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EDITORIAL
Heart failure and cardiomyopathies

Acetazolamide for acute heart failure: is ADVOR a riddle wrapped in a mystery inside an enigma?

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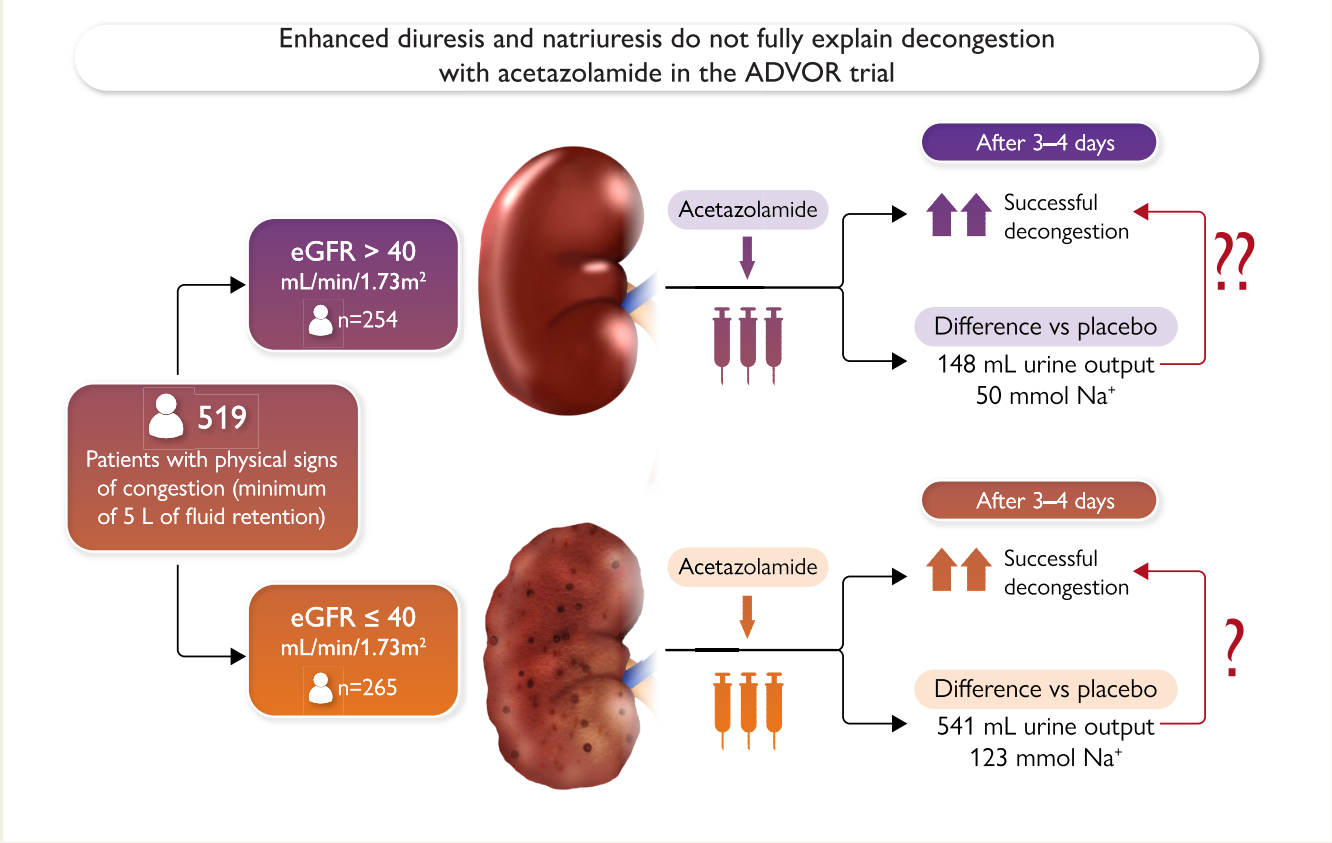
Graphical Abstract



Inability of diuresis and natriuresis to explain the reported effect of acetazolamide in alleviating physical signs of congestion. Abbreviations: eGFR = estimated glomerular filtration rate.

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The main cause of worsening symptoms in acute heart failure (AHF) is pulmonary congestion. Such congestion may be the consequence of a redistribution of blood volume due to the effect of the sympathetic nervous system to cause venoconstriction.[1] However, more commonly, congestion is related to sodium and water retention by the kidneys. Physical signs of congestion are typically seen only after the retention of at least 5 L of fluid.[2] In the latter instance, treatments to achieve decongestion represent a cornerstone of the management of AHF.[3] In most patients with AHF, systemic decongestion can be achieved by loop diuretics, which promote an important increase in urinary sodium excretion and urinary volume. If low doses of loop diuretics are insufficient, patients often respond to higher doses of furosemide or torsemide.[4,5]

The Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial reported the effects of the administration of acetazolamide to hospitalized patients with acute decompensated heart failure already receiving a loop diuretic. When compared with placebo, acetazolamide 500 mg intravenously daily for 3 days was reported to produce an increase in cumulative urinary sodium excretion, an increase in total urinary volume, and a 12% absolute increase in the proportion of patients who were considered to have 'complete decongestion' at discharge.[6] The use of acetazolamide was associated with 1 day shortening in the length of hospital stay, but this benefit was accompanied by a higher risk of transient worsening of renal function (WRF). Importantly, acetazolamide-treated patients did not have improved 3-month outcomes, assessed by the composite of heart failure hospitalization and all-cause mortality.

In this issue of *European Heart Journal*,[7] the investigators of the ADVOR trial report the influence of baseline renal function on the effects of acetazolamine. They note that the effects of acetazolamide on cumulative urinary sodium excretion and total urinary volume during the treatment period were more pronounced among patients with an estimated glomerular filtration rate (eGFR) below the median eGFR in the study ($\leq$40 mL/min/1.73 m^2), as compared with those with eGFR $>$ 40 mL/min/1.73 m^2. However, and importantly, the eGFR value before treatment did not influence the degree of decongestion produced by acetazolamide, with a similar decongestive effect reported in patients with an eGFR >40 L/min/1.73m^2 or $\leq$40 mL/min/1.73 m^2.

These observations might appear to be encouraging. Patients with heart failure who have renal dysfunction are likely to exhibit diuretic resistance, potentially related to a decrease in the delivery of tubular sodium to the loop of Henle as a result of a decline in glomerular filtration.[4] An action of acetazolamide to inhibit both carbonic anhydrase and sodium–hydrogen exchanger 3 in the proximal renal tubule might increase the distal delivery of sodium, specifically to the loop of Henle, thus enlarging the target for loop diuretics.[4,8] Inhibition of sodium reabsorption in the proximal tubule could conceivably be more attractive than adding thiazides, which act primarily on the distal nephron, but whose use is often accompanied by hypokalaemia and WRF.[9]

However, the new analyses presented by the ADVOR investigators raise additional questions (*Graphical Abstract*). In the original ADVOR report, when all patients were considered in the analysis, the increases in cumulative urinary sodium excretion and total urinary volume were modest. In absolute terms, when compared with placebo, acetazolamide produced an increase in urinary sodium that averaged 97 mmol of excreted sodium and an increase in urinary volume of 0.5 L over 2–3 days. Patients with physical signs of congestion (evident as meaningful peripheral oedema, ascites, and pleural effusion) have retained at least 5 L of fluid.[2] In these patients, resolution of congestion in an incremental 5%–10% of patients is typically accompanied by increases in urine volume in the active treatment group that exceed those in the control group by at least 1.5 L.[5] Therefore, resolution of the signs of congestion in ADVOR (which reported a 12% absolute increase in decongestion) would have necessitated an incremental diuresis of at least 2.0–2.5 L of urine, rather than the 0.5 L treatment effect that was reported in ADVOR.[6,7]

Furthermore, in the new analyses,[7] the 254 patients with an eGFR >40 mL/min/1.73 m^2 were reported to have experienced no significant natriuresis or diuresis. When compared with placebo, the magnitude of the effect of acetazolamine on urinary sodium excretion averaged only 50 mmol, and the effect of the drug on total urinary volume was only 148 mL (*Graphical Abstract*). Neither of these effects was statistically significant, and both of these effects are physiologically trivial. Yet, the ADVOR investigators report that the patients with an eGFR >40 mL/min/1.73 m^2 still experienced successful decongestion to a degree that was similar to those with impaired renal function. How is it possible for successful decongestion to be achieved without a drug-related increase in urinary sodium excretion or urinary volume?

Based on the new analyses, it seems unlikely that the physical decongestion reported in ADVOR was related to an effect of the drug to inhibit proximal renal tubular sodium reabsorption. Sodium–glucose co-transporter 2 (SGLT2) inhibitors also inhibit proximal renal tubular reabsorption, but their natriuretic effect is typically opposed by the counter-regulatory activation of sodium reabsorption in downstream nephron segments.[8,10] That explains why empagliflozin did not increase urinary sodium excretion in two trials of patients with acute heart failure (EMPAG-HF and EMPA-RESPONSE-AHF).[11–13] In a third trial (EMPULSE), clinical decongestion was reported after 15 days, but without any reported effect on urinary sodium or volume.[14] Yet, in the EMPULSE trial, decongestion was assessed by symptoms, and not by physical signs. Furthermore, in that trial, treatment with empagliflozin was maintained for the duration of follow-up (i.e. 90 days), whereas in ADVOR treatment with acetazolamide was administered for only 2–3 days.

How can acetazolamide have achieved decongestion of physical signs in 2–3 days in the absence of meaningful changes in urinary sodium and volume? In ADVOR, before randomization, the determination that patients had congestion was based on the observation that they had more than trace oedema or evidence of a pleural effusion or ascites, which was determined by physical examination and confirmed by imaging, typically ultrasound.[6] However, following randomization, the assessment of congestion was entirely dependent on the physical examination performed by the investigator, and no confirmatory imaging was performed. Although the investigator was blinded to the treatment assignment, physicians who were responsible for the assessment of the primary endpoint may have been aware of the effect of treatment on serum bicarbonate. Acetazolamide has a well-established effect on serum bicarbonate, which was measured in the ADVOR trial as a requirement of the protocol.[6] The mean change in bicarbonate in the acetazolamide group need not have been large to have influenced the judgement of site investigators in a meaningful fraction of patients.[15] This possibility might be one explanation for the resolution of physical signs of congestion in the absence of a natriuresis or diuresis in patients with preserved renal function.

Finally, it is important to consider the safety of acetazolamide. The authors conclude that acetazolamide is safe and effective to treat congestion across the entire range of renal function. However, as noted in the current report, use of the drug was accompanied by a three-fold increase in the risk of WRF. In their Supplementary

material online, the investigators note that an elevated baseline serum creatinine further heightened the risk of worsening renal function. We do not know the consequence of WRF following acetazolamide in patients with an already impaired GFR. Yet, these are the patients that the investigators would particularly target for treatment with acetazolamide.[7]

In summary, the results of ADVOR are worthy of a famous saying by Winston Churchill, who described the events during the outbreak of the Second World War as being 'a riddle wrapped in a mystery inside an enigma', suggesting that additional time and thought was required to understand the course of events. As the analyses from ADVOR are reported, the same advice seems to apply. The effects of acetazolamide in patients with acute heart failure and congestion clearly require further study.

Declarations

Disclosure of Interest

All authors declare no conflict of interest for this contribution.

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