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BCS Editorial

The known unknowns of managing acute heart failure

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Take Home Messages

- European and American heart failure (HF) guideline recommendations for the management of unplanned hospitalisations are based on limited randomised controlled trial evidence.
- Treating fluid overload is key, but how decongestion therapy is initiated and what treatment strategies are used within different local hospitals is not well reported. These variations in practice may impact on length of stay and patient outcomes.
- Patient views on heart failure treatment goals should be routinely sought particularly in complex, frail patients with multiple comorbidities.
- Future work will require more targeted research in these areas and a greater focus on shared decisions with patients with increasing awareness of how frailty and multimorbidity can impact on what 'best care' may look like for each HF patient.

Introduction

The lack of gold-standard randomised controlled trial (RCT) evidence to support clinical decision-making in acute cardiovascular care represents an area of particular unmet need, where significant variation in practice and underuse or overuse of clinical treatments can occur (1,2). Most recommendations are based on observational analyses rather than RCTs (1). Two recent sets of guidelines for heart failure, published by European and American societies, highlight the substantive gains made in improving patient outcomes wherever there is robust RCT evidence available (3,4). Optimal pharmacotherapy now includes new drug classes such as SGLT2 inhibitors and possible use in traditionally hard to treat groups such as heart failure with preserved ejection fraction (5). However, both guidelines have sections emphasising where gaps persist in the evidence. These 'known unknowns' represent areas of heart failure treatment that have suffered from a lack of RCTs to help guide best practice.

The growing case for addressing evidence gaps

The need to address deficiencies in evidence continues to grow. In the UK, heart failure inpatient work accounts for 1 million bed days per year and approximately 5% of all emergency admissions to hospital (6). With an ageing population, and the increasing prevalence of multiple long term conditions, the absolute number of hospital admissions for HF could increase by a further 50% over the next two decades (7). Recent analyses examining survival trends after a diagnosis of HF demonstrated between 6-7% absolute improvement in survival from 2000 to 2016, however one, five and ten year survival rates were still only 81%, 48% and 26% respectively (8).

About the author

Dr Yang Chen started his specialty training in 2017 as an NIHR Academic Clinical Fellow (ACF) in Cardiology at UCL. He has completed an MSc at the London School of Economics and Political Science and is currently undertaking a Clinical Research Fellowship funded by the NIHR BRC at UCLH, focusing on data science and pragmatic trials embedded within electronic health records.

The asymmetry between the significant costs of unplanned admissions, compared to the lack of investment in research that can generate insights into the optimal way to manage acute heart failure is stark. This editorial aims to highlight where specific knowledge gaps in acute heart failure care lie, and to provoke reflection and stimulation of debate on the differences in personal practice in these settings.

Task management in acute HF

The management of patients hospitalised with acute heart failure is often led by generalists such as emergency department or acute medical physicians. Data from the latest UK National Institute for Cardiovascular Outcomes Research (NICOR) Heart Failure audit demonstrates that almost one in five patients still do not receive specialist input during their inpatient admission (9). The aspects of patient care in a suspected or confirmed HF admission are summarised in Table 1.

This editorial will focus on the relief of symptoms which cause admission, namely the management of fluid overload (Task 2 from Table 1).

Treatable trait versus 'confirmed diagnosis'

One major challenge in conducting RCTs of different therapies used in acute heart failure is the timely and accurate identification of cases where the primary diagnosis is cardiac. The typical clinical signs (e.g. dependent oedema, ascites and pulmonary oedema) and symptoms (e.g. decreased mobility, tiredness and breathlessness) of 'fluid overload' may have other underlying causes including liver and renal disease. At the point of prescription of diuretic therapies clinicians may not be entirely certain of the diagnosis and indeed multiple pathologies may be present that contribute to fluid overload. Therefore by the time heart failure is confirmed, the window to enrol into a trial to detect any benefit for different treatment strategies may be lost.

Decongestion therapy

Emerging evidence from both registries and RCTs suggests that undertreatment of fluid overload (including residual congestion on discharge) is associated with a poorer prognosis (10,11). Treatment of fluid overload involves increasing urine output or decreasing fluid input. Loop diuretics (i.e. Furosemide) are the mainstay of decongestion therapy. Whilst there have been over 50 RCTs comparing different diuretics and their doses in HF (12), there are few studies that have examined diuretics in the acute setting. Perhaps the DOSE trial published over a decade ago remains the most salient (13) demonstrating no difference between infusion and bolus strategy for intravenous (IV) furosemide. Other studies have examined the role of less commonly used agents, such as metolazone (14) or torsemide in the soon to be published TRANSFORM HF trial (15). The current guideline recommendations for diuresis are summarised in Table 2.

	Tasks	Possible actions
1	Rule out cardiogenic shock which necessitates emergent specialist treatment in intensive care unit or shock centre	Consider transfer to regional/ specialist centre
2	Relief of symptoms which caused admission	Diuretics, oxygen, additional therapies
3	Recognition and treatment of any acute triggers	CHAMPIT[1] and also removing other triggers such as cessation of NSAIDs
4	Optimisation of prognostic medications	Goal directed therapy as best tolerated and with respect to individual patient factors and co-morbidities
5	Characterisation of underlying pathology	Echocardiography, cardiac MRI, additional imaging and investigation depending on clinical suspicion e.g. angiography
6	Characterisation of trajectory of illness	BNP, Creatinine and eGFR, Hb, weight and fluid balance

Table 1. Tasks for treating clinicians in the management of acute heart failure. *BNP = brain natriuretic peptide; CHAMPIT = Coronary syndromes, Hypertension, Arrhythmia, Mechanical, PE, Infections, Tamponade; eGFR = estimated glomerular filtration rate; Hb = haemoglobin; MRI = magnetic resonance imaging; NSAID = Nonsteroidal anti-inflammatory drugs.*

NICE Clinical guideline 187 (updated Nov 2021) (16)	ESC (or other relevant position statement/ state of the art review) (3,17)	ACC/AHA/HFSA (or other relevant position statement/ state of the art review) (4,18)
Starting IV diuretic dose (if not known to have HF)		
Offer IV diuretic therapy to people with acute heart failure. Start treatment using either a bolus or infusion strategy.	Diuretic treatment should be started with an initial IV dose of furosemide, or equivalent dose of bumetanide or torsemide. If the patient was not on oral diuretics, a starting dose of 20-40 mg of furosemide, or a bolus of 10-20 mg IV torsemide, can be used. Furosemide can be given as 2-3 daily boluses or as a continuous infusion.	Initial daily dose 20-40 mg. For patients not receiving long-term loop diuretics agents, 40–80 mg IV BID of furosemide or the equivalent is a reasonable empiric starting dose. Due to post-dosing Na+ retention, IV loop diuretic agents should usually be given at least twice daily.
Starting IV diuretic dose (if known HF and taking regular diuretics)		
For people already taking a diuretic, consider a higher dose of diuretic than that on which the person was admitted unless there are serious concerns with patient adherence to diuretic therapy before admission.	If the patient was already on diuretics, give a IV dose corresponding to 1-2 times the daily oral dose.	For patients on long-term loop diuretic agents, 2.5× their outpatient dose on a mg per mg basis demonstrated safety and efficacy in the DOSE trial.
Reassessment and dose escalation		
No advice given.	Diuretic response should be evaluated shortly after the start of diuretic therapy and may be assessed by performing a spot urine sodium content measurement after 2 or 6 h and/or by measuring the hourly urine output. A satisfactory diuretic response can be defined as a urine sodium content >50-70 mEq/L at 2 h and/or by a urine output >100-150 mL/h during the first 6 h. If there is an insufficient diuretic response, the loop diuretic IV dose can be doubled, with a further assessment of diuretic response.	Diuresis should not be discontinued prematurely because of small changes in serum creatinine, because elevations in the range of 0.3 mg/dL (27 umol/L) do not predict worse outcomes except when patients are discharged with persistent congestion. Max daily dose 600 mg /day.
Strategies for diuretic resistance		
Consider ultrafiltration for people with confirmed diuretic resistance.	If the diuretic response remains inadequate, e.g. <100 mL hourly diuresis despite doubling loop diuretic dose, concomitant administration of other diuretics acting at different sites, namely thiazides or metolazone or acetazolamide, may be considered. However, this combination requires careful monitoring of serum electrolytes and renal function.	If at 300 mg IV furosemide dose equivalent, consider combination nephron blockade: thiazide, acetazolamide, amiloride or diuretic dose of aldosterone antagonists.

Table 2. Overview of recommendations for decongestion therapy. *ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; HF = heart failure; HFSA = Heart failure Society of America; NICE = National Institute for Health and Care Excellence.*

One immediate reflection when examining Table 2 is to ask, how different is routine practice at your local hospital compared to the above recommendations? We do not have a systematic nationwide answer to this question. Whilst the NICOR HF audit focuses on quality metrics such as prescription of prognostic medications, there is no granular detail on the prescribing patterns of intravenous diuretics amongst generalist and specialist clinicians in the UK. The potential variation in practice represents a large 'known unknown' that may result in patient under- or over-treatment which can impact patient outcomes. In 2019-2020, the mean length of stay for heart failure admissions in the UK was between 5 to 25 days. How much front-end decongestion contributes to this large variation in length of stay is unknown.

Role of Fluid restriction

The role for improving the input side of the equation is also unclear. In fact, there is even less evidence for fluid restriction in the acute setting and therefore more chance for variation in practice. From the ESC (3): *'avoid large volumes of fluid intake. A fluid restriction of 1.5 to 2 L/day may be considered in patients with severe heart failure/hyponatraemia to relieve symptoms and congestion.' (McDonagh 2021, p.37)*

From the ACC/AHA/ HFSA (4): **'***CLASS IIb For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain (Level of Evidence: C)' (Heidenreich 2022, p75)*

There are no specific recommendations from NICE CG 187 with regards to fluid restriction (16). Given that oral fluid intake and overall fluid balance is difficult to accurately monitor (with the exception of ICU environments), one consideration for future research groups would be in designing trials that could be feasibly done in routine care circumstances with outcome measures that are meaningful and robustly captured. Collecting survey or service evaluation data on variation in practice at local sites may stimulate discussions with colleagues on experience and perceived benefits for fluid restriction. Gathering patients' views on their experience of adhering to 1 or 1.5 L of fluid a day may also impact on current or future thinking in this area.

Impact of comorbidity on fluid overloaded patients

Co-morbidity and frailty are common in heart failure patients, with >85% of patients having two or more additional chronic conditions (19). Recent post-hoc analysis of the GUIDE-IT HF trial by Khan *et al.* (20) linked frailty as an independent (almost doubling) multiplier of risk of adverse clinical outcomes. More shockingly, the study also highlighted that frail patients were significantly less likely during their hospitalisations to either have uptitration or initiation of optimal heart failure pharmacotherapies. The question raised is whether those in most need of evidence based medications are least likely to be given them. Patient choice and shared decision making around risks and benefits are crucial in complex cases, each case requiring a tailored approach.

Importantly, the focus should not solely be on pharmacotherapy or other medical interventions. The recent results from the landmark REHAB-HF trial (21) demonstrated that randomisation to an early rehabilitation intervention tailored to each HF patient resulted in significant improvements in physical function in the two thirds that completed the intervention. How meaningful factors such as mobility and functional capacity are to quality-of-life outcomes is individual to each HF patient.

Perhaps as important as ensuring the 'goldilocks' dose of beta blocker or ACE-inhibitor in our HF patients is to apportion dedicated time to consult with nurse specialist, physiotherapist and occupational therapist colleagues about the best use of non-pharmaceutical interventions to improve quality of life.

Unknown unknowns

Lastly, there is the tricky issue of considering unknown unknowns in acute heart failure management. Nobel Laureate Thomas Schelling's pithy comment of 'one thing a person cannot do…is to draw up a list of things that would never occur to them' is apt in describing this challenge. A readily available solution is to consult our patients at suitable opportunities, asking either formally as part of patient and public involvement work, or informally during clinical care, 'what are the top priorities for you/what can we do better when managing your heart failure in hospital and in the community?'.

In a recent priority setting paper for advanced heart failure set by the James Lind Alliance (22), one particular statement stood out from the patient perspective: 'what helps with symptoms from peripheral oedema experienced by people with advanced heart failure? For example, massage, exercise?'.

Conclusion

Whilst there remain gaps in the evidence base for treating fluid overload seen with decompensated heart failure, an unplanned admission to hospital is nevertheless a sentinel event for patients who stay on average at least 7 days in NHS hospitals. In this time, there are opportunities to improve patient care alongside uncertainties about the best way in doing so. Perhaps the most important known unknown for managing acute heart failure is to collect patient views more rigorously and to tailor broad recommendations from professional guidance into distinct, shared solutions for every HF patient that is treated.

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