Natriuretic peptides, heart failure and LCZ696 (Entresto®)

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Natriuretic peptides (NPs) – such as B-type natriuretic peptide precursor (BNP) and its N-terminal fragment (NT-proBNP) – are well-known and widely accepted as both useful and cost-effective biomarkers for heart failure (HF) diagnosis and therapy monitoring.

Both BNP and NT-proBNP are considered to be gold standard biomarkers of HF. Both of these are also incorporated into the majority of the national and international cardiovascular therapy guidelines. However, despite this, our understanding of their very complex nature is still far from being complete and comprehensive. Moreover, the constant development of new approaches in patient care and the implementation of new therapeutic agents generate new questions and challenges for the use of NPs for HF diagnostics and the monitoring of HF therapy.

The recently introduced HF medicine LCZ696 (Entresto®) that has been developed by Novartis and approved by the FDA is an example of the upcoming challenges in this field. “It’s been at least a decade since we’ve had a breakthrough of this magnitude” explained Dr. Clyde Yancy, Cardiology Chief at Northwestern University in Chicago and a former President of the American Heart Association. LCZ696 was reviewed under the FDA’s priority review program, which is applied to drugs that “…may provide a significant improvement over available therapy.”

The high potential of this new and seemingly promising HF drug has raised some important questions regarding the use of BNP and NT-proBNP as HF biomarkers along with LCZ696 therapy.

LCZ696 is made up of two components; the neprilysin inhibitor AHU377 and the angiotensin receptor inhibitor valsartan. Therefore, the effect of this drug is considered to be twofold: (i) Augmentation of NPs level (inhibition of their degradation by neprilysin) and (ii) Vasodilation (inhibition of the renin-angiotensin-aldosterone system via the angiotensin receptor II) (Figure 1).

The results of clinical studies are very promising: The trial data demonstrated marked improvement in outcomes with LCZ696 as compared to enalapril (an inhibitor of the angiotensin-converting enzyme) alone in patients with HF with a reduced ejection fraction (1).

Why was neprilysin chosen as a therapeutic target? Neprilysin is a widely expressed membrane-bound protease that has been shown to cleave and inactivate a number of potentially important peptides, including NPs, angiotensin II, glucagon, enkephalins, substance P, neurotensin, oxytocin, bradykinin and amyloid beta. All three members of the NP family – ANP, BNP and CNP – have been shown to be the substrates of neprilysin. However, neprilysin was shown to have only a modest direct effect on BNP.

As neprilysin is thought to be responsible for degrading BNP while having no shown effect on the breakdown of NT-proBNP, one may expect that patients who are treated with LCZ69 will have higher plasma BNP levels due to the inhibition of neprilysin activity. Conversely, NT-proBNP levels are not influenced by neprilysin inhibition. Indeed, as it follows from the recent study by the group of investigators and coordinators of the PARADIGM-HF trial, the plasma BNP levels were shown to increase during treatment with LCZ696, whereas NT-proBNP levels decreased (2).

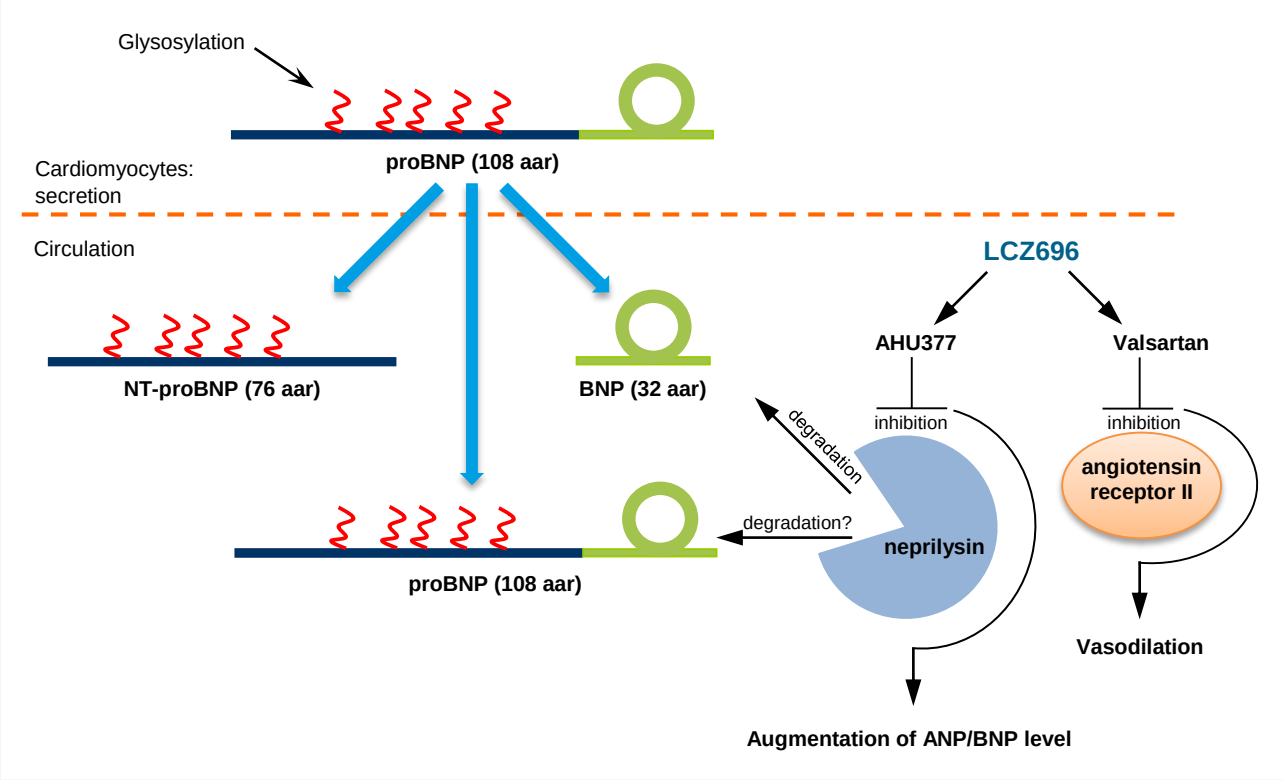

Figure 1. Schematic representation of BNP biosynthesis and the suggested pharmacological action of LCZ696. The beneficial effect of LCZ696 is thought to be achieved through the inhibition of neprilysin (which leads to the augmentation of the level of NPs) and the blocking of the angiotensin receptor II (which leads to vasodilation).

As the BNP levels are augmented by LCZ696 it has been argued that the measurement of BNP should not be used along with LCZ696 therapy and that NT-proBNP instead should be used to follow the therapy.

However, taking into account the complex biochemistry of proBNP-derived peptides and the diversity of HF forms, the answer to this question is clearly not obvious. There are several considerations regarding why this may be a far too simplistic view of a more complex system.

Firstly, the contemporary paradigm is that the NP system functions differently in different forms of HF and that, as a consequence, the effect of neprilysin inhibition with LCZ696 on NPs levels could be varied in different states of diseases. The beneficial effect of LCZ696 was shown in patients with HF with mild-to-moderate symptoms (reduced ejection fraction) although it remains to be seen how LCZ696 therapy affects patients with preserved ejection fraction or patients with acute HF, or in particular patients with chronic forms of HF.

Secondly, given the known diversity of proBNP-derived peptides, the puzzle of NPs, HF and LCZ696 becomes even more complex (3).The main form of plasma BNP-immunoreactivity is known to be represented by its uncleaved precursor – proBNP – along with multiple truncated forms of BNP. These are detected by current BNP immunoassays. Therefore, rather than considering the degradation of mere full length BNP (1-32), the effects of neprilysin and its inhibition with LCZ696 on the level of proBNP and different BNP fragments should be considered. Neprilysin has been shown to cleave mature BNP 1-32. However, there are currently no data demonstrating that neprilysin is capable of degrading intact proBNP or truncated BNP forms.

Thirdly, the recent data suggests that elevated BNP levels may inhibit the activity of circulating neprilysin (4). From a clinical perspective, this means that LCZ696 may have different effects in patients with low and high levels of circulating BNP due to the different activity of neprilysin. Therefore, one could conclude that BNP measurements are required to understand at what BNP level the LCZ696 therapy should be applied.

Fourthly, it should also be considered that the increase in circulating BNP might reciprocally reduce proBNP production and therefore as a consequence decrease the NT-proBNP level, which would then fail to reflect the improvement of cardiac function.

Whilst it has been suggested that NT-proBNP measurement should be used along with LCZ696 therapy, it could be argued that the suggestion is based on an overly simplified model of a complex biological phenomenon. Taking into account the complexity of the NP system and the diversity of HF states it remains open as to whether BNP or NT-proBNP alone should be used in order to fully understand the HF status of patients and the requirements for the appropriate treatment strategy. As our understanding of HF and LCZ696 increases it may become evident that both biomarkers or their ratio should be applied to fully utilize the diagnostic and prognostic value of these biomarkers. An increased level of BNP may serve as a read-out of an adequate LCZ696 dosing while NT-proBNP levels might reflect the effects of the drug on the functioning of the heart.

References

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