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REVIEW

Brugada syndrome: Diagnosis, risk stratification and management



Diagnostic, stratification du risque rythmique et prise en charge du syndrome de Brugada

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KEYWORDS

Brugada syndrome;
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Risk stratification

Summary Brugada syndrome is a rare inherited arrhythmia syndrome leading to an increased risk of sudden cardiac death, despite a structurally normal heart. Diagnosis is based on a specific electrocardiogram pattern, observed either spontaneously or during a sodium channel blocker test. Among affected patients, risk stratification remains a challenge, despite recent insights from large population cohorts. As implantable cardiac defibrillators – the main therapy in Brugada syndrome – are associated with a high rate of complications in this population, the main challenge is risk stratification of patients with Brugada syndrome. Aside from the two main predictors of arrhythmia (symptoms and spontaneous electrocardiogram pattern), many risk factors have been recently suggested for stratifying risk of sudden cardiac death in Brugada syndrome. We have reviewed these data and discuss current guidelines in light of recent progress in this complex field.

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MOTS CLÉS

Syndrome de Brugada ;

Résumé Le syndrome de Brugada est une arythmie cardiaque héréditaire rare, responsable de mort subite. En l'absence de cardiopathie structurale, le diagnostic repose sur l'ECG au repos ou lors d'un test de provocation pharmacologique. Comme le seul traitement ayant

Abbreviations: BrS, Brugada syndrome; ECG, electrocardiogram; EPS, electrophysiological study; ICD, implantable cardiac defibrillator; SCD, sudden cardiac death; VF, ventricular fibrillation.

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Pronostic ;
Diagnostic ;
Mort subite ;
Stratification du
risque

démontré sont efficacité est l'implantation d'un défibrillateur, mais qu'il s'accompagne d'un risque élevé de complication dans cette population, l'évaluation du risque rythmique est essentielle à la prise en charge de ces patients. Un aspect ECG spontané de syndrome de Brugada et la présence de symptômes restent les éléments les plus importants dans la stratification du risque mais de nombreux autres paramètres ont été récemment proposés pour stratifier le risque de mort subite. Nous discuterons l'analyse de l'ensemble de ces données au regard des dernières recommandations de prise en charge.

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Background

Brugada syndrome (BrS) is a rare inherited arrhythmia disease predisposing to ventricular fibrillation (VF) and sudden cardiac death (SCD), without identifiable structural abnormalities [1]. BrS mainly affects middle-aged patients (aged 45 years at diagnosis), with an eightfold higher diagnosis prevalence in men, despite an autosomal mode of inheritance [2,3].

Diagnosis is based solely on a specific but labile pattern on an electrocardiogram (ECG), defined as a ≥ 0.2 mV coved-type ST-segment elevation in the right precordial leads. However, the ECG can be silent, requiring sodium blockers to unmask the pathology. Identification of BrS patients is crucial to avoid sudden cardiac death (SCD), which is often the first symptom [2]. Among the general population, the prevalence of BrS appears to be very low, affecting 5 in 10,000 people [4], and its real impact on SCD is uncertain. In the absence of proven efficient drug therapy, implantable cardiac defibrillators (ICD) – the main therapy in BrS – have been suggested for primary prevention in many BrS patients. However, the risk of SCD among asymptomatic patients remains relatively low (0.5–1.5% per year) and the rate of ICD-related complications is high in this young population [2,5]. Consequently, the main challenge for the physician is the identification of patients at risk of arrhythmia who require specific treatment.

This review will focus on clinical aspects of the diagnosis of BrS, risk stratification and impact on management.

Clinical presentation and diagnosis

One-third of BrS patients are identified after symptoms (syncope or aborted SCD), most of which occur at rest with vagal symptoms or during the night [2]. Syncope can be caused by either non-sustained VF or a vasovagal episode without a relevant characteristic to distinguish arrhythmic from non-arrhythmic aetiology [6]. Fever, alcohol intake and medications can increase arrhythmia occurrence; these triggers can unmask a BrS ECG pattern in asymptomatic patients [7,8]. The increased prevalence of atrial fibrillation in BrS can also suggest a need for BrS screening to the physician, particularly for young men [9].

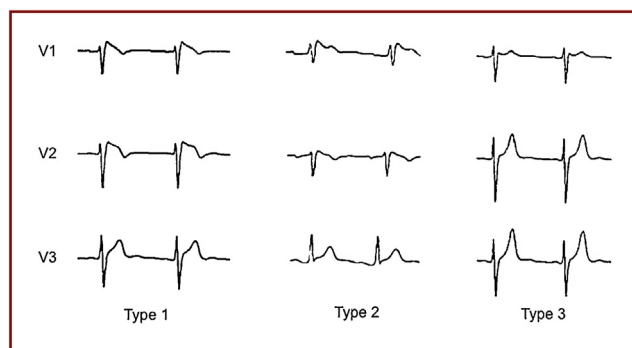


Figure 1. Electrocardiogram (ECG) patterns of Brugada syndrome. Modified from Ref. [27]. ECG patterns are represented from left to right in right precordial leads. Only a type 1 ECG allows diagnosis of Brugada syndrome.

Two-thirds of BrS patients are asymptomatic at diagnosis [2,10]. Of these, more than one-third are identified during familial screening [2]. Since the last guidelines were published, symptoms are not required for diagnosis that is based on a specific ECG pattern [1]. This ECG pattern, previously known as a type 1 ECG, consists of a coved ST-segment elevation in one right precordial lead of >0.2 mV, ending with a negative T wave (Fig. 1). Other ECG patterns are not sufficient for the diagnosis [11], but can suggest the need for a sodium channel blocker test to the physician, which can unmask a type 1 pattern. Ajmaline (1 mg/kg over 5–10 min), flecainide (2 mg/kg over 10 min) and procainamide can be used [1,12]. The respective sensitivities and specificities of these drugs have been evaluated with a genetic gold standard, but remain a matter of debate because of the genetic heterogeneity of the syndrome [13,14]. For now, it seems that flecainide and procainamide have a lower sensitivity than ajmaline [11,15]. Besides ventricular arrhythmia and the appearance of a type 1 ECG pattern, the sodium channel blocker test is usually stopped if the QRS widens to 130% of the baseline. However, some data argue against this criterion, which does not seem to be associated with the occurrence of complications [16]. Even if initial experiences reported a relatively high rate of complications during this test, more recent experiences have demonstrated that, under proper supervision, the risk is very low [17].

Table 1 Variables identified as being associated with sudden cardiac death in Brugada syndrome.

Variables	Definition	Effect on SCD	Main publications
Aborted SCD	—	Increased risk ^a	[2,5,10]
Syncope	Cause by arrhythmia	Increased risk ^a	[2,5,10]
Spontaneous ECG pattern	Type 1 ECG	Increased risk	[2,5,10]
Old age	Aged > 60 years	Decreased risk, but needs to be confirmed ^b	[37]
Sex	Female sex	Decreases risk ^b	[32,37]
EPS	VF occurrence	Increased risk, with conflicting data, particularly with three extra stimuli ^b	[2,10,52]
Sinus dysfunction	In females	Increased risk, but needs to be confirmed ^b	[33]
S wave in D1	S wave > 0.1 mV and/or > 40 ms	Increased risk, but needs to be confirmed ^b	[38]
QRS fragmentation	At least four spikes in one or at least eight spikes in all of the precordial leads	Increased risk, but needs to be confirmed ^b	[10,40]
Inferior type 1	Type 1 ECG in inferior or lateral leads	Increased risk, but needs to be confirmed ^b	[47]
Tpeak–Tend interval	Maximum Tpeak–Tend interval > 100 ms in precordial lead	Increased risk, but needs to be confirmed ^b	[48]
Early repolarization	J wave > 0.1 mV in two inferolateral leads	Increased risk, with conflicting data ^b	[39,45]
Post-exercise ST-segment elevation	≥0.05 mV in V1–V3 post exercise	Increased risk, but needs to be confirmed ^b	[56]
Type 1 ECG burden	24-h Holter monitoring	Increased risk, but needs to be confirmed ^b	[31]
Young age	Aged < 18 years	Conflicting data ^c	[34,36]
Family history of SCD	SCD in first-degree relatives	Conflicting data ^c	[2,10,39]
Genetic	SCN5A mutations	Conflicting data ^c	[2,10,34]
Atrial fibrillation	—	Conflicting data ^c	[2,9,10,38]
PR duration	PR > 200 ms	Conflicting data ^c	[41,44]
QRS duration	QRS > 120 ms	Conflicting data ^c	[41,44]
Late potentials	Two of three positive criteria	Conflicting data ^c	[42,44]
aVr sign	R wave ≥ 0.3 mV or R/q ≥ 0.75 in aVr	Conflicting data ^c	[2,10,43]

ECG: electrocardiogram; EPS: electrophysiological study; SCD: sudden cardiac death; VF: ventricular fibrillation.

^{a–c} An indication of the strength of data associating the variable with SCD (from ^a for consistent and prospective data to ^c for conflicting results).

The diagnosis of a type 1 ECG pattern is usually performed in V1–V3 leads at baseline or during the sodium channel blocker test. Diagnosis can also be performed by elevating V1–V2 leads in the third and the second intercostal space, as this increases sensitivity without modifying prognosis [18]. Based on a single tertiary-centre study, the latest consensus report also proposed acceptance of the diagnosis of BrS even in patients with only one lead showing the typical aspect [1,19]. Many conditions and diseases, including myocardial ischaemia, acute pericarditis, pulmonary embolism, right ventricular compression and metabolic disorder (hyper/hypokalaemia, hypercalcaemia), can exhibit a Brugada-like type 1 ECG pattern [1,20]. These BrS phenocopies cannot be differentiated from true BrS because of their identical ECG patterns, and argue for a systematic diagnostic approach to avoid misdiagnosis [21].

True congenital BrS has been shown to follow an autosomal mode of inheritance in families, and mutation identification has been suggested for diagnosis. Over 20 genes have been associated with BrS [13], and *SCN5A* has the majority of mutations. However, studies have shown that some previously associated variants are actually present in the general population, and are probably non-causal [22]. Furthermore, except for the *SCN5A* gene, the other BrS-associated genes present as many rare variants in cases as in controls, suggesting a minor role for these genes [23]. Interestingly, the concept of a more complex inheritance has emerged from the observation of incomplete penetrance among mutation carriers and of phenocopies among families [3], and has been recently illustrated by the discovery of frequent genetic variants (>10% in the general population) with an unexpectedly high impact on BrS susceptibility

[3,13,24,25]. Thus, the indication for *SCN5A* screening in clinical diagnostics may be restricted to the identification of patients at risk in a family [23].

Risk stratification

Once the diagnosis of BrS has been made, the main challenge is to stratify the risk of VF. Numerous variables have been suggested [26,27], but other than previous symptoms (syncope and aborted SCD) and spontaneous ECG pattern, all remain a matter of debate (Table 1).

Main risk factors

Symptoms

Patients with a history of SCD have a 10% annual risk of recurrence during the first 4 years [2,10]. Although this incidence subsequently decreases, it remains significant, and late recurrence can be observed [5]. Thus, ICD implantation is indicated for all cardiac arrest survivors [1].

Among patients who are diagnosed after syncope, the risk of arrhythmia has been consistently considered as significant [2,5,6,10]. With about 1.5%/year with VF, this risk is fourfold higher than in asymptomatic patients [2]. However, benign vasovagal syncope is also frequently described in BrS patients [2,6]. Although proarrhythmic effects of vagal stimulation have been described, only syncope probably caused by non-sustained VF has been consistently associated with SCD, increasing the risk to 5%/year [6,28]. Thus, in case of syncope of arrhythmic origin, there is no doubt that an ICD is needed.

However, the ability to differentiate arrhythmic syncope from neutrally mediated syncope remains a real challenge. A detailed clinical history, specific triggers (pain, seeing blood, micturition) and prodromes (palpitations, nausea, visual disturbance) may help to distinguish arrhythmic from non-arrhythmic syncope. Unfortunately, none of these variables is sufficient to provide accurate prognostic information [28]. Given the relatively high rate of complications after ICD implantation, the latest guidelines have restricted this implantation to "patients with a spontaneous type I ECG and history of syncope judged to be likely caused" by VF [1]. Although association with a spontaneous type 1 ECG increases the risk of SCD, a large number of patients are diagnosed after the sodium channel blocker test or with an uncertain clinical history, and thus remain in the grey zone for ICD implantation [2].

Spontaneous ECG pattern

Identification of a spontaneous pattern of BrS on an ECG has been consistently associated with an increased risk of SCD [2,10,29], ranging from 0.81%/year in asymptomatic patients to 2.3%/year in symptomatic patients [2]. Although the risk of appropriate ICD therapy for those with asymptomatic BrS patients is low, it is cumulative over time, reaching 12% at 10 years [5]. Regarding the extreme consequences without ICD implantation, it has been suggested that a multifactorial approach could help to stratify the risk of SCD [5,29]. However, because of the limited size of

population and follow-up, identification of patients with the highest risk remains a challenge.

A spontaneous type 1 ECG pattern is variable over time, with marked day-to-day variability in the J wave elevation [30]. Thus, long-term evaluation of the type 1 ECG burden using Holter recording appears to be an attractive tool to stratify the risk of arrhythmia [31]. Unfortunately, so far, essentially because of the lack of efficient tools to easily assess the ST segment over a long period, there is no clear demonstration of the value of this variable.

Clinical factors

Sex

As transmission of BrS is observed with an autosomal mode of inheritance, the prevalence of BrS is expected to be similar among men and women. However, BrS clearly has a high predominance in men, and a threefold increase in the risk of a type 1 ECG pattern and/or cardiac event [32,33]. However, male predominance is also observed in asymptomatic patients, which leads to a non-significant association with SCD [2,32].

As most risk factors for SCD were assessed in populations involving a large predominance of men, they appear to be less accurate for women. Identification of conduction disturbance and sinus dysfunction in women could be a better marker of risk than a spontaneous type 1 ECG and symptoms [32,33].

Age

SCD due to BrS is rare in children. However, the risk can be significant, particularly in children with previous symptoms and a spontaneous ECG pattern [34]. A drug-induced pattern has a good prognosis, but performing a sodium channel blocker test in children is questionable because of frequent complications and false negatives [35,36].

Limited data are available in older patients. However, the risk of arrhythmia appears to decrease significantly after the age of 60 years [37].

Family history and genetics

Given the genetic background of BrS, a family history of SCD and *SCN5A* mutations were suggested to stratify risk of arrhythmia [34,38,39]. However, large multivariable analyses did not confirm this association further [2,10]. Age, the number of SCDs and the degree of the relationship may modify the effect of family history on individual risk [34,38,39].

Atrial arrhythmia

Atrial fibrillation is more common in BrS, and can begin early, even in childhood [9,34]; it has been suggested, in case-control studies, to be associated with prognosis, but the relationship has not been demonstrated in a large cohort [2,9,10,38].

ECG variables

Many ECG variables have been associated with the prognosis of BrS patients, but with conflicting reports or without replication in an independent cohort [26,27] (Fig. 2, Table 1).

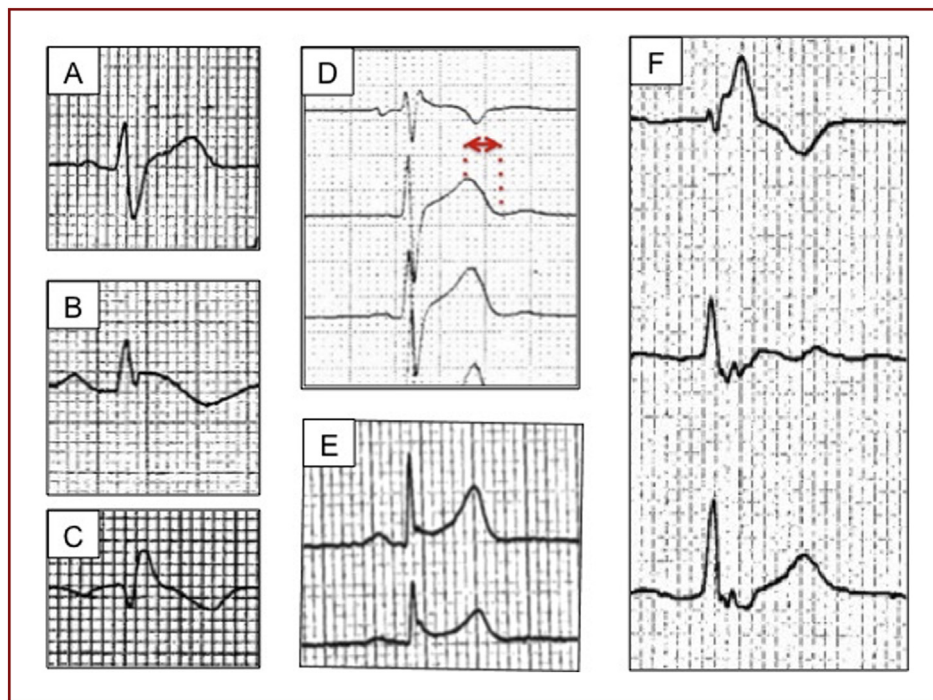


Figure 2. The main electrocardiogram (ECG) variables associated with prognosis in Brugada syndrome. The ECGs (25 mm/s with 0.1 mV/mm) illustrate: A: an S wave in D1; B: a type 1 ECG pattern in D2; C: aVr sign; D: a prolonged Tpeak–Tend interval in V1–V3 leads; E: early repolarization in D2 and D3; and F: fragmented QRS in V1–V3 leads.

Conduction disturbance

The presence of fragmented QRS complexes has been consistently associated with a twofold to ninefold increase in arrhythmia occurrence [10,40]. Of note, criteria definition and ECG recording filter settings varied among studies, limiting the scope of risk stratification, and explaining its absence from the latest guidelines.

Conduction delay has also been highlighted, in terms of QRS duration [41], late potential [42] and the aVr sign [43]. However, these variables were not confirmed in subsequent studies [2,10,44].

Caló et al. found that a wide or large S wave in lead I was a predictor of VF in a multivariable analysis of asymptomatic patients with a spontaneous BrS pattern [38]. Additionally, these authors provided an interesting finding regarding pathophysiology, as this S wave was associated with a conduction delay in the right ventricular outflow tract.

Repolarization variables

In BrS, some studies identified a more severe prognosis in the presence of an early repolarization pattern [39,45], whereas others did not find any relationship between early repolarization and the risk of arrhythmia [46]. The risk of SCD appears to increase when early repolarization is located in an inferior lead with a horizontal ST segment [39].

A type 1 ECG pattern in peripheral leads was additionally described in about 10% of patients, and was associated with an increased risk of SCD [47].

Finally, a Tpeak–Tend interval >200 ms, defining high transmural dispersion of repolarization, has been associated with increased occurrence of VF [48]; however, this was not confirmed in additional studies [49].

Electrophysiological study

From clinical variables, the incremental prognostic value of an electrophysiological study (EPS) is highly controversial. Whereas some authors have proposed an association between induced VF and cardiac events, large prospective studies have demonstrated that an EPS does not stratify the risk of arrhythmia [2,10,50,51]. The latest guidelines have restricted the use of an EPS to a class IIb for ICD implantation [1].

Although most case-control studies identify a high event rate after a positive EPS, the main question is whether to integrate this examination into the risk stratification of BrS. Sroubek et al. recently reported in a large meta-analysis that the induction of ventricular arrhythmia was associated with a twofold to threefold increased risk of VF (hazard ratio 2.55; $P=0.005$) [52]. However, the incremental value of an EPS appears to be small in patients with a high or low risk of arrhythmia, as defined by clinical variables. Considering intermediate-risk patients, the additional risk of a positive EPS does not exceed a 1%/year VF incidence. Considering the limitations in EPS reproducibility [10], and the fact that a negative EPS cannot exclude further arrhythmias, the place of an EPS in risk stratification still

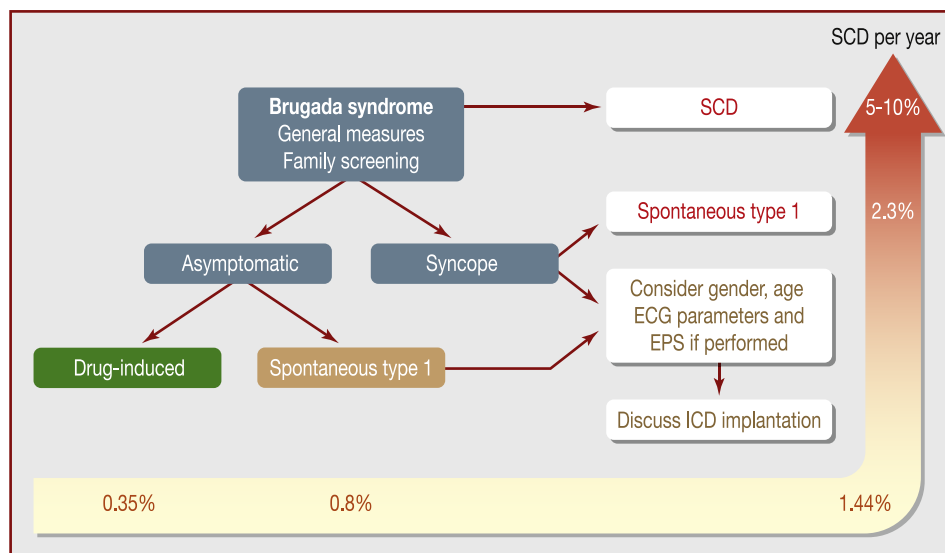


Figure 3. Indication for implantation of an implantable cardioverter defibrillator (ICD), according to the risk of sudden cardiac death (SCD). Modified from Refs. [1,2]. The risk of SCD is represented with a red arrow. The red boxes represents an indication for ICD implantation; the green box represents a patient who should not be implanted, according to the latest guidelines; the orange boxes are not addressed in the guidelines. ECG: electrocardiogram.

appears to be controversial, and it cannot be used as the only variable to define the management of the patient.

Management of BrS

Each patient should first be referred to a specialized centre for inherited arrhythmia. In France, the Cardiogen network involves three reference centres and 22 competence centres specialized in the management of inherited arrhythmia.

For all patients, the first step of management is focused on counselling in daily life: this includes avoiding excessive alcohol intake, treating fever aggressively and decreasing exercise activity progressively. A list of treatments that can increase the arrhythmia risk is given to the patient (the updated list is available on brugadadrugs.org). A familial screening should always be performed to achieve early identification of affected relatives who could be at risk of SCD [1].

After this first step, which applies to all patients, the discussion starts about which therapeutic approach to propose (Fig. 3). Until now, the only proven efficient therapy is ICD implantation, but other possibilities will certainly emerge in the next few years, such as catheter ablation, which is restricted to patients with frequent arrhythmia recurrences.

Asymptomatic patients with a drug-induced ECG pattern present with a very low risk of arrhythmia that does not indicate ICD implantation. By comparison, there is no doubt about the indication in symptomatic patients with a spontaneous ECG pattern.

The main question remaining relates to ICD implantation in patients with intermediate risk. A spontaneous ECG pattern in an asymptomatic patient defines a cumulative risk of VF reaching 12% at 10 years [5]. This risk appears higher than in symptomatic patients with vasovagal syncope, and argues for an early discussion with the patient about an ICD implantation [28]. In these cases, individual assessment

of associated risk factors should be performed to increase stratification accuracy. However, physicians have to recognize that, for now, even if we have a relatively clear picture of the risk at a population level, we are still unable to properly stratify patient risk at an individual level. Thus, in our view, it is essential to provide the patient with complete information about the limits of our knowledge. More importantly, the patient has to be involved with the decision, as the therapeutic choice will have a great psychological impact, regardless of the final decision.

Observational studies have suggested that quinidine should have a beneficial effect on arrhythmia; however, because of limited data, it cannot be encouraged in primary prevention [53,54]. High rates of hydroquinidine side effects and low numbers of arrhythmic events may prevent further evidence being obtained, even in high-risk patients [55]. The use of quinidine may be discussed on a case-by-case basis in highly specialized centres.

Conclusions and perspectives

Once the diagnosis is made, risk stratification, and therefore management, is often complex in BrS. Although a spontaneous ECG pattern and symptoms are the two main predictors of SCD, many variables have been suggested, and these require further evaluation in large populations. Identification of intermediate-risk patients underlies the need to increase the accuracy of such stratification and to improve therapy where prevalence of complications is a strong limiting factor. A combination of risk factors in an integrated clinical and genetic score could be the next step towards such personalized medicine.

The development of new defibrillation technology, such as a subcutaneous ICD, could facilitate the decision, by reducing the rate of complications arising from ICD implantation, and by making it possible to remove the system

easily in case of complication. Finally, catheter ablation, which is currently restricted to highly symptomatic patients, should be another means of decreasing the arrhythmic risk. Although promising, this technique still needs long-term studies before indications can include asymptomatic patients.

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Disclosure of interest

The authors declare that they have no competing interest.

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