The Efficacy, Side Effect, and Cost-effectiveness of Uperio for Heart Failure: A Literature Review

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Heart failure is a clinical syndrome that results when the heart is unable to provide sufficient blood flow to meet metabolic requirements or accommodate a systemic venous return. HF is a costly condition that consumes 1–2% of the total healthcare budget. Recently, angiotensin receptor/neprilysin inhibitors (ARNIs; sacubitril/valsartan, Uperio®) showed a highly significant and clinically relevant reduction in mortality and heart failure hospitalizations, and improvement of quality of life when added to current standard drugs in patients with heart failure with reduced ejection fraction.Sacubitril is an neprilysin inhibitor to slow down natriuretic peptide (NP) breakdown, effectively increasing their vasodilation effect. NP levels are elevated in patients with HF and other cardiac diseases for restoring normal circulatory conditions. As for valsartan, this is an angiotensin receptor blocker. It blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II. Although Uperio has fewer side effects, more effectiveness it is considered a high-priced heart failure medication and needs further economic impact.

Keywords: sacubitril/valsartan, heart failure, hypertension, side effects, cost

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Introduction

Heart failure (HF) is a syndrome resulting from cardiac disease, and is recognised clinically by a constellation of symptoms and signs produced by complex circulatory and neurohormonal responses to cardiac dysfunction.[1] Heart failure results from myocardial injury from a variety of causes including ischemic heart disease, hypertension, and diabetes.[2] In the United State of America (USA), the direct and indirect costs of total cardiovascular diseases (CVD), which include HF, were $422.3 billion in.1 There are several types of treatments available including Angiotensin-converting enzyme (ACE) inhibitors, Angiotensin-II-receptor antagonists (ARA), calcium-channel blockers (CCBs) and surgery. Angiotensin-converting—enzyme inhibitors reduce mortality and the need for hospitalisation and improve functional status in patients with heart failure. Despite such treatment, however, the mortality and morbidity rates associated with this condition are still high.[3] Cough is a side-effect of ACE inhibitors in up to 4% patients and may require withdrawal of therapy.[4] ARA could be used as an alternative to ACE inhibitors when side-effects that are specific to ACE inhibitors, such as cough, are encountered. Also, diuretics are undoubtedly successful at relieving breathlessness and oedema when overt fluid overload is present. Small randomised trials of older CCBs suggested no benefit or even a harmful effect in patients with heart failure.[5] Heart transplants, for the lucky few, are a highly successful way of managing severe heart failure. Donor organ supplies are low and dwindling. Mechanical left-ventricular assistance devices are now available for patients with end-stage heart failure.[6] Combination of an antagonist of the renin–angiotensin–aldosterone system (RAAS) has been introduced recently and effectively decreasing the blood pressure, with an inhibition of neprilysin, which is responsible for metabolising natriuretic peptides exerting antihypertensive and antifibrotic effects.

Uperio, which contains sacubitril and valsartan, is an angiotensin receptor-neprilysin inhibitor (ARNi). It's used to treat heart failure by enhancing the body's natural mechanisms to combat the condition. Sacubitril is a prodrug that inhibits neprilysin, an enzyme that breaks down natriuretic peptides. These peptides are important for blood volume and pressure regulation, promoting vasodilation and sodium excretion.[7] Valsartan blocks angiotensin II receptors, countering vasoconstriction and aldosterone release, which can increase blood pressure.[8] Together, they increase the levels of beneficial peptides while blocking harmful systems, effectively reducing strain on the heart.[7]

Uperio is indicated to reduce the risk of cardiovascular death and hospitalisation for patients with chronic heart failure and reduced ejection fraction. It's usually prescribed alongside other heart failure therapies, often replacing an ACE inhibitor or another ARB1.7 Clinical trials have shown that it significantly reduces the risk of death from cardiovascular causes and hospitalisation for heart failure compared to ACE inhibitor therapy alone.[8]

The purpose of this study is to conclude the efficiency of Uperio (valsartan/sacubitril combination), the cost difference with other drugs, the proper dosage of treatment, and the side effects for HF patients.

Method

With key words of (((heart failure) AND (uperio)) OR (angiotensin receptor-neprilysin inhibitor)) OR (sacubitril/valsartan) results from Google scholar and PubMed were narrowed down and we excluded irrelevant topics and languages except for English. Inclusion criteria specified characteristics studies must have to be considered about uperio treatment for HF patients, and obviously described specific populations, interventions, outcomes, and study designs. However, articles that were not relevant to the research and did not present the participants and protocol in detail were excluded. We compared and summarised a total of 14 papers to each other.

Discussion

The natriuretic peptide system

The natriuretic peptide (NP) system is an endocrine system that maintains fluid and pressure homeostasis by modulating cardiac and renal function. Several types of NPs have been described: atrial (ANP) brain- (BNP) and C-type natriuretic peptide (CNP). Whereas ANP and BNP are synthesised and secreted mainly from the cardiomyocytes in response to myocardial stretch.[9-10] CNP is released from endothelial cells in response to physiological agonists and by vascular injury NP levels are elevated in patients with HF and other cardiac diseases for restoring normal circulatory conditions.[11-13]

Their actions are modulated through guanylyl cyclase-coupled receptors A and B (NPR-A and NPR-B) and the more abundantly expressed G protein-linked

NP-clearance receptor (NPR-C) ANP and BNP bind selectively to NPR-A, while CNP binds to NPR-B and NPR-C and leads to activation of intracellular pathways.[9,14] By binding to NPR-C, natriuretic peptides are cleared from the bloodstream by endocytosis and intracellular inactivation.[15,16] NPR-A and NPR-B induce the generation of the second messenger cyclic guanosine monophosphate (cGMP), which mediates via protein kinase G activation and serine/threonine kinases most of the physiological effects of the NPs including natriuretic and diuretic effects, as well as various cardioprotective and antihypertensive mechanisms such as vasodilation, a reduced sympathetic nervous system (SNS) activity, inhibition of the RAAS (all more acute effects), induction of apoptosis and inhibition of fibrosis (long-term effects).[9,13,17] Unlike ANP and BNP, CNP does not act as an endocrine hormone, but as a paracrine factor in the vasculature, mainly as a vasodilator and inhibitor of vascular cell proliferation, although it is unclear whether CNP decreases blood pressure at physiological or pathological concentrations.[14,18-20]

Natriuretic peptides play a similar role as in the periphery, directly counteracting the effects of ANG II. Overall, main effects of natriuretic peptides include decreased salt and water intake, and inhibition of vasopressin, resulting in a decreasing in body fluid and lowering of blood pressure.[21]

Neprilysin

Neprilysin is an ANP-degrading zinc-dependent endopeptidase.[22] It was found that ANP was a substrate of NEP, also a multitude of other molecules such as ANP, BNP, CNP, angiotensins 1, 2, 3, 1-9, endothelin-1, endothelin-2, endothelin-3, adrenomedullin, and bradykinin.23 NEP is expressed in epithelial cells, neutrophils and fibroblasts, and it has been located in many tissues, such as renal proximal tubules, the heart, the brain, lungs, blood vessels and thyroid.[24-25] Inhibition of NEP activity, the goal is to slow down NP breakdown, effectively increasing their vasodilation effect.

Sacubitril/Valsartan (Uperio)

Sacubitril/Valsartan (previously known as LCZ696, and marketed under the name of Entresto®, Uperio®), a combination drug, has proven to be superior to conventional angiotensin-converting-enzyme (ACE) inhibition in reducing cardiovascular deaths and HF hospitalisation , in a large prospective randomised clinical trial.[26] The molecule consists of two active moieties in a 1:1 ratio, the well-documented ARB, valsartan and a NEPi pro-drug sacubitril (AHU337). The new class is called angiotensin receptor/neprilysin inhibitor.

Valsartan is an ARB. By having a much greater affinity for AT1R compared to AT2R, valsartan can inhibit the BP-raising and pro-fibrotic effects that are triggered by AT1R-mediated overproduction of reactive oxygen species causing hypertrophic cell growth, cell senescence, endothelial dysfunction, and cardiovascular and renal remodelling, without interfering with the beneficial antihypertensive and cardioprotective effects of AT2R.[27]

LBQ657 inhibits the neutral endopeptidase, an enzyme responsible for the degradation of NP. By preventing this process, the NP concentration increases and their cardioprotective and antihypertensive effects are enhanced.[28]

Uperio in hypertension

LCZ696 can significantly reduce blood pressure in patients with heart failure. According to a meta-analysis study by Geng, Qiang et al., this meta-analysis to determine the antihypertensive effect of LCZ696 in patients with hypertension. Compared with angiotensin receptor blockers (ARBs), LCZ696 100 mg caused a significant reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP). LCZ696 200 mg caused a significant reduction in SBP, DBP, 24-h ambulatory SBP , and 24-h ADBP . LCZ696 400 mg caused a significant reduction in SBP , DBP, 24-h ASBP, and 24 h ADBP . Compared with LCZ696 200 mg, LCZ696 400 mg caused a significant reduction in SBP , DBP , 24-h ASBP, and 24-h ADBP . Research found that the blood pressure-lowering effect of LCZ696 is dose-related. It confirms the antihypertensive effects of LCZ696.[29]

Three studies evaluated the effect of LCZ696 compared to olmesartan in the treatment of HT in Asian patients, in patients with essential HT not adequately responsive to olmesartan and elderly patients.[29-31] They all found LCZ696 to be superior in lowering the peripheral BP or CASP, although the effect seems to become non-significant over time.[31] Furthermore, the studies all point towards the same level of tolerability and AE for LCZ696 as for olmesartan.

Uperio in Heart Failure

The largest completed study so far is the PARADIGM-HF trial.[32] The study was a double-blinded, randomised,

phase 3 trial including 8442 patients with HFrEF (NYHA class II-IV) and with an EF of <40%. After a run-in period of 3–6 weeks, participants were randomised to an ACEi, enalapril (10 mg twice daily) or LCZ696 (200 mg twice daily) group in a 1:1 ratio. After a 27-month median follow-up period, the trial was stopped early because predetermined results for effects were achieved. The study showed a decreased hazard ratio of 0.8 (95% CI: 0.73–0.87; p < 0.001) for deaths due to CVD or hospitalizations and a reduction in physical symptoms (p < 0.001) with LCZ696. The study concluded LCZ696 to be 'superior to enalapril in reducing risk of death and of hospitalisation for heart failure'.33 McMurray et al. later showed that LCZ696 caused a reduction in CVD mortality and hospitalisation even as additional medication on top of BAA and mineralocorticoid receptor antagonists.[34]

Sacubitril was found to lessen cardiomyocyte cell death, hypertrophy, and impaired myocyte contractility by inhibiting PTEN, thus triggering a series of cascades that participate in cardiac remodelling. On the other hand, Valsartan improves cardiac remodelling by inhibiting the guanine nucleotide-binding protein family. More importantly, study found that the combination of Sacubitril and Valsartan acts synergistically against left ventricular extracellular matrix remodelling (LVEMR) and cardiomyocyte cell death, with Valsartan enhancing the effects of Sacubitril.[35]

Beneficial effect on glycemic control

Type 2 diabetes mellitus (T2DM) and HF often coexist, and the presence of both conditions in a patient typically indicates a poorer prognosis than either condition alone. This is partly due to the metabolic imbalances caused by T2DM, which can exacerbate the pathophysiology of HF. Glycemic control, typically measured by glycosylated haemoglobin (HbA1c) levels, is crucial in managing diabetes severity. It has been shown to be associated with the development and progression of HF. Optimal glycemic control is essential to mitigate these risks. Clinicians must carefully manage glycemic control in HF patients with T2DM, considering the individual patient's risk factors, comorbidities, and response to treatment. This personalised approach is vital to improving clinical outcomes and quality of life for these patients.[36]

There is evidence suggesting that treatment with a dual-acting angiotensin-receptor–neprilysin inhibitor (sacubitril/valsartan) resulted in improved glycemic control. This beneficial metabolic effect is most likely secondary to NEP inhibition and consequent modulation of its circulating substrates.[37]

Effects on Biomarkers of Extracellular Matrix Regulation

B-type natriuretic peptide (BNP) is a biomarker that plays a crucial role in the diagnosis and management of HF patients. Scientifically, BNP is a hormone produced by your heart's ventricles in response to excessive stretching of heart muscle cells (cardiomyocytes). This stretching can occur due to fluid overload, commonly seen in HF.[38]

At baseline, the profibrotic biomarkers aldosterone, sST2, TIMP-1, Gal-3, PINP, and PIIINP were higher, and biomarkers associated with collagen degradation, MMP-2 and -9, were lower than published referent control values. Eight months after randomization, aldosterone, sST2, TIMP-1, MMP-9, PINP, and PIIINP had decreased more in the sacubitril/valsartan than enalapril group. At baseline, higher values of sST-2, TIMP-1, and PIIINP were associated with higher primary outcome rates. Changes from baseline to 8 months in sST-2 and TIMP-1 were associated with change in outcomes.[39]

Biomarkers associated with profibrotic signalling are altered in HF with reduced ejection fraction, sacubitril/valsartan significantly decreased many of these biomarkers, and these biomarkers have important prognostic value. These findings suggest that sacubitril/valsartan may reduce profibrotic signalling, which may contribute to the improved outcomes.[39]

Side effects

A phase 2 trial aimed to evaluate the safety and tolerability of LCZ696 for HF patients (NYHA class II–IV), NCT01922089. The study was conducted as a randomised, double-blind, multi-centre trial in the United States, Europe and Turkey. The 498 participants were randomised into two groups up-titrating to 200 mg LCZ696 twice daily in 3 or 6 weeks, respectively. Common side effects were ('condensed' vs. 'conservative') hypotension (9.7% vs. 8.4%), renal dysfunction (7.3% vs. 7.6%) and hyperkalaemia (7.7% vs. 4.4%) and adjudicated angioedema (0.0%) , which occurred in patients.[40]

Cost

As for the cost, it can vary depending on the region and the healthcare system. For example, in Pakistan,

Uperio 100mg tablets are available, and there might be discounts offered on purchases.[41] Similarly, in Nigeria, the price for Uperio 100mg tablets (28 tablets) is listed, with potential discounts as well.[42] It's important to note that prices can fluctuate and it's best to consult a local pharmacy or healthcare provider for the most current pricing information.

The actual price of the drug has to be discussed. The treatment with Entresto (400 mg) will cost 48.42DKK (6.89$) a day. In comparison, equivalent doses of enalapril (20 mg) and valsartan (160 mg) will cost 0.27DKK (0.039$) and 1.2DKK (0.17$), respectively, per day. Therefore, the possible economic impact will need to be closely considered.

Conclusion

Combination of Angiotensin–Neprilysin Inhibition was beneficial in reducing hypertension, risks of death and hospitalisation for heart failure. Sacubitril was found to attenuate cardiomyocyte cell death, and hypertrophy, on the other hand, Valsartan improves cardiac remodelling. Also, they reduce profibrotic biomarkers which may contribute to improved outcomes. Uperio has a beneficial effect on glycemic control belongs to neprilysin inhibition. The proper dosage was 200 mg twice daily in 3-6 weeks. Although Uperio has fewer side effects, it is considered a high-priced heart failure medication and needs further economic impact.

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