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Is Sacubitril/Valsartan (Also) an Antiarrhythmic Drug?

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Sacubitril/valsartan is the first of a new class of drugs known as angiotensin receptor neprilysin inhibitors. In the pivotal PARADIGM-HF trial (Prospective Comparison of ARNi with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure),[1] published in 2014, 8442 patients with heart failure (HF) and reduced ejection fraction were randomized to receive either sacubitril/valsartan or enalapril. Patients in the sacubitril/valsartan group had a 20% relative risk reduction in the primary outcome cardiovascular death or HF hospitalization. Regarding the mode of death, most deaths in the study (1587; 80.9%) were because of cardiovascular factors, with sudden death being the most common cause of cardiovascular death (44.8%), followed by worsening HF (26.5%).[2] The reduction in mortality with sacubitril/valsartan was similar for sudden death and pump failure (20% and 21% relative risk reduction, respectively), although notably with no effect on incident atrial fibrillation. These results are more compelling if we take into account that the vast majority of patients in the PARADIGM-HF trial received optimal guideline-based medical therapy with drugs that have already been shown to reduce overall mortality and sudden death; 93% of patients were taking β-blockers and 55% were taking a mineralocorticoid receptor antagonist. The reduction in sudden death with sacubitril/valsartan was independent of protection with implantable cardioverter defibrillators (ICDs), present in only 15% of enrolled patients.[2]

SACUBITRIL/VALSARTAN AS A POTENTIALLY ANTIARRHYTHMIC DRUG

The mechanism by which sacubitril/valsartan further reduces mortality and sudden death, when given in addition to therapies with broadly proven efficacy, is not completely understood. Angiotensin receptor neprilysin inhibitors have a complex molecular mechanism of action involving multiple biological pathways that combine the effect of neprilysin inhibition with the blockade of the angiotensin-II receptor. Neprilysin is a ubiquitous metallopeptidase with several different substrates. In the cardiovascular system, neprilysin cleaves vasoactive peptides with vasodilating effects, such as natriuretic peptides, adrenomedullin, and bradykinin, as well as peptides with vasoconstrictor effects. The result of neprilysin inhibition is an increase in the circulating levels of natriuretic peptides, which have several cardioprotective effects that counteract the detrimental effects of renin-angiotensin system and sympathetic nervous system activation.[3] When coupled with their receptors NPR (Natriuretic Peptide Receptor)-A and NPR-B, natriuretic peptides increase intracellular cGMP and its effector molecule protein kinase G. This activates several signaling cascades that induce vasodilation, natriuresis, inhibition of the renin-angiotensin and sympathetic systems, and, most important, reduce cardiac inflammation, cell

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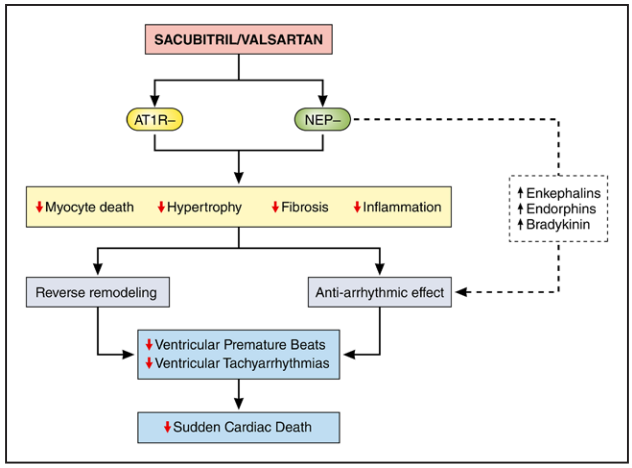

Figure. Proposed mechanisms whereby sacubitril/valsartan may exert antiarrhythmic effects.
By reducing myocardial cell death, hypertrophy, fibrosis, and inflammation, ARNI may reduce the substrate for ventricular arrhythmias. There could also be a more direct antiarrhythmic mechanism still not clearly understood (dotted line), where the different substrates of neprilysin may play a role, as suggested by preclinical data. ARNI indicates angiotensin receptor neprilysin inhibitors; AT1R, angiotensin II type 1 receptor; and NEP, neprilysin.

death, hypertrophy, and fibrosis, with the potential to reverse or reduce left ventricular remodeling (Figure).[4]

Is it possible that sacubitril/valsartan has direct antiarrhythmic effects, reducing ventricular arrhythmic events, which are the main cause of sudden death? Its lack of effect on the surface ECG argues against a direct electrophysiological (ie, ion channel) mechanism, but by reducing myocardial fibrosis and wall stretch, sacubitril/valsartan has the potential to reduce the incidence of ventricular arrhythmias. Myocardial fibrosis produces areas of electric inhomogeneity and slow conduction, which facilitate re-entry, the basic mechanism of ventricular arrhythmias in patients with cardiomyopathy. Myocardial stretch is also associated with a higher incidence of premature beats, which in an appropriate substrate may trigger lethal arrhythmias. Left ventricular function recovery by the reversal of pathological remodeling may also explain to a certain extent the reduction of sudden death, but there is no clear evidence yet that sacubitril/valsartan improves ejection fraction to a greater degree than standard therapy. ACE inhibitors and mineralocorticoid receptor antagonists act also by modulating cardiac remodeling, and β-blockers have well proven antiarrhythmic effects, so the additional antiarrhythmic benefit of sacubitril/valsartan may come from the promiscuous effects of neprilysin. Increased levels of enkephalins, endorphins, and bradykinin, which are also substrates of neprilysin, may play a role in the cardioprotective and antiarrhythmic effects of neprilysin inhibitors. The inhibition of the enzymatic breakdown of endogenous enkephalins by intravenous administration of acetorphan decreased the incidence of epinephrine-induced arrhythmias in rats. Further, the administration of an ACE/neprilysin inhibitor reduced the incidence of ventricular arrhythmias related to acute ischemia and reperfusion, and this effect was mediated by bradykinin.

There is some preliminary clinical evidence of the antiarrhythmic effects of sacubitril/valsartan. de Diego and colleagues[5] showed that, in patients with HF with a reduced ejection fraction (82% ischemic) who had an implanted ICD with remote monitoring capability, treatment with sacubitril/valsartan was associated with lower premature ventricular contraction burden, less nonsustained ventricular arrhythmias, and appropriate ICD shocks compared with previous therapy with an angiotensin-convertin enzyme inhibitor or an angiotensin receptor blocker. Although the nonrandomized design of the study and lack of a control group are acknowledged caveats, the results suggest that sacubitril/valsartan may have antiarrhythmic effects, either directly or via modulation of cardiac remodeling and neurohormonal pathways (Figure). More research is needed to confirm these findings and answer other questions, such as the effects of sacubitril/valsartan on atrial arrhythmias, which were not reduced in the PARADIGM-HF trial.

IMPLICATIONS FOR THE PREVENTION OF SUDDEN DEATH

Current guidelines recommend prophylactic ICD in patients with HF and an ejection fraction ≤35%. This recommendation is based on evidence from clinical trials conducted >10 years ago. More recent trials, such as DANISH, which included patients with nonischemic HF and optimal medical therapy according to more recent standards, failed to show a mortality benefit from the use of ICDs except in the younger patient subgroup, although the fact that the majority of patients in this trial had a cardiac resynchronization device could have influenced the results. No randomized ICD trials have been performed yet in patients receiving sacubitril/valsartan, but it is reasonable to assume that, as new therapies improve overall survival and reduce sudden death, the additional survival benefit provided by an ICD will become narrower. In this new era of HF management, we may need to reassess the role of ICDs in primary prevention for patients with HF in the context of angiotensin receptor neprilysin inhibitor therapy added to β-blockers and mineralocorticoid receptor antagonists, especially if evidence continues to suggest antiarrhythmic effects of sacubitril/valsartan.

ARTICLE INFORMATION

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Disclosures

None.

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