Worsening Heart Failure Events Despite Foundational Therapy in Patients with Heart Failure with Reduced Ejection Fraction: An Interview with International Cardiology Experts

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Interview Summary

Heart failure (HF) is a major and growing global health problem. It is a complex syndrome caused by a structural and/or functional cardiac abnormality which leads to a reduced cardiac output and/or elevated intracardiac pressures. HF with reduced ejection fraction (HFrEF) is typically considered if the ejection fraction is <40%.[1] A worsening HF event is defined as the need for intravenous diuretics with or without hospitalisation, or treatment of either existing therapy escalation or initiation of a new therapy, with or without intravenous diuretics.[2] Once patients with HFrEF have experienced a worsening HF event in an urgent care setting, the rate of recurrent hospitalisations and mortality rate increases.[1,3]

To better understand the impact of previous worsening HF events in patients with HFrEF, EMJ interviewed two leading figures in cardiology: Prof Jeroen Bax from the Netherlands and Prof Javed Butler from the USA. They acknowledged the poor prognosis of patients with HFrEF who have experienced prior worsening HF events and highlighted the current lack of guidance available for the management of this patient population. They commented on the need to use optimal medical therapy, including novel therapies, at an earlier stage in the disease process. Prof Butler addressed the need for additional treatments to be included in future guidelines, and Prof Bax summarised three recent trials that addressed patients with HFrEF and highlighted the importance of aligning the objectives of the clinician with those of the patient, particularly in those who have experienced worsening HF events.

INTRODUCTION

HF is a global problem, with an estimated 63 million patients worldwide living with the disease.[4] It is projected that the lifetime risk of developing chronic HF is one in five at 40 years of age, in both females and males.[5,6] This results in a high mortality rate but also leads to increased hospitalisation and has a significant burden on patients.

There are multiple risk factors for HFrEF, such as coronary artery disease, hypertension, or diabetes, which ultimately lead to left ventricular dilation and dysfunction. HFrEF is typically considered if the ejection fraction is <40%.[1] This then impacts on the left atrium and, with increasing HF, right ventricular failure will occur, with development of tricuspid regurgitation. This creates a vicious cycle of worsening cardiac dysfunction. Some patients with HF will have preserved ejection fraction, but the focus of this interview is on patients who have HFrEF.[1]

WORSENING HEART FAILURE EVENT: DEFINITION AND DIAGNOSIS

At some stage, patients with chronic HF experience a worsening HF event, marked by a deterioration in symptoms, explained Prof Bax. These patients are very vulnerable and at risk of poor outcomes. A worsening HF event is defined as the need for hospitalisation, with or without intravenous diuretics.[1,3] This acute, decompensated HF is an unstable situation. Prof Bax explained that this rapid progression of symptoms requires an adjustment in therapy, either by increasing the dosage of current treatments or introducing new treatments.

Prof Bax highlighted the need for diagnostic evaluation in these patients. This should include measurement of the cardiac biomarkers brain natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide (NT-proBNP), which are usually significantly elevated in these patients, as well as assessment of renal function. Left ventricular function is then assessed with two-dimensional echocardiography, which could show a sudden and significant deterioration. In Prof Bax's experience, a significant drop in ejection fraction is observed, with an increase in both left ventricular end-systolic and end-diastolic volume. He added that three-dimensional echocardiography is usually not available in the acute setting and MRI is not feasible in these patients with acute worsening HF.

Clinical Characteristics

"I tend to divide HFrEF patients [who have had a worsening HF event] into four categories," explained Prof Butler. The first category is those patients who are noncompliant with their medication for various reasons, such as failure to refill a prescription. The second category is patients who are unable to tolerate optimal medical therapy; for example, because of poor renal function or risk of haemodynamic instability or low blood pressure. The third category includes patients with worsening comorbidities, such as chronic obstructive pulmonary disease, anaemia, and thyroid dysfunction, which cause secondary worsening of HF. The fourth category is the patients who are compliant, able to tolerate optimal medical therapy, and whose comorbidities are not impacting upon their HF, yet their HF is progressing; they still develop worsening HF events and require hospitalisation or acute therapeutic intervention. Prof Butler emphasised that it is this group of patients that are a particular concern, as it "shows that optimal medical therapy is simply no longer sufficient." Both this group of patients and those who cannot tolerate standard guideline-directed medical therapy are in need of new treatment options.

Prognosis

Prof Butler explained that regardless of which category the patient falls into, the prognosis is relatively poor. He pointed out that "many clinicians don't recognise that the 1-year risk of death or hospitalisation for worsening HF events is approximately 25–30%," which he noted is extraordinarily high. "It really marks a change in the trajectory of the disease process; the risk worsens significantly with every subsequent hospitalisation," he added.

Prof Bax quoted data from a study conducted by Butler et al.,[3] which enrolled more than 11,000 patients with HFrEF. The study found that 56% of patients were re-hospitalised within 30 days of a HF event, indicating that too often these patients are not being stabilised. "The number of HF-related hospitalisations per patient increased exponentially over a 2-year period," he added.

"These patients require symptomatic stabilisation as well as stabilisation of cardiac size and function," stated Prof Bax. He continued: "Ideally, clinicians would aim for a decrease in left ventricular volume, together with an improvement in left ventricular function and ultimately a decrease in the number of worsening HF events. This would reduce the number of hospitalisations and, in turn, lead to a reduction in mortality."

Unmet Needs

Prof Bax explained that, because of limited data at the time of publication, current European and USA guidelines only provide guidance for stable patients, and therefore do not address the patients who have experienced a recent worsening event. He did add, however, that new European guidelines are currently in development.

Once patients with HFrEF develop worsening HF events, their treatment regimen must be adjusted or additional therapies added. If maintained on their existing treatment regimens, patients are at increased risk of future HF events, morbidity is increased, and there will usually be multiple hospitalisations.

Prof Bax highlighted the need for earlier identification of patients who are not stabilised on their current treatment regimens. A significant proportion of patients have worsening events despite guideline-directed therapy, resulting in a dynamic process, rather than a stable one. Clinical inertia is a real phenomenon. Optimal medication should reduce mortality and hospitalisation and improve quality of life, without having a negative effect on renal function or blood pressure. Prof Bax acknowledged the need for medications that do not have a detrimental effect on renal function or haemodynamics, pointing out that clinicians often discontinue medication because of a deterioration in renal function or a drop in blood pressure, and therefore optimal treatment is often not achieved. He also noted that it is important to consider the follow-up care once patients are discharged from hospital; patients need regular outpatient appointments with laboratory evaluation and systematic echocardiography, allowing for earlier adjustment of therapy when necessary.

With one in two patients with HFrEF readmitted to hospital within 30 days following a worsening event,[3] Prof Butler was asked whether there was a need for additional treatment options, complementary to background therapy. He responded: "Regardless of whether patients are on optimal medical therapy or not, there is clearly a place for additional treatments to further improve patient outcomes." He noted that: "Even for New York Heart Association (NYHA) Class II patients who are otherwise well, recent trials show that the 1-year primary endpoint event rate (hospitalisation or death) exceeds 10%." He explained that the residual risk of rehospitalisation or death is even higher in patients with comorbidities, who are unable to tolerate optimal medical therapy because of the associated side-effect profile.

AIMS OF TREATMENT: CLINICIAN AND PATIENT PERSPECTIVES

According to Prof Bax, physicians tend to focus on mortality figures. However, as is often seen in oncology patients, when the patient becomes more unstable and unwell, their perspective tends to change. Clinical trials focus on prolonging survival, however, when the patients are asked what their goal is, "they usually want to avoid hospitalisation and achieve stabilisation of symptoms," relayed Prof Bax. In his experience, Prof Bax has found that patients usually prioritise quality of life over longevity. He recalls patients requesting to "live a normal life and enjoy a simple life without being hampered by symptoms."

Asked about the attributes he looks for in a therapy to treat HFrEF, Prof Bax responded that, while keeping the patient's wishes in mind, key aims of therapy include "avoidance of future worsening HF events, preventing a further reduction in renal function, and trying to avoid further left ventricular dilation and impaired ventricular function."

Treatment Pathway

"I find it fascinating how clinicians think about different diseases and approach them differently," began Prof Butler. "You will never find a clinician who would not treat a patient with, for example, significant hypertension or uncontrolled diabetes, just because they are doing 'okay,' without many symptoms, and wait until their condition worsens before treating," he continued.

With this in mind, he described the importance of treating patients with HF appropriately early in the disease process to achieve the cumulative effect of therapy and prevent worsening HF events, and then to treat more aggressively when a worsening HF event occurs. "For some reason, patients with HF are often not optimally treated because they are perceived to be doing okay and clinicians often only escalate therapy once they develop worsening HF events," said Prof Butler.

"This approach is entirely inappropriate," he explained, because once worsening HF events occur the prognosis is already poor. In addition, many patients will die from sudden cardiac death before even experiencing a worsening HF event. According to Prof Butler, optimal medical therapy should be provided regardless of where a patient is in the disease process. However, he added that it is important to realise that once worsening HF events occur, the risk is substantially higher, and the treatment approach must be optimised and aggressive. "If there are novel therapies targeting worsening HF events, these therapies should be used," concluded Prof Butler.

NOVEL COMPOUNDS: CLINICAL STUDIES IN HEART FAILURE WITH REDUCED EJECTION FRACTION

Prof Bax highlighted three contemporary studies with novel compounds in HFrEF, all with nuanced patient populations, in an effort to stabilise patients. The studies all have positive results, however, demonstrate that "we can still only help these patients, but we cannot cure them," Prof Bax said. "I welcome these developments as this research is very much needed in our clinics," added Prof Bax. He subsequently summarised the key results from these studies.

In 2014, the double-blind PARADIGM trial of 8,442 patients with HFrEF compared treatment with the angiotensin receptor neprilysin inhibitor sacubitril–valsartan after a run-in period, versus the angiotensin-converting enzyme inhibitor enalapril.[7] Patients were only eligible for inclusion in the study if they had a plasma BNP level of ≥150 pg/mL (or NT-proBNP ≥600 pg/mL) or if they had been hospitalised for HF within the previous 12 months, with a BNP of ≥100 pg/mL (or NT-proBNP ≥400 pg/mL).[7] Patients receiving sacubitril–valsartan had reduced risks of cardiovascular-related death and hospitalisation for HF compared with patients receiving enalapril; however, these risks still remained. Death from cardiovascular causes or hospitalisation for HF occurred in 21.8% patients in the sacubitril–valsartan group versus 26.5% in the enalapril group, after a median follow-up of 27 months.[7]

In 2019, the DAPA-HF trial investigated the use of the sodium–glucose cotransporter-2 dapagliflozin versus placebo, in addition to recommended therapy. In total, 4,744 patients with NYHA Class II, III, or IV symptoms and an ejection fraction of ≤40% were enrolled.[8] Eligible patients were aged ≥18 years, with an NT-proBNP level of ≥600 pg/mL (or ≥400 pg/mL if they had been hospitalised for HF within the previous 12 months). Patients with atrial fibrillation or atrial flutter on a baseline ECG were required to have an NT-proBNP level of ≥900 pg/mL, regardless of their history of hospitalisation for HF. A significant number of patients in the dapagliflozin group (16.3%) died from cardiovascular complications or worsening HF over a median follow-up of 18.2 months. However, this risk was reduced when compared with placebo (21.2%), regardless of the presence or absence of diabetes.[8]

Results from the VICTORIA trial were presented at the American College of Cardiology (ACC) Annual Meeting earlier this year by Armstrong et al.[9] This is the first trial to focus entirely on symptomatic chronic HFrEF patients who experienced a worsening HF event; 84% had a HF hospitalisation in the 3-6 months leading up to the study, with the remaining 16% receiving intravenous diuretics in the emergency department. Patients enrolled had chronic HF (NYHA Class II, III, or IV) and an ejection fraction <45%. This trial assigned 5,050 patients to receive vericiguat (a novel oral soluble guanylate cyclase [sGC] stimulator) or placebo, on top of guideline-based therapy. This patient population was at the highest baseline risk of all three studies, with an approximately 38% annualised placebo event rate and an ejection fraction of 29%. Additionally, 41% of the patients were NYHA Class III–IV, with a very high NT-proBNP (2,800 pg/mL). The study showed an absolute annualised event reduction of 4.2 (all-cause mortality or first HF hospitalisation) at 3 months, with 24 being the number of patients needed to treat to prevent an event;[9] Prof Bax emphasised that this is a particularly good result.

TARGETING THE NO-sGC-cGMP PATHWAY

"Clinicians realised in the early 1990s that there are a lot of adverse neurohormonal systems that are activated in patients with HF," began Prof Butler. He continued to explain how it was thought that as the adverse neurohormonal level increased, its function needed to be attenuated. Current therapies block the adverse compensatory responses of the renin–angiotensin–aldosterone system, natriuretic peptide system and sympathetic nervous system (β-blockers); however, patients continue to experience worsening HF events.

Prof Butler explained that clinicians are now realising that there are inherent counter-regulatory hormones that regulate the adverse neurohormonal effects, and this occurs in the nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate (NO-sGC-cGMP) pathway. In this pathway, NO activates sGC, which then generates cGMP. In turn, cGMP activates the protein kinase G1α (PKG1α), which inhibits vasoconstriction, inflammation, hypertrophy, and fibrosis, thereby helping to maintain normal cardiovascular function.[10,11] In HF, NO availability and sGC activity is reduced, leading to decreased production of critical cGMP.

Therapies aimed at accentuating these positive neurohormonal pathways to achieve a balance between the adverse and positive neurohormonal systems are now in development, including the novel oral sGC stimulator vericiguat. In conditions such as HF with oxidative stress, there is impaired signalling of the NO-sGC-cGMP pathway. "If there was a means of directly stimulating sGC to activate downstream signalling of cGMP and PKG, you could see a lot of the beneficial effects of this pathway and improve patient outcomes," clarified Prof Butler.

CONCLUDING REMARKS

Prof Butler reiterated the importance of ensuring optimal medical therapy early in the disease process, rather than waiting until the patient deteriorates. He described how HF is unique in that, unlike other conditions, clinicians often wait until a worsening HF event has occurred, at which point "the vicious cycle has already begun."

Prof Bax also highlighted the importance of using novel treatments earlier in the disease course: "When the new guidelines are developed, I expect these treatments to be ranked highly in the algorithms for treatment of worsening HF events in patients with HFrEF." His final comments focussed on the need to be conscious of the patient's perspective. In his experience, the clinician tends to focus treatment regimens on increasing life expectancy, whereas the patient usually prioritises symptomatic relief and the ability to enjoy simple daily activities.

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