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EHRA SURVEY

EHRA European Heart Rhythm Association

Diagnostic, pharmacological, and ablation approaches for idiopathic ventricular fibrillation: the 2024 European Heart Rhythm Association survey

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Aims

The aim of the European Heart Rhythm Association (EHRA) physician-based survey was to assess current clinical practice regarding the diagnostic assessment and therapeutic management of idiopathic ventricular fibrillation (IVF) across European Society of Cardiology (ESC) countries and to evaluate adherence to the 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

Methods and results

An online 24-item was developed and disseminated by the Scientific Initatives Committee of EHRA. A total of 206 physicians from 41 countries completed the questionnaire. Respondents declaring a full diagnostic assessment of IVF, including at least coronary angiogram/cardiac computed tomography scan, electrocardiogram monitoring, exercise stress test, pharmacological challenges, and cardiac magnetic resonance, were 71 (35%). Cardiac magnetic resonance, sodium channel blocker test, and genetic testing were reported by 51, 34, and 43%, respectively. The most preferred first-line therapeutic strategy in case of recurrent implantable cardioverter-defibrillator (ICD) shocks was drug therapy (88%). In case of first-line strategy failure, the preferred reported strategy was ablation (53%).

Conclusion

This survey highlights a significant heterogeneity of the diagnostic approach to IVF with underuse of crucial examinations. In line with guideline recommendation, drug therapy is more often considered as first-line therapy and ablation as second-line therapy for recurrent ICD shocks. However, quinidine is considered as drug of choice by <25% of respondents.

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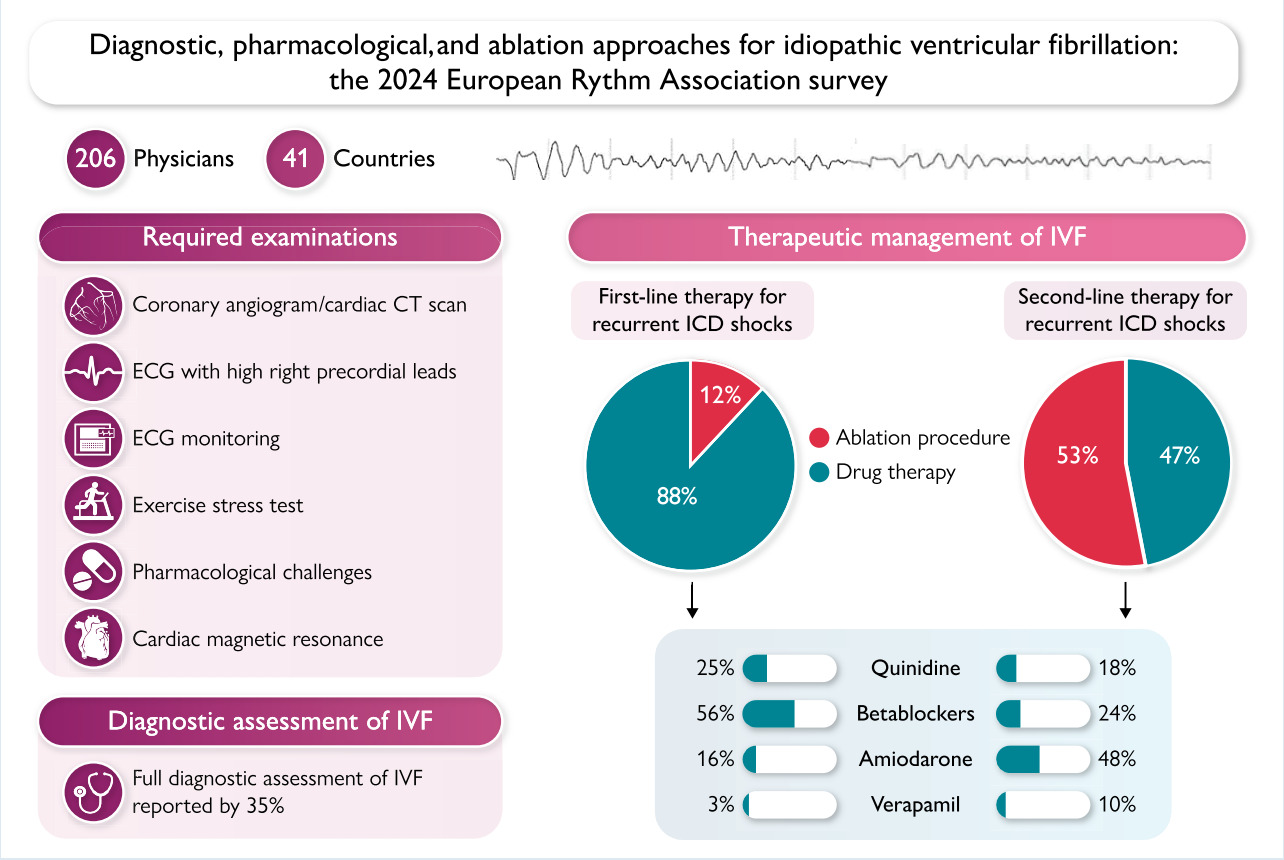
Graphical Abstract



Keywords Sudden cardiac death • Idiopathic ventricular fibrillation • Ablation • Diagnosis • Genetic testing • Ventricular arrhythmias • EHRA survey

Introduction

Idiopathic ventricular fibrillation (IVF) is a rare event occurring in nearly 1% of all out-of-hospital unexplained sudden cardiac arrests (SCAs) presenting with a shockable rhythm.[1–4] According to the 2022 European Society of Cardiology (ESC) guidelines on sudden cardiac death (SCD), the diagnosis of IVF in SCA survivors should be made after exclusion of structural, channelopathic, metabolic, or toxicological aetiologies.[1] A complete diagnostic assessment (and repeated diagnostic assessment over time) of any SCA of unexplained origin is therefore required before establishing a diagnosis of IVF.[1,3,5] Nevertheless, it has been reported that <50% of IVF cases receive a complete diagnostic assessment.[4]

An implantable cardioverter-defibrillator (ICD) implantation is recommended in all patients with IVF.[1] Chronic pharmacological and ablation strategies are considered (Class IIa recommendation) in patients with recurrent ICD discharges, with quinidine as first-line therapy and ablation as second-line therapy after drug therapy failure.[1,6]

The aim of this physician-based survey of the European Heart Rhythm Association (EHRA) was to assess current clinical practice with a main focus at the diagnostic assessment and therapeutic management of IVF across ESC countries and to evaluate adherence to the 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD.

Methods

The physician-based survey was developed and disseminated by the Scientific Initiatives Committee of EHRA. An online 24-item questionnaire was developed and circulated to the EHRA Research Network and dedicated social media channels between 21 December 2023 and 29 January 2024.

The physician-based survey was constructed to assess the current diagnostic and therapeutic approaches to patients with IVF and adherence to evidence-based recommendations. The online-based questionnaire consisted of single- and multiple-choice questions assessing physicians' daily practice in diagnostic examinations including electrocardiograms (ECGs), rhythm monitoring, exercise stress test, pharmacological provocative challenges (e.g. sodium or ergonovine testing), imaging studies [e.g. cardiac magnetic resonance (CMR)], coronary angiography/cardiac computed tomography (CT), genetic testing, and pharmacological/invasive approaches. Initial diagnostic assessment was considered complete if it included at least blood chemistry, ECG (including high lead), cardiac CT/coronary angiography, continuous rhythm monitoring by telemetry/Holter, exercise stress test, echocardiogram, sodium channel blocker testing, and CMR.[1]

The results of the anonymized data about participants, their institutions, and services were also collected in compliance with the European General Data Protection Regulation 2016/679. Survey results are expressed as categorical data (numbers and proportions). The statistical analysis was performed using SPSS Version 20 (IBM SPSS Statistics, New York, USA).

Results

A total of 224 participants agreed to participate to the survey and 206 (92%) from 41 countries successfully completed the questionnaire (56% aged 30–49 years, 77% males) and were included in the analysis. The most represented country was Germany (13%), followed by Italy (11%) and France (5%). Of the respondents, 51 (25%) were general cardiologists, 112 (54%) were cardiac electrophysiologists, and 10 (5%) had specific competencies in cardiogenetics, 22 (11%) in heart failure, and 7 (3%) in cardiac imaging. No interventional cardiologist participated to the survey. Respondents were affiliated with university hospitals ($n = 117$, 57%), non-university hospitals ($n = 62$, 30%), private hospitals ($n = 19$, 9%), or private practice ($n = 8$, 4%). Less than 10 years of practice was declared by 48 participants (23%), between 10 and 20 years by 60 (29%), and >20 years by 98 (48%).

Interdisciplinary evaluation of patients with idiopathic ventricular fibrillation

The involvement of general cardiologists for the assessment and management of IVF patients was reported by 144 respondents (70%), of cardiac electrophysiologists by 154 (75%), interventional cardiologists by 117 (57%), cardio-geneticists by 75 (36%), cardiac imaging specialists by 117 (57%), pathologists by 31 (15%), and psychologists by 28 (14%) (*Figure 1*). Approximately 138 respondents (67%) declared the presence of an interdisciplinary team at their institution dedicated to the assessment of patients with IVF. Most of these interdisciplinary evaluations (64%) were performed at university hospitals. There were 44 respondents (21%) declaring no case of IVF in the last year, 136 (66%) declaring <10 cases, and 26 declaring >10 cases (13%) (*Figure 2*).

Diagnostic assessment of patients with idiopathic ventricular fibrillation

A metabolic and toxicological screening was considered in any IVF case by 136 (66%) and 99 respondents (48%), respectively, only sporadically by 59 (29%) and 93 (45%), and not performed by 11 (5%) and 14 (7%) respondents.

One hundred eighty-four respondents (89%) considered the evaluation of a baseline 12-lead ECG after the arrhythmic event as essential to establish a diagnosis of IVF (*Figure 3*). Among them, 151 (82%) considered the diagnosis of IVF in the presence of a completely normal ECG. One hundred eighteen respondents (57%) reported regular ECG assessment with regard to the presence of repetitive short-coupled premature ventricular complexes (sc-PVCs) and 86 (42%) of a malignant early repolarization (ER) pattern. Regarding the definition of sc-PVCs, 99 (48%) had no specific cut-off value for the PVC coupling interval, 53 (26%) < 300 ms, 43 (21%) < 350 ms, and 11 (5%) > 350 ms.

An in-hospital telemetric continuous rhythm monitoring was considered indicated in all IVF cases by 149 respondents (72%), 12-lead ECG with Brugada high right precordial leads by 132 (64%), and exercise stress testing by 102 (49%).

Imaging studies, including 2D transthoracic echocardiography and CMR, were reported as routine examination by 206 (100%) and 105 (51%) respondents, respectively.

Provocative drug testing with sodium channel blocker agents was considered by 71 respondents (34%), and coronary angiography with ergonovine or acetylcholine test by 20 (10%). Genetic testing was considered by 88 (43%) and cardiac biopsy by 2 (1%). Among respondents considering genetic testing, 59 (67%) typically request gene panel sequencing, while 12 (14%) opt for whole-exome sequencing. The founder variant *DPP6* as part of the gene panel was reported by 26 (29%) and based on the patient's origin by 32 (36%). The remaining respondents were not aware of the adopted sequencing technique or genes included in the panel.

Complete initial diagnostic work-up and temporal reassessment of idiopathic ventricular fibrillation over time

Respondents declaring a full diagnostic assessment of IVF, including at least coronary angiogram/cardiac CT scan, ECG monitoring, exercise stress test, pharmacological challenges, and CMR, were 71 (35%). Most of these respondents (90%) were those reporting no or <10 IVF cases/year, indicating the rarity of the arrhythmic event in the presence of a complete initial diagnostic assessment.

The main reason for not providing a full diagnostic assessment of an unexplained VF was the absence of dedicated teams and interdisciplinary evaluations (74%), and the lack of awareness or a perceived added value (26%) (*Figure 4*).

Clinical re-assessment by repeated clinical and ECG evaluations was reported by 163 respondents (79%). Most of them (75%) reported a temporal strategy with evaluations every 2 years, while 14% had no specific temporal reassessment strategy. Routine first-degree assessment with ECG was reported by 105 (51%).

Therapeutic strategies to prevent idiopathic ventricular fibrillation recurrences

The most preferred first-line therapeutic strategy in case of recurrent ICD shocks was drug therapy, reported by 182 respondents (88%), and it was mostly based on the use of beta-blockers (56%), quinidine (25%), amiodarone (16%), and verapamil (3%). Ablation was considered as first-line strategy by 24 respondents (12%) (*Figure 5*).

In case of first-line strategy failure and recurrent ICD shocks, the preferred strategy was ablation for most respondents (108/206, 53%), followed by drug therapy (amiodarone 48%, beta-blockers 24%, quinidine 18%, and verapamil 10%) (*Figure 5*).

The most adopted ablation strategy was PVC triggers ablation (57%) followed by substrate mapping and ablation (i.e. diseased Purkinje system) reported by 43% of respondents. A right-sided, left-sided, and combined right–left Purkinje mapping was reported by 20%, 15%, and 65%.

A total of 137 respondents (67%) considered the 2022 VA SCD guidelines valuable for the evaluation and treatment of patients presenting with IVF.

Discussion

This report highlights different important features of current practice in the diagnostic and therapeutic management of IVF: (i) a complete diagnostic assessment of patients with IVF is reported only by a minority of respondents (35%); (ii) IVF is rarely encountered in the clinical practice if a complete diagnostic assessment is carried out; (iii) the lack of a complete diagnostic assessment is mostly related to the absence of dedicated interdisciplinary teams or to the absence of awareness or a perceived added value; (iv) in line with guideline recommendation, drug therapy is predominantly considered as first-line therapy and ablation as second-line therapy for recurrent ICD shocks; however, quinidine is considered as the preferred drug by <25% of respondents.

Diagnostic assessment of idiopathic ventricular fibrillation

The 2022 ESC guidelines state that 'the diagnosis of IVF is made in SCA survivors, preferably with documented VF, after exclusion of structural,

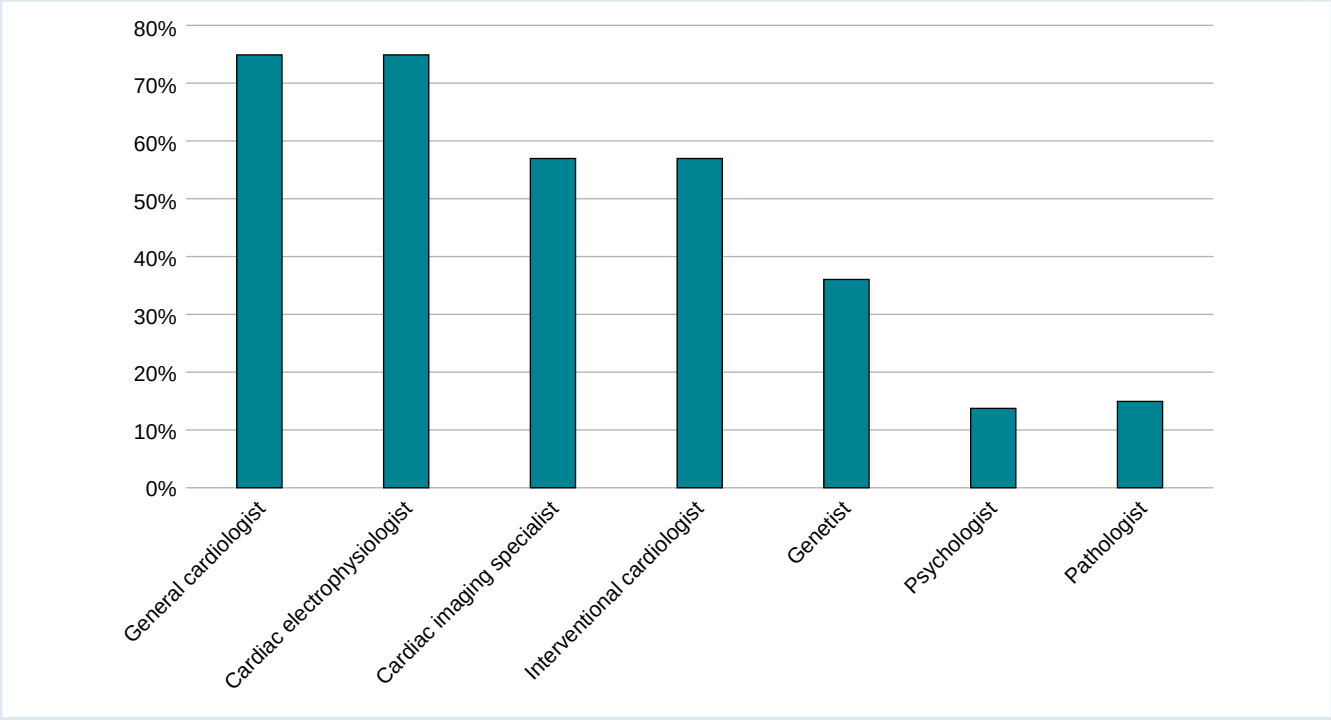


Figure 1 Interdisciplinary evaluations of IVF patients and rate of involved cardiac specialists.

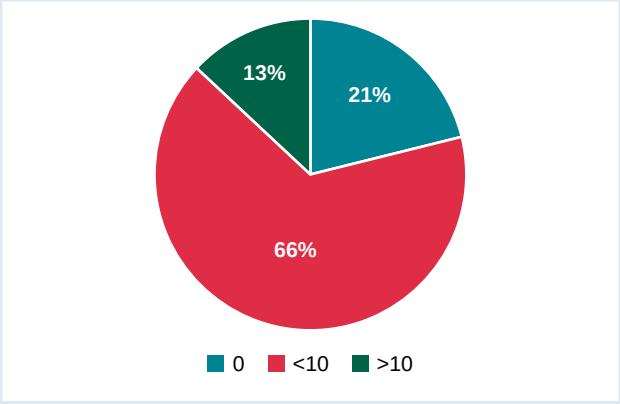


Figure 2 Number of new IVF diagnoses in the last 12 months.

channelopathic, metabolic, or toxicological aetiologies'. Moreover, there is a list of minimal studies required before accepting a diagnosis of IVF recommended by guidelines as Class I recommendations. These examinations include bidimensional transthoracic echocardiography, coronary angiogram, or cardiac CT scan, metabolic and toxicological investigations, 12-lead ECG with high right precordial leads, exercise stress test, 24h-Holter monitoring/telemetry, CMR, and pharmacological challenge with sodium channel blockers.[1]

In this survey, while the vast majority of respondents (95%) considered a metabolic and toxicological screening for patients with IVF, only a small proportion declared the exclusion of a channelopathy (e.g. catecholaminergic polymorphic ventricular tachycardia [CPVT]) by the means of exercise stress testing (reported only by 49%) and high right precordial leads ECG or sodium channel blockers test to exclude Brugada syndrome (reported by 64% and 34%, respectively). Moreover, imaging studies based on CMR to rule out structural cardiac abnormalities (e.g. presence of myocardial scar) were reported only by 51% of respondents. These data confirm the observation that many inherited cardiac conditions may be underdiagnosed among SCA survivors, due to the underuse of pharmacological challenges, misrecognition of ECG abnormalities/patterns (i.e. ER pattern or CPVT exercise-induced ventricular bigeminy).[3] A previous multicentre study reported that a complete diagnostic work-up is performed in 46% of IVF patients.[4]

The prevalence of true IVF in unexplained SCA survivors is low when a full diagnostic assessment is performed.[1–3] The reported rarity and its association to the diagnostic work-up are confirmed by this survey that highlights the fact that those respondents reporting a low annual rate of IVF (<10) were in most of cases those considering a full diagnostic assessment for their IVF cases.

The diagnostic yield of genetic testing in patients with IVF ranges from 3 to 17%. Guideline states that genetic testing for channelopathy and cardiomyopathy genes may be considered in IVF cases (IIb recommendation).[7] In our survey, <50% of respondents considered the genetic testing as part of the diagnostic assessment of IVF cases.

In selected SCA survivors with idiopathic VF, genetic testing for founder variants, where relevant, should be considered.[7] *A recent study from the Netherlands reported the genetic yield of causal LP/P variants in IVF is 5% but increases to 15% when including DPP6.*[7,8] In our survey, the Dutch founder *DPP6* variant testing was reported on a routine basis by 29% and based on patient's origin by 36%.

Interdisciplinary evaluations for patients with idiopathic ventricular fibrillation

In this survey, the majority of respondents (67%) declared the presence of interdisciplinary teams at their institution dedicated to the assessment of patients with IVF. However, the main reason for not providing a full diagnostic assessment was the lack of dedicated teams for IVF. The synergic involvement of general cardiologists, cardiac

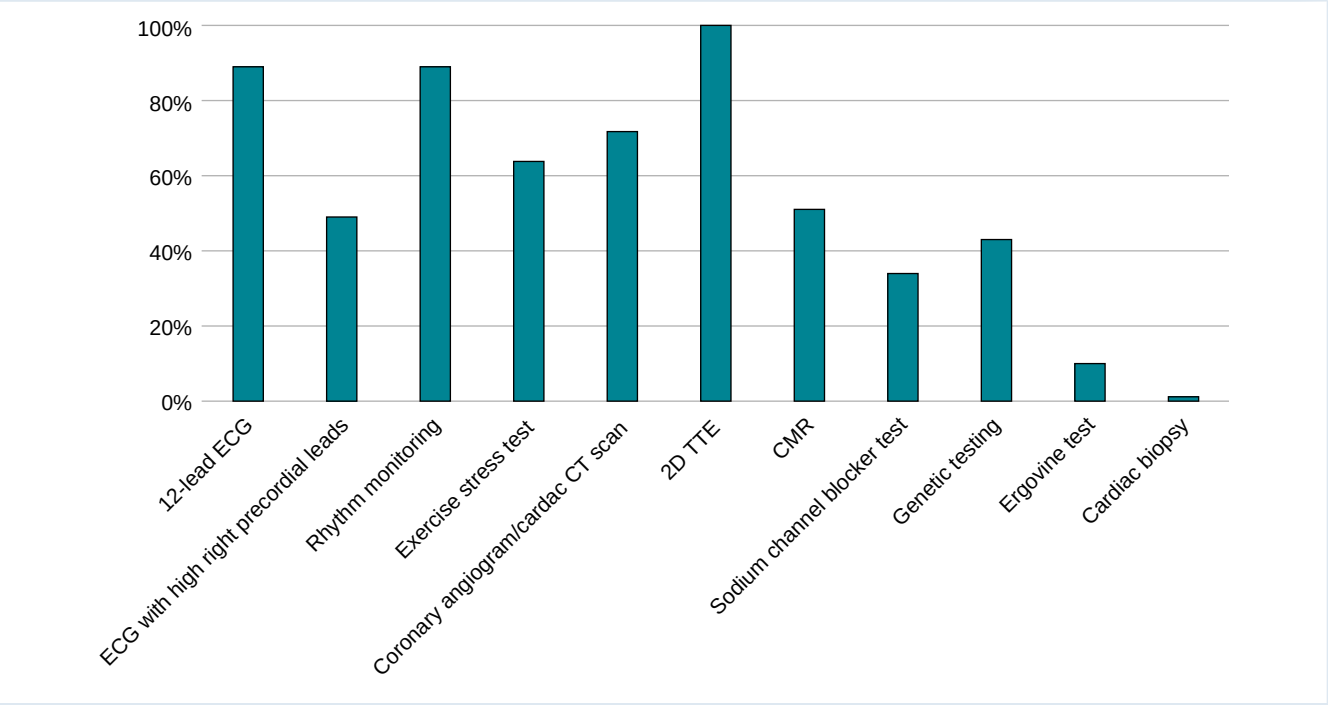


Figure 3 Diagnostic assessment with rate of reported examinations of IVF patients. CMR, cardiac magnetic resonance; CT, computed tomography; ECG, electrocardiogram; TTE, tranthoracic echocardiography.

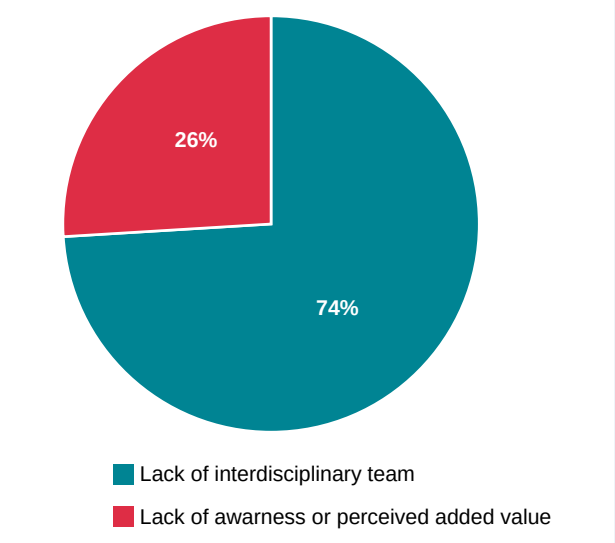


Figure 4 Reasons for not providing a full diagnostic assessment of IVF patients.

electrophysiologists, interventional cardiologists, cardiac imaging specialists, and cardio-geneticists in the initial assessment of a case of unexplained VF is of utmost importance to verify the absence of any other significant finding related to different diagnoses. Integration of clinical contributions by several cardiologists from distinct clinical subdisciplines into a comprehensive diagnostic assessment of IVF should be further and appropriately promoted and interdisciplinary IVF team should be ideally created. Education on the proper diagnostic assessment of unexplained SCA survivors should be adequately promoted and addressed.

Clinical reassessment and family members' evaluation

In this survey, the vast majority declared repeating a clinical and ECG assessment over time for any IVF case. Indeed, this strategy is important since in IVF patients, repeated ECG assessment during follow-up can result on changes of the initial diagnosis of IVF in up to 30% of cases.[3]

Guidelines recommend clinical evaluation (clinical history, ECG and high precordial lead ECG, exercise test, echocardiogram) of first-degree family members (Class IIb) considering its low diagnostic yield.[1] Indeed, Mellor *et al.*[9] have reported a low yield of family screening in relatives of (fully investigated) IVF probands patients (all with ECG, echo/MR, sodium channel blocker provocation, and 77% with genetic testing).

Therapeutic strategies

Idiopathic ventricular fibrillation patients with ER pattern and sc-PVCs (<350 ms) have a higher rate of VF recurrences during follow-up.[10,11] In this survey, almost half of respondents reported a regular assessment of the presence of ER pattern and sc-PVC in patients with IVF, highlighting the absence of awareness of the ECG signs possibly associated with arrhythmic VF recurrences.

Pharmacological and ablation strategies mostly rely on the IVF subgroup (PVC-triggered VF) and the presumed pathophysiological mechanisms. Quinidine in addition to an ICD may be appropriate for recurrent VF in PVC-triggered VF or IVF patients. Catheter ablation by experienced electrophysiologists may be appropriate in patients with IVF and recurrent episodes of VF triggered by a similar PVC nonresponsive to medical treatment.[6] Premature ventricular complexes most commonly originate from the Purkinje system and can be eliminated with a high acute success rate.[12] Detailed electroanatomic

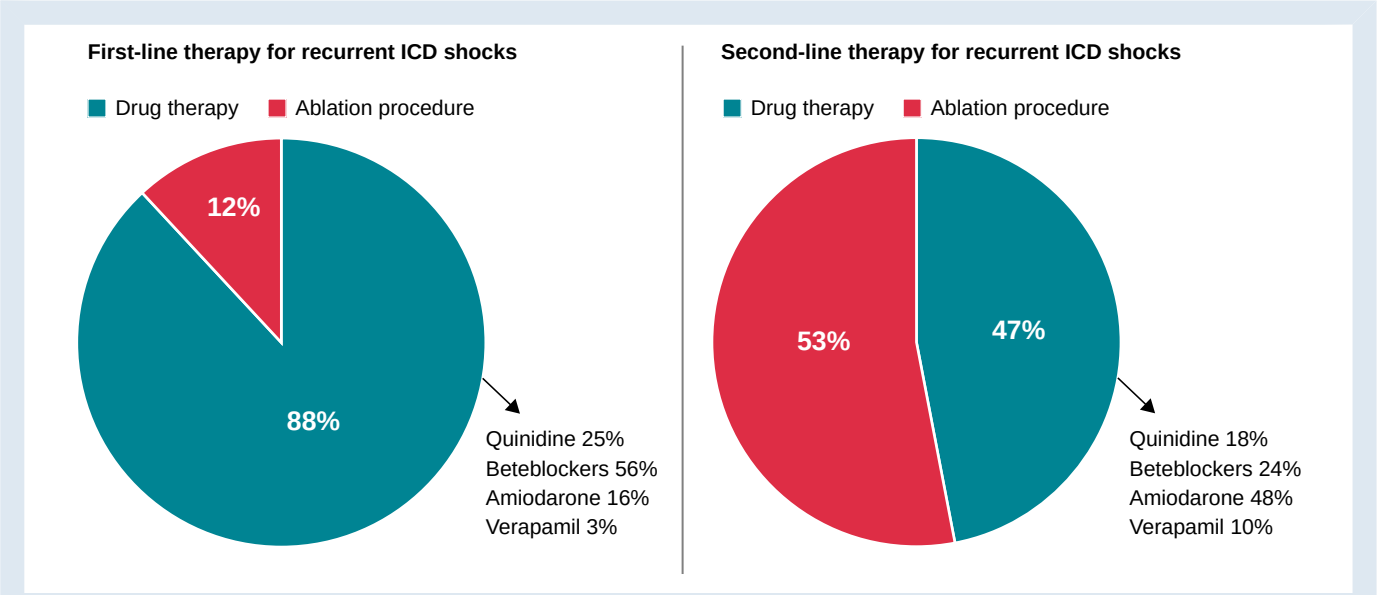


Figure 5 First- and second-line therapy for recurrent ICD shocks. ICD, implantable cardioverter defibrillator.

mapping may also reveal localized structural alterations in IVF patients.[12] Belhassen *et al.*[13] reported an 83% success rate for quinidine and 70% for ablation in patients with sc-PVC triggering IVF.

In line with guideline recommendation, drug therapy was more often considered as first-line therapy and ablation as second-line therapy for recurrent ICD shocks. However, quinidine (Class IIa recommendation) was reported as drug of choice by <25% of respondents. This low rate might be due to the limited availability of the drug in many countries. Further efforts should also be carried out to overcome the lack of accessibility of life-saving medications like quinidine.

Limitations

This survey has different limitations. Due to the relatively limited number of respondents, mainly electrophysiologists affiliated with university hospitals, and especially unequal representation among countries, the results cannot be extrapolated to different categories of practitioners and all ESC and European countries.

Conclusions

This survey highlights a significant heterogeneity of the diagnostic approach to IVF with underuse of crucial examinations. In line with guideline recommendation, drug therapy is predominantly considered as first-line therapy and ablation as second-line therapy for recurrent ICD shocks. However, quinidine is considered as drug of choice by <25% of respondents.

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Conflict of interest: none declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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