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Strength of clinical indication and therapeutic impact of the implantable cardioverter defibrillator in patients with hypertrophic cardiomyopathy

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ABSTRACT

Background: The implantable cardioverter defibrillator(ICD) has revolutionized the management of patients with hypertrophic cardiomyopathy (HCM) at risk of sudden cardiac death (SCD). However, the identification of ideal candidates remains challenging. We aimed to describe the long-term impact of the ICD for primary prevention in patients with HCM based on stringent (high SCD risk) vs lenient indications (need for pacing/personal choice).
Methods: Data from two Italian HCM Cardiomyopathy Units were retrospectively analyzed. Only patients >1 follow-up visits were divided into two groups according to ICD candidacy:stringent (high SCD risk) and lenient (need for pacing, patients' choice, physician advice despite lack of high SCD risk).
Major cardiac events (composite of appropriate shock/intervention and SCD) was the primary endpoint. A safety endpoint was defined as a composite of inappropriate shocks and device-related complications.
Results: Of 2009 patients, 252(12.5%) received an ICD, including 27(1.3%) in secondary prevention and 225 (11.2%) in primary prevention (age at implantation 49 ± 16 years; men 65.3%). Among those in primary prevention, 167(74.2%) had stringent, while 58(25.8%) had lenient indications.
At 5 ± 4 years, only stringent ICD patients experienced major cardiac events (2.84%/year, 5-year cumulative incidence: 8.1%, 95%CI [3.5–14.1%]).
ICD-related complications were similar across stringent and lenient subgroups. However, patients implanted >60 years had a significantly higher risk of adverse events.
Conclusion: One third of ICD recipients with HCM in primary prevention received a lenient implantation and had no appropriate intervention. ICD implantation due to systematic upgrade in patients requiring pacing and increased risk perception may offer little advantage and increase complication rates.

Abbreviations: AF, atrial fibrillation; ATP, anti-tachycardia pacing; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LA, left atrium; LGE, late gadolinium enhancement; LVOT, left ventricular outflow tract; NSVT, non-sustained ventricular tachycardia; PM, pacemaker; SCD, Sudden Cardiac Death; VF, ventricular fibrillation; VT, ventricular tachycardia.

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[2] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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1. Introduction

Over the last 20 years, the implantable cardioverter defibrillator (ICD) has revolutionized the management of patients with hypertrophic cardiomyopathy (HCM), providing reliable and consistent protection to individuals felt at greater risk of sudden cardiac death (SCD) (1). However, the identification of ideal candidates still remains challenging. While the indication of a device in secondary prevention is universally established, identification of high-risk patients in primary prevention is hindered by the heterogeneous clinical spectrum of the disease (2), with only a small minority of patients suffering potentially lethal arrhythmic events. Of those implanted due to a perceived increase in risk of SCD, only 2 to 3% per year receive appropriate shocks and about half of these interventions are due to arrhythmias that would likely self-terminate and therefore be non-lethal (3,4).

Based on over three decades of literature, algorithms have been developed to identify those HCM patients most likely to benefit from an ICD in primary prevention, and therefore maximize appropriateness (5–7). These algorithms have progressively penetrated medical practice, and most ICD implants reflect their clinical implementation. However, a substantial number of patients still receive an ICD despite the absence of high-risk criteria because they need permanent pacing due to bradyarrhythmias - and an ICD is preferred to a simple pacemaker - or simply due to the choice of patients and physicians. To what extent these less stringent indications represent appropriate preventive measures, when balanced against the risk of inappropriate shocks, device-related complications and costs, is unresolved. In the present study, we therefore assessed the therapeutic impact of the ICD for primary prevention in a large HCM patient cohort, based on the presence of stringent (i.e. according to standing guidelines) as opposed to lenient indications.

2. Methods

2.1. Study population

We retrospectively reviewed clinical and instrumental records of all HCM patients followed up at two national referral centres in Italy (Florence and Padua Cardiomyopathy Units, Italy), who were ≥ 16 years of age at first evaluation and had ≥1 year follow-up. HCM was defined by the presence of increased asymmetric left ventricular wall thickness > 15 mm in the absence of abnormal loading conditions at bidimensional (2D) echocardiography. Patients with non-sarcomeric HCM mimics (e.g. Fabry or cardiac amyloidosis disease) were excluded.

2.2. Indications for ICD implantation

Primary prevention was defined as ICD implantation in patients with no prior life-threatening events (6,8). Patients implanted from the first quarter of 2000 to first quarter of 2020 were included. Based on the strength of the indication, the primary prevention population was divided into two groups:

- *"Stringent",* i.e. *associated with a high risk profile,* defined before 2014 by at least 2 major risk factors (including non-vasovagal syncope, family history of SCD, non-sustained ventricular tachycardia (NSVT) on Holter monitoring, extreme LV hypertrophy and abnormal blood pressure response to exercise) (8) and after 2014 by an ESC score ≥ 6%/5 years (6) or presence of one or more of the following: LV apical aneurysm with transmural fibrosis at cardiac magnetic resonance (CMR) (9); end-stage HCM (defined LVEF<50% and/or restrictive diastolic pattern (10); extensive fibrosis (≥ 15% of total mass) at CMR (11).
- *"Lenient",* i.e. *not associated with a high risk profile:* including all other patients, in whom the decision to implant an ICD resulted from the need for pacing or was based on patients' personal choice (either due to physical, psychological or work reasons related to HCM diagnosis) or physician advice despite lack of high-risk features (differences in perceived risk attributed to individual risk factors like left ventricular wall thickness and family history of SCD independent of quantifiable SCD risk) (12).

Secondary prevention defined as ICD implantation following cardiac arrest due to ventricular fibrillation (VF) or hemodynamically significant sustained ventricular tachycardia (VT), were excluded.

2.3. Clinical management and follow up

All patients underwent routine 6–12 months visits, or more often if necessary, following a standardized protocol which included baseline 12-lead electrocardiogram, 24 or 48-h Holter recordings, and comprehensive 2D and Doppler echocardiography. Standard evaluation included 2D, M-mode, and Doppler study, according to the recommendations of the American Society of Echocardiography (13). Peak instantaneous left ventricular outflow tract (LVOT) gradient, due to mitral valve systolic anterior motion and mitral septal contact, was assessed with continuous wave Doppler under standard conditions. Genetic counselling was routinely offered to all patients since 2001. Next Generation Sequencing was adopted in 2012 and has been used ever since. All patients were offered genetic consultation and gene testing for HCM-associated variants in *MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *TPM1*, *ACTC1*, *MYL2*, *MYL3*, *TTR*, *GLA*, *LAMP2* and *PRKAG2* (variants in the last three, identifying HCM mimics, were a cause for exclusion).

2.4. Definition of outcome and study endpoints

Major cardiac events, defined as a composite of appropriate shock/intervention and SCD was the primary endpoint (14). Overall mortality, including SCD was also recorded in all patients, including those who were not referred to or refused ICD implantation. According to current guidelines, SCD was defined as an unexpected, nontraumatic, instantaneous collapse occurring unwitnessed or within an hour of the onset of symptoms (6). ICD were programmed by senior electrophysiology specialists according to current guidelines and manufacturer specifications (15). A safety endpoint – focusing on adverse events – was defined as a composite of inappropriate shocks, device-related infections or thrombosis, dislocations, and failure. Appropriate ICD intervention was defined by ATP or shock for VT >180 beats/min or VF according to expert consensus statement on optimal ICD arrhythmia detection times (15,16).

The study was approved by the Institutional Committee Review Board on Human Research at the authors' institution (Careggi University Hospital, Comitato Etico Area Vasta Centro and Padua University Hospital, Italy).

2.5. Statistical analysis

Continuous variables, reported as mean ± SD or as median and interquartile range (IQR; for non-normal distributions), were compared between groups ("stringent" vs "lenient") with Student's *t*-test or non-parametric tests, as appropriate. Categorical variables, reported as percentages, were compared between groups with chi-squared test (or a Fisher's exact test when any expected cell count was <5). For patients implanted with an ICD, follow-up was defined as the time from implantation to the last clinical visit or death. For all other patients not receiving an ICD, follow up was defined as the time from the first to last medical contact or death. Survival analysis was carried according to the Kaplan–Meier method and cumulative incidence functions were used to determine incidence of the endpoints. A two-sided *p*-value <0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Macintosh, Version 27.0 (Armonk, NY: IBM

Corp., USA) and GraphPad Prism v. 9.0.1.

3. Results

3.1. Baseline characteristics of patients referred to ICD implantation

Overall, 2187 patients with HCM were screened. Among these, 110 (5.0%) and 68 (3.1%) were excluded because had been diagnosed with Anderson Fabry disease or transthyretin cardiac amyloidosis caused by a genetic variant.

Of the 2009 patients, 252 (12.5%) received an ICD, including 27 (1.3%) in secondary prevention and 225 (11.2%) in primary prevention (mean age at implantation 49 ± 16 years; males 65.3%; Fig. 1 and Table 1). Among patients implanted in primary prevention, 167 (74.2%) had *stringent*, while 58 (25.8%) had *lenient* indications, as previously defined.

Patients in the stringent indication cohort were younger at both diagnosis and ICD implantation and were characterized by a higher ESC risk score and number of major risk factors (Table 1). Conversely, patients in the lenient indication group received an ICD because they needed a pacemaker ($N = 22$, 37.9%), chose to have an ICD despite the absence of a high-risk profile ($N = 14$, 24.1%), decided based on work-related issues (N = 1, 1.7%) or were referred to implant from the attending cardiologist ($N = 21$, 36.2%). Patients with lenient indications had more frequently been managed at peripheral hospitals with limited expertise in HCM. Pharmacological therapy did not differ among the groups with the exception of nondihydropyridine calcium channel blockers, more frequent in the lenient group, and angiotensin-converting-enzyme inhibitors, more frequent in the stringent group.

3.2. Long-term outcome

The 2009 patients were followed for 9 ± 5 years from initial evaluation. The 225 patients in primary prevention were followed for 5 ± 4 years after device implantation, with similar duration among the stringent and lenient indication subgroups (Table 2). Long-term, only stringent ICD patients experienced major cardiac events, with an annual incidence rate of 2.84%/year ($N = 26$ [15.6%], 5-year cumulative incidence: 8.1% 95% CI [3.5–14.1%]) (Fig. 2, Panel A). In particular, 15 (9.0%) experienced an appropriate shock (incidence rate: 1.6%/year), 7 (4.2%) anti-tachycardia pacing (incidence rate: 1.1%/year) and 4 (2.4%) had a SCD (incidence rate: 0.4%/year) (Table 2 and Fig. 1). By contrast, no major arrhythmic event was recorded in the lenient group.

By comparison, prevalence of SCD among 1757 patients without ICD was 2.1% over a mean of 9 ± 8 years ($N = 37$, incidence rate: 0.28%/year, 5-year cumulative incidence: 0.9% 95%CI [0.5–1.8]). Of these, two had a high-risk profile, but refused the ICD therapy; 4 had an intermediate risk, including 3 who also refused the device. Among patients in secondary prevention, 7 (25.9%, incidence rate: 5.18%/year) experienced an appropriate shock and 1 (3.7%, incidence rate: 0.73%/year) patient had a SCD.

3.3. Sudden cardiac death in ICD recipients

The 4 high-risk patients who died suddenly despite and ICD all had a hypokinetic-restrictive evolution with end-stage features, and likely suffered electromechanical dissociation: none experienced appropriate ICD interventions. The first patient had a positive family history for SCD, increased left atrium (LA) dimensions and increased arrhythmic burden (atrial fibrillation (AF) and NSVT); the second patient showed extensive transmural fibrosis at CMR associated with frequent arrhythmias (AF and NSVT); the third patient had a previous syncope, frequent NSVT, enlarged LA with AF and LVOT obstruction; the fourth patient died suddenly at the age of 28, with massive LV hypertrophy (40 mm), increased LA dimensions, LVOT obstruction and severe diastolic dysfunction.

3.4. ICD-related complications among primary prevention patients

Of the 225 patients in primary prevention, 55 (24.4%) patients experienced ICD-related complications, similar across the stringent and lenient indication subgroups (Table 2 and Fig. 1, incidence rate: 4.1 vs 5.5%/year in stringent vs lenient; 5-year Cumulative incidence: 12.4% 95% CI [7.5–20.5%] vs 14.7% 95% CI [5.7–31.4%] $p = 0.071$). Of note,

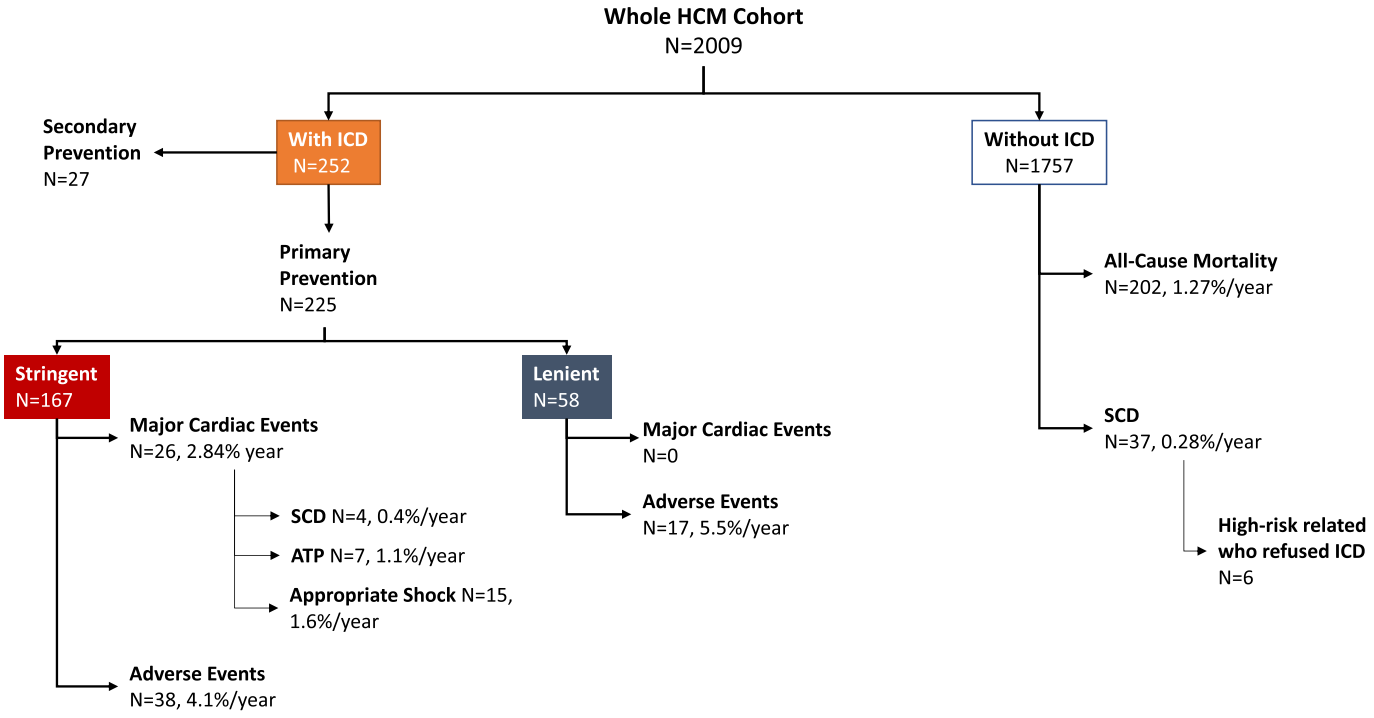

Fig. 1. Study Population by ICD presence and candidacy.

Table 1
Clinical characteristics of HCM patients undergoing ICD implantation for primary prevention, according to strength of indication.

	Stringent $N = 167$	Lenient $N = 58$	*P* value
Demographic characteristics			
Age at diagnosis, y	35.8 ± 18.3	44.0 ± 17.1	0.006
Age at implant, y	47.6 ± 16.1	53.3 ± 16.0	0.021
<40	50 (29.9)	10 (17.2)	0.009
40–60	72 (43.1)	22 (37.9)	
>60	45 (26.9)	26 (44.8)	
Males	112 (67.1)	35 (60.3)	0.354
NYHA III-IV	22 (13.2)	16 (27.5)	0.025
S-ICD	24 (14.4)	1 (1.7)	0.008
SCD Risk score	6.51 ± 3.66	3.75 ± 1.43	<0.001
Low	40 (23.9)*	32 (55.2)	
Intermediate	38(22.7)	26 (44.8)	
High	89 (53.3)	0	
Major Risk factors			
Syncope	51 (30.5)	16 (27.5)	0.665
Family history of SCD	49 (29.3)	17 (29.3)	0.996
NSVT	105 (63.8)	16 (27.6)	<0.001
LGE (≥ 15%)	74 (44.3)	0 (0)	<0.001
Apical aneurysm	4 (2.4)	0 (0)	0.577
End-stage	52 (31.1)	0 (0)	<0.001
Main Reason for Implant (for Lenient only)			
Need for pacing	n/a	22 (37.9)	–
Physician's advice	n/a	21 (36.2)	–
Patient's choice	n/a	14 (24.1)	–
Work-related issues	n/a	1 (1.7)	–
Genetic test**			
Number of P/LP variants			
0	20 (19)	12 (29.2)	
1	71 (67.6)	29 (70.7)	0.058
>1	14 (13.4)	2 (4.7)	
AF	72 (43.1)	29 (50)	0.383
CAD	14 (8.3)	4 (6.9)	0.884
Drug therapy***			
Beta-blockers	139 (87.4)	45 (81.8)	0.302
Calcium Channel Blockers	6 (3.8)	9 (16.1)	0.004
Disopyramide	7 (4.4)	5 (8.9)	0.205
Ranolazina	10 (6.3)	2 (3.6)	0.736
ACEi/ARB	52 (32.8)	10 (17.9)	0.033
Amiodarone	22 (13.8)	9 (16.1)	0.682
Echocardiogram			
Left atrial diameter	51±11	47±9	0.011
MLVWT	23±7	23±6	0.733
LVOT max gradient, median [IQR]	13 [5–44]	8 [5–30]	0.122
LVOTO	40 (24)	16 (27.6)	0.581

Categorical variables are presented as number of patients (%). Continuous values are expressed as mean ± standard deviation. LVOT max gradient as median [interquartile range]. Abbreviations: y: year; ACEi/ARB: Angiotensin Converting Enzyme inhibitors/Angiotensin Receptor Blockers; AF: Atrial Fibrillation; CAD: Coronary Artery Disease; ICD: implantable cardioverter-defibrillator; IVS: Interventricular Septum; LA: Left Atrium; LGE: Late Gadolinium Enhancement; LVOT(O): Left Ventricular Outflow Tract (Obstruction); MLVWT: Maximal Left Ventricular Wall Thickness; NYHA: New York Heart Association; NSVT: Non Sustained Ventricular Tachycardia; PM: Pacemaker; P/LP: Pathogenic/Likely Pathogenic; SCD = sudden cardiac death; S-ICD: subcutaneous ICD.
*: in these patients, High Risk warranting ICD implantation was not based on the ESC Risk score but rather on the presence of additional features such as: apical aneurism, progression to systolic dysfunction, presence of LGE at CMR., ** available in 146 patients (105 with high risk-related implantation). *** available in 215 patients (159 with high risk-related implantation).

patients implanted >60 years had a significant higher risk of adverse events (Fig. 2, Panels B and C). All device-related complications are summarized in Table 2. Notably, 29 patients (12.9%) experienced inappropriate shocks – mostly related to AF – with a trend towards a higher rate in the lenient cohort (18.9 vs 10.8%, $p = 0.142$). At least one device substitution was necessary in 57 individuals (25.3%).

Table 2
Events at follow up.

	Stringent N = 167	Lenient N = 58	P value
Follow Up, y	5 ± 4	5 ± 4	0.771
Major arrhythmic events	26 (15.6)	0	0.001
Appropriate shocks	15 (9.0)	0	
Appropriate ATP	7 (4.2)	0	
SCD	4 (2.4)	0	
ICD Replacements	41 (24.5)	16 (27.6)	
1	32 (78.0)	13 (81.3)	0.847
>1	9 (22.0)	3 (18.7)	
Acute Complications*	22 (13.2)	10 (17.2)	0.523
Adverse Events	38 (22.8)	17 (29.3)	0.317
<40 Years	13 (34.2)	1 (5.9)	0.275
40–60 Years	19 (50.0)	6 (35.3)	0.995
>60 Years	6 (15.8)	10 (58.8)	0.015
Adverse Events ≥2	4 (2.4)	0	0.576
Inappropriate Shocks	18 (10.8)	11 (18.9)	0.142
≥ 2 Shocks	6 (3.6)	2 (3.4)	0.914
Dislocations	1 (0.6)	1 (1.7)	0.463
Infections	8 (4.8)	1 (1.7)	0.451
Thrombosis	3 (1.8)	2 (3.4)	0.611
Device Failure	6 (3.6)	1 (1.7)	0.452
Upgrade to CRT	13 (7.8)	3 (5.3)	0.457

Categorical Variables Are Presented As Number Of Patients (%). Continuous Values Are Expressed As Mean ± Standard Deviation. Abbreviations: ICD: Implantable Cardioverter-Defibrillator; ATP: Anti-Tachycardia Pacing; CRT: Cardiac Resynchronization Therapy; SCD = Sudden Cardiac Death. * Up To 30 Days After Implantation.

4. Discussion

In the present study, we identified two different subsets of HCM patients who received ICD therapy for primary prevention of SCD. Two thirds of implants in this setting were stringent, due to a "high risk" profile as defined by the current international guidelines, either due to a sum of predictors, or to one major and established risk factor such as end-stage progression or an LV apical aneurysm. The remaining third, however, comprised individuals who did not qualify as high-risk but either required a pacemaker (upgraded to an ICD, given the need for an intravenous device in subjects with an arrhythmogenic disease) or shared this choice with the attending physician despite less than stringent indications, due to personal preference, work-related issue, or other reasons, often in peripheral hospitals with limited specific expertise in HCM. While need for pacing was the most common scenario (22 out of 58 patients with lenient ICD), a shared choice accounted for over one quarter of implants ($n = 15$, 26%). This finding likely reflects the degree of concern still raised by a diagnosis of HCM outside dedicated referral centres, where early descriptions of the disease as a rare and malignant entity, now outdated, still resonate (17).

Among patients implanted in primary prevention, the annual rate of major cardiac events was 2.84%, consistent with most recent literature (16). However, an important and novel finding was that this risk was not uniformly distributed, as appropriate interventions and SCD were recorded only in patients implanted in the stringent indication group, while none occurred in the lenient cohort. As expected, however, complication rates were similar between the two groups, with an annual incidence of 4.1% and 5.5% in patients with a stringent and lenient indication respectively.

These findings carry important clinical implications. Strategies for risk stratification that have evolved over the last two decades have overall been successful (despite evolving and sometimes conflicting data from the literature) in identifying HCM patients at high risk of SCD, with relevance of late gadolinium enhancement (LGE), among other risk factors, increasing sensibly (7). While sensitivity is unavoidably less that the ideal 100%, specificity is relatively good: in our cohort, 11 ICD implantations were necessary to prevent 1 SCD over 5 years – a satisfactory figure in a chronic disease with extended life expectancy and low

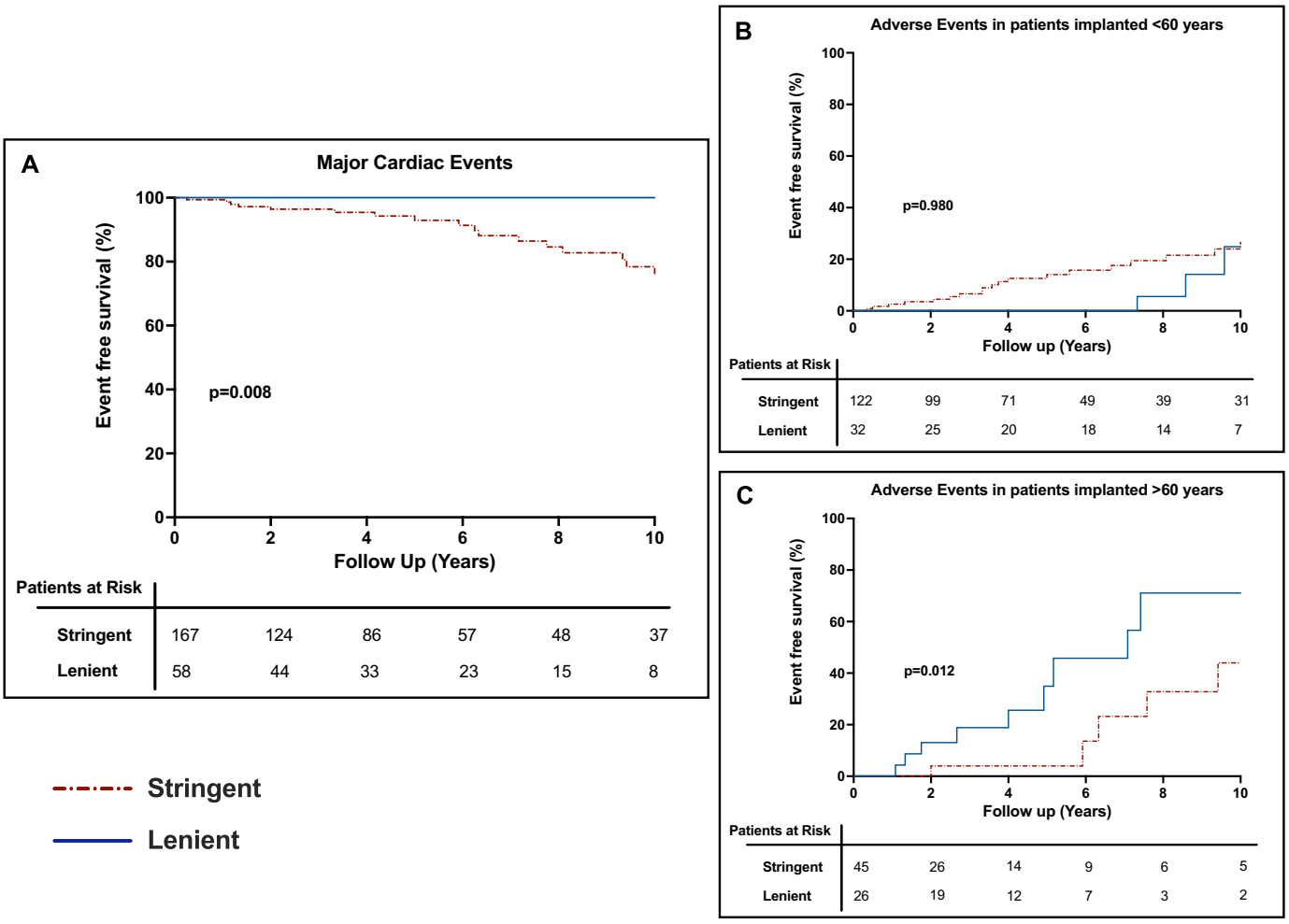

Fig. 2. Panel A: Kaplan Meier analysis of Major Cardiovascular Events according to ICD candidacy (stringent vs lenient). **Panels B and C:** Kaplan Meier analysis of the adverse events according to ICD candidacy (stringent vs lenient) in according to age at ICD implantation (Panel A: <60 years; Panel B: ≥60 years).

event rates. Furthermore, while it may be reasonable to implant an ICD in patients with less than high estimated risk, patients should be informed that the likelihood of device-related complications, which have been reported from 13 to up to 30% (7,16,18), (an annual rate of 5% in our study, with increasing incidence in older patients) far exceeds that of a life-saving event (4,16). Particularly in the case of pacing, the decision to implant an ICD rather than a pacemaker is often made by default by the physician, in an understandable effort to maximize protection. However, our data suggest that this should not be the case, and that the implications of this choice should be shared with the patients, including increased complication rates, increased frequency of battery substitution and shorter catheter duration. Since conduction disease is more common in older HCM patients, a subset considerably less exposed to SCD, this caveat may be all the more relevant to clinical practice. The same caution is required in patients with a lenient profile desiring an ICD (e.g. following the occurrence of SCD in a family member, in parents of small children, etc) or in whom the referring cardiologist has emphasized the need for a device. While all these indications may be reasonable in genetic cardiomyopathies with potential arrhythmic propensity, candidates to the ICD should be appropriately informed of the pros and cons in the light of the present findings. Of note, recent data sheds a positive light on the long-term impact of the ICD in HCM patients and suggests that even in patients who receive ICD interventions the device is safe and does not substantially impair psychological and physical well-being (19).

Our overall outcome data once again emphasize a different, more favourable profile of HCM, as outlined by recent literature, particularly with regard to SCD. In our population exceeding 2000 patients and followed over two decades, the rate of SCD among non-ICD recipients was as low as 0.28% per year. This is remarkable, given that our approach to the ICD was quite conservative compared to US institutions, but in line with other European centres, with a total implantation rate of about 12.5%, including 1.3% in secondary and 11.2% in primary prevention (12). While this may be due to a more selective "scrutiny" of patients with HCM, one may hypothesize that lenient indications for ICD implants are present also in other centres where referral to ICD implantation is higher.

A relevant issue regards the finding that the ICD may not confer absolute protection to HCM patients at high risk of SCD. Four individuals in our ICD cohort died suddenly despite a device during follow-up, representing less than 2% of patients with an ICD. These patients, having end-stage diseases with profound LV dysfunction and extensive myocardial fibrosis died of electromechanical dissociation. HCM associated heart failure due to systolic dysfunction or restrictive evolution is a severe condition with dismal outcome (10). These patients nevertheless represent excellent transplant candidates, with favourable long-term outcomes. The present study provides a further reason for early referral to cardiac transplantation in end-stage HCM patients, particularly in the presence of increased arrhythmic burden. In these patients, average degree of fibrotic replacement of LV myocardium approaches 40% (20). Therefore, although an infrequent occurrence, the ICD may fail as a bridge to transplant in these individuals due to the extreme

vulnerability of their hemodynamic state, exposing them to electromechanical dissociation or circulatory demise in the response to VT rates below detection threshold.

5. Conclusions

In conclusion, our long-term experience data showed that about one third of ICD recipients with HCM in primary prevention received a lenient implantation due to need for pacing, physician concern or patients' personal preference. These patients had no appropriate intervention, and their overall profile was comparable to that of low-risk patients not receiving a device. ICD-related complication rate was similar in the two groups: this suggests that systematic upgrade in patients requiring pacing or implantation due to concern raised by a diagnosis of HCM outside dedicated referral centres, and thus potentially against current recommendations, may offer little advantage and increase unnecessary complications rates, while better informed consultation may be a useful tool to drive shared decision making.

Authors' contributions

CF, VDF, CZ, and IO conceived the study collected and analyzed data, wrote and approved the final version of the manuscript; LT, MPR, GBR, AB, AC, BB, GC, NM, MZ, CC, MB, PP, and MDL contributed to conceive the study and/or critically revised the manuscript; DC conducted data management and analysis and critically revised the manuscript.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Declaration of Competing Interest

No conflict of interest to disclose for the present manuscript.

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