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SYSTEMATIC REVIEW ARTICLE

Ventricular Arrhythmias in Seniors with Heart Failure: Present Dilemmas and Therapeutic Considerations: A Systematic Review

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Abstract: ***Background*:** Heart Failure (HF) is a global public health problem, which affects over 23 million people worldwide. The prevalence of HF is higher among seniors in the USA and other developed countries. Ventricular Arrhythmias (VAs) account for 50% of deaths among patients with HF. We aim to elucidate the factors associated with VAs among seniors with HF, as well as therapies that may improve the outcomes.

***Methods*:** PubMed, Web of Science, Scopus, Cochrane Library databases, Science Direct, and Google Scholar were searched using specific keywords. The reference lists of relevant articles were searched for additional studies related to HF and VAs among seniors as well as associated outcomes.

***Results*:** The prevalence of VAs increases with worsening HF. A 24-hour Holter electrocardiogram may be useful in risk stratifying patients for device therapy if they do not meet the criterion of low ventricular ejection fraction. Implantable Cardiac Defibrillators (ICDs) are superior to anti-arrhythmic drugs in reducing mortality in patients with HF. Guideline-Directed Medical Therapy (GDMT) together with device therapy may be required to reduce symptoms. In general, the proportion of seniors on GDMT is low. A combination of ICDs and cardiac resynchronization therapy may improve outcomes in selected patients.

***Conclusion*:** Seniors with HF and VAs have high mortality even with the use of device therapy and GDMT. The holistic effect of device therapy on outcomes among seniors with HF is equivocal. More studies focused on seniors with advanced HF as well as therapeutic options are, therefore, required.

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1. INTRODUCTION

Heart Failure (HF) is a global public health problem, which affects about 23 million individuals worldwide and over 5.8 million people in the United States of America USA [1]. The incidence and prevalence of HF are higher among seniors in the USA and other developed countries [2, 3]. The incidence of HF is about 0.3 per 1000 in individuals less than 55 years, up to 18 per 1000 for those ≥ 85 years, and was estimated as high as 47 per 1000 in people in the ninth decade [4, 5]. HF is also the commonest cause of hospital re-admission among seniors [6, 7].

Sadly, despite the sophistication in medical and device therapy, HF is still characterized by a dismal prognosis as it is associated with a survival rate of about 50% at 5 years and 10% at 10 years [1]. Mortality due to HF may occur secondary to the progression of the disease (pump failure) or Sudden Cardiac Death (SCD) [8, 9]. Ventricular Arrhythmias (VAs) occur commonly in patients with HF [10-12]. Patients with HF, who have ventricular arrhythmias, especially Ventricular Tachycardia (VT) and Ventricular Fibrillation (VF), are at high risk of SCD [10-12].

VAs range from the relatively benign infrequent Premature Ventricular Contractions (PVCs) to the potentially fatal VF and VT [13]. VAs may act independently as a cause of SCD in patients with HF or may do so in concert with other factors [13]. There may be some other factors that modulate the presence and severity of VAs among patients with HF.

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Elderly patients may also have unique attributes that make them more susceptible to having both HF and VAs when compared to younger patients with HF [13, 14]. Guideline-directed Medical Therapy (GDMT) in HF management, as well as device therapy, have been shown to prolong survival of patients with HF [14]. These advanced therapies may have some limitations in their application among seniors. Some seniors may have intolerable side effects to one or more of the GDMT or outright contra-indications due to pre-existing co-morbidities or existing complications of HF. Device therapies for seniors with HF may be nuanced due to the peculiar physiology of seniors, and further exploration may be necessary before the generalization of their applicability in seniors.

Therefore, in the light of the above, a good understanding of all the factors associated with VAs among seniors with HF would be important in directing focussed research on therapies that would further improve quality of life and longevity among seniors.

We, therefore, aim to elucidate on the pathophysiology, clinical significance, existing dilemmas and therapeutic strategies for VAs among seniors with HF.

2. SEARCH METHODS

The search strategy for this review article was carried out using PubMed, Web of Science, Scopus, Cochrane Library databases, Science Direct, and Google Scholar. The reference lists of relevant articles were searched for additional studies related to HF among seniors as well as associated VAs and outcomes. Eight hundred and forty-eight (848) articles were obtained from the initial search. The search was further streamlined using filters, as outlined in Fig. (**1**) below. Some of the filters applied were randomized clinical trials, meta-analysis as well as study population involving people 65 years and above. Other filters were articles with clinical outcomes, such as mortality, hospitalization, and quality of life. Only full-text articles were considered. The authors, TOM and AOB, made the final selection of studies after the completion of an extensive literature search.

One hundred and forty-eight (148) articles were reviewed in detail, and only the most relevant articles were selected/referenced. Several search terms were used, such as "ventricular arrhythmias and heart failure and elderly," "elderly patients with heart failure and device therapy," "pathophysiology of ventricular arrhythmias among patients with heart failure," "prognosis of heart failure with ventricular arrhythmias," "therapeutic considerations among patients heart failure and ventricular arrhythmias."

3. PATHOPHYSIOLOGY OF VENTRICULAR ARRHYTHMIAS IN HEART FAILURE

In general, arrhythmias occur from one of the following mechanisms: electrical reentry, enhanced automaticity, and triggered activity [15]. Triggered activity may occur secondary to either Early After Depolarizations (EADs) occurring in the plateau phase of the Action Potential (AP) or Delayed After Depolarizations (DADs) occurring at the repolarized membrane potentials (E_m) [15].

At normal action potential duration and heart rates, DADs may predominate over EADs. DADs are enhanced by the stimulation of β-adrenergic receptors, which are usually heightened in patients with HF [15]. DADs are generally thought to be initiated by a spontaneous release of calcium (Ca^{2+}) from the sarcoplasmic reticulum leading to a Ca^{2+}-activated transient, depolarizing inward current (I_{ti}), which has been proposed to be carried by one of three different Ca^{2+}-activated currents [15]. The inward rectifying K current I_{K1} is crucial in stabilizing the resting membrane potential [15, 16]. I_{K1} has been noted to be decreased among humans with HF and may, therefore, be involved in the destabilization resting membrane potential of cardiac myocytes [15,16].

Electrical reentry is an important contributor to the occurrence of VT [15]. Reentry occurs when three criteria are met [15]. Firstly, there must be an obstacle, which may be, structural or functional, around which an action potential (AP) can circulate. Secondly, there should be differential properties in conduction such that the myocardial tissue ahead of the excitation wavefront remains excitable. Thirdly, a unidirectional conduction block must be present to perpetuate the wavefront. Therefore, upon trigger with, for instance, a PVC, the three conditions forming the arrhythmogenic substrate described above can sustain re-entry [15].

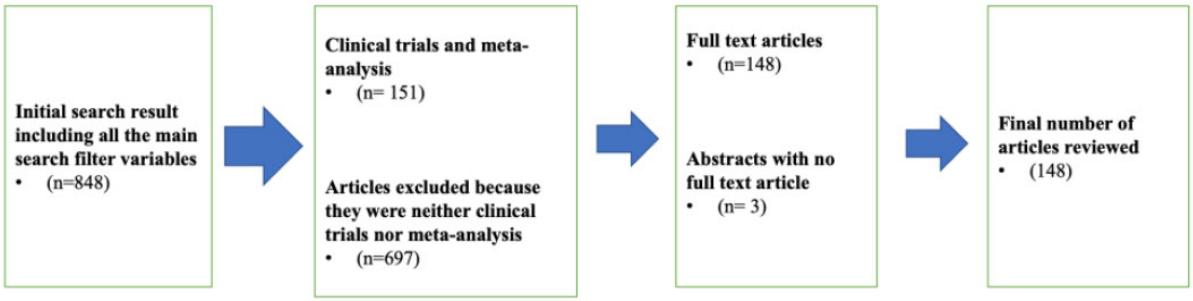

Fig. (1). Flow chart of review article selection process (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

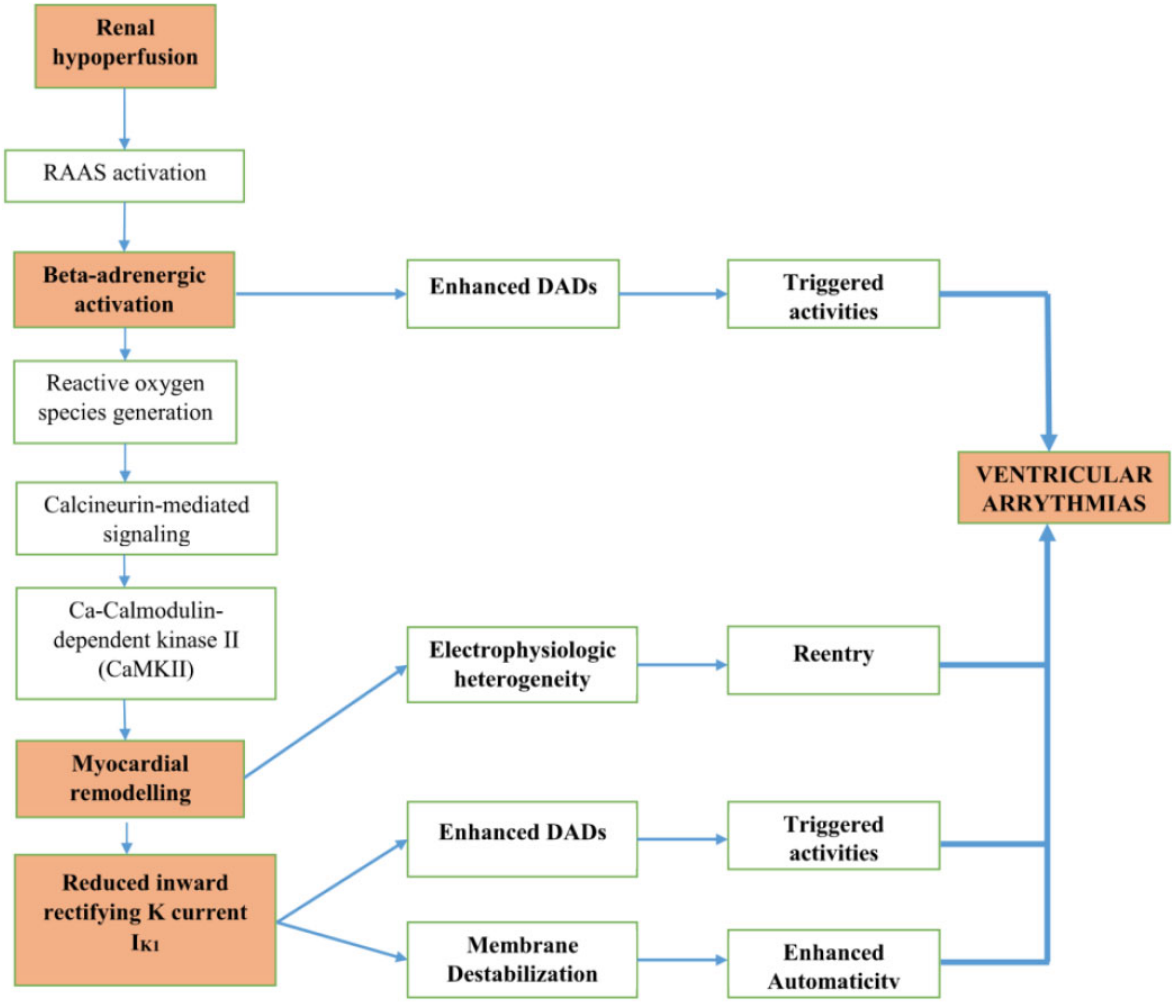

Fig. (2). Mechanism of Ventricular Arrhythmias in Patients with Heart Failure;
Abbreviations: RAAS: Renin Angiotensin Aldosterone System, DADs: Delayed After Depolarizations (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The main pathways implicated in the maladaptive remodeling process among patients with HF include the beta-adrenergic pathway, renin angiotensin aldosterone system (RAAS), Ca-Calmodulin-dependent kinase II (CaMKII), and calcineurin-mediated signaling [13-17]. These have, in turn, been shown to result in the electrophysiological substrate that triggers and sustains potentially lethal VAs [13, 17]. The remodeled and fibrosed myocardium has also been noted by earlier researchers to have distinctively longer action potential durations, marked alteration in myocardial calcium homeostasis, and increased heterogeneity in intercellular repolarization properties [13, 18-20]. This distorted electrical state makes it relatively easy for an ectopic beat to initiate an arrhythmia based on the mechanisms described above.

Each of the pathways described above could be targets of therapeutic interventions described below that may disrupt this arrhythmogenic cycle and consequently reduce the incidence and impact of ventricular arrhythmias among patients with HF.

A summary of this process is shown in Fig. (**2**).

4. VENTRICULAR ARRHYTHMIAS AND HEART FAILURE

Arrhythmias are a common accompaniment of HF irrespective of the method utilized in detecting them [12, 21]. VAs, as stated above, are a major cause of sudden death or resuscitated sudden death in HF [21, 22]. About 50% of all deaths in advanced HF are sudden and may be attributable to VT or VF [11, 22]. VT and VF are most commonly seen in patients with advanced HF, and as such, higher New York Heart Association (NYHA) functional class, low left ventricular ejection fraction (LVEF), and renal dysfunction have been associated with increased risk of SCD among patients

with HF [21-24]. This was corroborated by the findings of Saxon *et al.* [25] that an LVEF of less than 20% or NYHA functional class IV was strongly associated with an increased risk of SCD among patients with HF. The occurrence of malignant VAs is also proportional to the size of the left ventricle (LV) in diastole [13]. The Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial, which involved patients with ambulatory advanced NYHA functional class III/IV HF, revealed that the presence of an appropriate shock for sustained VAs was associated, not only with a significant increase in SCD (odds ratio [OR]: 2.97; $p = 0.03$) but also with a significant increase in pump failure death or hospitalization (OR: 2.45; $p < 0.0001$) [26].

Sustained VT is not the only type of VT associated with a poor outcome. Non-sustained VT also carries a high mortality risk among patients with HF [27]. The investigators in the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial concluded that the frequency of non-sustained VT was the most powerful predictor of mortality of all the measures of ventricular ectopy. However, multiple logistic regression demonstrated that non-sustained VT on ambulatory EKG did not offer much information on the predictability of mortality beyond what was obtained from other clinical parameters [28]. In one study, the mortality risk of appropriate shock was found to be associated with the underlying rhythm (monomorphic VT OR: 1.65; $p < 0.0001$; VF/polymorphic VT OR: 2.10; $p < 0.0001$) [29]. Also, in the Captopril-Digoxin Multicenter Study, PVCs, couplets, and non-sustained VT were univariate predictors of total mortality [30].

Interestingly, less severe forms of Vas, such as PVCs, which are benign in apparently normal patients, may have adverse consequences among patients with HF [31, 32]. The reason for this is not clear but may be related to the frequency and propensity of PVCs to degenerate into more grievous types' of VAs. The grading of PVCs by Lown and Wolf suggests that the higher the grade of the PVC, the higher the risk of a dangerous VA [33].

Therefore, by implication, almost all forms of VAs, irrespective of severity, are associated with a poor outcome among patients with HF. The question is, what form of VAs require therapy and what are the associated downsides of therapeutic interventions for VAs among seniors with HF?

5. DETECTING ARRHYTHMIAS

The best form of therapy is prevention, early detection, or at best identifying early harbingers of dangerous VAs. The routine 12-lead electrocardiogram (EKG) does not always capture dangerous arrhythmias except in patients with HF, who already have a severe burden of VAs [12, 14]. 24-Holter EKG or at the very least telemetry during hospitalization is better suited to pick up arrhythmias, with the former being capable of providing more useful information about heart rate variability and other indices of autonomic nervous system dysfunction [12, 14, 18].

A selected group of patients may need more invasive testing, such as electrophysiological study (EPS), to induce sustained VAs. This is not common at the present time because patients who meet criteria for ICDs, such as those with HF and LVEF of 35% in general, get an ICD [34]. Patients with HF and preserved EF (HFpEF) apart from those with ischemic heart disease have limited need for EPS because SCD is lower in this population compared to those with HF and reduced EF (HFrEF) [34]. However, patients with HFpEF are usually older and have multiple comorbidities than patients with HFrEF [34]. Also, as opposed to HFrEF, nearly a quarter of all deaths among patients with HFpEF are attributable to SCD [34].

Further risk stratification for patients with HFpEF was undertaken in the PRESERVE-EF (Risk Stratification in Patients with Preserved Ejection Fraction) trial [35]. The PRESERVE-HF study elaborated on risk stratification strategies that identify patients with HFpEF who would have needed ICD but would have missed out because of not meeting criteria due to LVEF. In this study, risk factors were stated to be present if at least one of the following 24-hour Holter derived indices were met: (greater than 30 PVCs/hour, non-sustained VT, late potentials, prolonged QTc, increased T-wave alternans, reduced heart rate variability, and abnormal deceleration capacity with abnormal turbulence) [34, 35]. Patients who met the above criteria underwent programmed ventricular stimulation, and if they had inducible VTs, they then had ICD implantation [35].

6. THERAPEUTIC CONSIDERATIONS

6.1. Beta Blockers

GDMT is advocated for all patients with HF irrespective of the presence or the absence of arrhythmias [25]. Some work has been done with regards to therapies that may reduce the occurrence of VAs and, in turn, SCD among patients with HF [36]. Metoprolol, bisoprolol and carvedilol have been shown to decrease the occurrence of VT or VF as well as the risk of SCD among HF patients [37-39]. These beta blockers are the most useful in patients with reduced LVEF, and their survival benefits stem from reduced adrenergic drive, improved balance of the autonomic nervous system as well as the reduction in the ventricular wall stress [40].

The use of beta blockers among seniors appears to be a problem because of the side effects such as hypotension, bradycardia, weakness, dizziness, among others [41]. Nebivolol was hypothesized to be more favorable among seniors because of its additional vasodilatory property [40]. The SENIORS Study (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure) was carried out to assess the effect of nebivolol on mortality and morbidity among seniors with HF, irrespective of the LVEF [40]. In this study, nebivolol did not appear to significantly reduce mortality compared to placebo for the secondary endpoint of all-cause mortality (15.8% *vs.* 18.1%; (Hazard Ratio (HR) 0.88, 95% CI

0.71-1.08; *P*=0.21). However, it appeared to be useful when the endpoint was death or cardiovascular hospitalization (31.1% *vs.* 35.3% in the placebo group; HR 0.86, 95% CI 0.74- 0.99; P = 0.039) [40].

Wikstrand *et al.* [41] conducted a large-scale placebo-controlled study to compare the four main beta blockers with the same baseline for comparison, which was reduced LVEF. Therefore, a subset of patients in the SENIORS trial with LVEF < 35% were compared with similar cohorts with decreased LVEF in the MERIT-HF, CIBIS-II and COPERNICUS trials. They concluded that bisoprolol, carvedilol and metoprolol CR/XL were similar in efficacy and tolerability among patients with HF irrespective of NYHA class or LVEF [41]. Nebivolol was noted to be less effective and not better tolerated [41].

6.2. Angiotensin Receptor Blockers/Angiotensin Converting Enzyme Inhibitors

Inhibitors of the RAAS have some antiarrhythmic properties in addition to mortality benefits among patients with HFrEF [42-44]. They mediate this by counteracting the proarrhythmic effects of angiotensin II, which can only be achieved when there is a complete blockade of the AT_1 receptor [45]. This complete blockade occurs only at higher doses (320 mg daily dose of valsartan in the Val-HeFT study [44] and 32 mg daily in the CHARM studies [19-21, 31]. Adverse effects, such as hyperkalemia, renal dysfunction, angioedema, intractable cough, hypotension, have limited the use of these agents in seniors, and even when they are used, these adverse effects limit achieving efficacious target doses [19-21, 31].

In fact, the reduced clearance of some angiotensin converting enzyme (ACE) inhibitors (such as enalapril or perindopril) among elderly patients with HF potentiate the antihypertensive effects and increase the risk of dizziness and falls [46, 47].

In the ELITE trial, losartan was associated with a 46% lower risk of mortality than that found with captopril among seniors with chronic HF (p = 0.035) [48]. The mortality reduction was thought to be largely due to the reduction of deaths due to SCD. SCD was apparently lower in the losartan group because, like an ARB; it blocks the AT_1 receptor without the concomitant increase in bradykinins that is associated with ACE inhibitors as bradykinin is proarrhythmic [48].

A large proportion of seniors were studied through the PARADIGM-HF trial, which involves a new class of drug therapy that includes the combination of sacubitril (a neprilysin inhibitor) and the angiotensin receptor blocker (ARB), valsartan [49, 50]. This study revealed that this drug combination reduces cardiovascular mortality and hospitalization for HF as well as all-cause mortality compared with enalapril alone [49, 50]. Interestingly, efficacy and side effect profile (hypotension, renal dysfunction, and hyperkalemia) were similar across all age groups in the sacubitril-valsartan arm compared to the enalapril group [51].

6.3. Aldosterone Antagonist

With regards to the use of aldosterone antagonist among seniors with HF, the EPHESUS [52], the RALES [53], and the more recent EMPHASIS-HF [54] trials showed a decreased risk of death irrespective of age. However, adverse events, such as hyperkalemia, renal dysfunction, and hypotension, may limit use among seniors and must be looked out for very closely [49, 52-54].

6.4. Adjunctive Therapy with Potassium Reducing Medications

Hyperkalemia is a common side effect of aldosterone antagonists, ACE inhibitors and ARBs [44-54]. Hyperkalemia may limit optimization or even result in cessation of these lifesaving medications, especially in seniors who may be more predisposed to having hyperkalemia as a side effect [44-54]. Newer medications (sodium zirconium cyclosilicate and patiromer) in addition to GDMT have ameliorated this side effect and may possibly enable a larger proportion of patients who hitherto would have had these useful medications discontinued because of hyperkalemia [55, 56]. The proportion by which use of these potassium-reducing medications affect outcomes (increasing the ability to prescribe and increase the doses of an aldosterone antagonist, ACE inhibitors and ARBs) is yet to be fully corroborated [55, 56]. More studies would be needed to see if the addition of these medications has a meaningful clinical effect.

6.5. Antiarrhythmic Medications

Antiarrhythmic agents among patients with HF in general have a controversial role ranging from their proarrhythmic effects to being contra-indicated when there is LV dysfunction [57]. As a result, only a few of these antiarrhythmic medications are useful in patients with HF and, even so, must be used with caution [57]. This line of thought stems from the findings of the Cardiac Arrhythmia Suppression Trial (CAST), where the mortality or nonfatal cardiac arrest rate (7.7%) was significantly higher among patients treated with flecainide or encainide compared with patients on placebo (3.0%), post-myocardial infarction [57, 58]. However, amiodarone appears to be one of the few medications that may be useful on its own or in combination with device therapy.

Piccini *et al.* [59] carried out a meta-analysis of 15 randomized controlled trials reviewing the use of amiodarone versus placebo/control SCD prevention among patients with HF. This meta-analysis showed that there was a non-significant reduction in all-cause mortality (p = 0.093], however, amiodarone decreased the incidence of SCD [7.1 *vs.* 9.7%; OR 0.71 (0.61-0.84), $P < 0.001$] and cardiovascular death (CVD) [14.0 *vs.* 16.3%; OR 0.82 (0.71-0.94), $P = 0.004$] [59]. This apparent gain was offset by the toxic effects of amiodarone as the researchers found that it was associated with a two- and five-fold increased risk of pulmonary and thyroid toxicity [59].

Other anti-arrhythmic medications, such as dofetilide, digoxin, dronedarone and azimilide (new class III antiarrhyth-

mic medication available only in Europe), have been studied and found not to be useful in the primary prevention of VT or VF among patients with HF patients [36, 57, 60].

Dronedarone was thought to be a medication that would be a game-changer with respect to arrhythmia care because of the lack of adverse effects associated with amiodarone due to the lack of iodine in its composition [60]. Dronedarone still has the electrophysiological properties of amiodarone but was noted to be associated with increased early mortality related to the worsening of HF when administered to patients with severe HF and LV systolic dysfunction [61].

Again, care must be taken when the use of anti-arrhythmic drugs is being contemplated for use among seniors with HF, especially as dose adjustments due to decreased hepatic and renal clearance as well as drug interactions have to be considered [57].

6.6. Catheter Ablation

Do patients with HF and supposedly benign Vas, such as PVCs and non-sustained VT, require therapy? Therapy may be useful because PVCs confer poor prognosis as stated above among patients with HF, but this must be balanced against the negative inotropic and proarrhythmic effects of antiarrhythmic drugs [62]. These arrhythmias are common following the intervention for myocardial infarction and are rarely hemodynamically significant [57]. In the rare event that hemodynamic compromise accompanies these arrhythmias (non-sustained VT); some researchers opine that a bolus of intravenous amiodarone may be useful [57]. On the other hand, if PVCs and non-sustained VT are prolonged and frequent, repeat angiogram/intervention may be required as they may suggest ongoing cardiac ischemia [57]. In some selected patients, cardiac ischemia may result in PVCs that degenerate into VT or VF storms [57]. Catheter ablation may be useful in this group of patients as well as a selected group of patients with PVC-induced cardiomyopathy [57, 62].

6.7. Implantable Cardioverter Defibrillator (ICD)

Two large trials, the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), demonstrated the role of ICD for the primary prevention of VT or VF for patients with HF who met certain criteria [63, 64]. These two trials indicate that ICD use is associated with a 23% and 31% reduction in all-cause mortality, respectively in patients with LV dysfunction. An ICD is usually recommended for symptomatic HF (NYHA classes II-III) associated with systolic dysfunction (LVEF $\leq$ 0.35) despite OPT for 3 or more months and in patients with an expected survival of more than one year with good functional status [49, 57]. The utility of ICD for primary prevention of SCD among asymptomatic patients (NYHA class I) with LVEF $\leq$35-40% or in patients with HF and preserved LVEF (40-45%) has not been established, therefore, it has not been recommended in these group of patients [57].

The literature is replete with regards to the usefulness of ICDs in secondary prevention for SCD among patients with HF [11, 62-64]. ICDs are superior to amiodarone in reducing mortality in patients with HF irrespective of LVEF with previous cardiac arrest or documented VF or sustained VT, or with syncope and clinical or inducible sustained VT (secondary prevention) as long as they have a life expectancy greater than one year [11]. It is important to note that ICDs do not prevent the occurrence of arrhythmias and the optimal use of medical antiarrhythmic agents' treatment to reduce symptomatic episodes is required [11].

ICDs may also be useful in patients with advanced HF who require a left ventricular assistance device (LVAD) as a bridge to heart transplant because of a strong association with VT or VF in the postoperative period [11]. ICDs have reduced the mortality rate following VT or VF in HF patients, but the mortality rate is still high among HF patients with these arrhythmias [11].

Having established the fact that ICDs are beneficial, the next question is if they are suitable options for seniors with HF. Chen *et al.* [65] assessed the efficacy of primary ICDs among seniors who received the device during hospitalization for acute decompensated HF, or other acute co-morbidities, with an emphasis on adjustment for early mortality and other factors that may indicate healthy candidate bias rather than the true effect of the ICD.

After adjustment for bias with latency analyses and the high dimension propensity score, seniors (age 66 years and above) who received an ICD during hospitalization for acute decompensated HF or other acute co-morbidities did not have a significantly different risk of death (HR 0.91, 0.82 to 1.00) or SCD (0.95, 0.78 to 1.17) than seniors who did not get an ICD during their acute hospitalization [65]. Therefore, from their findings, it appears that ICDs did not significantly alter the outcome among seniors with HF who were acutely admitted after taking into consideration adjustment for healthy candidate bias [65]. This finding is diametrically opposite to that reported above, which showed that primary ICDs decreased mortality by 23 to 31% among relatively healthier ambulatory patients with HF who met the criteria for ICD placement [63, 64]. Other important points to note are that the mean age of seniors in the study by Chen *et al.* [65] was markedly older than that in the MADIT-II and SCD-HeFT trials described above. Further studies would be needed to assess the risk-benefit ratio with regards to primary ICD implantation for seniors admitted acutely as opposed to waiting for these seniors to stabilize before electing primary ICD implantation.

Only a small proportion of very elderly patients with advanced HF receive primary ICD [66]. This cohort has been noted by Fudim *et al.* [66] to have a periprocedural complication rate of about 3.7%, mainly due to in-hospital death or cardiac arrest and one-year all-cause mortality that is more than 3-fold higher than that in seniors without advanced HF. These results are similar to the findings of Gandjbakhch *et al.* [67]. Several metanalyses have resulted in conflicting results with the one by Santangeli *et al.*, indicating ICDs were not associated with a significant reduction in mortality among patients aged $\geq$ 60 years (HR 0.81; 95% CI: 0.62 to

1.05) while a 35% reduction in mortality was seen in patients aged < 60 years (HR 0.65; 95% CI: 0.50-0.83) [49, 68]. On the other hand, the metanalysis by Kong and colleagues after pooling the results of four randomized clinical trials indicate that ICDs for primary prevention may be useful in patients older than 65 years as well as those older than 75 years but to a lesser degree [69]. It appears a decision on ICD implantation, for now, may have to be on a case-by-case basis with consideration of many factors since there is still a lot of ambivalence about the use of ICDs among seniors. Therefore, seniors with advanced HF may benefit from other strategies rather than primary ICD implantation..

The Prolongation of Reverse remOdelling period to avoid untimely ICD impLantation in newly diagnosed heart failure using the wearable cardioverter/defibrillator (PROLONG) study was meant to have a safe observation during the period of optimizing medical therapy and ensuring reverse ventricular remodeling and improvement of LVEF [70]. Since the improvement of LVEF is associated with a lower risk of SCD, the use of a wearable cardioverter/defibrillator for extended periods beyond the 3-month period after the first diagnosis may delay the need for primary ICD implantation [70]. The authors of the PROLONG study allowed an extension of the period of a wearable cardioverter/defibrillator, which was typically 3 months to allow a safe delayed reverse remodeling if one of the following indications were met: LVEF at a 3-month follow-up visit 30% to 35%, increase in LVEF of ≥ 5% compared to the previous visit and nonoptimized medications for HF [70]. Fifty-eight of the 166 patients in this study showed a persistent indication for primary preventive ICD [70]. Twelve appropriate wearable cardioverter/defibrillator shocks for VT/VF occurred in 11 patients.

The applicability of these findings may be limited among seniors as the mean age in this study was about 54 years. Extension of this study to the elderly patients with HF may result in improved appropriateness of ICD implantation by identifying those who may no longer meet the criteria for device therapy because of late improvement in LVEF due to reverse remodeling.

Other authors report that ICD among seniors 75 years and above may not be better than medical therapy alone [71-73]. Cortés *et al.* [71] conducted a single-center retrospective study of individuals who were 75 years with severe HF who met the criteria for ICD placement. They reported that the use of beta blockers was significantly higher in the ICD group, who were also significantly younger than the medical therapy group ($p < 0.001$ for both) [71]. After propensity score matching, the ICD and medical therapy only group consisted of 63 patients each, and the use beta blockers had mortality benefit but not ICD use [71]. Another study indicated that sacubitril/valsartan therapy among patients with HFrEF would be cost-effective by increasing survival at lower costs compared with an ICD [72].

6.8. Cardiac Resynchronization Therapy (CRT)

Cardiac resynchronization therapy **(**CRT) should be considered to reduce all-cause mortality and morbidity for symptomatic patients with HF in sinus rhythm with a QRS duration ≥ 150 msec and left bundle branch block (LBBB) QRS morphology and with LVEF ≤ 35% despite optimal medical therapy (class 1 indication) [74].

CRT mediates these benefits by electromechanical coupling, reverse structural remolding, creation of a more uniform distribution of myocardial blood, reducing LV volumes, increasing LVEF, and improving NYHA class, 6-minute walking test, quality of life, and peak oxygen consumption [75-78]. About 20% of patients with HF have a prolonged QRS of > 120 ms, while about 35% of the very ill patients with HF have a QRS > 120 ms [79, 80].

CRT is usually established by adding an LV pacing lead to a standard pacemaker or defibrillator system which has a right ventricular (RV) lead and possibly a right atrial lead [81]. Therefore, CRT may be implanted de novo as an upgrade to a pacemaker or together with an ICD (defibrillation function) [81].

When the two leads are active, the left and right ventricles pace is synchronised [81].

The mortality and morbidity benefit of CRT have been demonstrated in several large trials, however, there are not enough studies on the role of CRT in seniors, largely in part to under represent group in these trials [79]. The Multisite Stimulation in Cardiomyopathy (MUSTIC) trial (mean age 63 years) was one of the first trials that demonstrated CRT had beneficial effects of decreasing morbidity but not mortality among patients with HF [82]. The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) (mean age of 63.9 + 10.7 years) trial, on the other hand, was able to show CRT together with optimal medical therapy, which is effective in decreasing the secondary combined endpoint of HF hospitalization or death [83]. The Cardiac Resynchronization-HF (CARE-HF) (median of age is 66 years in the medical therapy alone group, and 67 years in the medical therapy plus CRT group) trial was able to demonstrate CRT independent of defibrillation function as having mortality benefit among patients with HF [84].

6.9. Cardiac Resynchronization Therapy in Combination with Implantable Cardioverter Defibrillator

In general, patients who meet the criteria for an ICD and who also have a broad QRS may need an upgrade to a combination of CRT with a defibrillator (CRT-D) [79]. In the light of this, the COMPANION trial assessed the mortality and morbidity benefits of three treatment groups, namely, OPT alone, OPT plus CRT with pacing only (CRT-P), or OPT plus CRT-D [85]. At one year of follow-up, only the CRT-D group had a significant decrease in the overall mortality compared to the group receiving OPT alone [85]. The CRT-P did not have the same effect, raising the suspicion that the mortality benefit may be solely due to the defibrillation function and not due to the effects of biventricular pacing [26, 85].

The RAFT and MADIT-CRT trials were able to show the role of CRT having survival benefit independent of defib-

rillation function when the implanted device had both CRT and ICD functionality among patients with HF [86, 87]. The additive benefits of CRT and ICD function was assessed in the MIRACLE ICD trial, which concluded that device therapy with dual ICD and CRT functionality resulted in an added advantage of improved functional status, exercise capacity, and quality of life among patients with moderate to severe HF, a wide QRS interval, and life-threatening arrhythmias [88].

Again, the use of these advanced therapies appears to be limited among seniors with HF. A meta-analysis involving six observational studies revealed that the aggregate implantation rate of ICDs was 37.9% compared to 64.3% for elderly versus younger patients, respectively (OR: 0.26; 95% CI: 0.14-0.46; $p < 0.0001$), receiving CRT [89]. Also, despite the fact that ischemic cardiomyopathy was commoner among the seniors compared to the younger individuals, ICD use in seniors was still significantly lower [89]. This is paradoxical because patients with ischemic cardiomyopathy are more likely to derive benefit from ICD implantation than those with nonischemic cardiomyopathy [90]. They concluded by opining that future studies that evaluate the effectiveness of ICDs in seniors with indications for CRT are required to guide the management of this rapidly increasing cohort [89].

6.10. Cardiac Resynchronization Therapy Non Responders

Sadly, CRT is not effective in about 30% of patients with HF, and these patients are referred to as CRT non responders [75-78]. The reasons are multifactorial, and research on how to reduce the non-responder rate of CRT among patients with HF is ongoing [75-78]. The prevention and prediction of non-response to CRT are paramount to improve the overall performance of CRT and lower its risk-benefit ratio [75-78]. This is of added importance among seniors because CRT is both invasive and expensive [91]. The presence of a dilated LV end diastolic diameter in diastole, or fragmented QRS were noted as strong predictors of non-response to CRT by Hu *et al.* [92]. They also noted that patients with these two predictors had a 46.2% probability of CRT non-response [92].

CRT nonresponders, in turn, have a higher mortality rate than individuals who have LV reverse remodeling (adequate response to CRT) at 6 months after CRT implantation [93].

It is, however, great to know that all is not bleak and gloom among CRT non responders, as sacubitril/valsartan therapy in this group of patients appears to significantly reduce the occurrence of cardiac death, heart transplant as well as LVAD implantation [94]. OPT should, therefore, be emphasized in all patients with HFrEF as they may have far-reaching benefits beyond the range known for OPT among patients with HF [94].

LIMITATIONS

The emerging area of interest with ongoing studies focused on the unique population of seniors with heart failure.

CONCLUSION

Ventricular arrhythmias are a major cause of morbidity and mortality among patients with HF. Optimized medical therapy for HF should be instituted before the use of anti-arrhythmic agents or device therapy. A better understanding of the pathophysiology of HF and these arrhythmias may provide more insight into the generation of better therapeutic agents than the present ones. Studies are ongoing on newer therapies that may improve outcomes of HF patients as the overall prognosis is still poor among HF patients with arrhythmias. Device therapy is complex, and more work is needed with regard to maximizing the benefits among seniors with advanced HF.

LIST OF ABBREVIATIONS

ACE	=	Angiotensin-Converting Enzyme
AP	=	Action Potential
ARB	=	Angiotensin Receptor Blocker
CaMKII	=	Ca-Calmodulin-dependent Kinase II
CARE-HF	=	Cardiac Resynchronization-HF
CAST	=	Cardiac Arrhythmia Suppression Trial
CHARM	=	Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity
CIBIS-II	=	Cardiac Insufficiency Bisoprolol Study II
COMPANION	=	Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure
COPERNICUS	=	Carvedilol Prospective Randomized Cumulative Survival
CRT	=	Cardiac Resynchronization Therapy
CRT-D	=	Cardiac Resynchronization Therapy with a Defibrillator
CRT-P	=	Cardiac Resynchronization Therapy with Pacing
DAD	=	Delayed Afterdepolarizations
EAD	=	Early After Depolarizations
EKG	=	Electrocardiogram
ELITE	=	Evaluation of Losartan in the Elderly
EMPHASIS-HF	=	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
EPHESUS	=	Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study

EPS = Electrophysiological Study
GDMT = Guideline Directed Medical Therapy
HF = Heart Failure
HFpEF = Heart Failure with preserved Ejection Fraction
HFrEF = Heart Failure with reduced Ejection Fraction
ICDs = Implantable Cardioverter Defibrillators
LV = Left Ventricle
LVAD = Left Ventricular Assist Device
LVEF = Left Ventricular Ejection Fraction
MADIT-CRT = Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy
MADIT-II = Multicenter Automatic Defibrillator Implantation Trial II
MERIT-HF = Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure
MIRACLE = Multicenter InSync Randomized Clinical Evaluation
MIRACLE ICD = Multicenter InSync Randomized Clinical Evaluation Implantable Cardioverter Defibrillator
MUSTIC = Multisite Stimulation in Cardiomyopathy
NYHA = New York Heart Association
OPT = Optimal Pharmacological Therapy
OR = Odds Ratio
PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
PRESERVE-EF = Risk Stratification in Patients with Preserved Ejection Fraction
PROLONG = Prolongation of Reverse remOdelling period to avoid untimely ICD impLantation in newly diagnosed heart failure using
PROMISE = Prospective Randomized Milrinone Survival Evaluation
PVCs = Premature Ventricular Contractions
RAAS = Renin Angiotensin Aldosterone System
RAFT = Resynchronization-Defibrillation for Ambulatory HF Trial
RALES = Randomized Aldactone Evaluation Study
SENIORS = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure
SCD = Sudden Cardiac Death
SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial
USA = United States of America
Val-HeFT = Valsartan Heart Failure Trial
VAs = Ventricular Arrhythmias
VF = Ventricular Fibrillation
VT = Ventricular Tachycardia

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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