Sudden cardiac death in cardiomyopathies: acting upon "acceptable" risk in the personalized medicine era

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Abstract

Patients with cardiomyopathies are confronted with the risk of sudden cardiac death (SCD) throughout their lifetime. Despite the fact that SCD is relatively rare, prognostic stratification is an integral part of physician–patient discussion, with the goal of risk modification and prevention. The current approach is based on a concept of "acceptable risk." However, there are intrinsic problems with an algorithm-based approach to risk management, magnified by the absence of robust evidence underlying clinical decision support tools, which can make high- versus low-risk classifications arbitrary. Strategies aimed at risk reduction range from selecting patients for an implantable cardioverter defibrillator (ICD) to disqualification from competitive sports. These clinical options, especially when implying the use of finite financial resources, are often delivered from the physician's perspective citing decision-making algorithms. When the burden of intervention-related risks or financial costs is deemed higher than an "acceptable risk" of SCD, the patient's perspective may not be appropriately considered. Designating a numeric threshold of "acceptable risk" has ethical implications. One could reasonably ask "acceptable to *whom*?" In an era when individual choice and autonomy are pillars of the physician–patient relationship, the subjective aspects of perceived risk should be acknowledged and be part of shared decision-making. This is particularly true when the lack of a strong scientific evidence base makes a dichotomous algorithm-driven approach suboptimal for unmitigated translation to clinical practice.

Keywords Cardiomyopathy · Sudden death · Risk stratification

Introduction

Cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease sufficient to explain the observed myocardial abnormality [1]. Cardiomyopathies are common causes of sudden cardiac death (SCD), especially in young individuals [2], but the absolute rate of events is small and the circumstances are largely unpredictable. Thus, major uncertainties exist regarding SCD risk stratification and clinical choices on preventative strategies such as implantable cardioverter defibrillators (ICDs), pharmacotherapy, and lifestyle counselling. The lack of randomized controlled trials and other sources of robust evidence compounds additional challenges to the endorsement of personalized pathways aimed at the holistic benefit for individual patients.

Current approaches are based on calculation of the "acceptable risk," which means that clinical strategies are

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dictated by the likelihood of a certain event to occur. However, the perception of "acceptability of risk" is subjective as numeric thresholds to define levels of risk are arbitrary: what is acceptable for the physician may not be so for the patient and vice versa. Although this "modus operandi" is commonly used in clinical medicine, there are many medical, scientific, and ethical dilemmas in the setting of SCD prevention in cardiomyopathy patients. The aim of this review is to discuss the concept of acceptable risk in the context of SCD prevention in cardiomyopathies by addressing key clinical and ethical questions, from patient autonomy to health economics and personalized patient choice.

The size of the matter

Cardiomyopathies are a heterogenous group of diseases that affect millions of patients worldwide. The natural history of these conditions has changed significantly in the last 3 decades with the advent and implementation of pharmacological and non-pharmacological therapies aimed both at symptom relief and at prognostic benefit.

The variable phenotypic expression and underlying genetic basis of these conditions make a deep understanding of the aetiology crucial in risk assessment and management. Patients with cardiomyopathies are often young and the burden of competing risk of non-sudden death is generally low, with a longer life expectancy in comparison with classical models of heart failure (HF). In this context, cardiomyopathies offer scenarios where risk stratification of SCD appears extremely relevant, but at the same time remarkably challenging, since the annual risk is low while exposure to risk is very extended and the efficacy of preventive strategies can only be judged in the long term.

Limitations of current strategies for risk prediction

Sudden death remains a leading cause of mortality in the general population, and is most often due to cardiovascular disease [3]. While coronary artery disease predominates in individuals over the age of 35, cardiomyopathies and channelopathies are the most frequent culprits in the young, and may be identified only at post-mortem examination [2]. When a cardiomyopathy is detected in vivo through clinical investigations, the next step is risk stratification. The assessment of risk has direct repercussions on management strategies which range from recommendations to avoid certain activities, such as competitive sport, to consideration of ICD implantation in primary prevention. However, identifying patients at the highest risk of SCD remains one of the greatest quandaries and is often a critical management priority in cardiomyopathies [4]. Studies on risk of SCD in this setting are often retrospective, based on small cohorts, and based on a small number of events, making interpretation of results and assessment of independent predictors difficult [5]. Sudden death remains a stochastic event with complex genesis often precipitated by a sum of circumstances. In order to increase statistical power, appropriate ICD shocks are often used as surrogates of SCD in studies addressing risk. However, this introduces a significant bias, since patients that have an ICD are by definition more likely to be at risk. Table 1 summarizes key studies on SCD in the main cardiomyopathy subtypes.

Taking hypertrophic cardiomyopathy (HCM) as an example, several risk factors have been shown to be associated with SCD [6, 7] (Table 2), all with high negative but very low positive predictive value when considered in isolation. Therefore, the individual risk profile is more accurately assessed in terms of a total burden of risk as opposed to the presence or absence of any given marker alone [8]. Both the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) have recently developed decision-making support tools [6, 7] to standardize the identification of those patients at highest risk. The ESC has promoted a linear regression risk score predicting SCD event rates at 5 years, comprised of 7 clinical variables in the attempt of providing a quantitative tool. The ACC/AHA have developed a risk score that utilizes 7 risk factors and the implantation of an ICD in primary prevention is recommended in the presence of at least one major clinical marker. Recently, two different scores have been developed for pediatric HCM patients, using a similar approach to the ESC adult score [9].

The development of risk calculators and algorithms represents a laudable effort that has provided clarity in the field and allowed substantial advances in clinical management and research. However, significant limitations exist and gaps in knowledge must be acknowledged in a frank discussion with patients, particularly when addressing the role of specific interventions [10].

Competing causes of non-sudden death

Strategies aimed at preventing SCD should be balanced with competing risks. This is particularly relevant to ICD implantation in primary prevention. For example, patients with advanced heart failure and reduced ejection fraction (HFrEF) are unlikely to benefit from ICD therapy because of the high rates of death from non-arrhythmic causes. This is reflected in guidelines that do not recommend ICD implantation for patients with NYHA class IV symptoms or for those with a life expectancy < 1 year. In elderly patients and in patients with high comorbidity burden, likely to die from non-sudden causes, the ICD has no beneficial role [11]. The Danish trial, a study of patients with symptomatic systolic heart failure not caused by coronary artery disease, showed a trend toward increased mortality with ICD implantation in patients > 68 years of age,

Table 1 Risk of sudden cardiac death and burden of alternative risks in main cardiomyopathy subtypes

	Annual incidence per 100 person-years	HCM	DCM	ARVC
Arrhythmic burden	**SCD**	1% [33]	1% [34]	1.6% [35]
		0.7% [36]	0.5% [37]	0.6% [38]
		0.7% [39]	1.9% [40]	0.1% [41]
		0.6% [42]	1.5% [12]	0.6% [43]
		0.5% [44]	0.2% [45]	0.4% [46]
		0.6% [47]	1% [48]	
		0.8% [5]	0.8% [49]	
		0.3% [50]	2% [51]	
			1.5% [51]	
			0.5% [51]	
			0.2% [51]	
	Appropriate ICD shock	3.3% [33]	2.4% [12]	2.1% [43]
		5.5% [52]	3.6% [53]	4.9% [54]
		5% [55]	7.2% [37]	10.7% [56]
		0.6% [47]	0.5% [51]	17.5% [57]
		4.8% [58]	0.6% [51]	12.9% [46]
		2% [50]	0.8% [51]	
		0.8% [59]	1% [60]	
		22.1% [5]		
		4.5% [61]		
Major complications	**Inappropriate shock**	2.1% [59]	1.2% [12]	3.9% [54]
		7.3% [52]	8.8% [37]	2.8% [56]
		7.5% [62]	2.6% [63]	5.5% [57]
		3.7% [64]		
		6.5% [61]		
	Device infection	0.2% [61]	0.9% [12]	0.5% [65]
		1% [52]	2% [53]	0.2% [54]
		1.2% [62]	0.2% [37]	

ICD, implantable cardioverter defibrillator; *SCD*, sudden cardiac death

in contrast to patients < 59 years of age who had a lower mortality with an ICD [12].

In general terms, competing risk is lower in patients with cardiomyopathies in comparison with classical models of heart failure, because of their younger age and lower comorbidity index. There are certain scenarios in which end-stage progression mandates evaluation of competing risk in the decision-making [13]. The prognosis of patients with DCM is affected by the severity of systolic dysfunction and a natural history characterized by progression toward pump failure and heart transplant is relatively common in patients with significant systolic impairment. In other cardiomyopathies, pump failure death is less common, but other forms of end-stage progression may occur [13].

Subjectivity in risk perception: physician versus patient perspectives

Although quantification of risk follows mathematical equations, the interpretation of numbers and perception of risk are largely subjective from both the physician and the patient viewpoints. It is not unusual to encounter a disagreement between physician and patient. A patient with HCM may perceive that a risk of SCD of 3% at 5 years is unbearable and may want to be protected with an ICD. However, such a patient would be classified as "low risk" by ESC guidelines, a class in which the ICD is generally not indicated (Fig. 1). The notion that there is some level of risk that everyone will find acceptable is a difficult idea to reconcile. If a patient, despite

Table 2 Risk factors for sudden cardiac death in main cardiomyopathy subtypes

Risk factors for SCD	HCM	DCM	ARVC
LVH	+ [66]	-	-
Early onset	± [67]	± [68]	± [69]
LVEF < 35%	+ [13]	+ [12]	+ [70]
NSVT	+ [33]	± [71]	+ [72]
RV severe systolic dysfunction	-	± [73, 74]	+ [70]
Myocardial fibrosis	+ [75]	+ [76]	+ [77]
LV outflow obstruction	+ [78]	-	-
Family history of SCD	+ [79]	+ [60]	± [80]
Syncope	+ [81]	+ [82]	+ [83]
NYHA > II	- [67]	+ [84]	+ [85]
Competitive sport	± [86, 87]	± [88]	+ [89]

+ : strong evidence of association between risk factor and SCD

± : dubious evidence of association between risk factor and SCD

- : no evidence of association between risk factor and SCD

ARVC, arrhythmogenic right ventricular cardiomyopathy; *DCM*, dilated cardiomyopathy; *HCM*, hypertrophic cardiomyopathy; *LV*, left ventricle; *LVEF*, left ventricular ejection fraction; *LVH*, left ventricular hypertrophy; *NSVT*, non-sustained ventricular tachycardia; *SCD*, sudden cardiac death

being not deemed at high risk, wants to have an ICD, are we in a position to disagree with this choice? There are many clinical and ethical aspects that should be taken in consideration. An ICD comes at a cost, both in terms of associated risks, including inappropriate shocks and device infections, and economic considerations. The physician evaluates the information available and proposes a strategy based on a combination of clinical details and data derived from available evidence. International guidelines support decision-making, providing a series of algorithms and flow charts that offer a relatively precise quantification of risk based on current evidence. However, they do not answer all the questions and potential dilemmas that may be encountered in caring for a specific patient. The intrinsic imperfection of risk calculators and recommendations, which are often based on dichotomous variables, and sometimes built on evidence from retrospective studies rather than randomized control trials, may be mediated by a holistic and individualized approach and by the clinician's judgement.

Many factors may impact a patient's perception of risk (Fig. 2). As medicine progresses from the outdated paternalistic approach to a physician–patient relationship based on autonomy where patients are decision-makers of their own health, subjectivity of risk appears particularly relevant. This is especially true when considering challenging choices, such as whether to implant an ICD for primary prevention or whether to advocate for athlete disqualification from competitive sport. Demographic, social, cultural, religious, and clinical factors have an impact on perception of risk. For example, a single parent of young children may have a different perception of SCD risk with respect to an individual without the responsibility of caring for a young family. Several studies have shown that older age and male sex lead to a decreased accuracy in estimation of risk [14, 15]. In order to understand health-related information and appropriately judge risk, patients must have a certain level of health literacy. Health literacy can be defined as "a constellation of skills, including the ability to perform basic reading and numerical tasks required to function in the health care environment" [16]. A key component of health literacy is numeracy, which in its broadest sense is the ability to understand and use numbers. In this framework, communication of risk is a crucial aspect of clinical consultation. Generally, when communicating risk, it is recommended to use simple numbers with clear explanations, as a more accurate perception of risk may be achieved when it is communicated in numerical rather than descriptive (such as "a small chance," "not very likely," "very likely") format [17]. When presenting information, it may be helpful to provide an interpretative standard or threshold, in order to aid understanding and also to personalize the risk to the individual [18].

The price to pay: lifestyle issues and risk of iatrogenic damage

Before the advent of ICDs in clinical practice, risk prediction in cardiomyopathies was limited by the absence of potentially life-saving therapies. The technological advances that led the development of smaller and more functional devices led to a progressive widespread use of ICDs from the early 2000s. After 20 years, increasing rates of iatrogenic complications provide a sobering lesson, and warn about the dangers and costs of overtreating. In the case of the ICD (particularly in the setting of primary prevention), these include device-related complications (currently occurring in about 15% of patients), most commonly inappropriate shocks triggered by supraventricular or sinus tachycardia, and atrial fibrillation as well as lead infections [7] (Table 1). A possible mitigation of additional risks attributable to transvenous ICDs, such as thrombosis and obstruction as well as other lead-related complications (e.g., fractures, replacement, and extraction), has stimulated interest in subcutaneous devices [19].

Furthermore, while avoidance of competitive sports may be judicious, discouraging regular exercise is considered detrimental in asymptomatic cardiomyopathy patients [20]. Recent studies have shown that obesity is highly prevalent among patients with HCM and is associated with increased likelihood of obstructive physiology and adverse outcomes [21]. In certain legal frameworks, the sporting organization or governing body may forbid the athlete to participate in competition. This is clearly aimed at preventing SCD, but

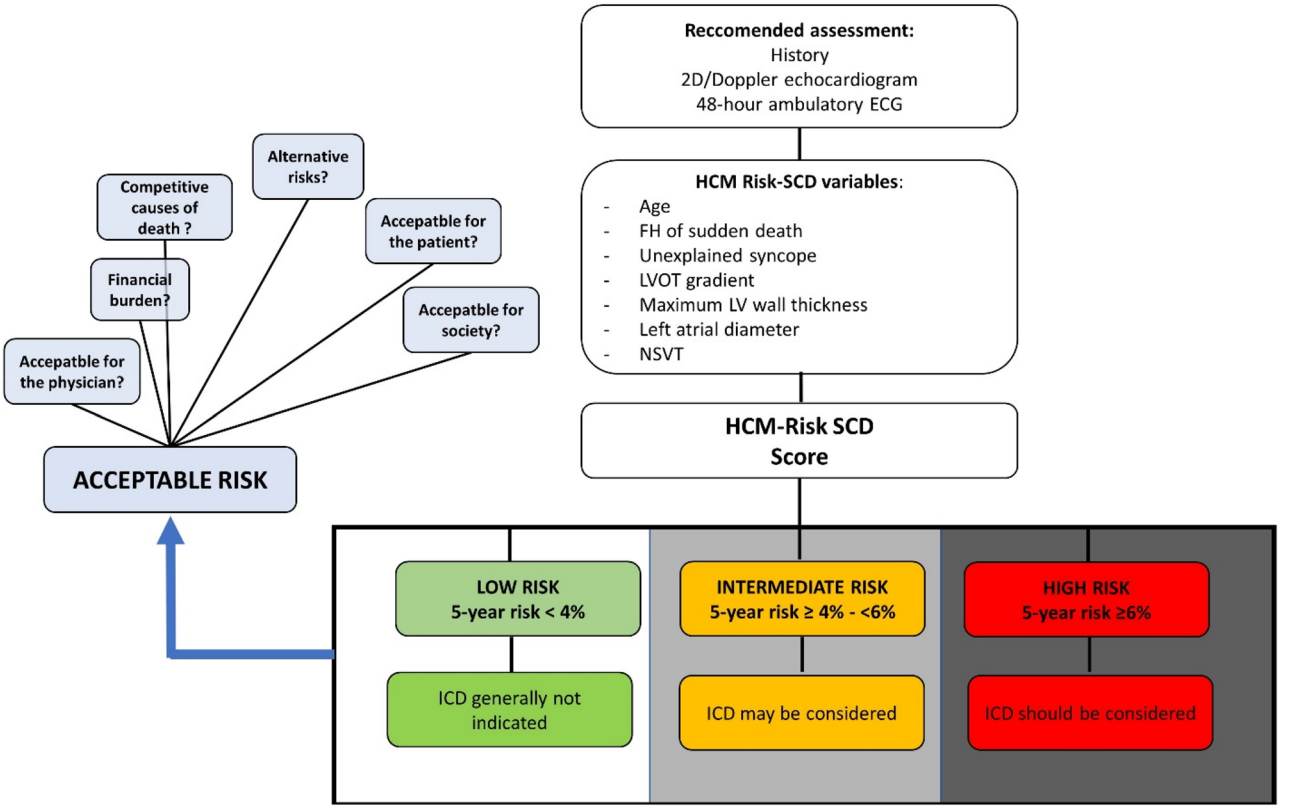
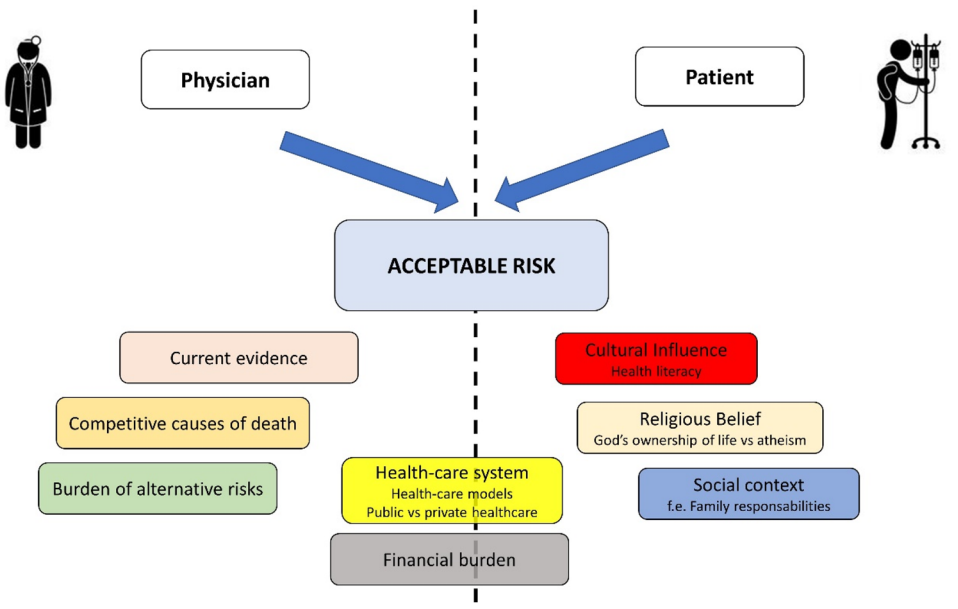


Fig. 1 European Society of Cardiology algorithm for the assessment of risk and indications for ICD in primary prevention in HCM (adapted from ESC guidelines). Abbreviations: FH: family history; HCM: hypertrophic cardiomyopathy; ICD: implantable cardioverter defibrillator; LVOT: left ventricular outflow tract obstruction; NSVT: non sustained ventricular tachycardia

the evidence of a possible relationship between exercise and risk of SCD is not robust in many cardiomyopathy subtypes [22]. Moreover, the consequences for the athlete may be deleterious, with a significant impact on his/her physical and psychological well-being. In the era of personalized medicine, care should be focused at the individual and not at the individual's disease. Emphasis of the risk of cardiomyopathy-related SCD should be balanced against the potential physical and psychological harm of neglecting other holistic considerations (Fig. 3).

Fig. 2 Acceptable and perceived risk (the physician and the patient perspectives)



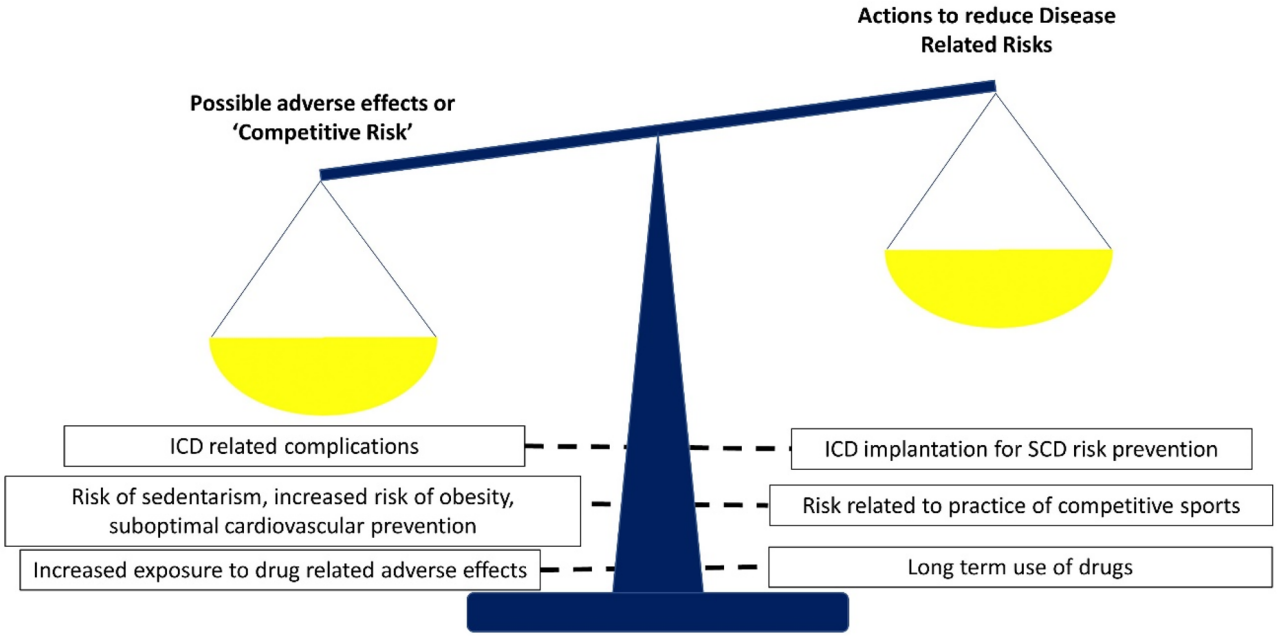


Fig. 3 Balance between actions aimed at reducing disease-related risks and competitive risks in the context of sudden death prevention. Abbreviations: ICD: implantable cardioverter defibrillator; SCD: sudden cardiac death

Financial implications of risk reduction strategies: another face of "acceptable risk"

We live in times when the prolonged survival of patients with chronic conditions has driven a substantial rise in healthcare expenditures worldwide [23, 24]. In the context of limited available resources, health systems are facing tremendous funding difficulties that challenge sustainability. Appropriateness is fundamental but it is a complex problem and a variable entity whose criteria and characteristics may change over the course of time and be influenced by various settings [25].

Incidence of SCD substantially differs across cardiomyopathy subtypes and age groups but invariably entails significant economic burden, especially when occurring in younger patients. Reduction of SCD conveys beneficial financial effects that may outweigh associated screening or treatment costs under specific diagnostic and therapeutic strategies. There is robust evidence suggesting that, despite the high upfront expenses, ICD is a cost-effective option in appropriately selected patients [26]. Of course, economic analyses are intricately linked to the willingness-to-pay threshold to gain an additional year of life — the economical equivalent of acceptable risk. While this parameter varies among policymakers, a cost-effectiveness ratio less than US$50,000 per life-year gained is considered economically attractive [27].

Based on incremental cost-effectiveness ratios (ICERs)—the difference in cost between two possible interventions, divided by the difference in their effect—cost evaluation studies have shown favorable ICERs for ICD therapy in patients with long QT syndrome (ICER: US$3,328 to US$19,393 per quality-adjusted life year [QALY] gained), HCM (US$17,526 to US$22,994 per QALY gained), and in high risk patients with Brugada syndrome (ICER: US$7,533 to US$10,138 per LYG and US$9,591 to US$14,667 per QALY gained, 2008 values) [28]. A dedicated study in the European healthcare setting underscored that primary prevention with ICD is cost-effective (ICER €43,993/QALY gained) among patients with left ventricular systolic dysfunction even when LVEF is > 40% and irrespectively of ischemic or dilated/non-ischemic aetiology [4]. The cost-effectiveness of ICDs is likely to be affected by the indication for use. If indications were to be broadened, an anticipated possibility if patient choice has an increasing role in decision to implant, the cost-effectiveness profile may be less favorable. This may have a deleterious effect on our resource-limited public healthcare systems.

Ethical implications

Designating a threshold of *acceptable* risk has ethical implications. One could reasonably ask "acceptable to *whom*?" While health economic analysis commonly uses tools to tally public acceptability of cost/benefit ratios, there is no indication that the patient has expressed an opinion as to what constitutes an acceptable risk of sudden death. Risk threshold above which ICD implantation is recommended has been framed as a clinical decision, but where the evidence base is not uniformly applicable (heterogenous subtypes of cardiomyopathy), this argument is less sound. Risk

versus benefit framed as number needed to treat versus numbers needed to harm may be seen as cynical when the benefit is an intervention that prevents death and the risk is one of less fatal complications. It broaches the interesting question of how and when society takes choices away from individuals in the name of public good. There are many ways to influence others, ranging from *nudging* to *soft* and then to *hard paternalism*. To justify the taking of individual autonomy, there often must be a perceived threat to others [29]. In the case of SCD risk stratification, this argument is weak.

Nudging is the act of arranging choice to encourage one to take a particular choice. Clinicians often do this in the way alternate treatment options are presented in clinical consultations [30]. Soft paternalism more strongly discourages undesirable choices, while hard paternalism diverges and disallows alternate choices [31]. The act of making eligibility decisions for ICD based on imperfect risk stratification with an absolute demarcation line could be considered unjustified hard paternalism if it takes choice out of the hands of the patient completely, not regarding personal life circumstances which may either modify risk or make a difference to how acceptable risk is to an individual.

Though a consequentialist approach (judging the goodness of a decision by the consequence) can be problematic to say the least, this is particularly challenging in the context of SCD risk as there is an element of uncertainty that translates to luck in outcome [32]. Often the case decisions dissected in hindsight result from instances in which there was a tragic failure to protect against SCD. However, this approach is dangerous as a decision, either for or against ICD implantation, may be the right decision even if the outcome is tragic. As Buchanan has pointed out, on a public health level, those patients with the most autonomy also have the best health, and the concept of a good life can vary from person to person [29]. Autonomy in this context is not libertarian, not free of responsibility or moral constraints, but rather a positive engagement in one's own and communities' health [29].

Certain life choices may increase risk of SCD; should these be considered prospectively in possible benefits of ICD insertion? For example, athletes who wish to continue competitive sports despite risk? Or women at borderline risk for SCD but planning high risk pregnancy? High risk choices that our patients should be empowered to make may thus alter the balance of risk and clinical indication. Given the above outlined context and circumstances, risk stratification tools are not fit for purpose as absolute indications for or against ICD implantation in cardiomyopathy patients. Instead, such decisions should be made within a multidisciplinary discussion, inclusive of and empowering the patient, and reflecting the patient's wishes, lifestyle choices, and first-person acceptability of best risk estimates.

Implications for management and future directions

Cardiomyopathies include a wide spectrum of diseases where risk of SCD is a common denominator. Challenges in risk stratification are many and faced in everyday practice. Although guidelines, algorithms, and risk calculators are of support in clinical choices, we rely on scarce evidence and often not on randomized clinical trials. The choice of implanting an ICD in primary prevention must always follow an open and bilateral discussion with the patients, sharing not only data but also doubts and trying to really understand what matters to the individual and the potential benefits and hazards (including psychological damage) of devices and lifestyle interventions. The ability to capture what really matters to patients and keeping an open mind is more important than strictly following guidelines. Because annual risk is generally low, decisions on primary prevention should not be rushed; waiting when there is uncertainty, in order to gain more information, is often beneficial. Patients that would be classified in the grey area of intermediate risk may exhibit worsening features along the course of the disease (such as non-sustained arrhythmias, worsening of symptoms, increased burden of fibrosis, and increasing biomarkers) which are clues that make the choices of certain management strategies more straightforward. Decisions should be reconsidered at each visit and based on up-to-date clinical information.

Algorithms and flow chart are useful tools in the hands of the clinicians; however, their complexity and constantly changing shape may prove to be extremely challenging rather than helpful in decision-making. Artificial intelligence, which is increasingly penetrating the world of medicine, may offer a different scenario, where computational analysis would allow to rapidly simplify complexity providing a road map to the clinician.

In this context, communication with patients is crucial and honest acknowledgement of scientific limitations should be part of the clinical consultation. The concept of "acceptable risk" should be replaced by the notion of "personalized risk" where numeric thresholds give way to a more holistic assessment with focus on the individual.

Conclusions

The notion of acceptable risk is increasingly under scrutiny, in an era when patient autonomy is a pillar of the physician–patient relationship. Specifically, acceptable risk of SCD in cardiomyopathies is often determined and quantified arbitrarily, despite the enormous impact that this can have, particularly in young patients, without acknowledging that numbers may be interpreted in very different ways and risk is perceived subjectively. Risk stratification of SCD in cardiomyopathies remains arduous and affected by the

lack of robust evidence and of randomized controlled trials, making the process of proposing and discussing management strategies even more challenging. In the personalized medicine era, it appears appropriate to abandon a dogmatic and paternalistic perspective, embracing an approach that communicates the limitations of current evidence and leaves adequate space for patient autonomy. The role of the physician in this context should not be to leave the choice in the hands of the patient, but instead to help illustrate the complexity of the issue, the repercussions on the patient, on society, and on the healthcare system. The physician should not be reluctant to recognize a "lack of knowledge" due to the paucity of robust evidence in certain aspects of care and management, embracing an honest discussion with patients.

We conclude with a citation from Robert Ludlum's novel "The Amber Warning" which encapsulates the constant challenge of decision-making: "Certainty does not exist in the real world of decision making. If we were to wait for complete certainty, action would be so delayed as to be irrelevant, and as the painful old saw remind us, 'Not to decide is to decide'. One cannot decide with no information. But one can't wait until one has complete information. There is a gradient between the two termini, and procedural integrity consists in the ability to choose the right points of partial knowledge."

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Declarations

Conflict of interest The authors declare no competing interests.

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