Vasopressin V1 receptor-mediated aldosterone production as a result of selective V2 receptor antagonism: a potential explanation for the failure of tolvaptan to reduce cardiovascular outcomes in the EVEREST trial

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Plasma volume expansion in patients with heart failure (HF) is associated with neurohumeral activation; symptom and signs of pulmonary congestion and peripheral oedema; an increase in hospitalizations for HF; and cardiovascular mortality.1 A reduction in plasma volume, as evidenced by haemoconcentration, has recently been suggested to be associated with an improvement in cardiovascular mortality.2 However, while loop diuretics reduce plasma volume and relieve the symptoms and signs of pulmonary congestion, they activate the renin–angiotensin–aldosterone system (RAAS) and, in experimental studies3 and some, although not all, retrospective clinical studies have been associated with an increase in cardiovascular mortality.4,5 Due to the controversy associated with the use of high-dose loop diuretics and their effect on cardiovascular mortality in patients with HF and a reduced left ventricular ejection fraction (REF) there has been increasing interest in alternative and or supplemental diuretic strategies to reduce plasma volume and to improve cardiovascular outcomes in patients with HFREF.

Tolvaptan, a selective V2 vasopressin antagonist, has been shown in pre-clinical and short-term studies in patients with HF to be a potent aquaretic with a resultant increase in urine output; a decrease in body weight; a decrease in pulmonary capillary wedge pressure; an increase in serum sodium concentration; without activation of the RAAS.6 However when studied over the longer term in patients with HFREF, it has not been shown to reduce natriuretic peptide levels or left ventricular remodelling,7,8 and did not improve cardiovascular outcomes despite an early improvement in symptoms of dyspnoea, a prolonged reduction in body weight, and normalization of serum sodium in hyponatraemic patients.9,9 The finding that tolvaptan failed to reduce natriuretic peptide levels and cardiovascular outcomes despite a reduction in body weight is especially notable since an increase in body weight post-discharge is the single most important predictor for readmission in patients with heart failure and a major predictor of mortality.10 The explanation for the failure of tolvaptan to improve ventricular remodelling, natriuretic peptide levels, and cardiovascular outcomes despite a reduction in body weight remains uncertain. Several explanations have, however, been proposed, including the suggestion that the dose of tolvaptan (30 mg/day) may have been inadequate; that patients selected for study did not have hyponatraemia; and the possibility that a reactive increase in vasopressin levels might over the long term stimulate the V1a receptor with a resultant increase in vasoconstriction, which might negate the beneficial effects associated with aquaretics.6,11 Without further prospective mechanistic studies it is difficult to confirm or refute these explanations. Recently, however, it has been shown that a deficiency of the V1a receptor causes hyporeninaemic hypoaldsteronism,12 and stimulation of the V1a receptor causes the adrenal production of aldosterone.13 The V1a receptor also affects the renal tubular effects of aldosterone.14 We postulate that these findings may explain the paradox of a persistent reduction in body weight despite the lack of an improvement in natriuretic peptide levels and cardiovascular outcomes associated with the use of tolvaptan in EVEREST.11 This hypotheses and its implications for the therapy of patients with HF will be briefly discussed below.

As noted above, V2 receptor antagonism results in a sustained reduction in body weight along with an early transient decrease in pulmonary capillary wedge pressure15 without activation of the RAAS.16 However, over the long term there is a reactive increase in vasopressin levels,6,17 with a resultant increased activation of the unprotected V1a receptor in the myocardium and vascular wall. This increase in vasopressin levels in patients receiving tolvaptan has recently been associated with an increase in aldosterone levels.17

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In patients with HF there is an up-regulation of the mineralocorticoid receptor (MR) in the myocardium and macrophages, along with an increase in plasma aldosterone levels. Aldosterone and activation of the MR decrease antioxidant reserves, increase reactive oxygen species (ROS), increase inflammatory cytokine activation, stimulate tissue angiotensin-converting enzyme (ACE) and angiotensin type 1 receptor (AT1R) expression, increase the levels of plasminogen activator-1 (PAI-1) levels, stimulate reactive myocardial and perivascular fibrosis, decrease nitric oxide availability, increase endothelial dysfunction, increase myocardial cell death, and reduce endothelial progenitor cell production and vascular repair. Thus it can be postulated that over the long term the beneficial effects of V2 receptor antagonism may be negated by V1a receptor stimulation with subsequent production of aldosterone, MR activation, sodium retention, and a tendency to increase plasma volume which could offset the reduction in plasma volume resulting from blockade of the V2 receptor and aquaresis.

There are several implications of our hypotheses both for the further evaluation of vasopressin antagonists and for the therapy of patients with HF. The combination of a V2 receptor antagonist and an MR antagonist (MRA) might be of interest especially in patients with acute decompensated HF (ADHF). The current dose of the MRAs spironolactone 25–50 mg and eplerenone 25–50 mg, while effective in reducing total mortality and hospitalizations in patients with chronic HFREF, are only mildly diuretic. Prior to the RALES study, a dose of spironolactone 100–200 mg day was suggested to be beneficial in overcoming diuretic resistance in patients with ADHF. The increased levels of aldosterone in patients receiving a V2 receptor antagonist might require these higher doses of MRAs to block the MR and to achieve diuresis. The combination of a V2 receptor selective antagonist and a high dose MRA could provide an increase in urinary output, an increase in sodium excretion, and a decrease in plasma volume, while preventing the activation of the MR with its adverse consequences. The safety of this approach will, however, require prospective evaluation. One might also consider the combination of a V2 receptor selective antagonist with a natriuretic peptide. For example, Costello-Boerrigter et al. have shown that tolvaptan alone increases systemic vascular resistance, blood pressure, and aldosterone levels. However, with the combination of tolvaptan plus brain natriuretic peptide (BNP) there is no increase in systemic vascular resistance, blood pressure, or aldosterone levels but an increase in urinary sodium excretion. Conversely, one might consider the use of a non-selective V1–V2 vasopressin receptor antagonist alone, which would not be expected to increase aldosterone levels above the level associated with the severity of heart failure. However, in view of the increase in aldosterone levels in patients with HF independent of the long-term use of a V2 receptor antagonist, it might be useful to consider a combination of a non-selective V1–V2 antagonist in conjunction with an MRA or natriuretic peptide such as BNP and(or the use of a non-selective V1–2 receptor antagonist alone or in conjunction with an MRA or natriuretic peptide holds the promise of a reduction in cardiovascular outcomes in patients with acute and chronic heart failure.

Conflict of interest: B.P. is a consultant for Pfizer, Merck, Novartis, Bayer, Takeda, and Astra Zeneca. M.G. is a consultant for Otsuka, Solvay Pharma, Novartis, Bayer, Sigma Tau, Debiopharm, Medtronic, Merck, Astellas, Cytokinetics CoThera, Inc., Pericor Therapeutics, GlaxoSmithKline, Johnson & Johnson, Abbott, Erreappa Terapeutici, Protein Design Laboratories, AstraZeneca, and Sanofi Aventis.

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