Sudden cardiac death in patients with myocardial infarction: 1.5 primary prevention

Yun-Tao Feng[1], Xiang-Fei Feng[2,*]

[1] *Dalian Medical University, 116044 Dalian, Liaoning, China*

[2] *Department of Cardiology, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, 200092 Shanghai, China*

*Correspondence: fengxiangfei@xinhuamed.com.cn (Xiang-Fei Feng)

Sudden cardiac death (SCD) is one of the most common causes of death in the world. Coronary heart disease (CHD) is the root cause of most patients with SCD, and myocardial infarction (MI) is the main cause of SCD among all types of CHD. Early identification of high-risk patients after an MI, and the application of related prevention strategies and disease-specific treatments will be the key to reduce SCD. The mechanism of SCD after MI varies over time, and the relevant risk prediction indicators are also dynamic and different. In the existing guidelines for MI patients, the static and slightly single stratification of primary (PP) and secondary (SP) prevention has significant room for improvement. The 1.5 primary prevention (1.5PP) is defined as patients with PP who also had the following risk factors: non-sustained ventricular tachycardia (NSVT), frequent premature ventricular contractions (PVCs), severe heart failure (left ventricular ejection fraction, LVEF <25%), and syncope or pre-syncope. The emergence of 1.5PP has provided a new method for the stratification and management of SCD after an MI.

Keywords

Sudden cardiac death; Myocardial infarction; Implantable cardioverter-defibrillator; Primary prevention; Secondary prevention; 1.5 primary prevention

1. Introduction

Sudden cardiac death (SCD) is defined by the American Heart Association (AHA) as a natural death caused by the heart that occurs within 1 hour after the onset of acute symptoms and is characterized by a sudden loss of consciousness [1]. In the United States, more than 370,000 people suffer from any type of sudden cardiac death, with an average annual rate of 97.1 per 100,000 people [2]. In addition, it has been reported that the risk of death from SCD is far greater than the total risk of all major cancers [3]. Therefore, reducing the incidence of sudden cardiac death is of great importance to reducing cardiovascular mortality.

There are many causes of SCD, including coronary heart disease (CHD), heart failure (HF), valvular heart disease, ion channel diseases, and myocardial diseases; such as obstructive hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy. Eighty percent of SCD is caused by CHD and its complications (Fig. 1) [4, 5]. The types of CHD include stable and unstable angina, nonfatal myocardial infarction (MI), and coronary death [6]. MI is the leading cause of SCD among all types of CHD and the risk of SCD among MI patients is 4–6 times higher than that of the general population [7, 8]. Therefore, the early prevention and management of high-risk patients after an MI is important to effectively reduce the incidence of SCD.

The risk of SCD after an MI is a dynamic process that is highly dependent on the incidence of myocardial death, changes in heart rhythm, and changes with time after an MI [9]. The predictive indicators of SCD are dynamic and varied. However, according to present guidelines, the primary (PP) and secondary (SP) prevention measures for SCD based on ICD (implantable cardioverter defibrillator) implantation still only depend on low left ventricular ejection fraction (LVEF) [10]. The proposal of 1.5 primary prevention (1.5PP) focuses on the prevention of four events in high-risk patients with SCD, including non-sustained ventricular tachycardia (NSVT), frequent premature ventricular contractions (PVCs, ≥10/h), severe HF (LVEF <25%), and syncope or pre-syncope [11], and helps to minimize the limitations of primary and secondary prevention.

In this review, we will summarize the current preventive measures for SCD after an MI and their shortcomings as the main preventive measures of SCD after an MI. The main mechanisms of SCD after an MI will be reviewed and their corresponding prediction indicators, and the related therapeutic interventions will be discussed according to the risk stratification method of 1.5PP.

2. Prevention strategy

2.1 Primary prevention

In patients with an LVEF of 35% or less that is due to ischemic heart disease who are at least 40 days post-MI and 90 days post revascularization, an ICD is recommended if meaningful survival of greater than 1 year is expected [12].

For the PP of SCD among high-risk patients after an MI, a number of clinical randomized controlled trials (RCTs), including MUSTT (Multicenter Unsustained Tachycardia Trial), MADIT-II (Multicenter Automatic Defibrillator Im-
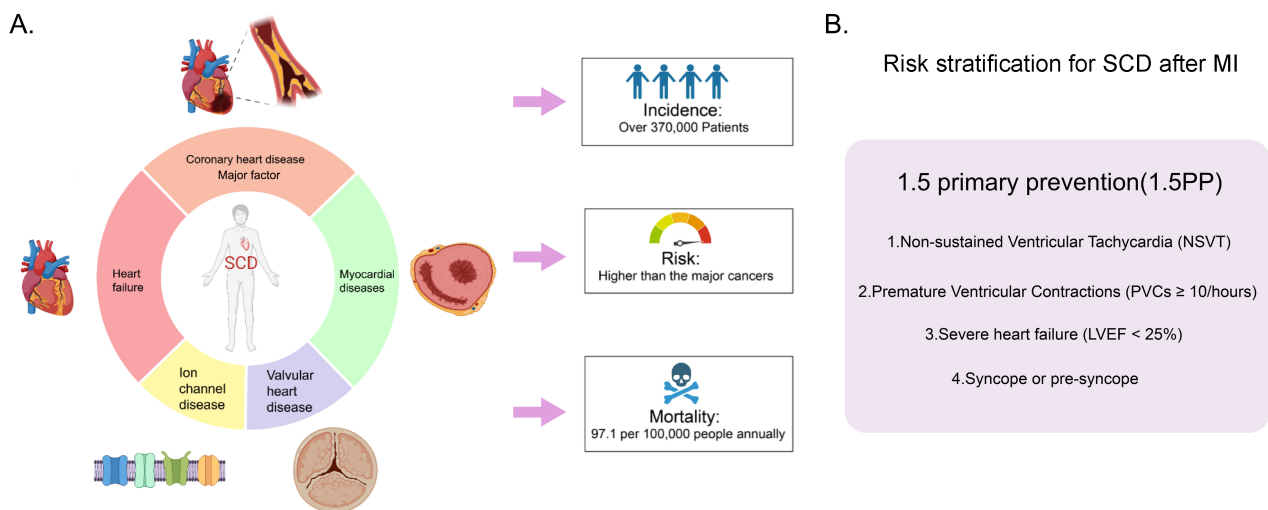
Fig. 1. Sudden cardiac death: (A) The causes (coronary heart disease, heart failure, channelopathies, etc) and dangers (incidence, risk and mortality) of sudden cardiac death (B) Risk stratification for SCD after MI (4 high-risk groups, 1.5PP). SCD, sudden cardiac death; MI, myocardial infarction; PP, primary prevention. This figure is rearranged and reprinted with permission from https://biorender.com/.

plantation Trial II), and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) [13–15], have demonstrated the use of ICD as the main preventive measure to reduce the incidence of SCD after an MI.

However, the primary preventive benefits of undergoing ICD treatment has limitations. For example, the application of ICD treatment guidelines excludes post-infarction patients with an LVEF ≥35% or an existing infarction [16]. In the Defibrillator in Acute Myocardial Infarction Trials (DINA-MIT) and Immediate Risk Stratification Improves Survival (IRIS) trials [17, 18], it was found that premature implantation of ICDs failed to improve the survival rate in early PP after an MI. Therefore, new technologies and treatments are needed to address the limitations of existing primary prevention techniques. For example, the use of a wearable cardioverter defibrillator (WCD) or subcutaneously implantable cardioverter-defibrillator (S-ICD) may circumvent the existing limitations of an ICD and provide a new direction for future PP.

2.2 Secondary prevention

The application of ICD therapy has resulted in preventing the recurrence of malignant arrhythmias and reducing SCD.

The three major milestone randomized trials for SP include the Antiarrhythmics vs. Implantable Defibrillator (AVID) trial, the Hamburg Cardiac Arrest Study (CASH), and the Canadian Implantable Defibrillator Study (CIDS) [19–21]. These studies have shown that ICDs can improve the survival of patients with fatal ventricular tachyarrhythmias (VTA) and reduce the incidence of death and that the efficacy is significantly better than anti-arrhythmic drugs in patients with resuscitated ventricular fibrillation (VF) arrest, syncope with persistent ventricular tachycardia (VT), LVEF ≤40%; patients with persistent VT; patients with resuscitated cardiac arrest and persistent ventricular arrhythmia; patients

who were evaluated after resuscitated VT/VF cessation, and those with persistent VT and syncope, persistent VT, and symptoms due to persistent depressed ventricular function.

However, a meta-analysis of these three milestone randomized trials suggests that the preventive effect of ICDs existed only in patients with an LVEF ≤35%. Furthermore, ICD implantation can result in potentially fatal complications such as recurrent and persistent VT/VF [22].

2.3 New prevention

Although the current guidelines detail the management of primary and secondary prevention of SCD, the prophylactic therapy of ICD implantation is still based on LVEF and its utilization varies greatly in different countries and regions [10, 23]. With the continuous emergence of new SCD risk assessment indicators, a new risk stratification approach is needed to update the current guidelines.

In order to further clarify the ICD therapy indications and supplement the new risk stratification, four risk factors related to the higher risk of sudden cardiac arrest (SCA), including non-sustained ventricular tachycardia (three or more consecutive beats at >100 beats per min lasting 30 s), frequent premature ventricular contractions (average of 10 or more PVCs per h), LVEF <25% and syncope or pre-syncope (due to suspected VT), were established as a new risk stratification approach for ICD implantation [23]. The prevention of PP patients with at least one of the four major risks is called 1.5PP.

A prospective, non-randomized, unblinded, global multicenter trial has been performed to explore the efficacy of ICD therapy in 1.5PP patients [11]. Through the analysis of a total of 3889 patients from 84 clinical centers in 17 countries or regions, ICD treatment was found to effectively reduce all-cause mortality by 49% for 1.5PP patients compared with 1.5PP patients without ICD implants. In the 1.5PP co-

hort, the number of patients who needed treatment (NNT) to save 1 life at 3 years was 10.0, while that of PP patients without a 1.5PP standard was 40.0. This indicates that ICD treatment confers strong mortality benefits to 1.5PP patients and supports the role of ICDs as an important intervention for global SCD management.

Although this clinical trial was non-randomized, and there were inconsistencies in the classification criteria for SD, the concept of 1.5PP provides a new method of risk stratification for ICD treatment and identifies four types of high-risk patients who can undergo ICD treatment for primary prevention. This study may provide a new model for the future hierarchical management of SCD prevention after a myocardial infarction.

3. Risk prediction indicators of SCD after MI

In complex cardiac conditions after an MI, risks are continuous and dynamic, so there is no absolute, single predictor of risk stratification for SCD [24]. In a review of autopsy records of the Valsartan in Acute Myocardial Infarction Trial (VALIANT) involving 14,000 patients with an MI, left HF, and left ventricular dysfunction (LVEF <35%), it was found that among 398 autopsies and 105 sudden deaths, non-arrhythmic deaths accounted for the highest proportion in the first month of sudden death after an MI, but 3 months later, 75 percent of sudden deaths were considered to be arrhythmic deaths [25]. Therefore, the distinction between non-arrhythmia (NAM) and arrhythmia (AM) mortality is of great significance in the risk stratification of SCD after myocardial infarction. There are different etiologies between NAM and AM. AM is caused by VF, VT, or cardiac arrest/pulseless electrical activity, while HF is the leading cause of NAM [26].

3.1 Non-arrhythmia mortality risk prediction indicators

An MI results in microcirculation dysfunction and its regulatory mechanisms, including ion channels, and the coronary circulation cannot meet the metabolic needs of the heart, leading to hypoxia, fibrosis, and tissue death, which ultimately leads to loss of myocardial function resulting in HF [27]. This can lead to myocardial stunning, cardiomyocyte necrosis, and acute mitral regurgitation due to papillary muscle dysfunction on the basis of ischemia. Late HF caused by ischemia reflects the consequences of cardiomyocyte death and scarring associated with ventricular remodeling [28].

For patients with HF, left ventricular dysfunction and HF are the most important predictors of SCD and their indices are closely related to LVEF [29]. For example, patients with an LVEF <30% after their most recent MI have an increased risk of death [30, 31], and the risk of SCD is 6–9 times that of normal people [32]. However, the risk of SCD in patients with low LVEF is not necessarily the same, so additional predictive factors independent of LVEF are needed to clarify their risk [33].

N-terminal pro b-type natriuretic peptide (NT-proBNP) levels measured after an MI are related to the occurrence of cardiac adverse events within one year and can be used as a predictor of cardiac syncope after an MI, and may help to predict who are those patients at risk for SCD after an MI [34, 35].

The evaluation of autonomic nervous function can also be used for risk stratification after an MI, including heart rate variability (HRV), baroreflex sensitivity (BRS), and heart rate turbulence (HRT) [36]. A systematic review of several retrospective and prospective studies has shown that the relative risk for abnormal values of HRT is a strong predictor of SCD [37]. The Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study showed that BRS <3.0 ms/mmHg and LVEF below 35% had a significant risk of cardiac death after myocardial infarction [38]. In addition, compared with data from the general population, low HRV has been shown to be an independent predictor of increased incidence of SCD in patients with a myocardial infarction [39].

3.2 Arrhythmia mortality risk prediction indicators

The main manifestation of an arrhythmia on an electrocardiogram (ECG) after an MI is tachycardia, including polymorphic VT or VF, which has become the major cause of death within 24 hours after an MI [40]. Potential triggers of VT or VF, including QT prolongation, unsustainable VTA, frequent PVCs, the high average late potentials on ECG reduced heart rate variability, or T-wave alternation (TWA) are associated with an increased risk of SCD after an MI [41, 42].

The interaction between myocardial triggers and pre-existing or abnormal substrates is the basis for the induction of persistent fatal arrhythmias [43].

Triggered activity refers to the depolarization activity generated by the atrium, ventricle, and the His-Purkinje System after an action potential, which is also called afterdepolarizations [44]. Afterdepolarizations includes early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs). EADs occur in phase 2 or phase 3 of the action potential, which is mainly related to the inward current, including the increases in the late sodium current (I_{Na}), the calcium current (I_{Ca}), or sodium-calcium exchanger (I_{NCX}) [45]. EADs and their evocative triggered activity are thought to underlie the arrhythmias observed in QT prolongation, such as pleomorphic ventricular tachycardia [46]. DADs appear in phase 4 of the action potential, which is mainly related to the calcium-sensitive currents caused by elevated spontaneous sarcoplasmic reticulum Ca^{2+} release [47]. The spontaneous release of calcium at the subcellular level in DADs was considered to be the triggered activity that induced PVCs [48]. A spontaneous action potential occurs when the EADs or DADs amplitude is large enough for the membrane to reach its threshold potential. Continual repetition of the trigger activity can precipitate tachyarrhythmias [49].

Substrates are electrophysiological abnormalities that are prone to reentry, including increased dispersion of conduction or repolarization, and abnormal restitution [44]. Due to a pre-existing or abnormal circuit in the myocardium, reen-
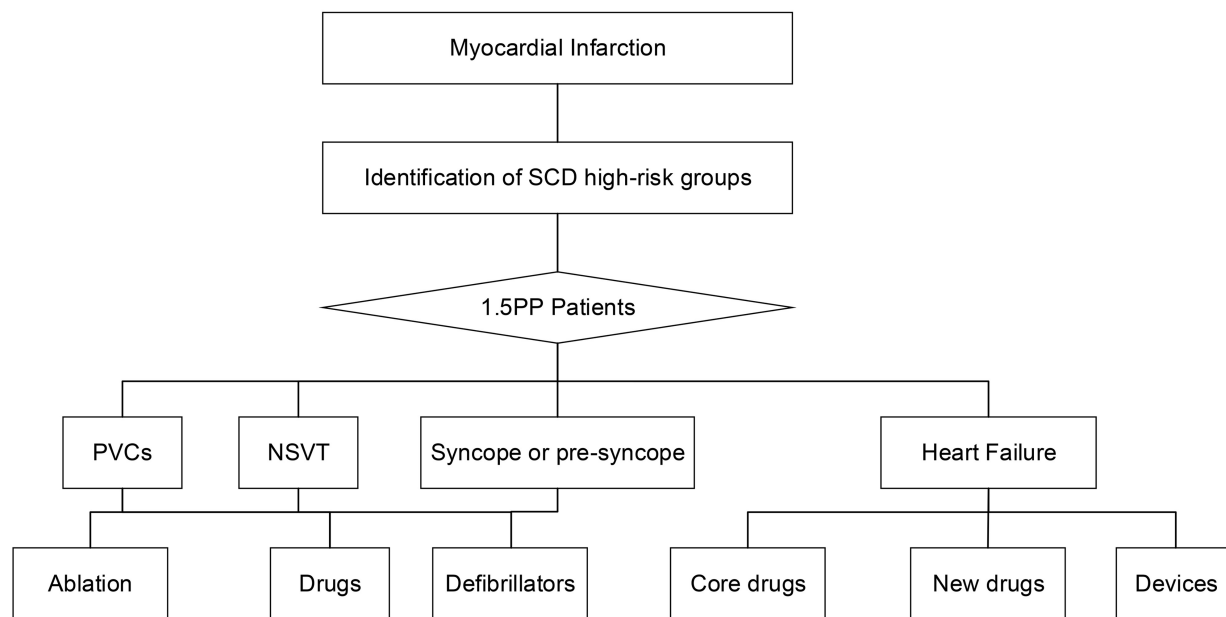
Fig. 2. Stratified management methods of high-risk patients with SCD after myocardial infarction. SCD, sudden cardiac death; PVCs, premature ventricular contractions; NSVT, non-sustained ventricular tachycardia; PP, primary prevention.

try occurs when the propagating impulse fails to die out after the normal activation of the heart and persists because of continuous activity around the circuit after the end of the refractory period, which causes the myocardium to continuously re-excite thus leading to arrhythmias, syncope, and even sudden death [44, 50]. TWA has been shown to be a risk factor and treatment indicator for patients with post-MI SCD in the Alternans Before Cardioverter Defibrillator (ABCD) trial and Risk Estimation Following Infarction Noninvasive Evaluation (REFINE) trial, and is best performed 10 to 14 weeks after the onset of an MI [51]. Its substrates are associated with repolarization dispersion that is histologically manifested as spatially concordant alternans and spatially discordant alternans, which promotes unidirectional conduction block and leads to reentry [52].

In addition, ischemia and hypoxia after an MI will lead to the increase of myocardial vulnerability and play an important role in the generation of re-entries [53]. HRV and the presence of the high average late potentials on ECG are also independent predictors of SCD and ischemic myocardial vulnerability after an MI [54].

4. Disease-specific therapy

For patients with an MI at high risk of SCD, professional care, and effective intervention are urgently needed to avoid fatal complications. Revascularization, including percutaneous coronary intervention (PCI) and surgical coronary artery bypass graft (CABG) surgery, is not only an important treatment but also a major preventive measure for SCD after an MI [55, 56]. Timing of revascularisation modifies the risk of SCD. Earlier revascularisation can lower the risk of SCD through the reduction of recurrent ischemia as well as the in-

cidence and degree of LV dysfunction [57, 58].

The selection of further treatment, including device therapy and drug therapy, depends on the SCD risk in MI patients. We used the 1.5PP stratification concept to summarize and list the specific management methods for patients in compliance with 1.5PP (Fig. 2).

4.1 PVCs/NSVT after MI

PVCs/NSVT are common after an MI, and the primary treatment for PVCs/NSVT is antiarrhythmic drugs (AADs) therapy or/and catheter ablation [59]. In addition, ICD implantation also has a significant preventive effect in this population [11]. Recently, statin therapy has been shown to be associated with improved survival in patients with ventricular tachyarrhythmias [60].

4.1.1 Antiarrhythmic drugs

It has been shown that type I AADs have no obvious effect in the prevention of SCD after an MI based on the experimental results of the Cardiac Arrhythmia Suppression Trial (CAST), the second Cardiac Arrhythmia Suppression Trial (CAST II), and the Cardiac Arrest Study Hamburg (CASH) [20, 61, 62]. Type I AADs also increase all-cause mortality. Therefore, they are not recommended for use in the primary prevention of SCD.

Class II β-blockers are an important part of the treatment of an MI, but they should be used only after HF resolves [63]. In the METOCARD-CNIC clinical trials, intravenous administration of metoprolol early before reperfusion reduced the infarct size and increased LVEF. In the long-term therapy following an MI, metoprolol helps to normalize LVEF, reduces the incidence of severe LV systolic dysfunction and the need for ICDs, and reduces the rate of hospital admissions for

HF [64]. In patients with an acute MI complicated with left ventricular systolic dysfunction, long-term treatment with carvedilol can reduce the frequency of all-cause and cardiovascular deaths and the recurrence of non-fatal MIs. In addition, in a retrospective study of 890 consecutive patients presenting with a NSTEMI, small doses of oral bisoprolol were protective against SCD in NSTEMI patients early after admission [65].

Amiodarone is an AAD with a class III effect and can be used for preventing SCD, especially in the first year after an MI. However, the EMIAT (European Myocardial Infarct Amiodarone Trial) failed to show any significant benefits of amiodarone on SCD [66]. A meta-analysis of 15 RCTs (8522 participants) showed that amiodarone could reduce the risk of SCD by 26% and that of all cardiovascular diseases by 18% in patients with cardiomyopathy, although it did not significantly reduce overall mortality. In addition, in another meta-analysis of 9997 participants with low-to-moderate quality evidence, amiodarone reduced SCD, cardiac, and all-cause mortality compared with placebo or interventions without primary prevention [67]. Therefore, amiodarone therapy may be reasonable for some patients who are at high risk for SCD.

In a multicentre, double-blind, randomized study enrolling 576 patients, diltiazem reduced the frequency of angina pectoris after a myocardial infarction by 49.7%. In addition, diltiazem can effectively prevent early re-infarction and severe angina after a non-Q wave infarction, and it is also safe and well-tolerated. However, the preventive effect against SCD after an MI remains to be seen.

4.1.2 Radiofrequency catheter ablation

Catheter ablation can eliminate abnormal electrical pathways from causing arrhythmias and reduce the risk of sudden cardiac death.

Catheter ablation is the most effective way to eradicate PVCs, which in addition to AADs is considered to be the first-line treatment in PVCs patients with decreased LVEF. However, there is still a need to conduct research to determine the best prevention and treatment methods for the underlying cause of PVCs to optimize treatment regimens while minimizing the risks [68].

In patients with recurrent VT, catheter ablation has become a recognized treatment option. In two prospective clinical trials, the Ventricular Tachycardia Ablation in Coronary Heart Disease (VTACH) and the Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia (SMASH-VT) trials, the time and frequency of recurrent VT/VF were significantly longer and decreased in patients who received ablation treatment [69, 70]. In addition, the incidence of ICD shocks in these patients was also significantly reduced. However, the timing of ablation of ventricular tachycardia in patients has always been a controversial topic, and this was the basis for the Preventive Ablation of Ventricular Tachycardia in Patients with Myocardial In-

farction (BERLIN VT) study [71]. In this trial, patients were randomly assigned (1 : 1) to either a prophylactic ablation strategy group or a delayed ablation strategy group, which received VT catheter ablation before ICD implantation or after the third appropriate ICD shock. Compared with the delayed ablation strategy, prophylactic VT ablation did not reduce the mortality or hospitalization rate of hospitalization due to worsening arrhythmia or HF within 1 year. Therefore, for secondary prophylaxis patients with ICD implantation indications, catheter ablation should be delayed until VT recurrence after ICD implantation is achieved to avoid the unnecessary risk of prophylactic ablation.

In the latest systematic review and meta-analysis of existing RCTs, preventive catheter ablation in patients with ischemic cardiomyopathy has been shown to reduce ICD treatment, ICD shock, and VT storms without increasing complications, especially in LVEF >30%. Appropriate ablation therapy is also associated with a significant reduction in the incidence of ICD shock, VT storm, and cardiac hospitalization [72]. In a multicenter, randomized, controlled trial, The Vasopressin vs. Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial, patients treated with AAD had more treatment-related adverse events than patients treated with ablation [73]. In order to explore whether catheter ablation is better than AADs in reducing mortality, the catheter ablation for VT in patients with an implantable cardioverter defibrillator (CALYPSO) pilot trial recruited 243 patients over 2 years. However, only 27 patients passed the screening because of prior AAD use, which resulted in the premature termination of the trial [74]. This trial highlights the difficulty in studying the current strategies that catheter ablation is used only after AAD fails. Recently, the VANISH2 trial (Ventricular Tachycardia Antiarrhythmics or Ablation in Structural Heart Disease 2, NCT02830360) enrolled 366 MI patients with a history of persistent uniform VT and randomized them to either catheter ablation or AAD, with the aim of determining the most appropriate first-line therapy for suppression of VT in persons with a prior MI by comparing the two strategies. And we look forward to encouraging results from this large clinical trial.

Another important aspect of ablation of ventricular tachycardia/sudden cardiac death is radiotherapy. Stereotactic arrhythmia radio ablation (STAR) is an emerging therapy for the treatment of VT. It has been shown to reduce the VT burden in patients who are difficult to treat with medication and/or catheter ablation or cannot tolerate catheter ablation [75]. However, there are significant differences in this emerging treatment between studies including a significant lack of consistency in the treatment protocols [76]. Therefore, more RCTs are still needed to establish a detailed treatment strategy.

4.2 Heart failure

Based on LVEF, HF is divided into HF with reduced ejection fraction (HFrEF, LVEF <40%) and HF with preserved ejection fraction (HFpEF, LVEF ≥50%). SCD comprises 25%

of all mortality in HFpEF patients and 40% of deaths in HFrEF patients [77]. Early reperfusion and early medication for HF are proven to be effective ways to improve the prognosis. Adding device treatments including ICD and cardiac resynchronization treatment (CRT) to avoid malignant arrhythmias will improve survival in these patients.

4.2.1 Basic drugs

According to the latest European Society of Cardiology/Heart Failure Association (ESC/HFA) consensus, the core treatment for HF contains beta-blockers, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB)/angiotensin receptor neprilysin inhibitor (ARNI), mineralocorticoid receptor antagonists (MRAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors [78]. Moreover, with the rational use of evidence-based drugs, rates of SCD in patients with HF declined substantially over time [79].

The activation of the RAAS system and the sympathetic nervous system is the key neurohumoral mechanism that causes HF. Blocking the production of angiotensin II (Ang II) and the activation of its related receptors plays an important role in blocking the RAAS cascade [80].

Among 2231 patients who survived MI and had LVEF ≤40%, captopril treatment reduced the risk of recurrent MI by 25% and the risk of death after MI recurrence by 32% [81]. In the Vasodilator-Heart Failure Trial II (V-HeFT II) trial, there was no significant difference between enalapril and isosorbide dinitrate/hydralazine in the treatment of patients with LVEF ≤45% who survived an MI. This provides further evidence that treatment with captopril and enalapril are important agents to prevent SCD after an MI.

Representative drugs in the ARB class include valsartan and losartan. In two prospective studies, the Acute Myocardial Infarction (VALIANT) trial and the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL), valsartan, and losartan were effective in treating acute MI patients. In addition, in patients with HF after MI, valsartan can down-regulate the occurrence of arrhythmic events, for example, NSVT, through cardiac reverse remodeling [82].

In the consensus guidelines between the Canadian Cardiovascular Society (CCS) and the American College of Cardiology (ACC), ARNI (sacubitril/valsartan) is prescribed as the first-line therapy [83, 84]. In the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial) trial involving 8442 patients with LVEF ≤40%, sacubitril/valsartan was shown to be superior to enalapril in reducing mortality and hospitalization rates in HFrEF patients [85]. In addition, sacubitril/valsartan also performed better than valsartan in reducing hospitalization rates in HFpEF patients [86]. However, whether ARNI prevents the development of HF after infarction and reduces SCD in patients with acute myocardial infarction (AMI) remains unknown.

To address this issue, the PARADISE-MI (Prospective ARNI vs. ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events after MI) trial enrolled 5661 patients with an AMI randomized 1 : 1 to receive sacubitril/valsartan or ramipril therapy [87]. The results show that although sacubitril/valsartan failed to reduce the primary endpoint in the AMI population compared with ramipril, the incidence of sacubitril/valsartan was low and a composite endpoint that included all HF events shows the advantages with sacubitril/valsartan over ramipril.

Mineralocorticoid receptor antagonists (MRAs) are recognized to be effective in reducing the mortality of patients with HF after MI. In a meta-analysis involving 25 RCTs and 19,333 patients, MRAs effectively down-regulated all-cause and cardiovascular mortality [88]. In addition, in a meta-analysis of three placebo-controlled randomized trials; the Randomized Aldactone Evaluation Study (RALES), Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), and the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), the risk of SCD in patients with HF treated with spironolactone or eplerenone was reduced by 23% [89].

According to the guidelines, SGLT2 inhibitors, such as Dapagliflozin, are recommended for patients with mild to moderate HF with reduced LVEF (≤40%) or coronary heart disease to improve symptoms and quality of life and reduce the risk of hospitalization and cardiovascular mortality [90].

4.2.2 Other new drugs

Other anti-heart failure drugs with different mechanisms of action have also been clinically effective, including vericiguat, omecamtiv mecarbil, and ivabradine. Vericiguat is an oral agonist for guanylate cyclase which improved outcomes in patients with an LVEF ≤40% [91]. Omecamtiv mecarbil is a novel selective cardiac myosin activator, which has been shown to improve cardiac function and reduce ventricular volume, heart rhythm, and N-terminal pro-B-type natriuretic peptide in patients with chronic HF. The combined incidence of cardiovascular death or HF events decreased significantly after omecamtiv mecarbil treatment [92]. Of the drugs used clinically, only ivabradine directly reduces the heart rate of sinoatrial node cells in the absence of other known cardiovascular system effects, which significantly reduced cardiovascular mortality or HF hospitalization rates [93].

4.2.3 Device treatment

An ICD is designed to detect and treat life-threatening arrhythmias and then automatically discharge and defibrillate to significantly reduce malignant ventricular rhythms. Patients with an LVEF ≤35% after an MI are the main beneficiaries of ICD management and prevention [94]. However, the majority of patients who die suddenly after an MI have LVEFs >35% and are ineligible for ICD treatment ac-

cording to current guidelines [95]. The Risk Estimation Following Infarction Noninvasive Evaluation - ICD Efficacy trial (Refine-ICD; https://clinicaltrials.gov/ Identifier NCT 00673842), an ongoing study, is expected to randomly select 1400 survivors of an MI to evaluate whether ICD treatment reduces mortality in patients with an LVEF between 36% and 50%, abnormal cardiac depolarization (TWA) and autonomic tension impairment (HRT) after an MI, which will complement the ICD implant evidence in the current guidelines.

Some patients with HF have atrioventricular, interventricular, and/or intraventricular dyssynchrony, which leads to decreased myocardial contractility. Cardiac resynchronization therapy (CRT) improves HF symptoms, exercise tolerance, quality of life, hospitalization rate, and significantly lowers mortality by improving atrioventricular, interventricular, and/or inventricular systolic synchronization and increasing cardiac output [96].

In pursuit of physiologic inventricular, interventricular, and atrioventricular synchronization, the pacing sites, and modes have been continuously improved and developed from biventricular pacing (BVP), to His bundle pacing (HBP), and the current left bundle branch pacing (LBBP) [97]. LBBP is defined as the capture of the left bundle branch (LBB) via a transventricular septal approach. Zhang *et al.* [98] performed LBBP in 11 patients with HF, and the results showed that the LVEF of all patients improved. Wu *et al.* [99] analyzed a total of 137 CRT patients with LVEF ≤40% who received BVP, HBP, or LBBP and found that patients treated with LBBP and HBP showed significantly better improvement in symptoms and left ventricular function than those treated with BVP. The R-wave amplitude and pacing threshold of LBBP were more satisfactory and stable than those of HBP [100]. However, many aspects of LBBP remain unknown and more RCTs are needed to explore its long-term safety and efficacy.

Further studies are necessary to determine whether using a more expensive defibrillator component such as (CRT-D) to CRT pacing (CRT-P) is needed. So far, no studies have provided clear evidence on the incremental survival advantage of CRT-D over CRT-P, in the ischaemic cardiomyopathy (ICM)/non-ischaemic cardiomyopathy (NICM) population [101]. The landmark COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial demonstrated that the addition of a defibrillator to cardiac resynchronization therapy does not significantly affect the combined outcome of death or hospitalization from any cause. However, the addition of a defibrillator to cardiac resynchronization therapy gradually increased the survival benefit, resulting in a significant 36% reduction in the risk of death compared to optimal pharmacologic therapy, and patients with NICM had a greater survival benefit using CRT-D than CRT-P [102]. Recently, a European observational, multicenter cohort study involving 5307 patients compared CRT-D with CRT-P treatment and showed that there was no survival benefit from the addition of an ICD in NICM patients compared to ICM patients [103]. The most reason-

able explanation for these results is that the proportional risk of SCD mainly determines the survival benefits of ICD implantation. This suggests that CRT-D has a greater benefit when the proportional risk of SCD is high while CRT-P has a greater benefit when the proportional risk of SCD is low [104]. However, more evidence is needed to identify the incremental survival advantage of CRT-D and the specific population that may benefit from it, so that patients can select the most appropriate device for treatment.

4.3 Management for patients with syncope or pre-syncope after MI

The survival rate of SCD is very low, so cardiopulmonary resuscitation (CPR) should be performed immediately in patients with a myocardial infarction in the event of syncope, coma, or cardiac arrest. In addition, in the 2017 guidelines, according to expert opinions, it is recommended that syncope patients with ischemic cardiomyopathy should be managed and treated following the guidelines, including the preventive effect of ICD on patients with cardiogenic syncope [105].

5. Conclusions

The occurrence of SCD after an MI is a major public health issue and the largest contributor to the global mortality risk. The impact of these tragic events is far-reaching and has a major impact on hospitals, communities, and families. In order to provide patients with appropriate management methods, more work is needed to define appropriate post-MI risk stratification. In addition, as the technology changes dynamically, guidelines for technical management should be gradually refined and adjusted, including the timing of ICD implantation and catheter ablation after an MI, and the criteria for the use of WCD, S-ICD, and CRT-D. The clinical therapeutic effects of new drugs with different mechanisms should be explored in order to provide more personalized treatment methods. Continued research in this field will be the key to reduce SCD after an MI.

Author contributions

YT wrote the original draft, and XF reviewed and edited the manuscript.

Ethics approval and consent to participate

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Conflict of interest

The authors declare no conflict of interest.

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