Title: The Therapeutic Benefit of Vasodilators in Acute Heart Failure: Absence of Evidence or Evidence of Absence?

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Main Text:

"Difference of opinion leads to enquiry, and enquiry to truth"
-Thomas Jefferson

The latest edition of the European Heart Journal: Acute Cardiovascular Care contains two manuscripts, one arguing for and one against the use of vasodilators in patients presenting with acute heart failure (AHF) [***insert reference to pro and contra manuscripts***]. Central to this debate are the 2021 European Society for Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure[1], which a downgrade in the class of recommendation for the use vasodilators in patients with AHF occurred (from a Class IIa, Level of evidence (LOE) B in the 2016 version, to a IIbB). This downgrade was supported by the results of the GALACTIC and the ELISABETH trials[2,3]. In the most recent version of the ESC Guidelines, the following recommendation is made for vasodilators in patients with AHF; *"In patients with AHF and SBP >110mmHg, i.v. vasodilators may be considered as initial therapy to improve symptoms and reduce congestion"*[1]. This recommendation was given a Class IIb, LOE B grading, indicating that the usefulness of vasodilators in patients with AHF is less well established by evidence. The intravenous vasodilators relevant to this recommendation, as per the supplement of the ESC guideline document, are nitroglycerine, isosorbide dinitrate and sodium nitroprusside[1].

Both sets of authors make cogent arguments to support their position regarding the use of vasodilators for the patient described in the clinical vignette [***insert reference to pro and contra manuscripts***]. So who are we to believe? How can our two sets of authors differ so widely in their opinions when faced with the same clinical question? In this editorial, we will analyse some of the arguments for and against vasodilators in AHF and attempt to shed light on this important issue. Before we attempt to answer any scientific question, it is important to first be specific with regard to the question that is being addressed. In this case, we are attempting to determine the scientific evidence supporting the use of vasodilators as the initial therapy for a hypotensive patient presenting with acute heart failure.

The authors of the manuscript arguing against vasodilator therapy [***insert reference to contra manuscript***] suggest that the best evidence supporting their stance is provided by two relatively recent randomised controlled trials (RCTs), the GALACTIC trial and the ELISABETH trial[2,3]. In the GALACTIC trial, patients with AHF were randomised to either early, intensive and sustained vasodilation or standard care[2]. Patients who were randomised

to early, intensive and sustained vasodilation received a combination of high and individualized doses of sublingual and transdermal nitrates, oral hydralazine for 48 hours and rapid up-titration of ACE inhibitors, ARBs, or sacubitril-valsartan according to pre-treatment and/or the preference of treating physicians, using a predefined safety corridor for systolic blood pressure of 90 to 110 mm Hg. Overall, there was no difference in the primary endpoint (all-cause mortality or AHF rehospitalisation within 180 days) between the two groups[2]. In the ELISABETH trial, which had a stepped wedge cluster randomised design, an intervention aimed at improving guideline adherence for the management of acute heart failure (which included intensive i.v. nitrate therapy) was compared to standard care in patients 75 years and older[3]. Intravenous nitrates were received by 96% of patients in the intervention group (median dose: 27.0 mg), compared to 25% of the control group (median dose: 4.0 mg, adjusted difference in doses, 23.8 mg [95% CI, 13.5-34.1 mg]). Despite this, the intervention did not improve survival at 30 days or result in an improvement in any of the clinical outcomes[3].

Like all trials, the GALACTIC and ELISABETH trials have their limitations. The main limitation for both is that neither directly compares i.v. vasodilators to placebo in a blinded fashion and therefore this complicates the interpretation of the results[2,3]. Patients with a blood pressure of <100mmHg were also excluded from both studies. It could also be suggested that the patient described in the clinical vignette referred to by the pro and contra authors would also have been too young to be enrolled in the ELISABETH study and that i.v. vasodilators were not used in the GALACTIC study. Therefore it could be argued that these trials do not wholly provide direct evidence for the patient in the clinical vignette, who has a blood pressure of < 100mmHg and is under 75 years of age or with regard to the recommendation in the 2021 ESC heart failure guidelines, which only refer to the use of i.v., not oral, vasodilator therapy[1]. However, despite these limitations, it must also be acknowledged that neither trial provided any support for an initial vasodilator based approach in patients with AHF.

The authors writing in favour of vasodilators cite the beneficial physiological effects of vasodilators in the setting of AHF as one reason supporting their use [***insert reference to pro manuscript***]. Some relevant lessons in this regard might be gleaned from trials of another class of vasodilating drugs that have been used in the setting of AHF, natriuretic peptides. A small RCT (N=127 patients) reported a benefit with nesiritide compared to placebo in reducing pulmonary capillary wedge pressure (PCWP) in AHF[4]. The FDA requested more data and the subsequent, larger VMAC trial, published in 2002, randomised 489 patients to

nesiritide (a recombinant B-type natriuretic peptide) (n=204), nitroglycerine (n=143) or placebo (n=142)[5]. The mean reduction in PCWP through to 3 hours was greater in patients assigned to nesiritide compared to those assigned to nitroglycerine and placebo, with no difference between the nitroglycerine and placebo groups. While it must be acknowledged that in this trial had some important limitations, including that the dose of nitrate may not have been appropriately titrated and that nearly two thirds of patients had not received diuretics, the favourable physiological effects on PCWP observed with nesiritide in the trial eventually led to FDA approval. However, 9 years later, the much larger ASCEND HF trial (N=7141 patients), comparing nesiritide to placebo, did not demonstrate a benefit in clinical outcomes with nesiritide[6,7]. In addition to its lack of clinical benefit, nesiritide was associated with an increase in the proportion of patients experiencing an episode of hypotension in ASCEND-HF[6] as well as increased renal dysfunction and mortality on meta-analysis of earlier results[8-10]. Similarly, the TRUE-AHF trial did not demonstrate a benefit in clinical outcomes with another natriuretic peptide (ularitide) compared to placebo, despite the observance of some favourable physiological effects in the ularitide arm[11].

Taken as a whole, these studies demonstrated that while natriuretic peptides may have provided some physiological benefits in AHF, they did not positively impact on hard outcomes. More concerningly, there was also a suggestion of potential harm[8,9]. An endpoint like 'reduction in PCWP' is an example of a 'surrogate endpoint', which can be defined as 'not an event, but rather a measurements that predicts events'[12]. The experience with natriuretic peptides highlights the potential limitations of surrogate endpoints in this setting. Some of the potential mechanisms by which an intervention can impact on a surrogate marker positively without improving clinical outcomes are demonstrated in **Figure 1**. This is not a situation unique to AHF and given that surrogate endpoints have not been shown to be predictive of clinical efficacy in a variety of settings in cardiovascular medicine, it seems only logical that we should not rely on studies demonstrating improvements in surrogate endpoints to guide our clinical practice recommendations[12]. Therefore we do not agree with the authors' contention that the mooted beneficial physiological effects of vasodilators can be used to justify their use for the patient described in the clinical vignette [***insert reference to pro manuscript***].

So what should our current approach to the use of vasodilators in the setting of AHF be? Based on currently available randomised evidence (suggesting an absence of efficacy), it does not appear that we can support the use of vasodilators as first line agents in a broad, unselected AHF population. In addition, given that a relatively common side effect of

vasodilators is hypotension, it seems logical that their use would be particularly unwise in hypotensive AHF patients (who were notably excluded from both the GALACTIC and ELISABETH RCTs).

However, when we consider any unselected AHF population, it is important to reflect that this population will consist of a heterogenous cohort of patients with a wide variety of underlying pathologies, across a spectrum of clinical severity. In addition, the underlying triggers for the AHF presentations will vary, including, amongst others; infection, ischemia, malignant hypertension, valvular heart disease and renal failure. Given this heterogeneity, it might be overly optimistic to suggest a 'one size fits all' approach could be adopted for all patients, across all severities of presentation. Accordingly, i.v. vasodilators might be more suitable for some AHF presentations than others. For example, there is some evidence from a small RCT (N=110 patients) to support the use of high-dose isosorbide dinitrate + low-dose furosemide in preference to high-dose furosemide + low-dose isosorbide dinitrate in patients presenting with severe, acute pulmonary oedema[13]. Of note, patients with a BP of less than 110/70 mm Hg were excluded from this study[13] and this is consistent with the current vasodilator recommendation in the HF guidelines[1]. It is also important to note that the recommendation in the latest HF guidelines refers only to the use of vasodilators as the initial therapy in AHF[1]. The role of vasodilators in patients with AHF who are failing to respond adequately to initial i.v. diuretic therapy is less clearly addressed in the scientific literature and there remains a clear unmet need for high quality randomized data in this regard.

With regard to future clinical trial design, it might be useful for triallists and physicians to draw a distinction between pharmacotherapeutic strategies aimed at the initial treatment goals of clinical stabilisation and symptom relief in AHF and those aimed at improving long term prognosis[14]. This may be particularly relevant in the treatment of AHF as the longer term outcome of these patients may be more dependent on the underlying HF aetiology than the management of the AHF presentation. Symptomatic improvement is an important therapeutic goal in patients presenting with AHF and we should not disregard safe pharmacotherapeutic strategies which provide effective early symptomatic relief and clinical stabilisation just because they do not also provide mortality benefit[15]. Challenges for future trials in this field include the often subjective nature of symptoms in AHF and the fact that the majority of patients with AHF will have initial improvements in symptoms early in their admission with standard therapy.

To summarise, both sets of authors in this edition of the journalmake some compelling arguments for the use of vasodilators in AHF in their pro and contra manuscripts

and we thank them for their contributions to this debate. However, based on current scientific evidence, we feel that the current HF guidelines provide an appropriate recommendation regarding the role of vasodilators in the initial treatment of AHF[1]. It is always important that when physicians prescribe a medication, they are cognisant of the benefit the medication will provide to the patient (if any) and whether this benefit relates to prognosis or to symptoms, to improvements in hard endpoints or merely to surrogate markers of efficacy. Even more importantly, we must always be mindful of the Hippocratic oath, 'primum non nocere' or 'do no harm'. When we consider the use of vasodilators in AHF through this lens, current scientific evidence suggests that the benefit (if any) of vasodilator therapy in the management of AHF may primarily be with respect to improvements in physiological parameters and symptomatic relief, rather than prognosis or hard clinical outcomes. A summary of the main outcomes associated with vasodilator therapy in comparison to standard care in patients with AHF are summarised in the **Central Illustration**. Based on the totality of currently available scientific data, these medications may be considered on a case by case basis but should not be first line, particularly in patients presenting with hypotension, who were excluded from the key RCTs.

As the Irish playwright, George Bernard Shaw, said; 'Beware of false knowledge, it is more dangerous than ignorance'. As a scientific community, it is important that we acknowledge both that there remains a large degree of 'ignorance' in our current understanding of the optimal management of patients with AHF and that more randomised data are urgently needed in order to ensure that our clinical practice is not based on 'false knowledge'.

Conflicts of Interest: The authors of this article have no conflicts of interest to declare.

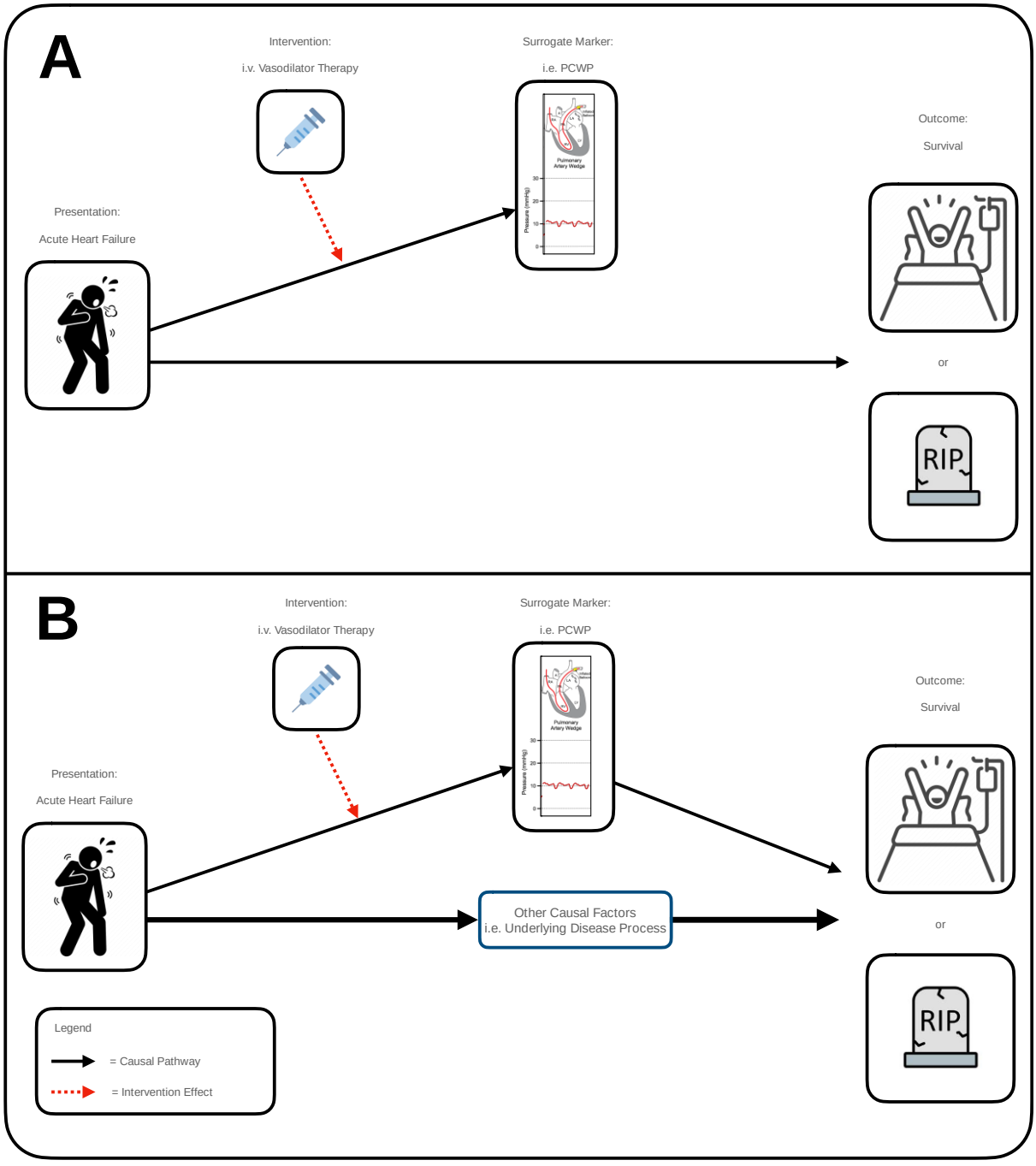
Figures.

Figure 1. Vasodilator Therapy in Acute Heart Failure: A Causal Pathway Analysis

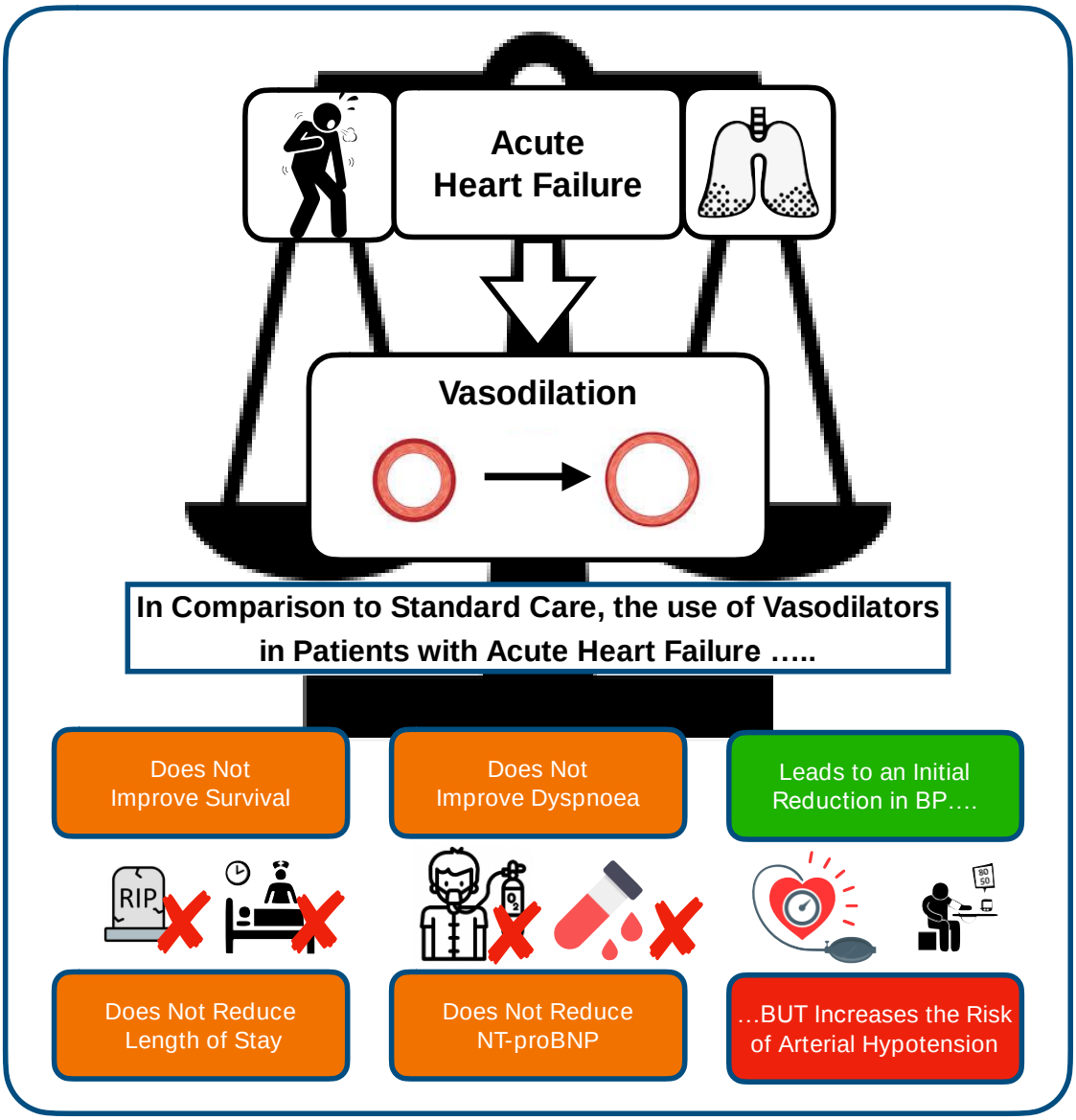
This figure demonstrates some of the potential ways in which an intervention (i.v. vasodilator therapy) can have a positive effect on a surrogate marker (pulmonary capillary wedge pressure, PCWP) in a specific clinical setting (acute heart failure) but fail to impact on a clinical outcome like survival. In **Panel A,** the surrogate is not in the causal pathway of the process leading to the outcome. As such, although the intervention has an effect on the surrogate, this does not impact on the clinical outcome. In **Panel B**, the surrogate is in a causal pathway of the process leading to the outcome. However, the intervention only impacts on this surrogate mediated causal pathway and not on another more important causal pathway, which is mediated by other causal factors, i.e., the underlying disease process. Therefore, although the intervention could potentially have an effect on the clinical outcome via the surrogate pathway, this is dwarfed by another, more important causal pathway.

Central Illustration. Vasodilator Therapy in Acute Heart Failure: Outcomes in Comparison to Standard Care

Figure 1. Vasodilator Therapy in Acute Heart Failure: A Causal Pathway Analysis



Central Illustration. Vasodilator Therapy in Acute Heart Failure: Outcomes in Comparison to Standard Care



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