages 1401–1409.

In 2009, the HEAAL investigators[1] reported that losartan 150 mg/day reduced the rate of death and admissions for heart failure with reduced ejection fraction (HFREF) compared with patients receiving losartan 50 mg/day, the dose previously recommended and evaluated in ELITE II[2] to compare losartan with captopril. This important contribution pointed out the necessity to determine the effective dose of a drug in patients with HFREF rather than relying upon the dose used to lower blood pressure in patients with essential hypertension. In this issue of the journal, the HEAAL investigators[3] report that investigator-reported adverse events (AEs), including kidney impairment, hyperkalaemia, and hypotension, were associated with an increased risk of death compared with those patients who did not experience them, and that these AEs were more frequent in the losartan 150 mg than the losartan 50 mg group. The median serum creatinine on the day of their investigator-reported AE was 1.8 mg/dL, potassium 5.8 mmol/L, and systolic and diastolic blood pressures were 86 and 60 mmHg, respectively. Independent of the dose of losartan, these AEs were more frequent in older patients, those receiving an aldosterone blocker, and in those who reported the incident AE as the reason for intolerance to angiotensin-converting enzyme inhibitor therapy, one of the criteria for treatment with losartan. Baseline levels of serum creatinine were predictive of subsequent renal impairment, while entry levels of serum potassium predicted the occurrence of hyperkalaemia, and baseline systolic blood pressure predicted subsequent hypotension. Diabetes mellitus, baseline haemoglobin, and diuretic use were also predictive of subsequent kidney impairment and hyperkalaemia. However, while these factors were predictive of subsequent AEs, the association between investigator-reported kidney impairment, hyperkalaemia, and hypotension and the excess risk of subsequent death and first hospitalization for HF was independent of these baseline factors. Also of note was the finding that the frequency of these AEs continued to increase over time and was not limited to the period surrounding initiation of therapy with losartan. On the basis of these findings, the HEAAL investigators[3] suggest close monitoring in patients with the baseline risk factors they identified and in patients treated with losartan 150 mg/day.

The finding that these AEs were associated with an increase in mortality, while not surprising, is nevertheless of importance and raises the issue of how we can avoid these AEs and how we should respond once they occur. It is important to emphasize that while there were significantly more AEs associated with the use of losartan 150 than 50 mg/day the strategy of losartan 150 mg significantly reduced cardiovascular events in comparison with 50 mg[1] and that the same AEs were associated with an increase in mortality when they occurred in patients on losartan 50 mg. While avoiding these AEs that were associated with an increase in mortality is desirable, it should be pointed out that these AEs are often difficult to predict in an individual patient and may be the cost of some strategies shown to be effective in reducing total mortality in patients with HFREF. One might conclude given the dictum 'primun non nocere' that since losartan 150 mg/day is associated with an increase in the incidence of AEs that resulted in an increase in mortality, it is better to avoid this strategy, especially in individuals at high risk for the development of these AEs with losartan such as those with chronic kidney disease, diabetes mellitus, or low haemoglobin, the very old, and those on an aldosterone blocker. These are, however, the very individuals who are at greatest risk and most in need of effective therapy to reduce their cardiovascular risk. Many clinicians have used this reasoning and have, for example, avoided the use of indicated aldosterone blockers in patients with HFREF[4] due to the fear of inducing hyperkalaemia, despite the evidence that aldosterone blockers reduce cardiovascular events even in these high-risk individuals.[5] While close monitoring should be instituted when prescribing losartan or similar agents to patients with the baseline risk factors identified by the HEAAL investigators,[3] the failure to attempt initiation may place the patient at greater risk than that associated with the development of these AEs.

A more difficult question is what should one do once these AEs occur in a patient with HFREF. Our initial impulse might be to withhold or reduce the dose of the drug thought to be responsible for

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the AE, such as losartan 150 mg/day or an aldosterone-blocking agent. On closer reflection, this impulse might be wrong. As the HEAAL investigators[3] point out, the occurrence of an AE such as hyperkalaemia or renal dysfunction might reflect progression of the underlying disease process and therefore might be an indication to continue the culprit drug rather than withdrawing it or reducing the dose. For example, aldosterone-blocking agents are known to be associated with an increased risk of hyperkalaemia, and it has been suggested that their dose be reduced if the serum potassium is 5.5 mmol/L and withheld if at any time on a non-haemolysed blood sample it is $\geq$ 6.0 mmol/L. Although this approach is reflected in current guidelines,[6,7] recent evidence from RALES[8] suggests that the use of spironolactone was associated with a reduction in mortality up to a serum potassium level of 6.0 mmol/L. Withholding losartan 150 mg or an aldosterone blocker from an otherwise indicated patient with HFREF and hyperkalaemia might in fact expose that patient to a far greater risk of death than that associated with hyperkalaemia. The risk of death associated with a given level of serum potassium is difficult to judge, and depends upon several factors including the rate of increase in serum potassium, pH, and serum calcium concentration. Unfortunately, the electrocardiogram has proven to be a poor guide to the risk of death associated with hyperkalaemia in an individual patient.[9] We need other markers to help us identify the level of serum potassium associated with an increased cardiovascular risk in an individual patient. Possibly measurement of tissue potassium as reflected by red blood cell potassium concentration[10] will be of value in this regard.

The implications regarding the cardiovascular risks associated with hypotension might be different from those associated with hyperkalaemia or renal impairment. Although hypotension was clearly associated with an increased risk of death in HEAAL whether on losartan 150 mg or 50 mg/day,[3] it is likely that many episodes of clinically significant hypotension were undetected. Mak *et al.*,[11] using ambulatory blood pressure monitoring in patients with HF treated with a neurohumeral blocking agents, noted a relatively high incidence of nocturnal hypotension that was unsuspected based upon office blood pressure monitoring or patients' symptoms. These nocturnal hypotensive episodes were associated with an increased cardiovascular risk. The level of hypotension at which one should be concerned in an individual patient with HF is, however, uncertain and may depend on the presence or absence of manifest and/or occult vascular disease. Possibly the use of biomarkers such as high sensitivity troponin might be of value in determining in an individual patient if a given degree of hypotension has been associated with ischaemic damage and therefore predisposes them to a subsequent increase in mortality. Withholding life-saving therapy such as losartan 150 mg/day after an episode of hypotension not associated with ischaemic damage may place the patient at far greater risk than continuing it. On the other hand, if one can detect evidence of tissue damage associated with the hypotensive episode, the proper response would be to reduce the dose or withhold the drug.

In conclusion, while the finding that investigator-reported AEs in HEAAL[3] were associated with an increase in mortality is not surprising, what is surprising is how little we know about the pathophysiology associated with the induction of these AEs, how to avoid them without exposing patients to an even greater risk, when to reduce the dose or withhold the suspected culprit drug, and when to continue it despite the occurrence of these AEs. This is an area for further investigation, and the HEAAL investigators should be congratulated for bringing this issue into focus. Good poker players understand that those who win most consistently know when to hold and when to fold. Similarly, good clinicians understand when to withhold a drug or reduce its dose and when to continue therapy despite the occurrence of these AEs. Some further insight into the means of evaluating the risk of these AEs in an individual patient might make us all winners and avoid exposing our patients to unnecessary risk.

Conflict of interest: B.P. is a consultant for Pfizer, Novartis, Bayer, Elli Lilly, Takeda, Amgen, Amorcyte, Cytopherx, Ardelyx, Gambro, Relypsa, BG-Medicine, and Aurasence, with stock options in Relypsa, BG-Medicine, and Aurasence; and has received grants from Novartis, Forrest Laboratories, and Medtronic.

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