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Review

Contemporary management of heart failure patients with reduced ejection fraction: the role of implantable devices and catheter ablation

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Heart failure (HF) is a complex clinical syndrome characterised by significant morbidity and mortality worldwide. Evidence-based therapies for the management of HF include several well-established neurohormonal antagonists and antiarrhythmic drug therapy to mitigate the onset of cardiac arrhythmia. However, the degree of rate and rhythm control achieved is often suboptimal and mortality rates continue to remain high. Implantable cardioverter-defibrillators (ICDs), cardiac resynchronization (CRT), and combined (CRT-D) therapies have emerged as integral and rapidly expanding technologies in the management of select patients with heart failure with reduced ejection fraction (HFrEF). ICDs treat ventricular arrhythmia and are used as primary prophylaxis for sudden cardiac death, while CRT resynchronizes ventricular contraction to improve left ventricular systolic function. Left ventricular assist device therapy has also been shown to provide clinically meaningful survival benefits in patients with advanced HF, and His-bundle pacing has more recently emerged as a safe, viable, and promising pacing modality for patients with CRT indication. Catheter ablation is another important and well-established strategy for managing cardiac arrhythmia in HF, demonstrating superior efficacy when compared with antiarrhythmic drug therapy alone. In this article, we provide a comprehensive and in-depth evaluation of the role of implantable devices and catheter ablation in patients with HFrEF, outlining current applications, recent advances, and future directions in practice.

Keywords

Heart failure; HFrEF; Catheter ablation; Implantable device; Atrial fibrillation; Ventricular tachycardia; Prevention

1. Introduction

Heart failure (HF) is a leading cause of morbidity and mortality worldwide. Cardiac arrhythmias, whether symptomatic or not, are common in all forms of HF. Atrial fibrillation (AF) and heart failure with reduced ejection fraction (HFrEF) are two of the most commonly encountered cardiac diseases that often co-exist and exacerbate one another [1]. Common mechanisms that underly the development of AF in HF include an elevation in left ventricular (LV) filling pressure secondary to systolic and diastolic dysfunction with concomitant atrial stretch, increased interstitial fibrosis leading to abnormal atrial conduction properties, dysregulation of intracellular calcium metabolism and alteration to depolarization patterns, and neurohormonal dysfunction [2]. AF may also precipitate the onset of HF by altering the efficiency of systolic and diastolic timing, leading to a shortened LV filling time, suboptimal rate control, and reduced myocardial contractility [3]. Ventricular tachyarrhythmias including ventricular tachycardia (VT) or ventricular fibrillation (VF) are also common in HF. These pathologies result from myocardial hypertrophy and sustained mechanical stretch, leading to stretch-induced ventricular arrhythmogenicity, and myocardial fibrosis and scar formation post-myocardial infarction with the induction of re-entrant VT [4].

Over the last few decades, beta-blockers, angiotensin receptor–neprilysin inhibitors (ARNis), and mineralocorticoid receptor antagonists (MRAs) have continued to demonstrate favourable reductions in mortality and hospitalization for HF [5]. Antiarrhythmic drug (AAD) therapy can also be used to reduce tachyarrhythmia-related symptoms, however many challenges continue to exist [6]. Catheter ablation has emerged as a superior alternative to pharmacological management especially in those who are drug intolerant or for

whom drug therapy is ineffective [7]. Device therapy has also become increasingly integral, encompassing a broad range of technologies for both acute (e.g., the intra-aortic balloon counterpulsation pump) and non-acute (e.g., left ventricular assist device) applications [8]. Their predominant indication however is to prevent sudden cardiac death (SCD) by treating VT or VF via an implantable cardioverter-defibrillator (ICD) or to provide cardiac resynchronization (CRT). Multiple clinical trials have since established the survival and quality of life (QoL) benefits of ICDs, CRTs, and their combination (CRT-D) in patients with HF [9, 10]. A flowchart illustrating treatment selection is presented in Fig. 1. His-bundle pacing has more recently emerged as a novel, safe, and alternative pacing modality to biventricular pacing in patients with HF and left bundle branch block (LBBB), and in patients with narrow QRS and PR prolongation [2, 11]. In light of recent advances, this review aims to provide a comprehensive and in-depth evaluation of the current role and future trajectory of implantable devices and catheter ablation in the contemporary management of HFrEF.

2. Implantable cardioverter defibrillators

2.1 Implantable cardioverter defibrillator versus pharmacological therapy

ICDs are an important component in the prevention of SCD in patients with VT, reducing all-cause mortality in both primary and secondary prevention populations with poor left ventricular ejection fraction (LVEF) due to ischaemic or non-ischaemic cardiomyopathy (Table 1, Ref. [12–17]). The Multicenter Automatic Defibrillator Implantation Trial II (MADIT)-II study by Moss *et al.* [13] was the first randomized trial to successfully demonstrate the lifesaving benefits of prophylactic ICD therapy. After randomization of 1232 post-myocardial infarction patients with LVEF $\leq$30% to ICD versus medical therapy, the primary outcome of all-cause mortality was significantly lower in the ICD arm at a mean follow-up of 20 months (14.2% vs. 19.8%, respectively; predominantly attributed to a reduction in SCD [18]). However, hospitalization for HF was notably more frequent in patients with ICD. Unlike MADIT-I, which demonstrated an early survival benefit with ICD, no mortality reduction was observed until nine months in MADIT-II [12].

The survival benefit of an implanted ICD was later shown to be in concordance with data from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Designed to investigate whether amiodarone or a conservatively programmed shock-only ICD would reduce the primary outcome of all-cause mortality among 2521 patients with NYHA class II/III and LVEF $\leq$35% [15], ICD implantation resulted in a 23% reduction in the risk of death from any cause and an absolute 7% decrease in mortality at a mean follow-up of 45.5 months. As with MADIT-II, worsening HF was the most common cause of mortality. This outcome may be attributed to the onset of inappropriate defibrillator shocks resulting in myocardial injury. Moreover, increased fibrosis may increase defibrillation thresholds, thus requiring higher energy defibrillations during subsequence arrhythmic events (fibrotic areas may also lead to new arrhythmogenic re-entry circuits) [19]. The induction of VF to test the correct sensing and defibrillation properties during implantation may also result in myocardial cell damage, and increased mortality may be due in part to the adverse psychological effects of an ICD stock, including anxiety and reactive depression [20]. Although no benefit was observed with amiodarone, its use will likely continue to be employed for the suppression of ambient ventricular arrhythmia amongst ICD recipients owing to its minimal pro-arrhythmic profile [21].

Regarding primary prevention therapy with ICDs in a non-ischaemic cardiomyopathy patient cohort, Kadish *et al.* [14] randomized 458 patients to single-chamber ICD plus medical therapy versus medical therapy alone in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) study, and demonstrated no significant difference in the primary endpoint of all-cause mortality at a mean follow-up of 26 months. However, a significant reduction in mortality due to arrythmia was reported with ICD use. These findings were later found to be in concordance with data from the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) [16], whereby randomization of 1116 patients with non-ischaemic cardiomyopathy to ICD versus usual clinical care demonstrated no statistically significant difference in all-cause mortality, death from cardiovascular causes, or safety events at a median follow-up of 68 months (despite a statistically significant reduction in SCD). Of note, an age-by-therapy interaction was observed as part of this study whereby younger patients derived a mortality benefit from ICD therapy whereas older patients (who are more likely to be at greater risk of complications e.g., lead fracture, device failure, infection necessitating system extraction, and death and HF-related hospitalization [22]) did not, highlighting the importance of careful patient selection. Moreover, it is possible that the relatively high rate of non-cardiovascular mortality may have led to an underestimation of the effects of ICD therapy.

In another study, the Prospective Comparison of ARNi with ACEi (angiotensin converting enzyme inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) by McMurray *et al.* [23] reported the superiority of the potentially antiarrhythmic ARNi versus enalapril in reducing the risk of death and hospitalization for HF in 8442 patients with NYHA class II-IV and LVEF $\leq$40%. However, it should be noted that a low percentage of patients within this study were in receipt of an ICD [24].

2.2 Subcutaneous implantable cardioverter defibrillators

In addition to transvenous ICDs, subcutaneous ICDs (s-ICDs) were originally designed to mitigate the risk of lead failure and systemic infection associated with the endovascular leads of transvenous devices [25, 26]. Although S-

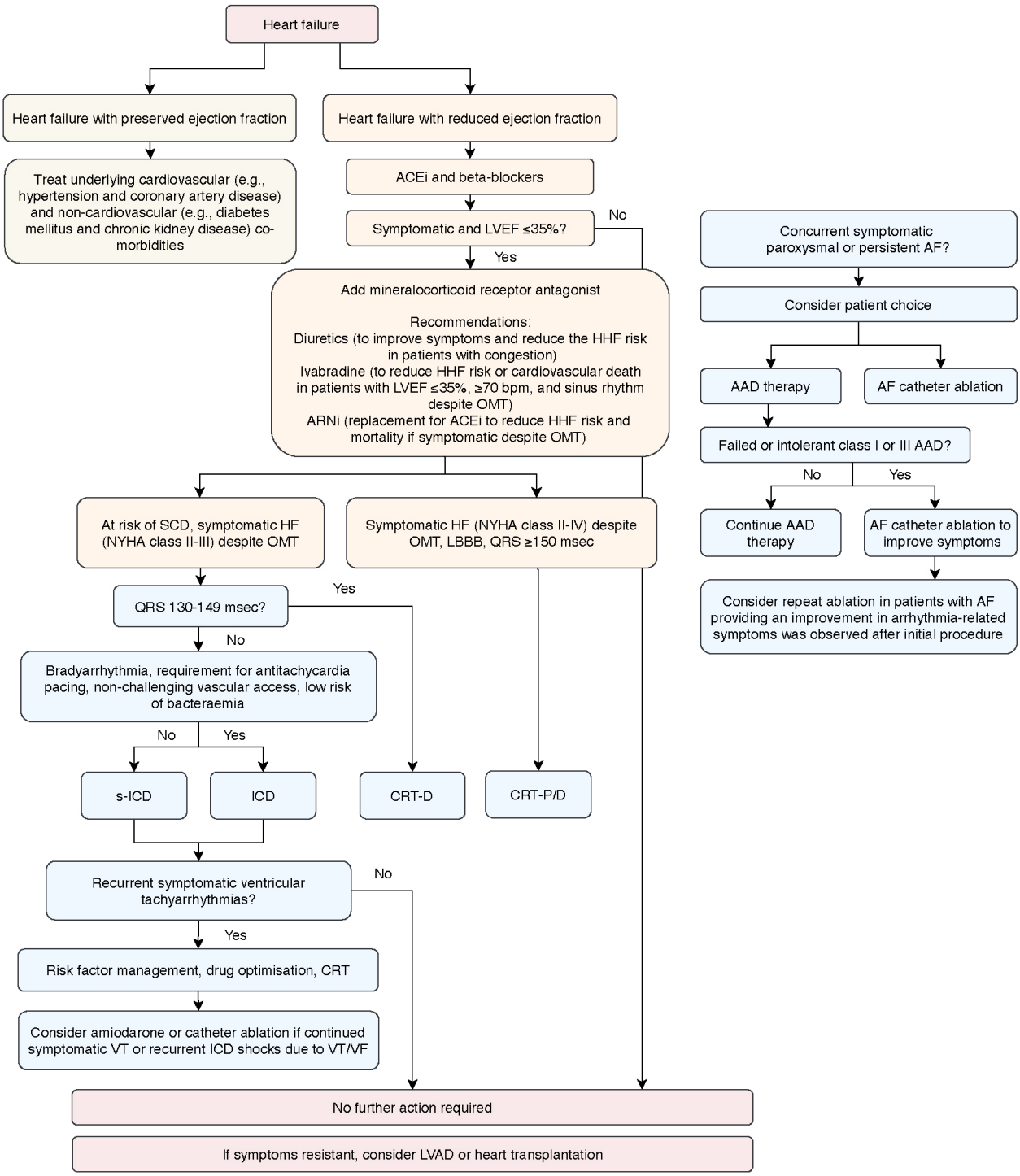

Fig. 1. Flowchart for treatment selection of device therapy or catheter ablation in patients with HF. AAD, antiarrhythmic drug; ACEi, angiotensin converting enzyme inhibitor; HHF, hospitalization for HF; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OMT, optimal medical therapy; SCD, sudden cardiac death.

ICDs are less prevalent than transvenous ICDs, their implantation is increasing [27]. The landmark Prospective Randomized Comparison of Subcutaneous and Transvenous Implantable Cardioverter Defibrillator Therapy (PRAETORIAN) study by Knops *et al.* [17] was the first randomized trial to compare subcutaneous versus transvenous ICDs. After randomization of 849 patients with class I or IIa indication for single-chamber ICD, device-related complications, inappropriate shocks, and hospitalization for HF were similar between groups at a median follow-up of 49.1 months. Although promising in its demonstration of the non-inferiority of s-ICDs relative to transvenous devices, notable differ-

ences were present between arms, including inappropriate shocks (driven by AF and supraventricular tachycardia in the transvenous arm and cardiac over-sensing in the s-ICD arm) and bleeding, albeit counterbalanced by infection. Limitations of this study include a short follow-up duration with respect to chronic complications and limited s-ICD longevity, the use of a non-inferiority margin, and a high percentage of patients lost to follow-up.

More recently, Gold *et al.* [28] evaluated the role of s-ICDs with standardized device programming in 1111 primary prevention patients with LVEF $\leq$35% in the Understanding Outcomes With the S-ICD in Primary Prevention Patients With Low Ejection Fraction (UNTOUCHED) study. Although a high level of freedom from inappropriate shocks, shock-free, and complication free rates was reported, notable limitations include a relatively short follow-up (18 months) and a non-randomized study design. Complementary data and longer term trends regarding the incidence of inappropriate shocks are due to be investigated in the EFFORTLESS (NCT01085435) [29] and PAS trials (NCT01736618) [30], while the ATLAS study will evaluate early and mid-term vascular and lead-related complications (NCT02881255) [31].

3. Cardiac resynchronization therapy

3.1 Cardiac resynchronization therapy versus pharmacological therapy

Cardiac resynchronization (CRT), or biventricular (BiV) pacing, is a therapeutic option in HF patients with prolonged QRS duration ($\geq$150 ms) and LBBB morphology, and in patients with a QRS duration of 130–149 ms with LBBB depending on NYHA classification [32]. The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) study was the first randomized clinical trial to evaluate the role of CRT or CRT-D versus optimal pharmacological therapy in a cohort of 1520 patients with NYHA class III/IV and QRS $\geq$120 ms (Table 2, Ref. [9, 10, 33–38]) [35]. At a median follow-up of 14.4 months, the primary outcome of all-cause mortality or all-cause non-elective hospitalization was significantly lower in the CRT arm. Moreover, the risk of death from any cause decreased by 24% with CRT-pacemaker (CRT-P) and 36% with CRT-D. Although earlier trials including the Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE; CRT vs. no pacing) trial [33] and MIRACLE-ICD (CRT with CRT capability turned on vs. turned off) [34] demonstrated improvements in QoL endpoints (e.g., 6-minute walk tests, NYHA functional class, and functional capacity) these were not powered to address the impact of CRT/ICD on mortality.

The survival benefits of CRT with or without defibrillator therapy were further supported by Cleland *et al.* [10] in the Cardiac Resynchronization - Heart Failure (CARE-HF) study. After randomization of 813 patients with NYHA class III/IV HF and QRS >120 ms to CRT versus optimal pharmacological therapy, a significantly lowered incidence of the primary endpoint (death from any cause or unplanned hospitalization for a major cardiovascular event) was reported in the CRT group at a mean follow-up of 29.4 months. Moreover, the authors reported a significant improvement in anatomical ventricular remodelling and neurohormonal measures (e.g., N-terminal pro-brain natriuretic peptide), reflecting the reverse modelling impact of CRT.

3.2 Cardiac resynchronization therapy with CRT capability turned on versus turned off

Although promising, the aforementioned findings were later countered by data from Ruschitzka *et al.* [37] in the Echocardiography Guided Cardiac Resynchronization Therapy (ECHO-CRT) study, which randomized 809 NYHA class III/IV HF patients to CRT with CRT capability turned on versus turned off and showed a non-significant increase in a predominantly cardiovascular death-driven all-cause mortality or first hospitalization for worsening HF. The participants of this study were notably selected for narrow QRS $\leq$130 ms (mean cohort duration: 105 ms; in contrast to COMPANION and CARE-HF, median cohort duration: both 160 ms), which may indicate the presence of potentially adverse effects in recipients of CRT with an exceptionally short QRS. Although the benefits of CRT are greater in patients with severe QRS ($\geq$150 ms) versus moderately prolonged (120–149 ms) [39], the effects of a mild-moderate QRS (e.g., 130–149 ms) has yet to be fully explored.

3.3 Cardiac resynchronization therapy versus implantable cardioverter defibrillator

The role of CRT in combination with ICD in less severe forms of HF have also been studied. In contrast to the CARE-HF trial, Moss *et al.* [9] (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy, MADIT-CRT study) randomized 1820 patients with LVEF $\leq$30%, QRS $\geq$130 ms, and NYHA class I/II HF to CRT plus ICD versus ICD alone. The primary endpoint of all-cause mortality or a non-fatal HF event was significantly reduced in the CRT-ICD arm at a mean follow-up of 28.8 months, driven predominantly by a 41% reduction in HF-related adverse events. These benefits were more evident in NYHA class II versus I recipients, highlighting the importance of risk stratification.

The survival benefit of defibrillator therapy in patients with mild-moderate NYHA class II/III HF, LVEF $\leq$30%, and QRS $\geq$120 ms (intrinsic) or $\geq$200 (paced) was later supported by Tang *et al.* [36] in the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). After randomisation of 1798 patients to CRT/ICD or ICD alone, the primary endpoint of all-cause mortality or hospitalization for HF occurred in 33.2% of CRT/ICD patients as compared with 40.3% of ICD patients at a mean follow-up of 40 months. However, as with MADIT-CRT, the 30-day post-implant incidence of adverse events was significantly higher in CRT/ICD, predominantly driven by lead dislodgement requiring intervention, which may reflect an increased complexity of the procedures performed.

Table 1. Key randomized controlled trials of implantable devices in patients with HF, with a focus on survival outcomes and hospitalization for HF.

Study	Year	Number of participants (N)	Follow-up (months)	Intervention	Death from any cause (HR; 95% CI)	Hospitalization for HF (HR; 95% CI)
				ICD		
MADIT [12]	1996	196	27	ICD vs. medical therapy	0.46 (0.26–0.82); $p = 0.009$	N/A
MADIT II [13]	2002	1232	20	ICD vs. medical therapy	0.69 (0.51–0.93); $p = 0.016$	Defibrillator group: 148 (19.9%) Medical therapy group: 73 (14.9%) (number of patients hospitalised for HF)
DEFINITE [14]	2004	458	26	ICD plus medical therapy vs. medical therapy	0.65 (0.40–1.06); $p = 0.08$	N/A
SCD-HeFT [15]	2005	2521	45.5	ICD vs. amiodarone vs. placebo	Defibrillator: 0.77 (0.62–0.96); $p = 0.007$ Amiodarone: 1.06 (0.86–1.30); $p = 0.53$	N/A
DANISH [16]	2016	1116	68	ICD vs. medical therapy	0.87 (0.68–1.12); $p = 0.28$	N/A
				s-ICD		
PRAETORIAN [17]	2020	849	49.1	Subcutaneous vs. transvenous ICD	1.23 (0.89–1.70); p-value not provided	1.08(0.79–1.49)

Table 2. Key randomized controlled trials of CRT in patients with HF, with a focus on survival outcomes and hospitalization for HF.

Study	Year	Number of participants (N)	Follow-up (months)	Intervention	Death from any cause (HR; 95% CI)	Hospitalization for HF (HR; 95% CI)
MIRACLE [33]	2002	453	6	CRT vs. no-CRT	0.73 (0.34–1.54); $p = 0.40$	0.50 (0.28–0.88); $p = 0.02$
MIRACLE-ICD [34]	2003	369	6	CRT with CRT capability turned on vs. turned off	CRT on: 25.7% (95% CI, 19.6–32.3%) CRT off: 25.9% (95% CI, 19.8–32.5%) $p = 0.69$ (probability of hospitalization for worsening HF or death from any cause)	CRT on: 47.4% (95% CI, 40.0–54.4%) CRT off: 48.3% (95% CI, 40.6–55.6%) $p = 0.88$ (probability of the risk of death or all–cause hospitalization)
COMPANION [35]	2004	1520	14.4	CRT-P vs. CRT-D vs. medical therapy	CRT-P: 0.76 (0.58–1.01); $p = 0.059$ CRT-D: 0.64 (0.48–0.86); $p = 0.003$	CRT-P: 0.66 (0.53–0.87); $p = 0.002$ CRT-D: 0.60 (0.49–0.75); $p < 0.001$ (death from or hospitalization for HF)
CARE-HF [10]	2005	813	29.4	CRT-P vs. medical therapy	0.64 (0.48–0.85); $p < 0.002$	0.48 (0.36–0.64); $p < 0.001$
MADIT-CRT [9]	2009	1820	28.8	CRT-D vs. ICD	0.66 (0.52–0.84); $p = 0.001$ (risk of death or HF)	0.59 (0.47–0.74); $p < 0.001$ (risk of HF)
RAFT [36]	2010	1798	40	CRT-D vs. ICD	0.75 (0.62–0.91); $p = 0.003$	0.68 (0.56–0.83); $p < 0.001$
ECHO-CRT [37]	2013	809	19.4	CRT with CRT capability turned on vs. turned off	1.81 (1.11–2.93); $p = 0.02$	1.16 (0.87–1.55); $p = 0.25$
BLOCK-HF [38]	2013	691	37	CRT-P or ICD with RV pacing vs. CRT-P or ICD with biventricular pacing	0.83 (0.61–1.14); p-value not provided	0.70 (0.52–0.93); p-value not provided

3.4 Biventricular versus right ventricular pacing

More recently, the superior long-term clinical and functional outcomes of BiV pacing in patients with high grade atrioventricular block (AVB) and mild-to-moderate LV dysfunction has been shown. In the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK-HF) study, Curtis *et al.* [38] randomized 691 patients with NYHA class I-III, LVEF $\leq$50%, and AVB to CRT-P or ICD with BiV versus right ventricular (RV) pacing. At a mean follow-up of 37 months, the incidence of death from any cause, urgent care visit for HF requiring IV therapy, or an increase in LV end-systolic volume index by $\geq$15% was significantly lower in the BiV group. In addition, the benefits of BiV pacing were found to persist irrespective of NYHA class (therefore, it is suggested that CRT may be the pacing modality of choice in patients with pre-existing HF who are likely to require a high degree of pacing support). Limitations include a high crossover rate, which may reflect a greater benefit of CRT, and placement of an LV lead in all patients, rendering it difficult to compare the rates of complication between groups.

3.5 His-bundle pacing

His-bundle conduction pacing (HBP) has more recently emerged as a viable alternative to BiV and RV pacing, achieving a physiological pattern of ventricular activation via the native His-Purkinje system. In particular, the use of HBP in conjunction with an LV lead (i.e., His-optimized CRT) has been shown to shorten LV activation times by $\geq$10 ms [40] as well as to reduce baseline QRS and to increase LVEF [11], reflecting an improvement in electrical synchrony. More recently, Sohaib *et al.* [2] showed AV-optimized HBP in 16 consecutive patients with HF and PR prolongation with either a normal QRS or right bundle branch block (RBBB) to improve acute haemodynamic function. Future complementary findings will be provided by the HOPE-HF study (NCT02671903) which aims to evaluate the role of AV delay optimisation via HBP on changes in exercise capacity in patients with PR interval $\geq$200 ms, LVEF $<$40%, and either narrow QRS ($\leq$140 ms) or RBBB, and the His-SYNC study (NCT02700425) which will investigate the safety and efficacy of HBP versus CRT.

Although promising, various clinical concerns are associated with HBP including a longer and more demanding learning curve [41], failed corrections of bundle branch block [42], and high HBP capture thresholds at implant and/or during late follow-up leading to premature battery depletion [43]. To address this, left bundle branch area pacing (LBBAP) has emerged as a safe and feasible technique for the delivery of physiological pacing in the event of failed HBP (demonstrating higher rates of implant success and lower lead-related complications [44, 45]), and as a valuable alternative to conventional CRT (demonstrating significant QRS narrowing and improvements in LVEF [46, 47]). However, future large prospective and randomized studies are needed to further verify the long-term safety and effectiveness of this pacing modality.

4. Left ventricular assist devices

Mechanical circulatory support via left ventricular assist device (LVAD) therapy is typically used in patients with drug-refractory end-stage HF as either a bridge to cardiac transplantation, bridge to recovery, or as destination therapy in terminal cardiac dysfunction. The landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) study by Rose *et al.* [48] randomized 129 patients with symptomatic end-stage HF and an ineligibility for cardiac transplantation to LVAD therapy versus optimal medical therapy. Although all-cause mortality was significantly lower in the LVAD group, this study reported significant morbidity and prolonged hospitalization alongside a 1-year survival rate of 52% in the LVAD group and 25% in the medical therapy group, and 2-year survival rate of 23% and 8%, respectively. In addition, the frequency of serious adverse events for LVAD was 2.35 times that of the medical therapy group, with a predominance of infection (28% at 3 months), bleeding (42% at 6 months), and risk of device malfunction (35% at 2 years) albeit countered by significant improvements in QoL as determined by SF-36 score, Beck depression inventory, and median NYHA class. Nevertheless, this study was the first to demonstrate a clinically meaningful survival benefit after LVAD therapy in patients with advanced HF, and its viability as a therapeutic option in select patients who are not candidates for cardiac transplantation. Recent meta-analyses have additionally supported the survival benefits of LVADs in comparison to medical management, with newer generations (e.g., HeartMate 3 and HeartWare) faring better than older generations (e.g., HeartMate II and HeartMate XVE/VE) for bleeding, device thrombosis, and stroke risk, albeit associated with worse adverse events e.g., drive-line exit-site infection [49]. Given the prevalence of comorbid conditions in HF, neither diabetes mellitus (DM) [50], pre-operative AF [51] nor prior CRT [52] have been shown via meta-analysis to significantly influence all-cause mortality post-LVAD.

5. Catheter ablation for atrial fibrillation

5.1 Catheter ablation versus rate control therapy

A number of clinical trials have demonstrated catheter ablation for AF in patients with HF to be safe and superior to pharmacological therapy, particularly if refractory or intolerant to medication [53]. The superiority of catheter ablation over rate control has been established in various small-scale trials and early randomized controlled trials (e.g., ARC-HF, CAMTAF, CAMERA-MRI). These studies showed an association between catheter ablation and significant improvements in LVEF, QoL (via Minnestoa living with HF questionnaire score), cardiopulmonary exercise performance (measured by peak oxygen consumption), B-type natriuretic peptide levels, and freedom from AF at follow-up (Table 3, Ref. [54–69]) [55–57, 59, 70].

Table 3. Key randomized controlled trials of catheter ablation for AF and VT in patients with HF.

Atrial fibrillation						
Study	Year	Number of participants (N)	Follow-up (months)	Intervention	Improvement in LVEF	Freedom from AF
PABA-CHF [54]	2008	81	6	CA vs. AV nodal ablation plus biventricular pacing	+8% vs. −1%	Patients receiving AADs: 88% Patients not receiving AADs: 71%
MacDonald *et al.* [55]	2011	41	12	CA vs. rate control	+4.5% vs. +2.8%	CA: 50% Rate control: 0%
ARC-HF [56]	2013	52	12	CA vs. rate control	+10.9% vs. +5.4	CA: 88% Rate control: rate criteria was achieved in 96% patients
CAMTAF [57]	2014	50	12	CA vs. rate control	+8.1% vs. −3.6%	CA: 73% Rate control: 0%
AATAC [58]	2016	203	24	CA vs. amiodarone	+8.1% vs +6.2%	CA: 70% Amiodarone: 34%
CAMERA-MRI [59]	2017	66	6	CA vs. rate control	+18% vs. 4.4%	CA: 100% Rate control: 0%
CASTLE-AF [60]	2018	363	60	CA vs. rate or rhythm control	+8.0% vs. +0.2%	CA: 63.1% Rate or rhythm control: 21.7%
AMICA [61]	2019	140	12	CA vs. rate or rhythm control	+8.8% vs. +7.3%	CA: 73.5% Rate or rhythm control: 50%
CABANA-AF [62]	2019	2204	60	CA vs. rate or rhythm control	N/A	CA: 84% Rate or rhythm control: 74%
CIRCA-DOSE [63]	2019	346	12	Contact force–guided radiofrequency ablation vs. 4-minute cryoballoon ablation vs. 2-minute cryoballoon ablation	N/A	53.9% vs. 52.2% vs. 51.7% (Freedom from any atrial tachyarrhythmia, after a single ablation procedure, with 90-day blanking period)
Ventricular tachycardia						
Study	Year	Number of participants (N)	Follow-up (months)	Intervention	Survival	Freedom from VT
SMASH-VT [64]	2007	128	22.5	CA plus ICD vs. ICD	99% vs. 83%	CA plus ICD: 88% ICD: 67%
VTACH [65]	2010	110	24	CA plus ICD vs. ICD	90.4% vs. 92.7%	CA plus ICD: 47% ICD: 29%
HELP-VT [66]	2014	227	12	CA in dilated non-ischaemic CM vs. ischaemic CM	87.3% vs. 92.1%	Non-ischaemic CM: 40.5% Ischaemic CM: 57.0%
VANISH [67]	2016	259	27.9	CA vs. rhythm control	72.7% vs. 72.7%	CA: 57.6% Rhythm control: 57.5% (Freedom from appropriate ICD shock at any time)
SMS [68]	2017	111	27.6	CA plus ICD vs. ICD	90.2% vs. 80.7%	CA plus ICD: 49% ICD: 52%
BERLIN-VT [69]	2020	163	12	Preventative VT ablation vs. deferred VT ablation	92.1% vs. 97.6%	Preventative: 60.3% Deferred: 51.8% (Freedom from sustained VT)

ARC-HF, A Randomized Trial to Assess Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Chronic Heart Failure; CA, catheter ablation; CAMERA-MRI, Catheter Ablation versus MEdical Rate control in Atrial fibrillation and heart failure – An MRI guided multi-centre randomized controlled trial; CAMTAF, Catheter Ablation Versus Medical Treatment of Atrial Fibrillation; PABA-CHF, Pulmonary-Vein Isolation for Atrial Fibrillation in Patients with Heart Failure.

5.2 Catheter ablation versus antiarrhythmic drug therapy

The Ablation versus Amiodarone for Treatment of Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted ICD/CRT-D (AATAC) study by Di Biase *et al.* [58] was the first randomized trial to compare the efficacy of catheter ablation versus amiodarone. After randomization of 203 patients with persistent AF, NYHA II/III, LVEF $\leq$40%, and an implanted dual chamber ICD/CRT-D, a 45% relative risk reduction in unplanned hospitalizations and a 56% relative risk reduction in mortality was reported in the catheter ablation group at 2-year follow-up. Although limited in design (i.e., providing a comparison against an AAD with significant known toxicities) these findings importantly highlighted the superiority of catheter ablation over AADs in achieving and maintaining sinus rhythm.

The Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) study by Marrouche *et al.* [60] was later conducted to assess cardiovascular outcomes in catheter ablation versus standard treatment. After randomization of 363 patients with symptomatic paroxysmal or persistent AF, NYHA II-IV, LVEF $\leq$35%, and a prior implanted ICD/CRT-D, catheter ablation was associated with a significant 16.1% absolute reduction in death or hospitalization for HF, with a greater proportion of patients in sinus rhythm versus standard treatment (63.1% versus 21.7%, respectively), at 5-years follow-up. Whether these findings are equally applicable in ischaemic and non-ischaemic aetiologies, as well as asymptomatic AF, remains unclear. Nevertheless, this study was able to provide the first critical step toward the suggestion that catheter ablation may represent a reasonable first-line treatment in patients with HF.

In another prospective trial, Kuck *et al.* [61], the Atrial Fibrillation Management in Congestive Heart Failure With Ablation (AMICA) study investigated the influence of catheter ablation versus best medical therapy on the primary outcome of LVEF in addition to 6-minute walk test, QoL, and NT-proBNP, in a persistent or longstanding persistent AF and LVEF $\leq$35% patient cohort. Prematurely terminated due to futility, this study did not report a significant difference in LVEF nor in the restoration of sinus rhythm at 1-year follow-up. This observation may be partly explained by the enrolment of a patient population with lower baseline LVEF and NYHA as well as a short duration of follow-up. Notably, the 1-year increase in LVEF following catheter ablation was similar between AMICA, CASTLE-AF, and AATAC trials.

The influence of catheter ablation in patients with new-onset or untreated AF was more recently investigated by Packer at al. in the Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA-AF) study [62]. Although randomization of 2204 patients to either catheter ablation or medical therapy failed to demonstrate the superiority of catheter ablation with respect to the primary endpoint of death, disabling stroke, serious bleeding, or cardiac arrest at 5-year follow-up, patients randomized to catheter ablation did, however, demonstrate a significant reduction in AF recurrence as well as the rate of death or cardiovascular hospitalization. Although promising, it is important to highlight the heterogeneous nature of the drug therapy arm that was used in addition to the single-blinded study design. The latter may explain the high crossover rate, which may have led to an underestimation of ablation benefit.

Recent advances in the delivery of catheter ablation for AF have emerged in the form of contact-force-guided radiofrequency ablation and second-generation cryoballoon ablation. To explore these technologies, the Cryoballoon versus Irrigated Radiofrequency Catheter Ablation: Double Short vs Standard Exposure Duration (CIRCA-DOSE) study by Andrade *et al.* [63] was established to evaluate the efficacy and safety profile of newer contact force-guided radiofrequency (RF) ablation technologies. This was performed in 346 patients with symptomatic paroxysmal AF refractory to Class I/II AADs and referred for a first catheter ablation procedure, randomized to contact-force irrigated RF ablation, cryoballoon ablation using 2-minute cryoapplications (CRYO-2), or cryoballoon ablation using standard 4-minute cryoapplications (CRYO-4). At 12-months follow-up, no significant difference in freedom from recurrent atrial tachyarrhythmia on continuous rhythm monitoring, symptomatic AF or AF burden, nor in the frequency of complications was reported. In addition to demonstrating equal effectiveness, this study showed that a 4-minute freezing duration is not necessarily required in place of a shorter 2-minute cryoapplication.

Complementary data on this topic will be provided by the RAFT-AF study (NCT01420393) which will investigate whether catheter ablation, with or without AAD therapy, reduces all-cause mortality and hospitalization for HF versus rate control in patients with a high burden of AF and NYHA class II/III.

6. Catheter ablation for ventricular tachycardia

6.1 Catheter ablation and ICD therapy

ICD therapies are used to terminate VT by antitachycardia pacing (ATP) or the delivery of a direct current shock, however they cannot prevent the recurrence of VT. Since ICD shocks are associated with increased morbidity and mortality, owing to physiological distress and physical trauma, the main treatment options to reduce the frequency and recurrence of VT include AADs or catheter ablation [71].

The Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia (SMASH-VT) study by Reddy *et al.* [64] was established to evaluate whether prophylactic VT ablation within 6 months after secondary prevention ICD implantation, in patients with spontaneous VT/VF and a history of myocardial infarction, would reduce the incidence of ICD therapy (Table 3). After randomization of 128 patients to defibrillator with adjunctive catheter ablation versus defibrillator implantation alone, the primary endpoint of survival free from any appropriate ICD therapy, in addition to free-

dom from ICD shocks, was significantly greater in catheter ablation patients at a mean follow-up of 22.5 months. Although overall mortality was lower with catheter ablation, this did not reach statistical significance.

A strategy of prophylactic catheter ablation for VT plus ICD versus ICD alone was later evaluated by Kuck *et al.* [65] in the Ventricular Tachycardia Ablation in Coronary Heart Disease (VTACH) study. After randomization of 110 patients with haemodynamically tolerated VT, prior myocardial infarction, and a LVEF $\leq$50%, the primary outcome of median time to first VT or VF episode was significantly greater in the prophylactic ablation group at 2-year follow-up. Moreover, the event-free survival rate was statistically significant between groups as was the mean number of appropriate shocks per patient per year (0.6 vs. 3.4, respectively). Although mortality was similar between groups, as with SMASH-VT, this study added to an increasing body of evidence to support the prophylactic use of VT ablation among patients with an underlying ischaemic pathology.

In contrast to SMASH-VT and VTACH, the Substrate Modification Study (SMS) was more recently conducted to determine whether prophylactic catheter ablation of the arrhythmogenic substrate in 111 patients with unstable VT, LVEF $\leq$40%, and coronary artery disease reduces or prevents the recurrence of VT/VF [68]. Although a similar 2-year event-free survival was observed between groups at 27.6 months follow-up, the number of spontaneous ventricular arrhythmia episodes was significantly reduced in the ablation group (2.8 vs. 8.1, respectively) including the number of episodes requiring ATP or shock (2.8 vs. 12.9, respectively).

The role of preventive versus deferred VT ablation among patients undergoing an ICD implant has since been investigated in the Preventive Ablation of Ventricular Tachycardia in Patients With Myocardial Infarction (BERLIN-VT) study, which randomized 163 patients with a history of prior MI with stable ischaemic CM and LVEF 30–50% [69]. Terminated due to futility, the primary outcome of a composite of all-cause death and unplanned hospitalization for either symptomatic ventricular arrhythmia or worsening HF was significantly higher in the preventative group. However, several secondary endpoints were in favour of prevention including the incidence of sustained ventricular arrhythmias and the incidence of ICD therapies. Together with SMASH-VT and VTACH, these studies were able to provide evidence to support the use of preventative VT ablation in post-infarction patients.

Whether the long-term arrhythmia-free survival benefits of catheter ablation for VT would extend to a non-ischaemic cardiomyopathy patient cohort was investigated by Dinov *et al.* [66] in the Heart Center of Leipzig VT (HELP-VT) trial. Although the difference in VT-free survival at 1-year follow-up in non-ischaemic versus ischaemic cardiomyopathy did not reach statistical significance, there were various limitations to this study, including a non-randomized design and the reporting of outcomes after a single VT ablation procedure. As a whole, it is recommended that a more comprehensive approach to VT management, including repeat VT ablation, epicardial mapping, and aims for complete VT non-inducibility, are used in patients with non-ischaemic cardiomyopathy.

6.2 Catheter ablation versus rate or antiarrhythmic drug therapy

With the exception of beta-blockers, existing pharmacological therapy has not been shown to be effective in the management of patients with ventricular tachyarrhythmia [72]. In the Ventricular Tachycardia Ablation versus Escalated Antiarrhythmic Drug Therapy in Ischemic Heart Disease (VANISH) study, Sapp *et al.* [67] performed the first randomized trial to compare VT ablation with escalation of AAD therapy in 259 patients with ischaemic cardiomyopathy, ICD, and persistent VT despite AADs (predominantly amiodarone). At a mean follow-up of 27.9 months, the primary outcome of a composite of death, VT storm, or appropriate ICD shock after 30-days of treatment occurred in 59.1% of patients in the ablation group and 68.5% of patients in the escalated AAD group. In the ablation group, this finding was predominantly driven by a reduction in the rates of appropriate ICD stocks and VT storm. The superiority of VT ablation was, however, not associated with a significant difference in mortality. Although high impact in its demonstration of the ability of ablation to be more effective at reducing recurrent VT than escalation of AAD, this trial suffered from a number of important limitations, including the use of an open-label design and inadequate power for detecting differences in mortality.

In a more recent retrospective analysis of the 2002–2014 Nationwide Inpatient Sample, the efficacy and safety profile of VT ablation in HFrEF versus medical therapy was shown to significantly lower in-hospital mortality, in contrast to VANISH, albeit with high rates of post-operative haemorrhage, myocardial infarction, and pericardial and neurological complication [73]. Although future prospective trials are needed to fully investigate and verify these outcomes, factors that have been postulated to act as barriers to the recruitment of patients and the completion of long-term endpoints in trials of VT ablation include funding challenges, patient referral as a 'last resort', and factors that may dissuade patients from continuing enrolment (e.g., randomization to a non-ablation arm).

7. Discussion

HF is a highly debilitating condition and major public health concern associated with significant morbidity and mortality worldwide. Several large-scale clinical trials have since established the role of implantable devices in the management of HF, which has evolved significantly over the past few decades. LVAD systems have undergone substantial progress in durability and reliability as destination therapy for end-stage HF, while ICDs continue to be used in the primary prevention of SCD. Although s-ICDs were designed to address the limitations of transvenous ICD systems, these patients must be carefully selected due to a propensity for

t-wave oversensing, an inability to provide antitachycardia pacing nor CRT, and limited capacity for continuous bradycardia pacing [74, 75]. Contraindications to s-ICD use therefore includes a previously implanted unipolar pacemaker, VT that is known or anticipated to be responsive to antitachycardia pacing, HF and LBBB indicated for CRT, and symptomatic bradycardia requiring permanent pacing [74]. In general, s-ICDs are considered in younger patients, those with congenital cardiomyopathies or genetic arrhythmia syndromes, candidates for ICD without concurrent need for pacing, patients at high risk of bacteraemia (e.g., dialysis), or in the event of challenging vascular access [74].

In addition to ICDs, CRT systems have continued to demonstrate meaningful improvements in clinical outcome with respect to mortality and hospitalization for HF. However, there continues to exist a group of patients for whom the indication for CRT is controversial (i.e., RBBB), and approximately one third of patients with an indication for CRT have a suboptimal clinical response (i.e., "non-responders") [76]. Causes of non-response include mechanical dyssynchrony, presence and extent of myocardial scar, and suboptimal LV lead position [77–79]. Other factors that have been shown to influence response to CRT include QRS width and morphology pattern, device optimization, and post-implant programming [80, 81]. With respect to future directions, alternative modes of LV pacing with the capacity to overcome the limitations of non-response include isolated LV pacing (potential as a tiered therapy) [82], endocardial pacing (LV end-systolic volume reduction in patients enrolled after CRT non-response) [83], septal pacing (short-term haemodynamic improvements and electrical resynchronization on par with BiV pacing) [84], and multipoint LV pacing (reductions in hospitalization for HF, improved LVEF on follow-up, and an increase in CRT response) [85]. Risk stratification has also become increasingly important to help identify those patients most likely to benefit. Selection is supported by circulating biomarker red cell width distribution and platelet count levels (which independently predict long-term all-cause mortality and reverse LV remodelling in CRT) [86], ScREEN scoring (Sex category, Renal function, ECG/QRS width, Ejection fraction and NYHA class) [87], contractile reserve [88] and the Charlson Age-Co-morbidity Index (CACI) [89]. In addition to non-response, a therapeutic gap continues to exist in the treatment of patients that are ineligible for CRT. Ultimately, restoring conduction to near-normal physiology is the predominant aim, and in those with suitable anatomy, conduction system pacing has been shown to be a viable alternative or potential first-line approach.

Catheter ablation is superior to pharmacological therapy in providing rhythm control in patients with symptomatic AF and in improving functional status, QoL, LVEF, frequency of hospitalization for HF, and mortality parameters in patients. These underlying pathophysiological benefits stem from the successful restoration of sinus rhythm, emphasizing the importance of timely intervention. Radiofrequency (RF)-based circumferential pulmonary vein isolation (PVI) remains the cornerstone approach irrespective of AF type, and mounting epidemiological evidence and randomized data have increasingly highlighted the importance of risk factor management in improving successful post-procedural outcomes (e.g., obesity and sedentary lifestyle) [90]. Importantly, this should involve risk stratification and optimal patient selection based on individualized clinical assessment and physiological characteristics, together with the risks of ablative technology.

Although multiple-procedure success rates of PVI in patients with AF range 50–80%, efficacy remains suboptimal in patients with persistent and long-standing persistent AF [91]. The success of ablation therefore depends on various physiological factors, including the type and duration of AF (e.g., paroxysmal versus persistent), structural heart remodelling, atrial wavelets and multiple macro re-entry circuits that complicate procedural success, in addition to insufficient lesion formation during the index procedure [92]. Innovative tools that have more recently emerged to overcome the limitations of existing ablative technology include single-shot pulmonary vein isolation modalities in the form of cryoballoon (e.g., CRYO4PERSISTENT AF trial, demonstrating a 61% single-procedure success at 12 months post-ablation) [93, 94], cardiac magnetic resonance imaging-guided LA substrate modification in addition to standard PVI using cryoablation [95], laserballoon ablation (demonstrating similar efficacy as wide-area circumferential PVI using irrigated RF in persistent AF) [96], in addition to the use of markers of ablation lesion quality (e.g., ablation index) [97] and contact force-sensing technologies [98]. Irreversible electroporation may overcome the complications of thermal ablation including pulmonary vein stenosis and oesophageal ulceration via the generation of a high electrical field, however this has yet to be investigated clinically [99]. In patients with VT, challenges including the identification of optimal timing for VT ablation and the most suitable indications with respect to patient parameters remain.

Additional advances in the field of implantable devices and catheter ablation are likely to involve further incremental improvements to design and integrated telemetric programmability. The future of HF management may also see the rise of novel technologies complexed with biologically active components to reverse myocardial dysfunction.

8. Conclusions

Implantable device therapy and catheter ablation have progressed significantly over the past few decades. However, there continues to remain numerous areas of active investigation aimed at reducing the incidence of patients with HF that do not respond to CRT and to minimizing the recurrence of arrhythmia post-ablation. Although numerous management strategies have emerged to address this, future large scale and randomized trials are needed to confirm their feasibility of implementation, long-term safety, and effectiveness in clinical practice.

Author contributions

CS, SA, AB, GS and NP wrote the original draft. EA and NTS reviewed and edited the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

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