To master heart failure, first master congestion.

John G.F. Cleland MD [1,2], Pierpaolo Pellicori MD [1]

1. Robertson Centre for Biostatistics and Glasgow Clinical Trials Unit, Institute of Health and Wellbeing, University of Glasgow, Glasgow Royal Infirmary, Glasgow, UK.

2. National Heart & Lung Institute, Imperial College London, UK

Address for Correspondence

Robertson Centre for Biostatistics & Glasgow Clinical Trials Unit,

University of Glasgow, UK. G12 8QQ

john.cleland@glasgow.ac.uk

846 Words; 12 references

The GUIDE-HF team (1) should be congratulated on attempting to master congestion, a key driver of symptoms, signs and progression of heart failure. Controlling congestion is associated with an excellent prognosis (2), a key consideration for a new universal definition of heart failure (3). Symptoms and signs are late, subjective, and insensitive measures of congestion compared to blood biomarkers, ultrasound and haemodynamics (3;4). Raised (>15 mmHg) pulmonary artery (PA) diastolic pressure, reflecting left atrial pressure, indicates haemodynamic congestion, although not necessarily congestion in tissues (ie:- oedema) (3). In GUIDE-HF, PA pressure was measured using a trans-venously implanted, wireless 'chip', powered externally by radio-frequency energy, enabling daily transmission of snapshot recordings to remote healthcare providers, avoiding in-person visits and facilitating home telemonitoring (5;6).

Previous research suggests that PA pressure monitoring might reduce hospitalisations for heart failure (7-10). GUIDE-HF was simple in concept but complex to implement. Patients were blind to assigned group, but all were contacted regularly. Research staff in the same centre could be blinded or not depending on their role (1). This was a good design for testing a technology but less so for a whole system of care. Participants had devices implanted before randomisation; 98% of attempts succeeded. Complications were rare and patient-adherence to data-transmission was good, whether assigned to disclosure or concealment of PA pressures. Targets were 15-35 mmHg for systolic, 10-25 mmHg for mean and 8-20mmHg for diastolic PA pressures. Disappointingly, only mean PA pressures are reported.

Of 1,000 patients randomised, about 20% were aged ≥80 years, left ventricular ejection fraction (LVEF) was >40% in 47% [for whom guidelines provide few therapeutic recommendations], only 56% were hospitalised within the previous year and baseline PA diastolic pressure was already in target-range for about 50%. Plasma concentrations of natriuretic peptides were grossly elevated, possibly because most patients (60%) had a history

of atrial fibrillation. Clinical signs of congestion were not reported. Most patients with an LVEF ≤40% received loop diuretics and beta-blockers and had defibrillators or cardiac resynchronisation devices but many were not prescribed other guideline-recommended therapies. About 7% of patients were lost to follow-up.

Overall, the trial was neutral for its primary endpoint, recurrent heart failure events (hospitalizations or visits) or all-cause mortality at 12 months, although women, older and Black patients and those with milder symptoms might have benefited. Monitoring was not associated with improvements in exercise capacity or quality of life and therefore, by inference, symptoms. Cardiovascular mortality was 5% at 12 months; low considering participants' age and multi-morbidity. Fewer events than planned occurred in the control group, partly explained by a decline in heart failure hospitalisations after the advent of COVID, as observed elsewhere (11). Possible explanations, which might provide clues to improving heart failure management, include reduced consumption of salt-laden processed food during lockdown, increases or decreases in exercise, better remote care, or avoiding hospitals because of fear of COVID or to protect overloaded services. Adjusting for pandemic-effects, PA pressure-guided management was associated with fewer heart failure hospitalisations, about 53 compared to 38 per hundred patient-years, leading to a 19% reduction in the primary endpoint, which just reached conventional statistical significance.

Loop diuretics are essential for managing congestion, reducing blood volume and shrinking atrial and ventricular diastolic volumes (12). There were more changes in diuretics with monitoring, but it is unclear if cumulative dose increased. Fewer patients received guideline-recommended therapies at 12 months compared to baseline. Lack of information on systemic arterial pressure and renal function, which were not monitored, might have hampered effective pharmacological management (5).

The median value for mean PA pressure at baseline was 31 mmHg that, if held constant for a year, would generate 11,315 mmHg-Days [365 days x 31 mmHg] but if lowered to 20 mmHg, only 7,300 mmHg-Days; 4,000 mmHg-Days less. The observed mean reduction in pressure with monitoring was only -793 mmHg-Days (7% lower), which was only slightly more than for the control group [-583 mmHg-Days; 5% lower]. Intense monitoring for the first three-months was required, but this did not confer a substantial between-group difference in pressures until 6-8 months. During 12 months of follow-up, mean PA pressure averaged about 2 mmHg lower compared to baseline with monitoring, which is less than in observational studies (9;10), but similar to previous randomised trials (8). The reduction in mean PA pressure with monitoring was statistically but not substantially larger than in the control group (-1.5 mmHg). Of course, large reductions in PA pressure are not always appropriate or feasible if they cause systemic hypotension or renal dysfunction. More sophisticated analyses are required to translate information on PA pressure monitoring into clinical practice.

In summary, GUIDE-HF did not enrol an ideal group of patients for demonstrating the efficacy of PA pressure monitoring, many had baseline pressures in the target range with little possibility of short-term gain (9;10), follow-up was too short and interventions did not substantially change PA pressure. Monitoring alone cannot improve outcome; consequent actions might. The GUIDE-HF results are encouraging but inconclusive. They should inform further research; possibly a large, simple, open-label trial investigating a system of care rather than a single technology.

Conflict of interest statements.

Dr. Cleland reports personal fees from Abbott, outside the submitted work.

Dr Pellicori has nothing to disclose.

Reference List

(1) Lindenfeld JA, et al. A Randomized, Controlled Trial of Hemodynamic-Guided Management of Heart Failure. Lancet 2021.

(2) Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro FJ, Zannad F et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet 2020 July 11;396(10244):121-8.

(3) Cleland JGF, Pfeffer MA, Clark AL, Januzzi JL, McMurray JJV, Mueller C et al. The struggle towards a Universal Definition of Heart Failure-how to proceed? Eur Heart J 2021 April 1;42:684-96.

(4) Pellicori P, Platz E, Dauw J, Ter Maaten JM, Martens P, Pivetta E et al. Ultrasound imaging of congestion in heart failure: examinations beyond the heart. Eur J Heart Fail 2020 October 29.

(5) Cleland JGF, Clark RA, Pellicori P, Inglis SC. Caring for people with heart failure and many other medical problems through and beyond the COVID-19 pandemic: the advantages of universal access to home telemonitoring. Eur J Heart Fail 2020 June;22(6):995-8.

(6) Cleland JFG, Clark RA. Telehealth: delivering high-quality care for heart failure. Lancet 2018 September 22;392(10152):990-1.

(7) Abraham J, Bharmi R, Jonsson O, Oliveira GH, Artis A, Valika A et al. Association of Ambulatory Hemodynamic Monitoring of Heart Failure With Clinical Outcomes in a Concurrent Matched Cohort Analysis. JAMA Cardiol 2019 June 1;4(6):556-63.

(8) Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011 February 19;377(9766):658-66.

(9) Shavelle DM, Desai AS, Abraham WT, Bourge RC, Raval N, Rathman LD et al. Lower Rates of Heart Failure and All-Cause Hospitalizations During Pulmonary Artery Pressure-Guided Therapy for Ambulatory Heart Failure: One-Year Outcomes From the CardioMEMS Post-Approval Study. Circ Heart Fail 2020 August;13(8):e006863.

(10) Angermann CE, Assmus B, Anker SD, Asselbergs FW, Brachmann J, Brett ME et al. Pulmonary artery pressure-guided therapy in ambulatory patients with symptomatic heart failure: the CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF). Eur J Heart Fail 2020 October;22(10):1891-901.

(11) Shoaib A, Van Spall HGC, Wu J, Cleland JGF, McDonagh TA, Rashid M et al. Substantial decline in hospital admissions for heart failure accompanied by increased community mortality during COVID-19 pandemic. Eur Heart J Qual Care Clin Outcomes 2021 May 27.

(12) Pellicori P, Cleland JG, Zhang J, Kallvikbacka-Bennett A, Urbinati A, Shah P et al. Cardiac Dysfunction, Congestion and Loop Diuretics: their Relationship to Prognosis in Heart Failure. CARDIOVASC DRUGS THER 2016 December;30(6):599-609.