Sacubitril/Valsartan
The Newest Neurohormonal Blocker for Guideline-Directed Medical Therapy for Heart Failure

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KEYWORDS

• Sacubitril • Valsartan • Neurohormonal blocker • Heart failure

KEY POINTS

- The burden of heart failure is projected to increase over the next decade, and it is predicted that 1 in every 33 Americans will be affected by heart failure.
- The recent addition of the combination of sacubitril/valsartan (LCZ696) to guideline-directed medical therapies should ameliorate this burden.
- Neprilysin inhibition is associated with significant improvements in survival.
- Despite substantial reductions in mortality with neprilysin inhibition, the mortality rate among patients with heart failure remains high around 20% over 2 years in the intervention arm of Prospective comparison of ARNi with ACEi to Determine Impact on Global Mortailty and morbidity in Heart Failure (PARADIGM_HF) suggesting that opportunities to reduce mortality in heart failure remain.

INTRODUCTION

The burden of heart failure is projected to increase over the next decade, and it is predicted that 1 in every 33 Americans will be affected by heart failure.[1] Given that heart failure currently results in more than 1 million hospitalizations every year and the estimated 5-year mortality is approximately 50%, therapies that will improve survival and the economic burden are urgently needed. It is anticipated that the cost of managing heart failure is going to be approximately $70 billion in 2030.[2] Therefore, the recent addition of the combination of sacubitril/valsartan (LCZ696) to guideline-directed medical therapies should ameliorate this burden.

PHARMACOLOGY

Sacubitril, a prodrug, is an inhibitor of neprilysin, a neutral endopeptidase, that is responsible for degradation of biologically active vasoactive peptides, including natriuretic peptides (brain natriuretic peptide [BNP] and N-terminal [NT]-proBNP) and bradykinin (Figs. 1 and 2). ProBNPs convert into NT-proBNP and BNP. BNP acts by natriuresis, diuresis, vasodilatation, antiproliferative vascular effects, and decreased sympathetic tone. Degradation of BNP into breakdown products is inhibited neprilysin resulting in an increase in natriuretic peptides, including BNP, which have vasodilator properties, facilitate sodium excretion, and most likely have effects on cardiac remodeling. Therefore, when patients are on neprilysin inhibitors, BNP cannot be used to monitor therapy; in fact, NT-proBNP is a biomarker of choice in patients on neprilysin inhibition.

NEUROHORMONAL BLOCKADE

The Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF[3])

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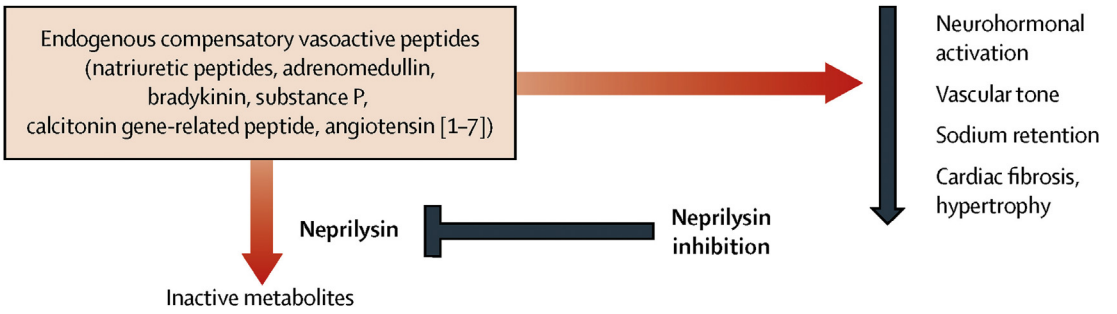

Fig. 1. The actions of vasoactive peptides in heart failure. Many endogenous compensatory vasoactive peptides act to antagonize the maladaptive mechanisms of heart failure (neurohormonal activation, vascular tone, sodium retention, and cardiac hypertrophy and fibrosis). Because these peptides are degraded by a common enzyme (neprilysin), their favorable actions are enhanced when a neprilysin inhibitor is included as part of the neurohormonal inhibitory strategy used to treat chronic heart failure. (*From* Packer M, McMurray JJV. Importance of endogenous compensatory vasoactive peptides in broadening the effects of inhibitors of the renin-angiotensin system for the treatment of heart failure. Lancet 2017;389:1832; with permission.)

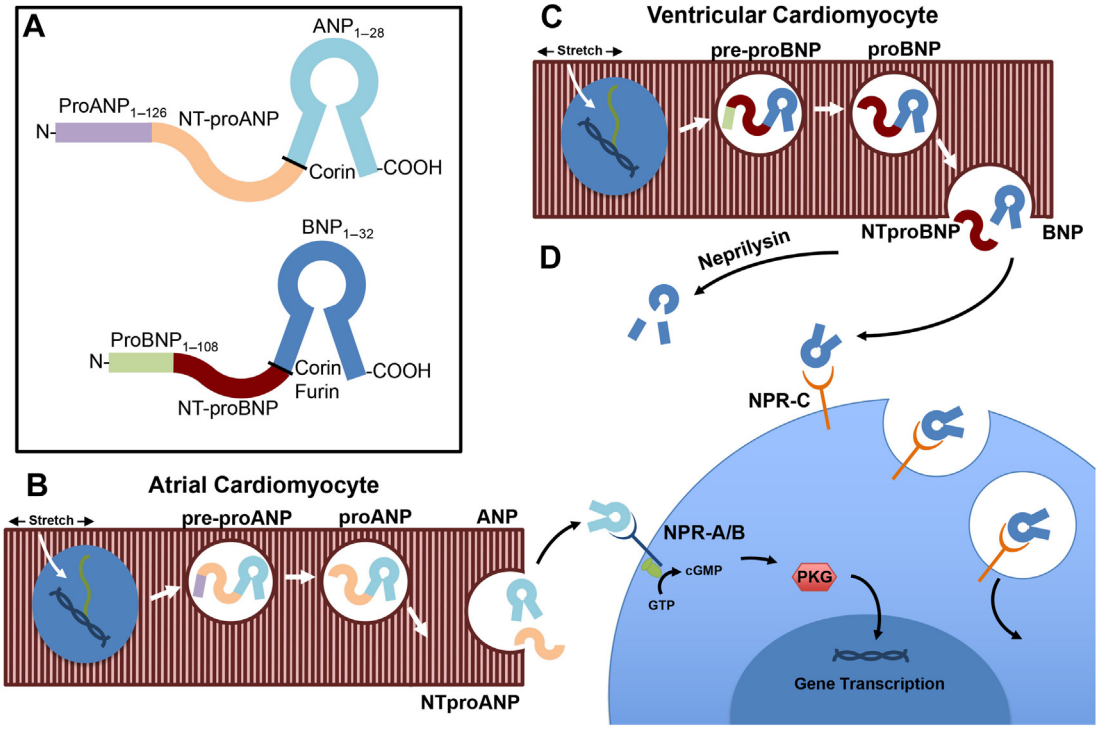

Fig. 2. Atrial natriuretic peptide (ANP) and BNP physiology. (*A*) Molecular structure of ANP (*top*) and BNP (*bottom*) showing enzymatic cleavage sites and end-product fragments. (*B*) Production and processing of ANP by atrial cardiac myocyte in response to mechanical stretch stimulus. (*C*) Production and processing of BNP by ventricular cardiac myocyte in response to mechanical stimulus. (*D*) Effects of ANP and BNP on target tissues. Both ANP and BNP bind natriuretic peptide receptor (NPR)A and NPR-B on target cells, inducing cleavage of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) by cytoplasmic G proteins, initiating an intracellular cGMP signaling cascade involving protein kinase G (PKG), ultimately leading to downstream transcription of genes involving smooth muscle cell relaxation, diuresis, and natriuresis (depending on target tissue). Both ANP and BNP are broken down in serum by circulating endogenous peptidases, including neprilysin. ANP and BNP are also degraded (to a lesser extent) by cellular uptake through binding NPR-C, undergoing receptor-mediated endocytosis and intracellular breakdown by lysosomes. (*From* Maisel AS, Duran JM, Wettersten N. Natriuretic peptides in heart failure. Heart Fail Clin 2018;14:15; with permission.)