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Short Communication

Heart Failure and Ventricular Arrhythmias: The Role of Drug Therapy

Andrea Pozzi*

Cardiology Division, Valduce Hospital, Como, Italy

ABSTRACT

Heart Failure (HF) is a pandemic disease, affecting more than 30 million people in Europe. Patients with chronic HF are classified according to Left Ventricular Ejection Fraction (LVEF) in HF with reduced (LVEF ≤ 40%), mild reduced (LVEF 41-49%) and preserved Ejection Fraction (LVEF ≥ 50%). Patients with reduced Ejection Fraction (HFrEF) have an increased risk to develop life threatening arrhythmias such as ventricular tachycardia or fibrillation.

Keywords: Heart failure; Ventricular tachycardia; Arrhythmias; Congestive heart failure; Drug therapy

DESCRIPTION

Noteworthy, there is a complex interaction between ventricular arrhythmias and HF, since the arrhythmic burden can accelerate the HF progression whereas HF may trigger the development of arrhythmias [1,2]. Of note, the neurohormonal activation plays a crucial role for the development of arrhythmic substrate. In this regard the Renin Angiotensin Aldosterone System (RAAS) and the sympathetic nervous system, promote structural changes such as ventricular hypertrophy and fibrosis, increase oxidative stress which affects myocytes in the mechanical and electrical functions [3].

Over the years different classes of drugs have been studied in HFrEF patients to assess whether they may decrease ventricular tachycardia. Due to the antiarrhythmic propriety, different antiarrhythmic drugs have been deeply studied, achieving unexpected results. At the beginning of the '90, the CAST trial was prematurely interrupted since flecainide and encainide demonstrated an increased risk of ventricular arrhythmias and death compared to placebo [4]. After a decade, the Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure trial (SCD-HeFT), showed any difference between amiodarone and placebo in the reduction of all cause of death [5]. Conversely, this trial demonstrated a significative reduction of all cause of death in the Implantable Cardioverter Defibrillator (ICD) arm. As consequence, the SCD-HeFT trial had a massive impact on guidelines recommendation on ICD therapy in HFrEF patients.

Conversely to the previous anti arrhythmic drugs, beta-blockers demonstrated significative reduction in ventricular arrhythmias [6,7]. Particularly, in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial, carvedilol significantly reduced ventricular fibrillation compared to the placebo (p=0.019) in a HFrEF population with severe reduced ejection fraction (LVEF<25%) [7]. This result has been recently confirmed in study, wherein the role of beta-blockers in prevention of ventricular tachyarrhythmias has been assessed among HFrEF patients with an ICD [8]. In this observational study, metoprolol and carvedilol were examined at three different doses (low, intermediate, and high), demonstrated a significative reduction of ventricular tachycardia or ventricular fibrillation without any differences between the two drugs. Noteworthy, the reduction of ventricular arrhythmic burden was observed only in the high dose arm. Beyond the result regarding the reduction of arrhythmias, this study further reinforced the importance for an appropriate drugs titration to achieve an effective reduction of outcome in HF patients. Although the RAAS have a paramount influence on the pathophysiology of HF and promote arrhythmia by increasing myocardial fibrosis, the effects of the RAAS-inhibitors on ventricular arrhythmias have not been exhaustively studied, and a few contrasting data is available so far.

In a post-hoc analysis of the Vasodilator Heart Failure Trial II (V-HeFT II), patients treated with enalapril experienced a reduction in the frequency of ventricular tachycardia of 27% compared with baseline after 12 months of follow-up; whereas in the hydralazine-isosorbide dinitrate arm this reduction was not seen [9]. Conversely, the Effect of Enalapril on Survival in Patients with Left Ventricular Ejection Fraction and Congestive Heart Failure (SOLVD) trial, did not show any difference regarding the reduction of no sustained ventricular tachycardia at 4 and 12

Correspondence to: Andrea Pozzi, Cardiology Division, Valduce Hospital, Como, Italy, E-mail: andreawellsvabg@gmail.com

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months in patients treated with enalapril or placebo [10]. According to the effect of mineralocorticoid receptors antagonist on ventricular arrhythmias, in the Randomized Aldactone Evaluation Study (RALES) trial, there was any difference between spironolactone and placebo in the prevalence of ventricular arrhythmias in 6632 HFrEF patients [11]. Importantly, the aforementioned studies have been conducted before guidelines recommended the introduction of ICD therapy in patients with HFrEF. In this regard, due to the lack of device arrhythmic detection, the number of ventricular arrhythmic episodes could have been underestimated especially among asymptomatic patients, representing an important bias for the assessment of the effect of RAAS-inhibitors on ventricular arrhythmias.

In the last decades, a new class of drug, the Angiotensin Receptor-Neprilysin Inhibitors (ARNI), showed a significative reduction of outcome in HFrEF patients [12]. In a recent post hoc analysis of the Angiotensin-Neprilysin Inhibition *versus* Enalapril in Heart Failure (PARADIGM-HF) trial, Curtain, et al. demonstrated a significative of ventricular arrhythmias (p=0.002) and the composite endpoint of ventricular arrhythmias, ICD shock and resuscitated cardiac arrest (p=0.039) among patients treated with sacubitril/valsartan, compared to enalapril [13]. These data have been also confirmed in a recent meta-analysis which considered both Randomized Controlled Trials (RCT) and no-RCT studies [14]. Notably, all patients enrolled in the no-RCTs had an ICD which allowed a reliable detection of ventricular arrhythmias, showing an effective reduction after ARNI treatment. The newer class of drug in HF treatment, Sodium Glucose Cotransporter 2-Inhibitors (SGLT-2I), demonstrated a massive reduction of cardiovascular outcome irrespectively from LVEF, although the exact mechanisms related to the beneficial effect in HF patients are not completely known [15,16].

CONCLUSION

Surprisingly, data coming from RCTs, did not show any reduction of ventricular arrhythmias, among patients treated with SGLT-2Is so far. In conclusion, although four classes of drugs improve prognosis in HFrEF, only beta blockers and ARNI have been clearly associated with a reduction in ventricular arrhythmias. Guidelines recommended ICD therapy to treat life threatening arrhythmias, however a well up-titrated drug therapy may reduce the arrhythmic burden with a beneficial effect on both life expectancy and quality of life (less ICD-shock).

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