Implanted haemodynamic telemonitoring devices to guide management of heart failure: a review and meta-analysis of randomised trials

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Abstract

Background and aims Congestion is a key driver of morbidity and mortality in heart failure. Implanted haemodynamic monitoring devices might allow early identification and management of congestion. Here, we provide a state-of-the-art review of implanted haemodynamic monitoring devices for patients with heart failure, including a meta-analysis of randomised trials.

Methods and results We did a systematic search for pre-print and published trials in Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) on the 22nd of September 2021. We included randomised trials that compared management with or without information from implanted haemodynamic monitoring devices for patients with heart failure. Outcomes selected were hospitalisation for heart failure and all-cause mortality. Changes in treatment associated with haemodynamic monitoring resulted in only a small reduction in mean pulmonary artery pressure (typically < 1 mmHg as a daily average), which generally remained much greater than 20 mmHg. Haemodynamic monitoring reduced hospitalisations for heart failure (HR 0.75; 95% CI 0.58–0.96; \( p = 0.03 \)) but not mortality (RR 0.92; 95% CI 0.68–1.26; \( p = 0.48 \)).

Conclusions Haemodynamic monitoring for patients with heart failure may reduce the risk of hospitalization for heart failure but this has not yet translated into a reduction in mortality, perhaps because the duration of trials was too short or the reduction in pulmonary artery pressure was not sufficiently large. The efficacy and safety of aiming for larger reductions in pulmonary artery pressure should be explored.
Graphical abstract

Implanted haemodynamic telemonitoring devices to guide management of heart failure: a review and meta-analysis of randomised trials

Data search
- Medline (PubMed), Embase (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL)
- Up to 22nd of September 2021

Participants
- 4 studies, 2,224 patients
- Median age: 55 to 71 years
- 66% male

Interventions
- Chronicle
- Chronicle/ICD
- CardioMEMS

Findings
- Study 1: Chronicle
- Study 2: Chronicle/ICD
- Study 3: CardioMEMS

Conclusions
- Monitoring pulmonary artery pressure in patients with heart failure reduces the risk of heart failure hospitalisations but this has, as yet, not translated into a reduction in mortality

After selecting key words, a systematic review for implanted haemodynamic telemonitoring devices was performed in different dataset and 4 randomised clinical trials were identified and included in this meta-analysis. Three different devices (Chronicle, Chronicle/ICD and CardioMEMS) were tested. All-cause mortality and total heart failure hospitalisations were selected as outcomes. No reduction in all-cause mortality rate was reported but a potential benefit on total heart failure hospitalisation was identified.

Keywords
Tele-monitoring · Pulmonary hypertension · Implantable devices · Heart failure

Abbreviations
- ACE-I/ARBs: Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers
- FDA: Food and Drug Administration
- HFrEF: Heart failure with reduced ejection fraction
- HFpEF: Heart failure with preserved ejection fraction
- HR: Hazard ratio
- ICD: Implantable cardioverter defibrillator
- NYHA: New York Heart Association
- PA: Pulmonary artery
- PAP: Pulmonary artery pressure
- PAPd: Pulmonary artery diastolic pressure
- ePAPd: Estimated pulmonary artery diastolic pressure
- PAPm: Pulmonary artery mean pressure
- PAPS: Pulmonary artery systolic pressure
- PCWP: Pulmonary capillary wedge pressure
- PH: Pulmonary hypertension
- RHC: Right heart catheterisation
- RR: Risk ratio
- RV: Right ventricle
- SGLT2-Is: Sodium glucose cotransporter-2 inhibitors
- TR: Tricuspid regurgitation

Introduction
Heart failure can be defined as cardiac dysfunction associated with interstitial or intravascular water and salt retention, otherwise known as congestion. Congestion is not only a cause of symptoms and signs but may also cause cardiac dysfunction, remodelling and arrhythmias, which are all associated with a poorer prognosis [1]. Identifying, quantifying and treating congestion at an early stage is a key task for good management of heart failure, but it is currently done sub-optimally.

Symptoms and signs have traditionally been used to guide therapy but are not specific for heart failure and may only be obvious once decompensation is severe [2]. High plasma
concentrations of natriuretic peptides correlate with symptoms and with the severity of cardiac dysfunction [1] and are associated with an increased risk of hospitalisation and death due to heart failure; although measurement of natriuretic peptides facilitates initial diagnosis, their serial evaluation has not been shown—convincingly—to improve heart failure management [3]. The requirement for more than a drop of blood for point-of-care measurement makes monitoring by patients at home difficult [4].

Echocardiography is not only widely available and frequently used for non-invasive, real-time assessment of cardiac structure and function but can also provide information on congestion. However, it requires expertise to acquire and interpret images, and there is little evidence, as yet, that serial ultrasound can be used to guide diuretic treatment. There is also a lack of robust evidence that other non-invasive approaches to estimate the amount of body water and its distribution, such as weighing scales, bio-impedance or remote dielectric sensing, improve management and outcomes for patients with heart failure [5].

Elevated pulmonary artery (PA) or right ventricular pressures also reflect congestion and identify patients with heart failure who are at greater risk of hospitalization or death [6]. Recently, implantable miniaturised sensors have been developed and tested to assist clinicians in the management of patients with symptomatic heart failure, allowing treatments to be haemodynamically tailored for each patient individually in the hope that this will improve well-being, reduce hospitalisation and, hopefully, increase longevity [7].

In this manuscript, we summarise the rationale and the current state-of-the-art of implanted haemodynamic monitoring devices for patients with heart failure. We also conducted a systematic review and meta-analysis of randomised trials to investigate the effects of this strategy on heart failure hospitalisations and mortality in this population.

Pulmonary hypertension and heart failure: a vicious circle

Recently, updated guidelines reduced the threshold for diagnosing PH from a mean PAP of 25 mmHg down to 20 mmHg, assessed at rest during a right heart catheterisation (RHC) [8]. However, the median value for a resting PAPm in a healthy population is approximately 15 mmHg, with a normal range of about 11–17 mmHg [9]. Data from a broad range of patients, mostly men, in the VA-CART programme (> 20,000 patients, 97% men, 2473 with heart failure) found that the risk of hospitalisation and mortality starts to increase, progressively, when an invasively measured PAPm exceeds 19 mmHg [10].

In routine clinical practice, ultrasound is often used to identify PH, combining information from tricuspid regurgitation (TR) peak velocity and inferior vena cava diameter and collapsibility to estimate PA systolic pressure (PAPs) [11]; an echocardiogram will also help identify causes of PH, such as mitral valve or left ventricular disease. PAPs measured by ultrasound generally correlate well with invasively measured values [12]. However, peak TR velocity may underestimate PAPs when tricuspid regurgitation is severe or in case of right ventricular dysfunction, necessitating invasive assessment to confirm a diagnosis or quantify the severity of PH [8].

Persistently elevated left atrial pressures, due to left ventricular dysfunction or mitral valve disease, are transmitted backwards to the pulmonary circulation, leading to a rise of pulmonary artery pressure (PAP) [13]. At first, PAP pressures may be largely dictated by left atrial pressure, rising only with exercise or episodes of decompensation. However, over time, increases in pulmonary vascular tone and hypertrophy of the pre-capillary pulmonary vascular smooth muscle may develop. Pathophysiologically, this may protect the pulmonary capillaries from increases in pulmonary arterial, although not pulmonary venous, pressure. Eventually, vascular remodelling may lead to relatively fixed pulmonary hypertension that is independent of left atrial pressure and may be relatively unresponsive to pulmonary vasodilators, which may even have deleterious effects by increasing perfusion to poorly aerated lung regions (ventilation perfusion mismatch) [14–16]. An elevated PAP increases the load on the right ventricle (RV), which may cause dilation and dysfunction, leading to tricuspid regurgitation and increasing systemic venous congestion. Once this happens, the risk of decompensation, hospital admission and death increases substantially [17, 18].

PH is common in patients with heart failure, but its reported prevalence depends on the criteria used to define it and the severity of heart failure [19–21]. Perhaps all patients with chronic heart failure have some PH and it is not really a question of prevalence but only of severity. For most patients with heart failure, the severity of PH at rest is mild. A study in a broad population of heart failure, defining PH as a PAPs of > 45 mmHg by ultrasound, suggested a prevalence of PH less than 10% [6, 22]. Defining PH as a PAPs ≥ 35 mmHg provides much higher estimates of prevalence ranging from about 30–50% amongst patients with heart failure and preserved left ventricular ejection fraction (HFpEF) [6, 17, 23, 24]. Similarly, a series of reports suggests that most patients with heart failure and reduced ejection fraction (HFrEF) have PH, with the prevalence varying by the stringency of the diagnostic criteria for PH [20, 25–28] (Table 1).

Patients with PH generally have more severe heart failure, are older [23, 29] and are more likely to have atrial fibrillation [20, 23, 26, 28], poorer renal function [20, 25], higher plasma concentrations of natriuretic peptides [20, 25] and to be treated with loop diuretics [6, 20, 22, 25] (Table 1).
Indeed, patients who do not have distinctly elevated plasma concentrations of natriuretic peptides often do not have sufficient tricuspid regurgitation to measure velocities accurately and do not appear to have PH. In other words, plasma natriuretic peptides can be effectively used to exclude the presence of PH in clinical practice [6]. Both for patients with HFrEF and HFpEF, increasing PAP is associated with a poorer prognosis [20, 24].

Monitoring pulmonary artery pressure: a new approach for heart failure management

The ESCAPE trial [30] investigated whether invasive haemodynamic monitoring—target pulmonary capillary wedge pressure (PCWP) of 15 mmHg and right atrial pressure of 8 mmHg—would improve outcome compared to clinical assessment alone for patients hospitalised with heart failure. The results were disappointing; haemodynamic monitoring did not increase days alive out of hospital or reduce plasma concentrations of B-type natriuretic peptides. A subsequent meta-analysis conducted to assess the impact of invasive haemodynamic assessment by pulmonary artery catheter on the management of critically ill patients (13 studies, > 5000 patients, including those enrolled in the ESCAPE trial), suggested no clinical benefit [31].

The chronicle device [32]

The Chronicle device had a lead-mounted pressure sensor placed in the outflow tract of the RV. The lead was connected to a box, implanted subcutaneously in the pectoral area and containing the electronic components and power source. The pressure sensor used the principle of variable capacitance to provide measures of RV systolic and diastolic pressures and to assess the maximum rate of the pressure increase and decrease (max $dP/dt$) used to estimate the pulmonary artery diastolic (ePAPd) pressure that closely correlated with the pulmonary artery diastolic (ePAPd) pressure that closely correlated with the pulmonary artery diastolic pressure (PAPd), measured prior to the randomisation.

### Table 1: Prevalence of pulmonary hypertension in cohorts or trials of patients with heart failure

| Year of publication | Country | Number of patients | Clinical setting | Diagnostic method | Blood tests | Therapy |
|---------------------|---------|-------------------|----------------|------------------|-------------|---------|
| 2001                | Italy   | 377               | Outpatients    | RHC              | Creatinine (mg/dl) 1.6 (vs 1.4) | NT-proBNP (pg/ml) 13.1 (vs 13.2) |
| 2010                | UK      | 1380              | Outpatients    | Doppler          | NT-proBNP (pg/ml) 1.6 (vs 1.4) | NT-proBNP (pg/ml) 13.1 (vs 13.2) |
| 2011                | US      | 463               | Outpatients    | Doppler          | NT-proBNP (pg/ml) 1.6 (vs 1.4) | NT-proBNP (pg/ml) 13.1 (vs 13.2) |
| 2011                | Israel  | 550               | Mixed          | Doppler          | NT-proBNP (pg/ml) 1.6 (vs 1.4) | NT-proBNP (pg/ml) 13.1 (vs 13.2) |
| 2011                | US      | 326               | Mixed          | Doppler          | NT-proBNP (pg/ml) 1.6 (vs 1.4) | NT-proBNP (pg/ml) 13.1 (vs 13.2) |
| 2020                | US      | 203               | Mixed          | Doppler          | NT-proBNP (pg/ml) 1.6 (vs 1.4) | NT-proBNP (pg/ml) 13.1 (vs 13.2) |
| 2021                | Canada  | 550               | Mixed          | Doppler          | NT-proBNP (pg/ml) 1.6 (vs 1.4) | NT-proBNP (pg/ml) 13.1 (vs 13.2) |
| 2022                | US      | 570               | Mixed          | Doppler          | NT-proBNP (pg/ml) 1.6 (vs 1.4) | NT-proBNP (pg/ml) 13.1 (vs 13.2) |

**Key characteristics of patients with (or without) pulmonary hypertension**

ACE-I/ARBs angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, AF atrial fibrillation, BBs beta-blockers, BNP B-type natriuretic peptides, eGFR estimated glomerular filtration rate, HFrEF heart failure with reduced ejection fraction, MRA mineralocorticoid antagonists, NT-proBNP amino-terminal pro-brain natriuretic peptide, PAPm pulmonary artery mean pressure, PAPs pulmonary artery systolic pressures, PH pulmonary hypertension, PVD pulmonary vascular disease, PVR pulmonary vascular resistance, RHC right heart catheterization, RVGT right ventricular tricuspid gradient, SBP systolic blood pressure, UK United Kingdom, US United States

*Patients with pulmonary vascular disease are defined as PVR ≥ 1.74 WU at 20 W of exercise, measured prior to the randomisation.

The prevalence rate of PH in the GUIDE-HF is not provided by the authors: the value reported in this table is an estimate obtained considering the average of PAPm, the standard deviation and the number of specimens of the study population, assuming a normal distribution.

This data refers only to ACE-I. Data are reported as $n$ (%) and mean. Data on the REDUCE-LAP section are reported as $n$ (%) and median.
been assigned a class IIb recommendation (level of evidence PAP using a wireless haemodynamic monitor system has
in symptomatic patients with heart failure, monitoring of
Systematic review and meta-analysis

sub-optimal control of congestion at an earlier stage.
exercise. Assessing PA pressure during exercise might detect
ures PA pressure directly. However, a potential limitation
entailed risks and complications; CardioMEMS also meas-
not require a surgical implantation procedure with the
sensor is always exposed to PA pressures, it is not cur-
only few minutes of PA pressures are transmitted. Thus, although
the sensor is always exposed to PA pressures, it is not cur-
Currently, the device measures pressures continuously but store only a sample in memory that could be transmitt-
ed; this was usually the 8.5 min prior to each transmission. Patients could be instructed to rest or take exercise prior to
transmitting data.

Chronicle ICD system [33]

This device represented an evolution of the Chronicle, with
the pressure-sensing system incorporated into an ICD. A
single-chamber ICD lead was placed in the RV apex and an
additional lead positioned in the RV outflow tract to measure
pressures.

CardioMEMS system [34]

CardioMEMS measures PAP using micro-electromechanical
system (MEMS) technology and requires neither batteries nor leads. The sensor is 15-mm long and 3-mm wide and
is permanently implanted in a distal branch of the PA via
RHC. Two loops at the ends of the sensor serve as anchors
and allow automatic sizing to the width of the vessel. The
PA sensor consists of a three-dimensional coil and pressure
sensitive capacitor. The coil electromagnetically couples
the pressure sensitive capacitor to the electronics system,
allowing the remote measurement of the resonant frequency
then it is converted to a pressure measurement. Collection of
haemodynamic data requires the patient to lie on an external
pillow-like device which injects radiofrequency energy into
the sensor, receives back signals to generate the waveform and
transmits the data to a remote service facility that then
relays the results to the patient’s healthcare provider. Only a
few minutes of PA pressures are transmitted. Thus, although
the sensor is always exposed to PA pressures, it is not cur-
ently possible to obtain 24 h pressures.

Compared to the Chronicle device, CardioMEMS does
not require a surgical implantation procedure with the
entailed risks and complications; CardioMEMS also meas-
ures PA pressure directly. However, a potential limitation of
CardioMEMS is the difficulty in capturing data during
exercise. Assessing PA pressure during exercise might detect
sub-optimal control of congestion at an earlier stage.

Systematic review and meta-analysis

In symptomatic patients with heart failure, monitoring of
PAP using a wireless haemodynamic monitor system has
been assigned a class IIb recommendation (level of evidence B) by the 2021 European Society of Cardiology (ESC) heart
failure guidelines [35] in order to improve clinical outcomes.
The current guidelines on heart failure, provided by the
AHA/ACC/HFSA [36], were recently updated. Consistent
with ESC guidelines, they assigned a class IIb recommenda-
tion for the use of PAP haemodynamic monitors, but they
restricted this indication only to the patients in New York
Heart Association (NYHA) functional class III who had pre-
viously been hospitalised for heart failure or had elevated
plasma concentrations of natriuretic peptides. They also
highlighted that PAP monitoring was of uncertain benefit in
reducing the risk of subsequent heart failure hospitalisation.
Earlier in 2022, the US Food and Drug Administration
(FDA) extended the indications for the CardioMEMS PA
pressure monitor to include patients with heart failure ‘who
have either been hospitalized for heart failure in the previous
year and/or have elevated natriuretic peptides’, opening the
way to more widespread use of this technology.

To further evaluate the validity of these recommendations, we conducted a meta-analysis (graphical abstract) after the
publication of the largest trial to date, GUIDE-HF trial [37].

Our primary and secondary outcomes were total heart
failure hospitalisations and all-cause mortality, respectively.
Full methods are shown in the supplementary material.
Briefly, on the 22nd of September 2021, we searched Med-
line (PubMed), Embase (Ovid) and the Cochrane Central
Register of Controlled Trials (CENTRAL) databases for
randomised trials that investigated the use of implantable
haemodynamic systems to monitor PAP in patients with
heart failure.

Only fully peer-reviewed manuscripts written in English
were considered for inclusion. After removing duplicates
(n = 406), a further 4818 records were excluded by screen-
ting titles and abstracts; the remaining 431 articles were fully
evaluated. We finally identified eight papers from four cli-
nical trials: the cardioMEMS Heart Sensor Allows Monitor-
ing of Pressure to Improve Outcomes in NYHA Class III
Heart Failure Patients (CHAMPION, four papers) [38–41],
the Chronicle Offers Management to Patients with Advanced
Signs and Symptoms of Heart Failure (COMPASS-HF, two
papers) [42, 43], the Reducing Decompensation Events
Utilizing Intracardiac Pressures in Patients With Chronic
Heart Failure (REDUCEhf, one paper) [44] and the haemo-
dynamic-GUIDEd management of Heart Failure (GUIDE-
HF, one paper) [37]. Figure 1 shows the results of our search
strategy (PRISMA flow diagram), whilst table S1 (supple-
mentary material) summarises the baseline characteristics of
enrolled populations. All the trials we found were conducted
in North America between 2008 and 2021 and all patients
enrolled had a monitoring device implanted, regardless of
allocation; however, the information acquired by the sensors
were disclosed to physicians only for patients in the inter-
vention arm. A key strategy that differentiated the design
of CHAMPION and GUIDE-HF was the introduction of specific algorithms that guided the clinicians on the implementation of therapy according to haemodynamic readings. More detailed information about these trials are summarised in Table 2. Overall, compared to standard care, the use of implanted haemodynamic sensors reduced the risk of total heart failure hospitalisation by 25% (2224 patients; HR 0.75; 95% CI 0.58–0.96; \( p = 0.03 \)) (Fig. 2A), using data from the longest follow-up available, but was not associated with a reduction in the risk of all-cause mortality (RR 0.92; 95% CI 0.68–1.26; \( p = 0.48 \)) (Fig. 2B).

Discussion

Considering the cost and complexity of haemodynamically guided monitoring for patients with heart failure, the results of randomised trials conducted, so far, are rather disappointing. Although haemodynamic monitoring might reduce hospitalisations for heart failure, the confidence intervals around the estimate are wide and the statistical certainty low. There are many potential explanations for why a reduction in hospitalisations and PA pressure might not translate into a reduction in mortality. Longer follow-up might be required for such small reductions in PA pressure to translate into reductions in mortality; more intense management to normalise PA pressure might lead to a greater reductions in hospitalisations and mortality but with the risk of more side effects. Perhaps the therapeutic algorithms are too cautious; perhaps current treatments are just not sufficiently effective [45, 46].

In order to improve management of heart failure by haemodynamic monitoring, measurements should be accurate in order to avoid false alerts and detect true ones and must be followed by changes in management to correct the perceived problem (a low or a high PA pressure). The optimal target PAP may differ from one patient to the next. A too low pressure due to intensification of heart failure therapy may lead to a fall in cardiac output, systemic arterial pressures and renal function. Patient engagement is essential. Unless patients are given the correct advice and follow management recommendations, haemodynamic monitoring will not be of any help. There is a long ‘delivery chain’ including the sensor, the patient taking the measurement, transmission to the service centre, relay on to the care team, the formulation of recommendations by the care team, the transmission of those recommendations back to the patient and the patient acting on the advice. There is a lot that could go wrong: the chain is only as strong as its weakest link.

In the COMPASS-HF [42] trial, heart failure therapies, particularly loop diuretics, were adjusted more frequently in patients assigned to the haemodynamic-guided arm than controls but trialists did not define an ePAPd target of treatment and, as a consequence, the mean ePAPd of the whole population remained high, at around 28 ± 7 mmHg throughout the entire study [42–44], suggesting either that investigators failed to recommend more intense treatment or that patients did not or could not (due to side effects) implement it. This failure is important, as a retrospective analysis using pooled data from three studies of the Chronicle programme (\( n = 790 \) patients) suggests that only a substantial reduction in ePAPd during follow-up reduced mortality; however, a decrease of 3 mmHg, or more, between baseline and 6 months was observed in less than 20% of patients [47–49].

In CHAMPION [38], haemodynamic-guided therapy was associated with a 28% reduction in heart failure hospitalisations, compared to the control group, during 6 months of follow-up, with similar encouraging results considering data from the entire follow-up (mean 18 months). CHAMPION provided instructions to investigators on how to modify treatment, mainly diuretics—followed by vasodilators, to achieve pre-specified ‘optimal’ haemodynamic readings. During follow-up, not only diuretics and vasodilators but also other neuro-hormonal antagonist therapies were adjusted more frequently in those assigned to active monitoring [39, 47]. Rather than responding to measurements thought to reflect an imminent problem, CHAMPION investigators attempted to adjust treatment constantly to maintain PAP as close to ideal as possible [50]. However, treatment guided by haemodynamic monitoring reduce PAPm by only ~ 5% in relative terms and only ~ 1.6 mmHg in absolute terms compared to no changes observed in the control group. Findings from CHAMPION also confirmed the close relationship between PH and adverse outcome [38]. Of the 537 patients enrolled and with complete baseline haemodynamic data, the 320 (59%) who met the criteria of Group II PH [8] had a higher rate of heart failure hospitalisations and greater risk of death than those without PH.

GUIDE-HF is the largest trial of haemodynamic monitoring conducted so far. By design, each patient was to be followed for only 12 months. Investigators were asked to contact participants twice a month for the first 3 months and then monthly until the end of the trial. Haemodynamic monitoring may provide less benefit when clinical care in the control group is frequent and of a high quality. Unfortunately, the COVID-19 pandemic struck when only about 40% of patients had completed 12 months of follow-up. An analysis [51] comparing findings prior and after the spread of COVID-19 pandemic was published recently, after our systematic search. The GUIDE-HF trial appeared to be on course for a positive result consistent with CHAMPION prior to COVID but then something remarkable happened. With the advent of COVID, PA pressures improved in the control group to the same extent as the intervention group. It appears that patients with heart failure during COVID might...
have become more adherent to their treatments and may have modified their lifestyle. Once the difference in pressures was lost, so was the difference in event rates. In a sense, this proves that better control of PA pressures is effective but questions whether we need frequent haemodynamic monitoring to achieve it. Perhaps monitoring every few months by a non-invasive approach, such as ultrasound, would be similarly effective. However, the reduction in PA pressures even prior to COVID was modest [45]. Both CHAMPION and GUIDE-HF show that we need more effective means of controlling PAP, either better implementation of existing interventions or new treatments.

The rate of hospitalisation in CHAMPION and GUIDE-HF appears to be much higher, both in the intervention group and in the control arm, compared to many other landmark trials of heart failure (Table S3, supplementary material). Differences in the characteristics of the population, in the design of the trial or the number of contacts between patients and physicians, during follow-up, both in the treatment and control arms, could explain the high rates of hospitalisation. Patients in GUIDE-HF may have been in a worse functional class than most other trials and had poorer renal function but they did not have a higher plasma NT-proBNP or annual mortality.

Although many patients with elevated PAP must have been enrolled in landmark trials of beta-blockers and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACE-I/ARBs), the effects of these therapies on PAP have been rarely evaluated. In animal models, mineralocorticoid receptor antagonists improve RV function and reverse PH, but studies in patients with heart failure and PH are lacking [52]. Indeed, no trial has ever evaluated the effects of loop diuretics on pulmonary pressures, even if they are the most commonly used drugs to decongest patients with evidence of elevated PAP.

Tran and colleagues [53] reported a rapid fall in mean (−3.6 mmHg), systolic (−6.5 mmHg) and diastolic (−2.5 mmHg) PA pressures when treatment with ACE-I/ARBs was switched to sacubitril/valsartan in 18 patients with HFrEF with a CardioMEMS implant. Consistent with these results, Khan and colleagues [54] reported a reduction in PAPd (−2.5 mmHg), PAPs (−3.6 mmHg) and PAPm (−3.2 mmHg) following initiation of treatment with sacubitril/valsartan in 13 patients with HFrEF who also had been implanted with a CardioMEMS device.

Sodium glucose cotransporter-2 inhibitors (SGLT2-Is) have recently been shown to be highly effective for the treatment of heart failure [55]. In a single-centre observational study, dapagliflozin reduced CardioMEMS PAPm from 42 ± 9 to 38 ± 10 mmHg, after seven days from initiation of the treatment [56]. In the EMBRACE-HF trial [57], 65 patients with heart failure (mean age 66 years, 97% on loop diuretics) and a CardioMEMS system (mean PAPd 22 mmHg) were randomised to empagliflozin or placebo. Compared to those assigned to placebo, empagliflozin 10 mg/day reduced the PAPd (averaged between 8 and 12 weeks, primary endpoint) by ~1.5 mmHg, regardless of heart failure phenotype. A greater proportion of patients assigned to empagliflozin also achieved a ≥20% reduction in plasma amino-terminal pro-brain natriuretic peptide values at 12 weeks (34% versus 7%; \(p = 0.01\)).

The real-world clinical experience with CardioMEMS provides the opportunity to evaluate the combined effects of intensification of treatment on PAP in patients with heart failure but also the long-term safety of this approach. Using data from a post-approval registry of 1200 patients with severe heart failure symptoms implanted with CardioMEMS, Shavelle and colleagues [58] showed that intensification of medications reduced PAPm during 1 year of observation in those with baseline PAPm ≥ 35 mmHg (−4.8 ± 6.2 mm Hg), but when PAPm was < 25 mmHg at baseline, pressures rose (+1.5 ± 5.8 mm Hg). Patients with a baseline PAPm of 25–34 mmHg had an intermediate response (−1.3 ± 5.0 mmHg).

These findings replicate those previously reported by Heywood and colleagues [59], who used de-identified PAP data from the first 2000 patients with heart failure implanted with a CardioMEMS who had at least 6 months of follow-up. They found that patients with a
### Table 2: Key characteristics of the trials included in the meta-analysis

| TRIAL                        | COMPASS-HF [42,43] (2008) | REDUCE-HF [44] (2011) | CHAMPION [38-41] (2011) | GUIDE-HF [37] (2021) |
|------------------------------|----------------------------|-----------------------|-------------------------|----------------------|
| **Device used**              | Chronicle                  | Chronicle-ICD         | CardioMEMS              | CardioMEMS           |
| **Country (Enrolling Sites)**| US (28)                   | US (53)               | US (64)                 | US and Canada (118)  |
| **Follow up length**         | 6 months                   | 12 months             | Standard care           | Standard care        |
| **Scheduled visits**         | 1.3 and 6 months           | 1.3, 6.9 and 12 months| 1.3, 6 and 12 months   | 6 months and 12 months|
| **Blinding**                 | Single blind†              | Single blind†         | Single blind†           | Single blind‡        |

#### Main inclusion criteria

- **Functional class**: NYHA III-IV
- **Previous HFH**: Within 6 months
- **Other**: -ICD indication

#### Main exclusion criteria

- **CKD**: Serum creatinine ≥ 3.5 mg/dL
- **COPD**: Severe
- **Advanced HF**: Likely HTx or LVAD
- **Other**: -ICD indication

#### Efficacy

- **HF hospitalisation or urgent visits**: Treatment vs control
- **HF hospitalisations**: Treatment vs control

#### Safety

- **Device-related complication**: Treatment vs control
- **Device failure**: Treatment vs control

#### Haemodynamic changes

- **PAPm AUC (mmHg-days)**: Treatment vs control
- **Change in ePAPd at six months (mmHg)**: Treatment vs control

#### Medication changes during follow up

- **All-drugs (per month-patient)**: Treatment vs control
- **Diuretic (during follow up)**: Treatment vs control

#### Safety end-point

- **Freedom from device related complication (%)**: 91.5, 96.5, 98.6, 99

#### Outcomes results

- **All-cause death**: HR [95%CI]
- **HF Hospitalisation**: HR [95%CI]

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*Note: Table includes detailed data on key characteristics of the trials, including device used, country (enrolling sites), patients, control, follow up length, scheduled visits, blinding, main inclusion criteria, main exclusion criteria, efficacy, safety, haemodynamic changes, medication changes during follow up, and safety end-point.*

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*AUC area under the curve, BMI body mass index, CKD chronic kidney disease, COPD chronic obstructive pulmonary disease, CRT cardiac resynchronization therapy, eGFR estimated glomerular filtration rate, HF heart failure, HFH heart failure hospitalisation, HR hazard ratio, HTx heart transplantation, ICD implantable cardiac defibrillator, LVAD left ventricular assist device, NYHA New York Heart Association, ePAPd estimated diastolic pulmonary artery pressure, PAPm pulmonary artery mean pressure, US United States*

*Only participants but not the investigators were blinded*

*Patients without previous heart failure hospitalisation meet inclusion criteria if they report elevated natriuretic peptides in the 30 days prior to the consent (prespecified thresholds defined brain-type natriuretic peptide ≥ 250 pg/ml or amino-terminal pro-brain natriuretic peptide values ≥ 1000 pg/ml)*

*If not compatible with the monitoring device*

*Emergency room access evaluations following by intravenous diuretic therapy*

*These data refer only to the HFpEF cohort*
PAPm ≥ 35 mmHg at implantation had a fall in pressure (from 44 ± 7 to 37 ± 10 mmHg), whilst for those with a baseline PAPm < 25 mmHg (from 21 ± 3 to 22 ± 7 mmHg) or 25–34 mmHg (from 30 ± 3 to 29 ± 7 mmHg) pressures were unchanged.

Of the 5,500 CardioMEMS implanted in the US during the first 3 years after FDA approval, the reported rate of adverse events was relatively low (155 events; 2.8%), including PA injury (28 reports, 6 of which culminated in death), 46 sensor malfunction or migration (1%), 15 (0.3%) bleeding or infection at the vascular access and 5 pulmonary embolism or device thrombosis [60]. Experience from Germany [61] and the UK [62] confirms that tailoring treatment according to PAP using CardioMEMS is safe and feasible also in the European health care systems.

Uncertainty remains about the cost-effectiveness of the CardioMEMS. Further research is required to estimate, more accurately, the financial sustainability at scale [63]. Whether these devices should be restricted to patients with PH is uncertain. The devices are expensive and therefore may not be cost effective in sick patients with a short life expectancy nor in well-controlled patients who may have few events. There will be a ‘sweet spot’ where patients are neither too well nor too sick to benefit [64].

Technological developments now allow pulmonary artery pressure to be combined with other vital signs, to allow clinicians to individualise treatments with greater precision and without the need of clinical visits [65].

Most of the circulating blood volume is contained in the highly compliant venous system, which might buffer the impact of an increased circulating volume on PAPm. The CardioMEMS device can measure PCWP, which reflect left atrial pressure, but it appears the snapshots that the device takes may be less reliable and therefore treatment recommendations are not based on them. Devices implanted in the atrial septum to measure left atrial pressure are being investigated [66]. Monitoring venous capacity by ultrasound or other means might be an even better approach to detect and correct haemodynamic problems (both under- and over-filling) than measuring PAP [67, 68].

**Limitations**

We were only able to access to published information, and not to individual patient data, which precluded more detailed analysis. Additional limitations include the heterogeneity of the devices used in the trials and changes in practice.
Conclusions

Monitoring pulmonary artery pressure in patients with heart failure reduces the risk of total heart failure hospitalisations, but not mortality. The results of our meta-analysis not only support recently updated professional guidelines but also highlight the need for further research before recommending widespread use of these currently costly technologies. Better patient selection, better patient engagement and education, better therapeutic algorithms, more ambitious haemodynamic targets and more effective and well-tolerated interventions to achieve them could yet make haemodynamic monitoring a cornerstone of care for patients with heart failure.

Further research is required to implement these therapeutic strategies and to identify patients more likely to benefit, thereby justifying the additional costs.

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