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Review Article

Sudden cardiac death prevention in the era of novel heart failure medications

I. Koev [a,d,1], M. Yarkoni [a,d,1], D. Luria [a,d], O. Amir [a,b,d], Y. Biton [a,c,d,*]

[a] Department of Cardiology, Hadassah Medical Center, Jerusalem, Israel
[b] The Azrieli Faculty of Medicine in the Galilee, Bar-Ilan University, Safed, Israel
[c] Heart Research Follow-Up Program, University of Rochester Medical Center, Rochester, NY, USA
[d] Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel

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ABSTRACT

Sudden cardiac death (SCD) occurs unexpectedly and is usually a result of ventricular arrhythmia in patients with structural heart disease. The implantable cardioverter-defibrillator (ICD), with or without biventricular pacing, has been proven to be protective for heart failure patients with reduced ejection fraction of <35 % (HFrEF). This device therapy prevents SCD, with additional optimal medications, namely angiotensin-converting enzyme-inhibitors, angiotensin-II receptor-blockers, beta-blockers and mineralocorticoid receptor-antagonists. HFrEF patients present the majority of SCD incidents, as they are characterized by cardiac fibrosis, the main arrhythmogenic element. The introduction of angiotensin-receptor-neprilysin inhibitors, sodium-glucose co-transporter-2 inhibitors and guanylate-cyclase stimulators was associated with reduction of SCD. Additionally, clinical trials have evaluated the improved outcome of these new medications on left ventricular ejection fraction, arrhythmias and HFrEF. These beneficial effects could possibly lead to important changes in decision-making on ICD implantation for primary prevention in patients with HFrEF and reduce the need for device therapy. In this review, we highlight the pathophysiological mechanisms of the new drug agents, and evaluate the possible effect they could have on the role of device therapy as a primary prevention of SCD.

1. Introduction

Sudden cardiac death (SCD) is defined as sudden and unexpected death occurring within an hour of onset of symptoms, or occurring in patients found dead within 24-hours of being asymptomatic, presumably due to cardiac arrhythmia or hemodynamic catastrophe [1]. SCD is usually a result of ventricular tachycardia (VT) which progresses into ventricular fibrillation (VF) in patients with structural heart disease [2]. Mechanisms involved in the diseased heart, such as increased tissue heterogeneity, cellular membrane voltage, and calcium uptake all increase the predisposition to a wave break, resulting in re-entry and VF [3]. Oxidative stress with hydrogen peroxide is another process which promotes VT/VF through early after-depolarization and triggered activity [4]. Yet, cardiac fibrosis is the main arrhythmogenic substrate in heart failure patients with reduced ejection fraction (HFrEF) of <40 %. Cardiac fibrosis can potentially stimulate triggers, create a vulnerable substrate for re-entry, and produce a pro-arrhythmic environment [5]. HFrEF patients present the majority of SCD incidents. The implantable cardioverter-defibrillator (ICD) with or without biventricular-pacing has been proven to be protective for HFrEF patients as part of prevention of SCD [6]. This is in addition to the optimal medical therapy, angiotensin-converting enzyme-inhibitors (ACEis), angiotensin-II receptor-blockers (ARBs), beta-blockers and mineralocorticoid receptor-antagonists (MRAs). Recently, three new drugs were introduced and effectively improved survival, including angiotensin-receptor neprilysin-inhibitors (ARNIs) (also known as sacubitril/valsartan), sodium-glucose co-transporter 2-inhibitors (SGLT2is) [7–9] and vericiguat [10]. In this review, we will evaluate the effects of these new agents on SCD, arrhythmia and possibly on the indications for device therapy for primary prevention.

2. Prevention of SCD with ICD with or without biventricular-pacing

In patients who have experienced ventricular arrhythmia (VA), ICD

* Corresponding author at: Heart Institute, Hadassah Medical Center, Jerusalem 9112001, Israel.
E-mail address: bitony@hadassah.org.il (Y. Biton).
[1] The first two authors contributed equally to the manuscript preparation.

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implantation with or without biventricular pacing is justified as secondary prevention [11–15]. The decision about defibrillator implantation for primary prevention is more complicated. ICD implantation reduces the risk of SCD secondary to an arrhythmic event [16]. MADIT and MADIT-II trials showed that in patients with coronary artery disease and left ventricular ejection fraction (LVEF) <35 % survival is improved, and patients meeting these criteria benefit from this therapy [17,18].

Prior to considering ICD implantation with or without biventricular-pacing as primary prevention, there are two fundamental points to account for. The first is related to implantation in patients with non-ischemic cardiomyopathy (NICMP). In the DEFINITE trial, fewer SCD events were observed in patients with NICMP and implanted ICD, but no significant differences in all-cause mortality were observed [19]. The DANISH trial, confirmed these results, showing that ICDs reduced SCD but not all-cause mortality events [20].

Timing of implantation is another critical point to consider regarding ICD implants as primary prevention. The DINAMIT trial did not show any significant improvement for patients with LVEF ≤35 % who underwent ICD implantation in the first 40-days post-myocardial infraction (MI) [21]. In another study confirming these results, IRIS, no significant difference in overall mortality was seen in patients with heart rate > 90 beats per minute and LVEF ≤40 % following ICD implantation between 5 and 31 days post-MI [22]. In both trials, a statistically significant decrease in mortality was found secondary to SCD, yet a significant increase in mortality by non-SCD. The VEST trial [23] studied the risk of arrhythmogenic mortality in patients with LVEF ≤35 % at 90 days post-MI. This study showed that wearing a cardioverter-defibrillator in addition to optimal medical therapy (OMT) 18-hours per day did not decrease significantly the rate of primary outcome arrhythmic mortality *vs.* control with OMT alone.

Another requirement on the efficiency of ICD implantation is a balanced therapy between anti-tachycardia pacing and shock. In analysis of the Israeli ICD registry, Sabbag et al. present a real-world contemporary era data on the rate of appropriate shock therapies [24]. Their study showed low ICD therapy rates in real-life settings, probably due to improved ICD-programming, better pharmacological treatment and more cardiac resynchronization therapy defibrillator (CRT-D) implantations in the last decade. Their results correlate the MADIT-RIT trial [25], underlying the significance of patient selection for appropriate management and the importance of risk stratification. Goldenberg et al. [26] suggested five criteria (New York Heart Association, NYHA functional class >II, age > 70 years, BUN >26 mg/dl, QRS duration > 0.12 s, and atrial fibrillation), whereby a U-shaped pattern presented the ICD efficacy, with ICD implantation most beneficial for intermediate-risk patients.

Defibrillator implantation also has potential risks including displacement, pneumothorax, hematoma and infection, assessed in 9.1 % of patients and after 16 months [27]. By reducing inappropriate shocks and considering existing risks, there is a demand for redefining the guidelines on primary prevention of SCD in HFrEF patients.

3. Medical therapy for prevention of SCD

In patients with ischemic heart disease, treatment with statins and platelet aggregation inhibitors reduces SCD risk [28,29] as part modifying risk factors. ACEis, ARBs, beta-blockers and MRAs have a synergetic effect on decreased SCD risk in patients with newly diagnosed HFrEF, and improve LVEF through reverse remodeling [30–32]. In addition, ACEis and beta-blockers reduce the possibility of SCD through increased sympatholytic activity [33]. Owing to this evidence, it is recommended that prior to decision-making on ICD implantation with or without biventricular pacing, newly diagnosed HFrEF patients should be on OMT at least 3-months [6,34].

Accordingly, the decision on defibrillator implantation is not always straightforward, and relies on 2 European Society for Cardiology (ESC) guidelines, which underline its importance. In the ESC guidelines on VAs and SCD prevention [12], defibrillator therapy for primary prevention of SCD is recommended in patients with symptomatic heart failure (HF) (NYHA class II-III) and LVEF 35 % after three months of OMT. In the ESC guidelines on HF, OMT is specified and lists ACEis/ARNIs, beta-blockers, MRAs and SGLT2is, as this currently is the cornerstone therapy to reduce mortality in these patients [6].

4. Novel treatments for heart failure

ARNIs are relatively new medications for HFrEF. According to current ESC Guidelines for HF, it is recommended for ambulatory HFrEF patients who remain symptomatic despite the long-established OMT with ACEis, beta-blockers, and MRAs [6].

Several studies have shown supremacy of ARNIs over ACEis in patients with LVEF <40 %. In the PARADIGM-HF trial, ARNIs reduced the risk of cardiovascular death or hospitalization for HF by 20 % compared with enalapril [35], and prevented the clinical progression in surviving HF patients more effectively than ACEis [36]. In PIONEER-HF, ARNIs significantly decreased N-terminal pro-hormone B-type Natriuretic Peptides (NT-proBNPs) concentration *vs.* enalapril therapy among patients hospitalized for acute-decompensated HF [37].

Several studies tried to assess the effect of ARNIs on LVEF (Table 1). In PROVE-HF the patients improved the mean LVEF by 5.2 % after 6-months and by 9.4 % after 12-months of treatment with sacubitril/valsartan 97/103 mg b.i.d. [38]. A slight benefit in LVEF with ARNIs (target dose 97/103 mg b.i.d.) similar to that with enalapril was presented in the EVALUATE-HF study. Further, ARNIs promoted repair in other parameters of LV reverse remodeling, suggesting improved LVEF restoration in the long-term with ARNIs, compared to enalapril [39,40]. Two additional studies of Martens et al. confirmed that improvement of at least 5 % in LVEF could be reached within the first year after initiation of ARNIs treatment [41,42]. The investigators highlighted that a higher drug-dose independently predicted significant improvement in LVEF ($p = 0.001$) and significant reduction in LVESV ($p = 0.001$). El-Battrawy et al. presented similar results, as mean LVEF in their patient population improved by 5 % during 12-months with ARNIs [43]. In all studies, significant improvement of LVEF is longer than the 3-month recommendation of OMT before defibrillator implantation in the current guidelines (Fig. 1).

Less information is provided on the effect of ARNIs with VT, VF or SCD, compared with LVEF. Two studies show improvement for these outcomes (Table 2); however data is still limited. In the PARADIGM-HF study, although not a primary endpoint in analysis on the cause of death, slightly lower SCD incidence was observed in patients treated with maximal dose of 97/103 mg b.i.d. sacubitril/valsartan, compared to those treated with enalapril [44]. The retrospective study by Martens et al. showed better efficacy on VAs with maximal tolerable dose ARNIs in 151 patients with previously implanted ICD/CRT and available telemonitoring data [42]. Treatment with ACEis/ARBs was replaced with an equivalent dose of ARNIs, after which incident and antecedent (364 days each) were assessed. Their study showed a significant reduction in all VA events, including number of patients with VT/VF episodes, total VT/VF episodes, total appropriate therapy episodes, mean sum non-sustained ventricular tachycardias (NSVTs) per patient and mean premature ventricular contractions (PVCs) per hour. The percentage of biventricular-pacing increased from 96 % to 99 %, and the biventricular-pacing of <90 % was significantly reduced. However, El-Battrawy et al. presented that the composite number of VA events was increased 12-months after initiation of ARNIs. Nonetheless, treatment with MRAs was interrupted in 25 % of the patients, which further highlights the importance of OMT [43]. De Diego et al. present similar results in their observational prospective study on patients with previously implanted defibrillator and telemonitoring [45]. They compared arrhythmia events during 9-months of ACEis/ARBs treatment and for 9-months following replacement with ARNIs. They observed a reduction in NSVT episodes, sustained VT events, appropriate ICD shocks and PVCs

Table 1
The effect of ARNI on LVEF.

Study name	Patients	Study design	Aims	Inclusion criteria	Median follow-up	Primary endpoints	Secondary endpoints	LVEF assessment
PROVE-HF[a]	794	Prospective, single-group, open-label	Correlation between changes in the log2-NT-proBNP concentration and cardiac remodeling	NYHA functional class II, III, or IV LVEF ≤40 % Stable dose of loop diuretics for 2-weeks prior to study initiation	12 months	Correlation between changes in the concentration of NT-proBNP and cardiac remodeling from baseline to 12 months for different parameters		Improved, LVEF at baseline 28.2 % Mean increase at 6 months 5.2 %, p < 0.001 Mean increase at 12 months 9.4 %, p < 0.001
Martens et al.[b]	125	Prospective, assessor-blinded, single-center	Assessment of the reverse remodeling response to sacubitril/valsartan	NYHA class II-IV LVEF below 35 % Pre-treatment with individual optimal dose of ACEi or ARB for at least 4 weeks	118 days	Improved LVEF Improved LVESV (147 ± 57 ml *vs.*129 ± 55 ml; p < 0.001) Improved LVEDV (206 ± 71 ml *vs.*197 ± 72 ml; p = 0.027)		Improved LVEF (29.6 % to 34.8 %; p < 0.001)
EVALUATE-HF[c]	464	Randomized, double-blind, double-dummy, parallel group, active-controlled, forced-titration multicenter	Assessment of HFrEF treatment with sacubitril-valsartan *vs.* enalapri, in improving central aortic stiffness and cardiac remodeling	HF LVEF ≤40 %	12 weeks	Changes in aortic characteristic impedance (Zc), a measure of central aortic stiffness No significant differences between the two groups (p = 0.78)	Changes in EF	Improved LVEF Mean increase at 12 weeks with Entresto: 34 % to 36 % Mean increase at 12 weeks with Enalapril: 33 % to 35 %
El-Battrawy et al.[d]	59	Observational retrospective	Comparing incidence of arrhythmias before and after initiation of sacubitril/valsartan	NYHA II-IV despite OMT LVEF < 40 % Implanted PM, ICD, CRT-D or loop recorder Received ARNI	12 months	VA burden increased in the first 12 months after ARNI initiation	Improvement of LVEF in HFrEF patients	Improved LVEF at 12 months follow up 25 % to 30 %

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin-receptor-neprilysin inhibitor, sacubitril/valsartan; CRT-D = cardiac resynchronization therapy defibrillator; EF = ejection fraction; HFrEF = heart failure with reduced ejection fraction; HF = heart failure; ICD = *implantable cardioverter*-defibrillator; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NT-proBNP = N-terminal pro-hormone B-type Natriuretic Peptide; NYHA = New York Heart Association; OMT = optimal medical treatment; PM = pacemaker.

[a] Januzzi JL, Jr., Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, Camacho A, Pina IL, Rocha RA, Shah AM, Williamson KM, Solomon SD, Investigators P-H. Association of Change in N-Terminal Pro-B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment With Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction. *JAMA* 2019:1–11.

[b] Martens P, Belien H, Dupont M, Vandervoort P, Mullens W. The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction. *Cardiovasc Ther* 2018;36:e12435.

[c] Desai AS, Solomon SD, Shah AM, Claggett BL, Fang JC, Izzo J, McCague K, Abbas CA, Rocha R, Mitchell GF, Investigators *E*-H. Effect of Sacubitril-Valsartan *vs* Enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. *JAMA* 2019:1–10.

[d] El-Battrawy I, Pilsinger C, Liebe V, Lang S, Kuschyk J, Zhou X, Borggrefe M, Roger S, Akin I. Impact of Sacubitril/Valsartan on the Long-Term Incidence of Ventricular Arrhythmias in Chronic Heart Failure Patients. *J Clin Med* 2019;8.

per hour, while the biventricular-pacing in patients with CRT-D increased from 95 % to 98.8 %.

SGLT2is were approved recently for the management of HFrEF. Zelniker et al. [46] summarized the results of three studies, EMPA-REG [47], DECLARE-TIMI-58 [48] and CANVAS [49], in their meta-analysis, demonstrating positive cardiovascular outcomes in patients with diabetes, treated with SGLT2is in addition to standard OMT. Later, DAPA-HF and EMPEROR-Reduced trials showed improved cardiovascular outcome of Dapagliflozin 10 mg daily and Empagliflozin 10 mg daily, respectively, in patients with HFrEF regardless of diabetes (Table 3) [8,9]. In their meta-analysis of DAPA-HF and EMPEROR-Reduced trials, Zannad et al. show that SGLT2is minimize the number of hospitalizations, improve renal outcomes and reduce all-cause and cardiovascular mortality in patients with HFrEF [50]. While these studies led to important changes in the management of HFrEF patients, based on valuable clinical outcome, the effect of SGLT2is on LVEF was not assessed. In a retrospective study of 202 patients with HF and diabetes type-2, Hwang et al. demonstrated that Dapagliflozin 10 mg/day and Empagliflozin 10 mg/day improve LVEF from 36.1 % to 45 % after a median follow-up of 13-months [51]. Their outcome shows promise for future trials, assessing the effect of SGLT2is on LVEF in HFrEF patients, regardless of diabetes. Requena-Ibanez et al. [52] describe the possible mechanisms of SGLT2is, *i.e.*, reductions in epicardial adipose tissue, myocardial fibrosis, aortic stiffness, and inflammatory biomarkers compared with placebo.

Cyclic guanosine monophosphate (cGMP) is known for its protective cardiovascular and kidney effect [53,54]. It is the new “target” to improve management and outcomes of HFrEF. In HF, vascular dysfunction and increased inflammation have a negative effect on NO bioavailability, leading to a reduction in cGMP synthesis [55]. The VICTORIA trial evaluated *vericiguat* 10 mg daily (an oral soluble guanylate-cyclase stimulator) in patients with NYHA class II-IV and LVEF<45 % [10]. It presented reduced composite primary outcome of cardiovascular death or first HF hospitalization (35.5 % *vs.* 38.5 %). A

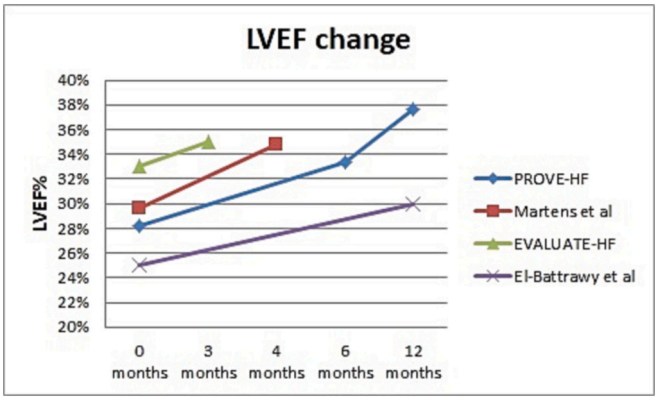

Fig. 1. Left ventricular ejection fraction (LVEF) change after initiation of treatment with ARNIs.
ARNI = angiotensin-receptor-neprilysin inhibitor; LVEF = left ventricular ejection fraction.

limitation to this study was the relatively short median follow-up of 10.8 months (compared to 18-months in DAPA-HF and 16-months in EMPEROR-Reduced trials) [56]. SOCRATES-REDUCED trial showed improvement in LVEF after 12-weeks of treatment with vericiguat 10 mg daily (+3.7 %, p = 0.02; descriptive analysis; mean LVEF 29.6 % at inclusion of the patients) [57] The effect of longer therapy with vericiguat on reducing cardiovascular death rates and LVEF needs to be assessed in future trials.

In the last twenty years, many attempts have been made in providing medication to improve contractility and increase cardiac function, as systolic dysfunction is the main property of HFrEF. The synthesis of *omecamtiv mecarbil (OM)* is considered the long-awaited breakthrough in this area as a first-in-class selective cardiac myosin activator. It binds and stabilizes the myosin heads in a confirmation which enables greater force during each cardiac contraction, or systole [58]. GALACTIC-HF trial indicated that treatment with OM (using pharmacokinetic-guided doses of 25 mg, 37.5 mg, or 50 mg twice daily) reduced the primary composite efficacy endpoint of cardiovascular death or HF events *versus* placebo in patients with HFrEF on standard-of-care (SOC). No significant reduction in the secondary endpoint of cardiovascular death was observed. Rates of adverse events, including major ischemic cardiac events, were well-balanced between treatment arms [55,58]. Future studies need to assess the effect on LVEF, as positive outcomes could affect the decision-making of defibrillator implantations.

Another medication which improves prognosis in patients with HFrEF is *ivabradine*. It is a "funny" channel blocker (If-channel in the sinus node) and due to its unique mechanism of action, ivabradine is now considered a well-established drug in the treatment of chronic-HF in patients with sinus rhythm, with a Class IIA recommendation in the latest ESC guidelines [6]. Three large trials, CARVIVA HF [59], SHIFT [60] and INTENSIFY [61] assessed the effect of ivabradine on HFrEF patients showing a reduction in re-hospitalizations and improved quality of life. Reduction in HF hospitalizations is one of the main targets in HFrEF management, as each decompensation event is related to reduced life expectancy [62,63]. The clinical indications for ivabradine include all patients with symptomatic HFrEF (with LVEF ≤35 %) in sinus rhythm and who remain with heart rates above 70 bpm, despite OMT, including maximally tolerated doses of beta-blockers [64].

Table 2
The effect of ARNI on arrhythmias.

Study name	Patients	Study design	Median follow-up	Primary endpoints	VT/VF/SCD
PARADIGM-HF[a]	8442	Randomized, double-blind, parallel group, active-controlled, two-arm, event-driven trial	27 months	Composite of CV death or hospitalization for HF	SCD in ARNI *vs.* Enalapril groups (6 % *vs.*7.4 %; p = 0.002)
Martens et al.[b]	151	Retrospective; Antecedent and incident analysis	2 years (1 year antecedent analysis; 1 year incident analysis)	VT/VF burden NSVT burden PVCs burden Reduced occurrence of appropriate therapy Improved BiV pacing	VT/VF episodes dropped (51 *vs.*14; p < 0.001) VT/VF burden dropped (19 *vs.*10) Appropriate therapy episodes dropped (20 *vs.* 6; p = 0.007) NSVT burden dropped (7.7 ± 11.8 *vs.* 3.7 ± 5.4; p < 0.001) PVCs burden dropped (14 *vs.* 2; p < 0.001) BiV pacing improved (96 ± 4 *vs.* 99 ± 1; p < 0.001)
De Diego et al.[c]	120	Observational prospective	9 months on RAASi followed by 9 months on ARNI	Sustained VT and Appropriate ICD shocks NSVT burden PVCs burden Improved BiV pacing	Sustained VT and appropriate ICD shocks dropped (6.7 % *vs.*0.8 %; p < 0.02) NSVT burden dropped (15 ± 1.7 *vs.* 5.4 ± 0.5; p < 0.002) PVCs burden dropped (78 ± 15 *vs.* 33 ± 12; p < 0.0003) BiV pacing improved (95 ± 6 *vs.* 98.8 ± 1.3; p < 0.02)
El-Battrawy et al.[d]	59	Observational retrospective	12 months	VA burden after initiation of ARNI	Composite of VAs was increased in the first 12 months after ARNI initiation

ARNI = angiotensin-receptor-neprilysin inhibitor, sacubitril/valsartan; BiV = biventricular pacing; CV = cardiovascular; ICD = *implantable cardioverter*-defibrillator; NSVT = nonsustained ventricular tachycardia; PVCs = premature ventricular contractions; RAASi = Renin-angiotensin-aldosterone system inhibitors; SCD = sudden cardiac death; VA = ventricular arrhythmias; VF = ventricular fibrillation; VT = ventricular tachycardia.

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[b] Martens P, Nuyens D, Rivero-Ayerza M, Van Herendael H, Vercammen J, Ceyssens W, Luwel E, Dupont M, Mullens W. Sacubitril/valsartan reduces ventricular arrhythmias in parallel with left ventricular reverse remodeling in heart failure with reduced ejection fraction. *Clin Res Cardiol* 2019;108:1074–1082.

[c] de Diego C, Gonzalez-Torres L, Nunez JM, Centurion Inda R, Martin-Langerwerf DA, Sangio AD, Chochowski P, Casasnovas P, Blazquez JC, Almendral J. Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices. *Heart Rhythm* 2018;15:395–402.

[d] El-Battrawy I, Pilsinger C, Liebe V, Lang S, Kuschyk J, Zhou X, Borggrefe M, Roger S, Akin I. Impact of Sacubitril/Valsartan on the Long-Term Incidence of Ventricular Arrhythmias in Chronic Heart Failure Patients. *J Clin Med* 2019;8.

Table 3
SGLT2i in HFrEF.

Study name	Patients	Study design	Aims	Inclusion criteria	Median follow-up	Primary endpoints & outcome	Secondary endpoints & outcome	LV EF assessment
DAPA-HF[a]	4744	Prospective placebo-controlled trial	Assessment of SGLT2i effect in HFrEF patients, irrespective of diabetes status	EF ≤ 40 % NYHA class II-IV Elevated NT-proBNP OMT	18 months	Composite of worsening HF or CV death (16.3 % *vs.* 21.2 %; p < 0.001)	CV death or HF hospitalization (16.1 % *vs.* 20.9 %; p < 0.001) Total hospitalizations for HF and CV deaths (567 *vs.* 742; p < 0.001) Change in KCCQ total symptom score at 8 months (6.1 ± 18.6 *vs.* 3.3 ± 19.2; p < 0.001) Worsening renal function (1.2 % *vs.* 1.6 %) Death from any cause (11.6 % *vs.* 13.9 %)	LVEF at baseline ≤40 %
EMPEROR – Reduced[b]	3730	Prospective placebo-controlled trial	Assessment of Empagliflozin safety and efficacy in symptomatic HFrEF patients, irrespective of diabetes status	EF ≤ 40 % NYHA class II-IV Elevated NT-proBNP HF hospitalization within 12 months OMT	16 months	Composite of worsening HF or CV death (19.4 % *vs.* 24.7 %; p < 0.001)	HF hospitalizations (388 *vs.* 553; p < 0.001) eGFR decline rate (−0.55 ml/min/1.73 m^2/year *vs.* −2.28 ml/min/1.73 m^2/year; p < 0.001)	LVEF at baseline =27.7 %

eGFR = estimated glomerular filtration rate; HFrEF heart failure with reduced ejection fraction; HF = heart failure; KCCQ = *Kansas City Cardiomyopathy Questionnaire;* NT-proBNP = N-terminal pro-hormone B-type natriuretic peptide; *NYHA = New York Health Association;* OMT = optimal medical treatment; SGLT2i = Sodium-glucose co-transporter 2 inhibitors.

[a] McMurray JJV, DeMets DL, Inzucchi SE, Kober L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sabatine MS, Sjostrand M, Solomon SD, Committees D-H, Investigators. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail* 2019;21:665–675.

[b] Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Bohm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F, Investigators EM-RT. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020;383:1413–1424.

The INTENSIFY study [61] also provides insight on the effect of ivabradine on LVEF. At baseline, 26.6 % of patients had an LVEF ≤35 %, which declined to 17.4 % after 4-months. In support of this finding, Tsutsui et al. [65] presented a dose-dependent recuperation of LVEF with ivabradine 2.5 mg b.i.d., a 5.4 ± 7.0 % improvement compared to placebo (p = 0.0472), and with ivabradine 5 mg b.i.d., a 6.4 ± 9.9 % improvement *versus* placebo (p = 0.0359).

There is still insufficient evidence regarding ivabradine's effect on VAs. In the SHIFT study and its Holter sub-study, the prevalence of VT and PVC did not vary between ivabradine and placebo groups [60,66,67].

These medications improve the previously well-established OMT and advance the management of HF. To explain further these improvements, we outline herein the importance of several pathophysiological mechanisms involved.

5. Pathophysiological mechanisms with the novel medications

The mechanisms of improving outcome *via* ARNIs, SGLT2is, and vericiguat are illustrated in Fig. 2a, and OM and ivabradine in Fig. 2b. ARNIs promote the treatment of ARBs by the additive effect of sacubitril as neprilysin-inhibitors and by valsartan, directly inhibiting the renin-angiotensin-aldosterone system (RAAS). The concurrent effect of these two elements focuses on two pathophysiological mechanisms leading to HF: activation of RAAS and reduced sensitivity to natriuretic peptides (NPs) [68]. Neprilysin is a metallopeptidase which affects the cardiovascular system by decaying vasodilating peptides, such as NPs, adrenomedullin and bradykinin [69]. As a result of neprilysin inhibition, there is in an increase in circulating levels of NPs and a concurrent reduction of NT-proBNP, both which reverse the negative effects driven by the activation of RAA and sympathetic nervous system (SNS) [70]. The blockade of the neprilysin neurohormonal pathway also improves natriuresis which leads to reduction in LV end-diastolic pressure and has a progressive effect on LV remodeling [69]. In addition, this reduces doses of loop-diuretics [71], which moderates neuro-hormonal levels and associated electrolyte imbalance [63]. The positive results from the ENTRESTO-SAS study [72] further indicate an improvement of sleep apnea, an independent risk factor of congestive-HF morbidity and mortality [73,74], in patients treated with sacubitril/valsartan. Sleep apnea is a common comorbidity among patients with HFrEF (up to 76 %) [75], and this study demonstrated that similar mechanisms of ARNIs improve the outcome in these patients as in congestive-HF patients; some of these pathophysiological mechanisms include extracellular fluid overload, cardiac injury, and sympathetic nervous system activation [76].

The prevention of elevated filling pressures, an indicative independent predictor of arrhythmia [77], as well as improved expression of potassium channels and stabilized action potentials [78], seem all to be feasible reasons to reduce SCD. The mechanisms participating in these improvements include recovery of contractile function, reduced fibrosis, reduced wall stress, and reconstruction of ion-channels. ARNIs induce the expression of potassium channels [35] and diminish the reduction of L-type calcium current. ARNIs' effects on RAAS pathway, reducing pro-arrhythmic remodeling and providing anti-arrhythmic function, modulate cardiac electrophysiology at various scales which influence both atrial and ventricular tachyarrhythmias [79].

SGLT2is also contribute to cardiac hemodynamics, functioning to improve HF and reduce SCD risk. Their diuretic effect results in better clearance of fluid from the interstitial space rather than from the circulation, possibly ensuing congestion relief with minimal impact on blood volume, arterial filling and organ perfusion [80]. In addition, Verma et al. [81] reported that SGLT2is enrich cardiac energy metabolism by enhancing production from glucose and from fatty acid oxidation and therefore improve the energy supply to the “deprived”

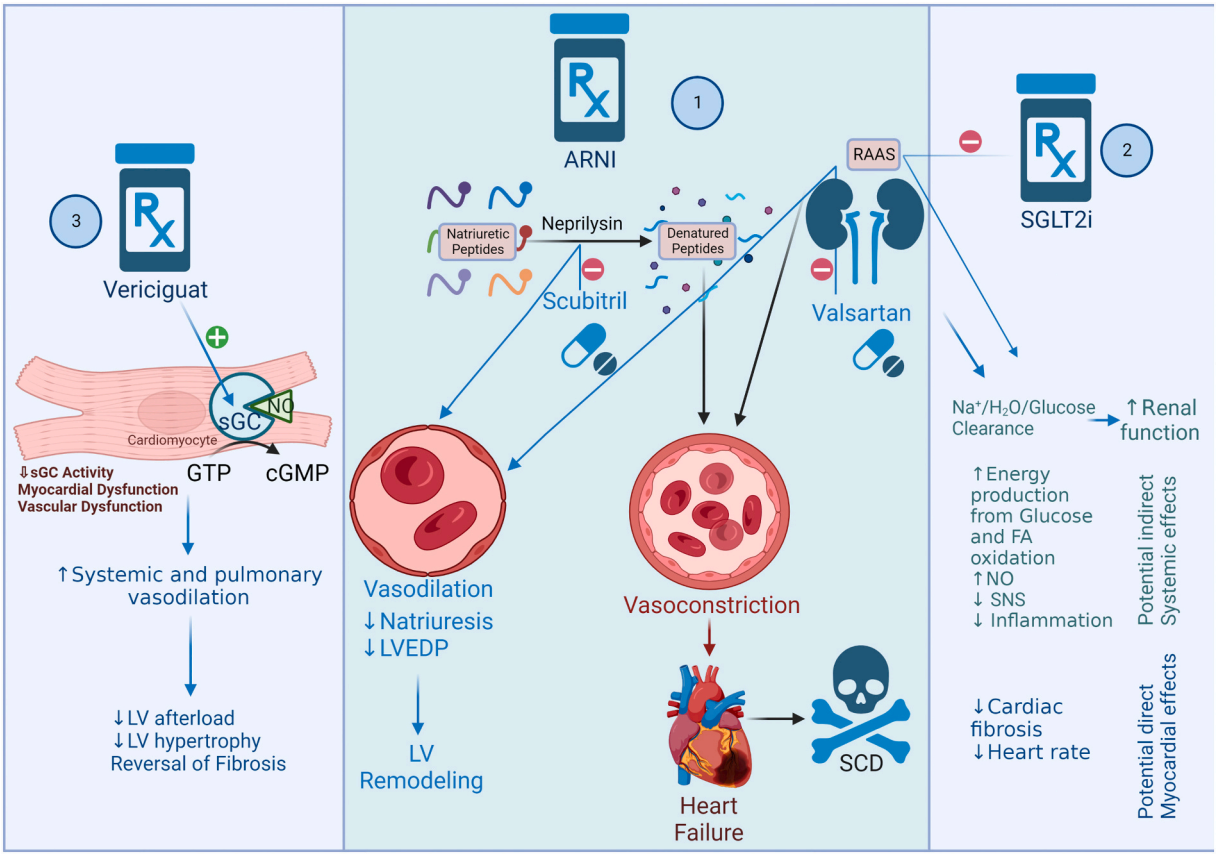

Fig. 2a. Physiological mechanisms of the new medications ARNIs, SGLT2is and vericiguat.
(1) ARNIs have additive concurrent effects inhibiting both ARBs with valsartan and neprilysin with sacubitril. Valsartan inhibits the RASS pathway improving renal function and cardiac outcome by clearance of sodium, water and glucose from the interstitial space rather than from the circulation. Valsartan improves vasoconstriction. Sacubitril increases the circulating levels of natriuretic peptides and the concurrent reduction of NT-ProBNP, both which reverse the negative effects driven by the activation of RAA and SNS. Sacubitril reduces natriuresis and LVEDP, an independent predictor of arrhythmia, and improves LV remodeling. (2) SGLT2is also inhibit RAAS for a better clearance of fluid from the interstitial space. Potential indirect systemic effects include: increased energy production from glucose and FA oxidation, increased NO, decreased SNS function, decreased inflammation. Potential direct myocardial effects include: decreased fibrosis and decreased heart rate. (3) cGMP deficiency results in low NO, inflammation, myocardial and vascular dysfunction. Vericiguat targets the sGC-cGMP pathway by enhancing sGC sensitivity to endogenous NO. The increasing levels of cGMP improve systemic and pulmonary vasodilation, decrease LV afterload and hypertrophy, eventually reversing fibrosis.
ARBs = angiotensin II receptor blockers, ARNIs = angiotensin-receptor-neprilysin inhibitors, cGMP = cyclic guanosine monophosphate, FA = fatty acid, HCN = Hyperpolarization-activated cyclic nucleotide–gated, LV = left ventricular, LVEDP = left ventricular end-diastolic pressure, NO = nitric oxide, NT-proBNPs = The N-terminal prohormone of brain natriuretic peptides, RAAS = renin-angiotensin-aldosterone system, SCD = sudden cardiac death, sCG = soluble guanylate cyclase, SGLT2is = sodium-glucose co-transporter 2 inhibitors, SNS = sympathetic nervous system.

weak heart. Another positive effect of SGLT2is on the cardiovascular system is the notable improvement in myocardial oxidative stress injury and cardiac fibrosis [82]. Several additional cardioprotective effects of SGLT2 inhibition were also recently described, such as inflammation decline, inhibition of the sympathetic nervous system, SGLT1, and the sodium-hydrogen exchanger, prevention of ischemia/reperfusion injury, reduction in hyperuricemia and epicardial fat mass, and increase in autophagy and lysosomal degradation, erythropoietin levels and circulating pro-vascular progenitor cells [83].

Vericiguat is a soluble guanylate cyclase (sGC) stimulator and affects a different pathway to treat HF. It targets the NO-sGC, cGMP pathway by enhancing sGC sensitivity to endogenous NO [84]. Experimental studies suggested various potential positive effects of sGC stimulators including prevention of LV hypertrophy and reversal of fibrosis. Furthermore, systemic and pulmonary vasodilatation associated with sGC stimulation could result in LV reduction after-load [85]. Only sacubitril/valsartan and vericiguat, among therapies increasing cGMP, improved patient outcome over the standard combination of ACEis/ARBs, beta-blockers, and MRAs [55] in HFrEF by targeting two distinct mechanisms. This is a reason for optimism that a potential positive collective effect could be expected for improved outcome of both LV-remodeling and SCD reduction.

Ivabradine's beneficial effect on HFrEF is based on heart rate reduction at rest and/or exercise with improvement of heart rate variability, which prolongs diastolic perfusion time, improves coronary blood flow, increases exercise capacity and increases stroke volume. Taken together, these mechanisms provide an anti-remodeling effect, improving LV structure and function [64].

Cardiac rehabilitation *via* non-drug management was investigated thoroughly by some authors for remodeling and improving LVEF over time. The beneficial effects of lifestyle changes including smoking and alcohol cessation, fluid and salt restriction and weight loss in obese patients, were not striking. In the CROS-HF meta-analysis, Bjarnason-Wehrens et al. presented no decline on mortality or hospitalizations in HFrEF patients, although exercise-based cardiac rehabilitation increased quality-of-life and exercise capacity [86].

6. Discussion

With new insights on medical therapy of HFrEF, the decision on

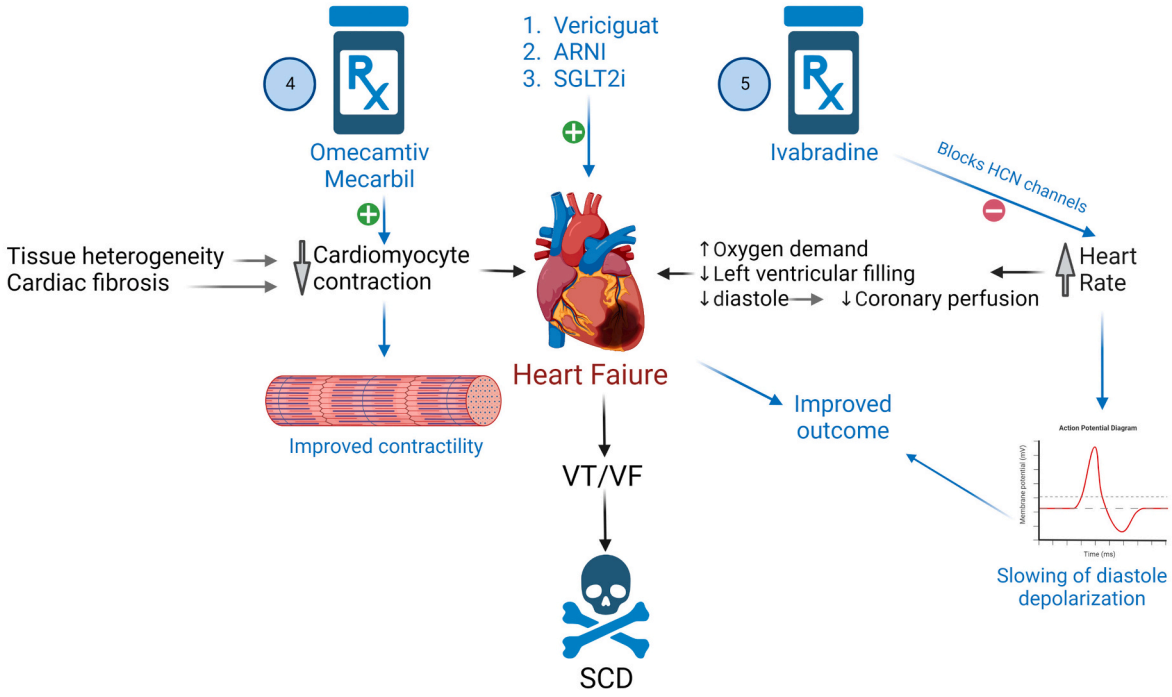

Fig. 2b. Physiological mechanisms omecamtiv mecarbil and ivabradine.
(1–3) The new medications, vericiguat, ARNIs and SGLT2is improve heart failure, VT/VF and consequently reduce SCD. (4) Omecamtiv mecarbil improves cardiomyocyte contraction and reverses the heart malfunctions caused by tissue heterogeneity and cardiac fibrosis. (5) Ivabradine blocks HCN channels located on cardiomyocytes and slows diastole depolarization, slowing the heart rate. This improves pathologies of oxygen demand, LV filling, diastole and coronary perfusion, which morbidly lead to heart failure VT/VF and finally to SCD.
ARBs = angiotensin II receptor blockers, ARNIs = angiotensin-receptor-neprilysin inhibitors, cGMP = cyclic guanosine monophosphate, FA = fatty acid, HCN = Hyperpolarization-activated cyclic nucleotide–gated, LV = left ventricular, LVEDP = left ventricular end-diastolic pressure, NO = nitric oxide, NT-proBNP = N-terminal pro-hormone B-type Natriuretic Peptide, RAAS = renin-angiotensin-aldosterone system, SCD = sudden cardiac death, sCG = soluble guanylate cyclase, SGLT2is = sodium-glucose co-transporter 2 inhibitors, SNS = sympathetic nervous system, VT = ventricular tachycardia, VF = ventricular fibrillation.

primary prevention of SCD is even more complicated now. Encouraging data regarding the effect of ARNIs on LVEF, ventricular events, SCD and survival need further study, to evaluate similarly the roles of the other recently adjoined medications in the treatment of HFrEF.

On the other hand, the role of defibrillators is on the rise, as are telemonitoring devices. In the IN-TIME trial [87], Hindricks et al. attest that patients benefit from telemonitoring through their ICD with or without biventricular pacing, resulting in a better composite clinical score (all-cause mortality, overnight hospital admission for HF, change in NYHA class, and change in patient global self-assessment). They suggest that three mechanisms attributed to these results, (1) early detection of the onset or progression of ventricular and atrial tachyarrhythmias, (2) early recognition of suboptimal device function, and (3) patient interview prompted by telemonitoring, which occasionally revealed symptomatic worsening or noncompliance to drugs.

We believe that supplementary treatment with ARNIs, SGLT2i and vericiguat to the conventional HF therapy would significantly improve LVEF and probably for longer periods than those proposed in the current guidelines. The combined effect of the new four-pillar therapy of HFrEF (ARNIs, beta-blockers, mineralocorticoid receptor-antagonists and SGLT2is) on LVEF is yet to be evaluated, but an improvement of 5 % or more seems achievable. Eventually, this would mainly affect the management of patients with LVEF 30 %–35 % as they seem the cohort of patients that would mostly benefit from the treatment. This could lead to less defibrillator implantations, and hopefully to reduced risk and better management of the patients. Eventually, positive results over longer intervals with OMT could precede to another question, is the time waiting for improvement in LVEF under OMT worth the risk of longer waiting time between HF diagnoses and defibrillator implantation?

Several studies showed that ARNIs and SGLT2is reduced all-cause mortality. PARADIGM-HF trial and Zelniker et al.'s systematic review both demonstrated a respective reduction in all-cause mortality with ARNIs or SGL2is, respectively, 14 % and 15 % reduction in these reports [35,46]. Tromp et al. [88] showed that the combination of ARNIs, beta-blockers, MRAs and SGLT2is reduce all-cause mortality by 61 % compared to placebo, whereas all-cause mortality with the previous "gold standard" therapy of ACEis, beta-blockers and MRAs was reduced only by 48 %.

Supporting studies for the guideline recommendations on ICD implantation for primary prevention are over 20 years old, and the new drugs were not available at that time. Using combination novel therapy in HFrEF patients could potentially affect the outcomes of older studies that assessed the requirement for ICD implantation for primary prevention. For example, in the DANISH trial in 2016 which is the most recent of those studies, ICD implantation was not associated with a significantly lower all-cause mortality compared to usual clinical care. In this trial, in the absence of new medications ARNIs and SGLT2is in the control group, the all-cause mortality rate was 5.0 events per 100 person-years compared to 4.4 events per 100 person-years in the ICD group patients [20]. In theory, if these medications were used as

indicated in the current guidelines during the DANISH trial; specifically, if they were to be used in the control group, we can argue that mortality could be about 29 % lower, because of a possible additive effect of these two medications. We can further reason a lower incidence if a synergistic effect between these two drugs does exist. This would make any benefit from adding an ICD even less likely.

In other trials using new HF medications, VICTORIA with vericiguat, GALACTIC-HF with OM, and SHIFT with Ivabridine, all-cause mortality did not change significantly [10,58,60]. Still, a synergistic effect between these drugs and others mentioned in this review, could potentially lead to a considerable decrease in mortality; this assumption needs further research. Meaningful reduction in all-cause mortality with new medications could potentially improve the risks *versus* benefits regarding defibrillator implantations. The ideas presented in this review could improve clinicians' decision-making regarding which HFrEF patients would benefit from an ICD with or without biventricular pacing implantation, as a primary prevention of SCD. Further studies are essential, as the new revolution of HF treatments is currently on the rise.

7. Conclusion

The effects of ARNIs, SGLT2is and guanylate-cyclase stimulator on HF hospitalizations were consistent in the trials. New studies suggest that these new agents could also improve LVEF and reduce the events of cardiovascular death in patients with HFrEF and decrease overall mortality perhaps to a degree that an ICD will provide no additional benefit. This improved outcome could possibly lead to important changes in decision-making on ICD implantation with or without biventricular pacing for primary prevention in patients with HFrEF and reduce the need of device therapy.

CRediT authorship contribution statement

I. Koev: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **M. Yarkoni:** Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **D. Luria:** Conceptualization, Methodology, Supervision. **O. Amir:** Conceptualization, Methodology, Supervision. **Y. Biton:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The corresponding author has authority over manuscript preparation and the decision to submit the manuscript for publication. The corresponding author confirms that the first two co-authors drafted the manuscript and that all authors read and approved the manuscript.

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