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ORIGINAL RESEARCH

How Many CPVT Patients Need an ICD?

The Impact of Left Cardiac Sympathetic Denervation

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ABSTRACT

BACKGROUND The management of catecholaminergic polymorphic ventricular tachycardia (CPVT) patients with drug refractory cardiac events (CEs) is challenging.

OBJECTIVES This study sought to assess the efficacy of left cardiac sympathetic denervation (LCSD) in 162 CPVT patients, focusing on those symptomatic without a high-risk genotype and compliant to therapy (main subanalysis, n = 118) of whom 41 had syncope on medical therapy. CEs included syncope, sudden cardiac arrest (SCA), sudden cardiac death (SCD), and appropriate implantable cardioverter-defibrillator (ICD) interventions.

METHODS A retrospective study including 162 CPVT patients (51% female, 80% probands, 79% *RYR2* positive) who underwent LCSD worldwide.

RESULTS Most (n = 139; 85%) of the 162 patients experienced ≥1 CE before LCSD, 84 (52%) had CEs despite medical therapy, and 43 (27%) had previous SCA. Overall, 93% received a beta-blocker (nonselective in 85%), 53% both a beta-blocker and a class I antiarrhythmic drug, and 55% (89) had an ICD before LCSD. During a median of 48 months (Q1-Q3: 12-111 months) after LCSD, 28 of 162 patients (17%) had ≥1 CE, including 10 of 28 (36%) during noncompliance. Of the 118 patients (main subanalysis), 13% suffered CEs after LCSD, including 3 SCAs and 1 SCD despite an ICD (3%). Of the 41 with syncope on medical therapy, 6 (15%) experienced CEs after LCSD, including the SCD despite an ICD (3%). LCSD improved quality of life by reducing ICD shocks by 67% and electrical storms by 80%.

CONCLUSIONS Our data suggest that probably <5% of symptomatic CPVT patients compliant to medical therapy require an ICD after LCSD. ICDs do not reliably prevent SCD. (JACC Clin Electrophysiol. 2026;■:■-■) © 2026 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

βB = beta-blocker

CE = cardiac event

CPVT = catecholaminergic polymorphic ventricular tachycardia

ICD = implantable cardioverter-defibrillator

LCSD = left cardiac sympathetic denervation

LQTS = long QT syndrome

NSVT = nonsustained ventricular tachycardia

RCSD = right cardiac sympathetic denervation

SCA = sudden cardiac arrest

SCD = sudden cardiac death

VT = ventricular tachycardia

Different diseases associated with risk for sudden cardiac death (SCD) have different problems when pharmacologic therapy looks insufficient and a more invasive approach, such as the use of an implantable cardioverter-defibrillator (ICD), appears necessary. For high-risk patients with ischemic heart disease, heart failure, and even for those with most cardiomyopathies, an ICD is often considered and pursued. This is in contrast to 2 channelopathies, long QT syndrome (LQTS) and especially catecholaminergic polymorphic ventricular tachycardia (CPVT).[1]

The reason, in addition to the frequent adverse events directly related to the ICD and common in young patients,[2] lies in the exquisite sensitivity of these 2 syndromes to catecholamines, which easily trigger electrical storms after an appropriate shock, often leading to the exhaustion of all ICD available therapies, a condition known as end of-treatment. Furthermore, in CPVT only, ICD shocks, though effective for ventricular fibrillation, often fail to terminate polymorphic/bidirectional VTs,[3,4] leading to ineffectiveness-related end-of-treatment. Additionally, noncompliance to medical therapy is an alarming and often under-reported issue for LQTS and CPVT patients, concurring to increase the risk of deadly electrical storms among ICD recipients.[5,6] Lastly, both for LQTS and CPVT, the existence of particularly high-risk genotypes is well established.[7,8] A recent international cohort study concluded that, when dealing with CPVT patients, the decision to implant an ICD should be weighed against the potential risks of severe ICD-related complications and recurrent shocks.[9]

These concerns are a heavy burden for cardiologists who are requested to decide on how to proceed when a CPVT patient has a breakthrough arrhythmic event despite appropriate beta-blocker (βB) therapy, largely because of opposing views in the published data about the value of ICDs in reducing mortality among high-risk CPVT patients.[10,11] Furthermore, from these discussions it seems that only cursory attention has been given to the possibility that left cardiac sympathetic denervation (LCSD)[12] might tilt the balance in favor of a less invasive/aggressive treatment option than ICDs.

In 2008, we assessed for the first time the potential value of LCSD in managing CPVT patients not fully protected by βBs[13] and in 2015 we performed the first study in a large cohort of CPVT patients.[14] That specific experience prompted the objective of the present study: given the frequent and potentially serious adverse events caused by ICDs, how many CPVT patients really need an ICD if their therapy with βBs with or without flecainide[15] is complemented with LCSD? Accordingly, we gathered data on the largest data set ever reported for CPVT patients on medical therapy having also undergone LCSD to provide further insights on the long-term efficacy of LCSD.

METHODS

This study included 162 CPVT patients who underwent LCSD at 10 referral centers worldwide between 1988 and 2025: Italy, the United States (specifically Rochester, Minnesota), United Kingdom, Germany, Norway, Russia, Iran, and Israel. The coordinating center in Milan collected deidentified baseline and follow-up data via web-based forms. CPVT diagnosis was established clinically with or without genetic confirmation of a pathogenic (P) or likely pathogenic (LP) CPVT-associated variant. Cardiac events (CEs) either before or after LCSD were defined as arrhythmic syncope, sudden cardiac arrest (SCA), SCD (after LCSD), or appropriate ICD therapies (those delivered for rapid ventricular tachyarrhythmias within the programmed detection parameters). Electrical storms were defined as ≥3 episodes of sustained VT/ventricular fibrillation in 24 hours (in patients without ICD) or ≥3 ICD shocks in 24 hours (in patients with ICD). End-of-treatment was defined as ICD therapy exhaustion due to serial shocks. Patients were considered as symptomatic before LCSD if they had experienced ≥1 CE. All therapies were prescribed at the physician's discretion. Medical therapy consisted of βBs, with or without a class IC antiarrhythmic drug (flecainide[15] or propafenone[16]), at the maximum tolerated dose, considering as targets ≥1 mg/kg/d of nadolol or 2 mg/kg/d of propranolol. In all centers, LCSD was performed

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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correctly (ie, by removing the lower half of the stellate ganglion [T1] and the ipsilateral sympathetic ganglia from T2 to T4), because any form of incomplete denervation is medically unacceptable and ethically disquieting.[17] Documented nonsustained (≥triplets) ventricular arrhythmias despite medical therapy prompted us to consider an ICD implant and/or LCSD even in absence of CEs. High-risk genotypes included *CASQ2* and those associated with atypical forms of CPVT, including *CALM*, *TECRL*, and *TRDN*.[8]

The main objectives of the present study were to assess the efficacy of LCSD in patients with CPVT, to identify predictors of CEs after the procedure and to establish a management strategy for patients with syncope despite medical treatment and no previous SCA. Due to its high clinical relevance, a particular focus (main subanalysis) was directed toward symptomatic CPVT patients without high-risk genotypes compliant on medical therapy.

The study was approved by the Istituto Auxologico Italiano Ethics Committee (2021_05_18_06_CHAREG), and the subsequent amendments by the Comitato Etico Territoriale Lombardia 5 (CE 2242737_1) as well as ethical committees at collaborating centers.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD or median (Q1-Q3) and categorical variables as percentages. Continuous variables are compared with Student's *t*-test or Mann-Whitney U test, as appropriate. Absolute and relative frequencies are reported for categorical variables and compared by the Fisher exact test or the chi-square test, as appropriate. CEs incidence after LCSD was compared across groups based on pre-LCSD clinical status (asymptomatic, previously symptomatic with and without CEs on medical therapy), underlying genotype (high-risk vs no high-risk), post-LCSD medical therapy adherence (on-treatment and intention-to-treat), and ICD presence at LCSD.

Event-free survival was estimated using Kaplan-Meier curves and compared by log-rank test. A multivariable Cox proportional hazards model featuring only variables significant ($P < 0.05$) in univariable logistic regression-assessed predictors of CEs after LCSD. The proportional hazards assumption was assessed using Schoenfeld residuals for all variables in the final Cox models. Where the proportional hazards assumption was violated ($P < 0.05$), the Cox model was stratified by the violating variable. Due to variable drug combinations, ongoing medical therapy was analyzed categorically, with ßB monotherapy as the reference group compared to ßB plus class IC antiarrhythmic drugs or other regimens (combined). Statistical significance was defined as $P < 0.05$. There were no missing data for any of the key variables analyzed in this study. Consequently, all analyses were conducted on complete cases.

Computations and images were carried out using IBM SPSS Statistics (version 27.0), MedCalc Statistical Software (version 20), GraphPad Prism (version 8.0.0, Dotmatics), and Python 3.13.0.

RESULTS

STUDY POPULATION. A total of 162 CPVT patients (83 females, 51%; 129 probands, 80%) were included in the study (Table 1). Video-assisted thoracoscopic surgery was performed in most patients (141, 87%), whereas the remaining underwent either a supraclavicular or transaxillary approach. Genotyping was performed in 153 (94%) and showed P/LP *RYR2* variants in 84%. Most patients (139, 85%) experienced ≥1 CE before LCSD, including 32 (23% of those with CEs) who presented with SCA as their first symptom. Mean age was 10 ± 7 years at first symptom, and 14 ± 9 years at diagnosis.

Overall, 151 patients (93%) received a βB (in 85% a nonselective βB) and 86 patients (53%) a combination medical therapy including both a βB and a class I antiarrhythmic drug. Additionally, 89 patients (55%) had an ICD before LCSD, including 32 (36%) after syncope on medical therapy, 31 (35%) after SCA either on (n = 3) or off (n = 28) treatment, and 26 (29%) due to nonsustained ventricular tachycardia (NSVT) on medical therapy.

Of the 162 patients, 84 (52%) underwent LCSD because of CEs on prescribed medical therapy. Importantly, LCSD was performed in 55 (34%) previously symptomatic patients without CEs on medical therapy and in 23 (14%) previously asymptomatic patients (primary prevention), because of NSVT while on medical therapy (Figure 1).

OUTCOME OF LCSD. Mean age at LCSD was 19 ± 10 years (range 2-58 years), with a median follow-up after surgery of 48 months (Q1-Q3: 12-111 months) during which 2 additional ICDs were implanted. No major complications occurred. Minor, transient complications affected 11 patients (7%), including neuropathic pain in 7 (4%), left eyelid ptosis in 3 (2%), and pneumothorax in 1 (1%). Video-assisted thoracoscopic surgery produced a mild, permanent ptosis in 3 patients (2%); none requiring plastic surgery.

After LCSD, 28 of 162 patients (17%) (Table 1) had ≥1 post-LCSD CE, including 4 (2%) who died suddenly, 5 (3%) who had SCA, 19 (12%) who

TABLE 1 Baseline Characteristics of the Study Population

Characteristic	All Patients (N = 162)	No Recurrences (n = 134)	Recurrences, ITT (n = 28)	*P* Value
Female sex	83 (51)	69 (52)	14 (50)	0.9
Mean age at diagnosis, y	14 ± 9	15 ± 10	10 ± 4	**0.008**
Proband status	129 (80)	102 (76)	27 (96)	**0.016**
Genotyped	153 (94)	126 (94)	27 (96)	0.615
RYR2 pos	128/153 (84)	107/126 (85)	21/27 (78)	0.363
Gen neg	10/153 (7)	9/126 (7)	1/27 (4)	0.513
High-risk genotype	15 (9)	10 (8)	5 (18)	0.085
CASQ2 hom	9 (5)	6 (5)	3 (11)	0.188
CALM/TECRL/TRDN	2/1/3 (4)	2/0/2 (3)	0/1/1 (7)	0.108
CEs ever before LCSD	139 (85)	112 (84)	27 (96)	0.077
SCA before LCSD	43 (27)	34 (25)	9 (32)	0.462
ICD before LCSD	89 (55)	76 (57)	23 (82)	**0.012**
βB before LCSD	151 (93)	126 (94)	25 (89)	0.365
Non-selective βB before LCSD	128/151 (85)	106/126 (84)	22/25 (88)	0.623
IC AADs before LCSD	91 (56)	77 (57)	14/28 (50)	0.470
Flecainide	85/91 (93)	73/77 (95)	12/14 (86)	0.210
CEs on medical therapy before LCSD	84 (51)	65 (49)	19 (68)	**0.039**
Mean age at LCSD, y	19 ± 10	20 ± 11	13 ± 4	**0.002**
Median FU after LCSD, mo	48 (12-111)	39 (9-96)	90 (45-129)	**0.009**
Noncompliance to medical therapy after LCSD	10 (6)	0 (0)	10 (36)	**<0.001**

Values are n (%), mean ± SD, n/n (%), or median (Q1-Q3). Bold values are statistically significant.

AAD = antiarrhythmic drug; βB = beta-blocker; CEs = cardiac events; FU = follow-up; Gen = Genotype hom = homozygote; IC = class I; ICD = implantable cardioverter-defibrillator; ITT = intention to treat; LCSD = left cardiac sympathetic denervation; neg = negative; pos = positive; SCA = sudden cardiac arrest.

had ≥1 ICD shock as their worst CE, and 1 who had an arrhythmic syncope. Median time to the first CE after LCSD was 25 months (Q1-Q3: 7-72 months). Of extreme importance, noncompliance to medical treatment was systematically involved in 10 of these 28 patients (36%) with CEs after LCSD. Thus, the actual incidence of CEs among compliant patients was of 18 of 152 (12%).

During follow-up, 39 of 162 patients (24%) had therapy changes, mostly (27 of 39, 69%) not prompted by CEs (see the Supplemental Appendix and Supplemental Table 1 for details).

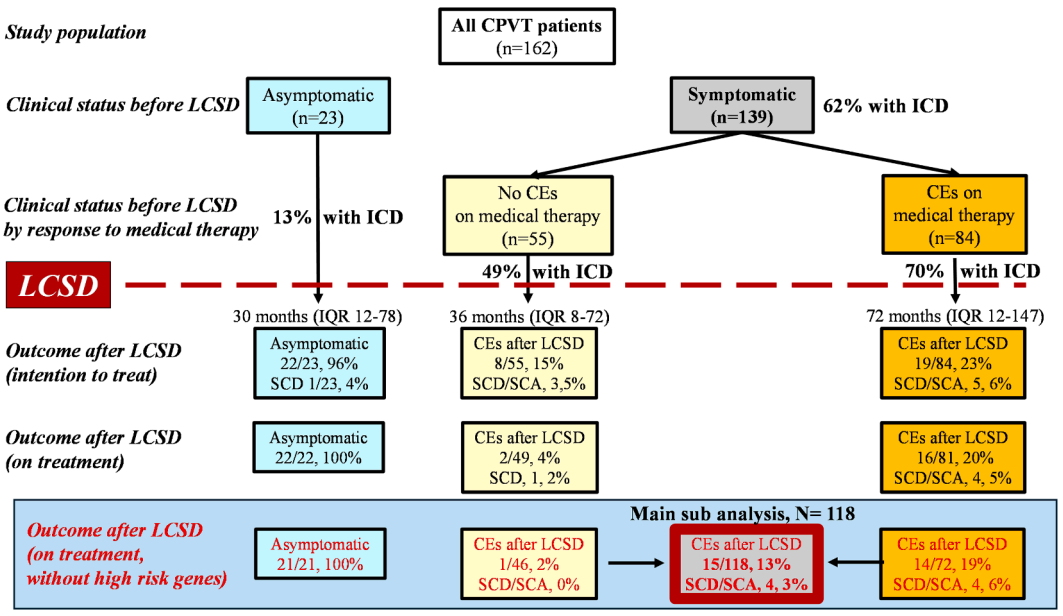
Figure 1 summarizes outcomes after LCSD, stratified according to the clinical status before LCSD. Asymptomatic patients adherent to therapy experienced no CEs during a median follow-up of 30 months (Q1-Q3: 12-72 months) (**Figure 1**, bottom left); as a significant warning, the only patient not compliant to medical therapy died suddenly. In symptomatic patients without any CEs on medical therapy, LCSD resulted in only 1 CE (of 46, 2%) when excluding high-risk genotypes, and in 2 CEs (of 49, 4%) when including them (**Figure 1**, bottom, second box).

CEs rates after LCSD among previously symptomatic patients despite medical therapy were 23% (intention-to-treat), 20% (on-treatment), and 19% (on-treatment excluding high-risk genotypes) during a median follow-up of 72 months (Q1-Q3: 12-147 months) (**Figure 1**, right column).

Table 2 provides details about the 9 patients with SCA (n = 5) or SCD (n = 4) after LCSD, including 5 with an ICD. Two SCAs and 2 SCDs (44%) occurred under declared noncompliance; avoidable triggering factors were involved in the other 2: multiple energy drinks in 1 and switching from nadolol to metoprolol in the other. Data retrieved from ICD interrogation showed refractory ventricular arrhythmias in all 5 cases with a device, thus representing an ICD failure. Overall, none of the patients without a high-risk genotype, complaint to medical therapy, and on a nonselective ßBs died suddenly.

PREDICTORS OF CEs AFTER LCSD. Cox regression analysis (AUC: 0.789; 95% CI: 0.718-0.861) in the entire cohort (n = 162; 28 events), adjusted for proband status, identified noncompliance with post-LCSD medical therapy (HR: 11.91, 95% CI: 5.09-27.88; $P < 0.0001$) and ICD presence at LCSD (HR: 3.15; 95% CI: 1.16-8.60; $P = 0.024$) as independent predictors of post-LCSD events. Given violation of the proportional hazards assumption for noncompliance (Schoenfeld residuals $P = 0.041$), the model was stratified by this variable. Following

FIGURE 1 Clinical Status Before LCSD and Outcome Afterwards According to Therapeutic Compliance



The diagram shows the number of catecholaminergic polymorphic ventricular tachycardia (CPVT) patients subdivided according to the clinical status before and therapeutic status after left cardiac sympathetic denervation (LCSD). Boxes represent status and outcomes, with colors indicating pre-LCSD clinical status: blue (asymptomatic), gray (symptomatic), light yellow (symptomatic without cardiac events [CEs] on medical therapy), and orange (symptomatic with CEs on medical therapy). The red dashed LCSD line shows progression to post-treatment outcomes, with time points at 30, 36, and 72 months, respectively, in the 3 groups, capturing, for each box, all CEs and only sudden cardiac death (SCD)/sudden cardiac arrest (SCA) events. Outcomes are presented for 1) all patients (intention-to-treat) (first line), 2) medical therapy-compliant patients (second line), and 3) medical therapy-compliant patients without high-risk genes (third line). The third line includes the 118 symptomatic patients of the main subanalysis. ICD = implantable cardioverter-defibrillator.

stratification, ICD presence at LCSD remained an independent predictor of CEs post-LCSD (stratified HR: 4.69; 95% CI: 1.38-15.88; $P = 0.013$).

PRIMARY SUBANALYSIS. Critical to clinical practice are the outcomes of LCSD patients symptomatic prior to LCSD without a high-risk genotype, on and compliant to medical therapy (n = 118; 59 female, 50%; 107 probands, 91%) (**Table 3**). The majority of patients (72, 61%) had CEs on medical therapy prior to LCSD. **Figure 2** shows the long-term cumulative event-free survival considering all CEs (**Figure 2A**) and only SCAs/SCDs (**Figure 2B**).

Overall, 15 of these 118 patients (13%) had CEs during a median follow-up of 48 months (Q1-Q3: 8-111 months) after LCSD, including 11 (9%) with ICD shocks, 3 with SCA (3%), and 1 SCD (1%) (**Table 2**). The incidence of CEs after LCSD was not significantly different among patients with (7 of 40, 18%) or without (8 of 78, 10%) a history of SCA before LCSD ($P = 0.266$). Impressively, only 1 of the 48 patients without an ICD suffered a CE (a SCA) after LCSD, as opposed to 14 of 70 (20%) among those with an ICD ($P = 0.004$). The proportion of patients on a class I antiarrhythmic drug associated with a ßB did not significantly change after LCSD (68% vs 60%; $P = 0.196$) (see the Supplemental Appendix).

In a Cox regression analysis (AUC: 0.77; 95% CI: 0.73-0.82) of this subgroup (n = 118; 15 CEs), adjusted for CEs on medical therapy before LCSD, prior ICD implantation was the sole independent predictor of CEs after LCSD (HR: 7.89; 95% CI: 1.03-69.64; $P = 0.074$). Despite the limited sample size, the proportional hazards assumption was met. Combination therapy (ßB plus IC antiarrhythmic drug) was not associated with reduced/altered CEs risk post-LCSD compared to ßB alone, a finding supported by survival curves (Supplemental Figure 1) and sensitivity analysis in patients with CEs before LCSD on medical therapy (Supplemental Figure 2).

MANAGEMENT OF PATIENTS WITH SYNCOPE DESPITE MEDICAL THERAPY. A total of 41 patients (22 female, 54%, 35 probands, 85%) had ≥1 previous

TABLE 2 Patients With SCA/SCD After LCSD

Sex	Genotype	Age At First Symptom (y)	SCA Before LCSD	Age at ICD (y)	No. CEs on Medications Before LCSD	Medications at LCSD in mg/kg/d	Age at LCSD (y)	Latest Medications After LCSD	CEs After LCSD Details
M	RYR2+	6	No	8	1	Nad 0.5	9	Nad 0.5+ Propaf 3.8	Single SCA 273 mo after LCSD while playing basketball at camp
F	RYR2+	7	Yes	17	1	Nad 1.3+ Fleca 4.4	18	Nad 1.3+ Fleca 4.4	Single SCA 83 mo after LCSD requiring 3 AED shocks; energy drinks and vaping involved
M	CASQ2	5	No			Nad 0.8+ Fleca 3.1	17	Nad 0.4+ Fleca 3.1	SCD 4 mo after LCSD, previous sustained VT at loop recorder
M	RYR2+	–	No			Nad 0.7	15	Nad 1.3+ Fleca 3.3	Single SCD 48 mo after LCSD, noncompliant
M	RYR2+	9	No			Nad 2	14	Nad 1+ Fleca 6.7	Single SCA 120 mo after LCSD, noncompliant
M	RYR2+	9	No	10	2	Nad 1+ Fleca 3.1	15	Nad 1+ Vera 2.0	Single SCA 84 mo after LCSD, noncompliant
M	RYR2+	6	No	12		Nad 1+ Propaf 4	15	Nad 1+ Propaf 4	SCD 168 mo after LCSD, with previous multiple AD, noncompliant
F	RYR2+	3	No	9	67	Nad 1+ Mexi 7	14	Meto 100 mg twice daily	Single SCD 8 mo after LCSD, after switch from nadolol to metoprolol
M	RYR2+	9	Yes		5	Nad 1+ Fleca 6	9	Nad 1+ Fleca 6	Documented SCA due to VF 136 mo after LCSD, than ICD implantation, 3 separate ICD shocks leading to RCSD. No further events thereafter

AED = automated external defibrillator; AD = appropriate discharges; F = female; Fleca = flecainide; M = male; Meto = metoprolol; Nad = nadolol; Propaf = propafenone; RCSD = right cardiac sympathetic denervation; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Table 1.

syncope on medical therapy without a history of SCA before LCSD. Most of them (27, 66%) received an ICD first and then LCSD (in 23 cases due to recurrent ICD shocks, in 4 because of documented NSVTs), whereas the remaining 14 were treated with LCSD only without an ICD. The majority (22 of 41, 54%) were treated with a ßB plus a class I antiarrhythmic drug at the time of LCSD. During a median follow-up of 53 months (Q1-Q3: 8-138 months) post-LCSD, 6 patients (15%) experienced CEs, always ICD shocks, including 1 SCD (2%) after ßB change from nadolol to metoprolol. Accordingly, the incidence of CEs after LCSD was 6 of 27 (22%) among ICD recipients, as opposed to 0 of 14 (0%) among patients without ICDs ($P = 0.078$).

IMPACT OF HIGH-RISK GENOTYPES. A total of 15 patients (n = 8; 53% male) were harboring a high-risk genotype, represented by *CASQ2* homozygosity (ie, CPVT2) in 9 cases (60%) (Supplemental Table 2). Most of them (93%) were symptomatic before LCSD, with a mean age at first symptom of 6 ± 5 years, which was significantly lower than the rest of the population (10 ± 7; $P = 0.002$). There was a trend for a higher incidence of CEs after LCSD among these 15 patients with a high-risk genotype (5 of 15, 33%), compared to the rest of the population (23 of 147, 15%; $P = 0.08$), thus reinforcing the concept that high-risk genotypes are always more difficult to protect.[18] The SCA/SCD incidence after LCSD was not different (1 of 15, 7% vs 8 of 147, 5%; $P = 0.8$), but the only case of SCD occurring during regular compliance to proper medical therapy was in a patient with *CASQ2*-mediated CPVT2.

IMPACT OF LCSD IN PATIENTS WITH AND WITHOUT ICD. Of 89 patients with ICDs before LCSD, 51 (66%) underwent LCSD for ICD shocks, including 17 with electrical storms (19%) and 11 (12%) with end-of-treatment conditions. Overall, 23 of 89 patients (26%, $P < 0.001$ compared to before) experienced ≥1 appropriate ICD interventions (all shocks) post-LCSD, including 5 (6%) who developed end-of-treatment conditions leading to SCA in 3 cases and SCD in 2, highlighting that ICDs do not guarantee complete protection. Crucial for the quality of life, among the 15 patients with recurrent ICD shocks, the median number significantly decreased from 7 (Q1-Q3: 3-15; maximum 109) to 0 (Q1-Q3: 0-1; maximum 9) after LCSD ($P < 0.001$) during a median follow-up of 72 months (Q1-Q3: 12-144 months). Two patients received an ICD post-LCSD: 1 for ventricular fibrillation-related SCA and 1 for persistent syncope due to noncompliance. The incidence of CEs was

TABLE 3 Baseline Characteristics of the Main Subanalysis Population

Characteristics	All Patients (n = 118)	No. CEs After LCSD (n= 103)	CEs After LCSD (n= 15)	*P* Value
Female sex	59 (50)	51 (50)	8 (53)	0.791
Mean age at diagnosis, y	14 ± 9	15 ± 9	8 ± 2	**<0.001**
Proband status	107 (91)	92 (89)	15 (100)	0.355
Genotyped	111 (93)	97 (94)	14 (93)	1.00
RYR2 pos	101 (86)	88 (85)	13 (87)	1.00
Gen neg	10 (8)	9 (9)	1 (7)	1.00
CEs ever before LCSD	118 (100)	103 (100)	15 (100)	1.00
SCA first symptom	29 (25)	25 (24)	4 (27)	1.00
SCA before LCSD	40 (34)	33 (32)	7 (47)	0.381
ICD before LCSD	70 (59)	56 (54)	14 (93)	**0.004**
βB before LCSD	112 (95)	98 (95)	14 (93)	0.566
Nonselective βB before LCSD	92/112 (82)	80/98 (82)	12/14 (86)	1.00
IC AADs before LCSD	71 (60)	63 (61)	8 (53)	0.583
Propafenone + βB	5 (4)	4 (4)	1 (7)	0.499
Flecainide + βB	62 (52)	56 (54)	6 (40)	0.408
Flecainide monotherapy	4 (3)	3 (3)	1 (7)	0.424
CEs on medical therapy before LCSD	72 (61)	58 (56)	14 (93)	**0.009**
LCSD as monotherapy	2 (2)	2 (2)	0 (0)	1.00
Mean age at LCSD, y	19 ± 10	19 ± 10	13 ± 4	**0.008**
Median FU after LCSD, mo	48 (8-111)	41 (7-93)	103 (78-144)	**0.022**

Values are n (%), mean ± SD, n/n (%), or median (Q1-Q3). **Bold** values are statistically significant.
Abbreviation as in Table 1.

significantly higher among patients with an ICD compared to those without (26% vs 7%; $P = 0.002$), whereas the incidence of SCA/SCD was similar (6% vs 5%; $P = 1.0$). Differences in the main patients' characteristics and treatment before and after LCSD according to the presence of ICD at LCSD are reported in Supplemental Table 3 and support a higher risk profile of patients with ICDs.

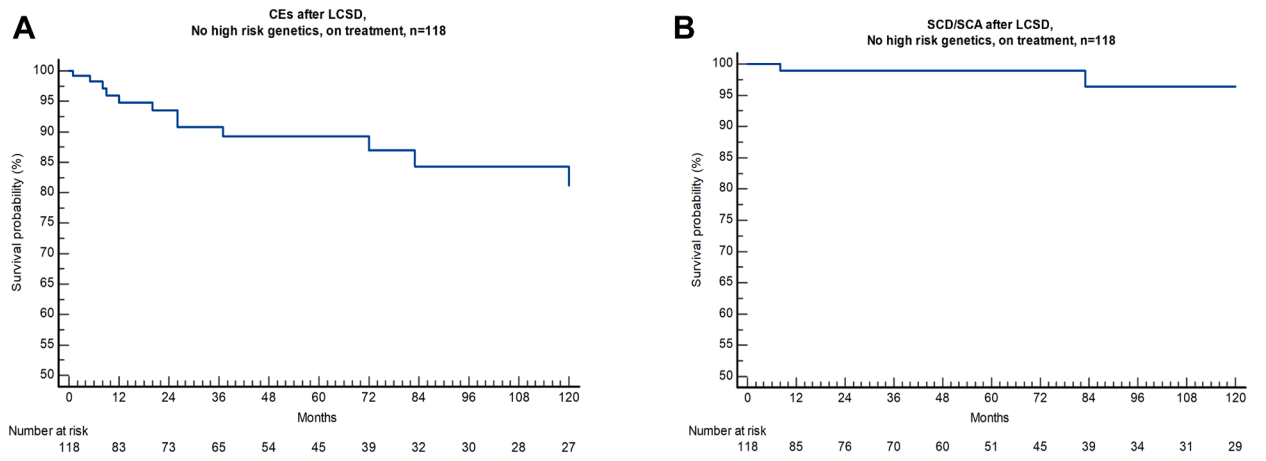
LCSD, NONCOMPLIANCE, AND ICDs. Non-compliance-related CEs occurred both in patients with an ICD (7 of 23, 30%; including 1 SCA and 1 SCD) and in patients without ICDs (3 of 5, 60%; including 1 SCA and 1 SCD; $P = 0.103$), leading to a worrisome equal (3%) incidence of SCA/SCD among patients with and without ICDs adherent to medical therapy. In compliant patients, LCSD significantly reduced ICD shocks by 67% (from 46 of 79 to 15 of 79; $P < 0.001$) and electrical storms by 80% (from 15 of 79 to 3 of 79; $P = 0.003$). A potentially important but nonsignificant 67% reduction was observed in end-of-treatment conditions (from 9 of 79 to 3 of 79; $P = 0.08$). Figure 3 shows survival free from all CEs (Figure 3A) and from SCA/SCD according to ICD presence, in compliant patients without high-risk genotypes.

RCSD FOLLOWING LCSD. Right cardiac sympathetic denervation (RCSD) following LCSD was performed in 4 patients, in 3 because of CEs despite compliance to medical therapy without any subsequent CE. The fourth patient underwent RCSD because of a 13-beat NSVT on exercise stress testing, despite full-dose propranolol and flecainide. RCSD prevented the NSVT to occur while significantly reducing peak heart rate on the same medication regimen (from 186 beats/min [90% of predicted] to 117 beats/min [57% of predicted]).

DISCUSSION

Our study addressed 2 exquisitely clinical questions: What protection can we expect and which are the predictors of CEs after LCSD performed in CPVT patients not fully protected by traditional medical therapy (nonselective βBs with or without a class IC antiarrhythmic drug, typically flecainide)? How should these patients be managed? The answers to these questions could help physicians and families decide whether ICD implantation is justified. Indeed, the management of CPVT patients not fully protected by medical therapy involves a significant medical

FIGURE 2 CEs and SCA/SCD Free Survival After LCSD in the Main Subgroup



Survival free from all CEs (A) and from SCA/SCD (B) after LCSD in the main subgroup (118 symptomatic patients with no high-risk genetics, compliant to medical therapy). Abbreviations as in Figure 1.

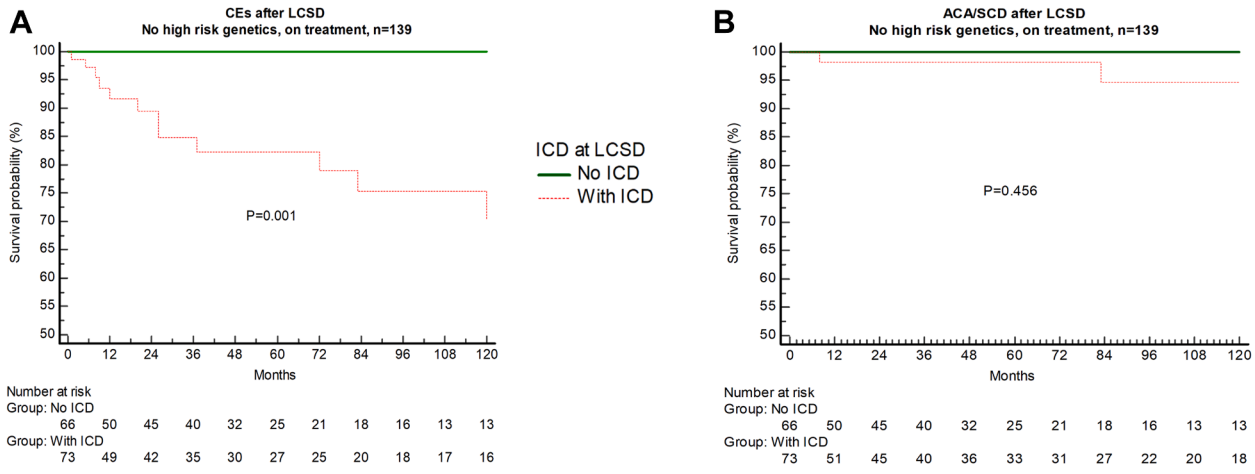
responsibility, and its complexity is compounded by the fact that, as opposed to ICDs, practical and theoretical expertise on LCSD is far from widespread and is missing even at several referral centers. In this delicate clinical scenario, given that ICDs are ubiquitous but not at all devoid of adverse events, it is of the utmost importance to provide large and solid clinical data on the therapeutic efficacy of LCSD for patients with CPVT. We uncovered several significant findings, resulting from the largest cohort of CPVT patients treated with LCSD reported so far. Clinical features were similar to those reported in other CPVT cohorts,[19] but ours had an earlier event onset and a higher percentage of patients with aborted SCA as the first symptom, reflecting a higher proportion of severely symptomatic patients and high-risk genotypes.

Importantly, despite the inherent limitations of a retrospective study, LCSD appears even more effective in protecting CPVT patients from life-threatening events than what was previously thought.[12,14] ICDs not only fail to provide a complete protection from SCD but appear to be associated with a higher number of electrical storms, end-of-treatment conditions and CEs, probably due to a combination of higher inherent arrhythmic risk of these patients, reduced ICD efficacy/proarrhythmic potential of ICDs in CPVT, and intervention on otherwise likely asymptomatic NSVTs. By contrast, LCSD has a major impact on the quality of life of the patients compliant to medical therapy because it impressively reduces ICD shocks and electrical storms (Central Illustration).

MANAGEMENT OF PATIENTS NOT FULLY PROTECTED BY βBs. Nonselective βBs, such as nadolol and propranolol, are the cornerstone for the prevention of arrhythmias in CPVT, consistently outperforming β1-selective drugs.[11,20] However, recurrent CEs still occur in about 30% of symptomatic patients despite βB treatment, a rate consistently reported across studies,[21] including a non-neglectable 6% incidence of SCA/SCD in a large cohort of 329 symptomatic patients with CPVT1.[20] Suboptimal βBs daily dosages and noncompliance play a major role in βBs failures, highlighting the importance of drug titration and the inherent limitations of therapies dependent on patient adherence, particularly in the young.[6] The exercise stress test is reliable and consistent within the same CPVT patient in inducing ventricular arrhythmias,[22] making it useful for both diagnosis and long-term therapeutic optimization. Flecainide has been reported to reduce exercise-induced ventricular arrhythmias[23] and to show long-term clinical benefit;[15] however, its efficacy compared to that of LCSD remains unknown. When facing a CPVT patient with syncope despite βBs, most doctors around the world decide to proceed with ICD implantation. Our data show that, probably in >80% of cases, this decision is not warranted.

ISSUES WITH ICDs. ICD use in CPVT requires disease-specific considerations[24] beyond the general concern for adverse events.[2] Optimal programming is crucial to minimize unnecessary and potentially proarrhythmic interventions. Nonetheless, ICD

FIGURE 3 CEs and SCA/SCD Free Survival After LCSD According to ICD Presence of Main Patient's Characteristics and Outcome



Survival free from all CEs (A) and from SCA/SCD after LCSD, according to the presence or absence of an ICD at LCSD. Abbreviations as in Figure 2.

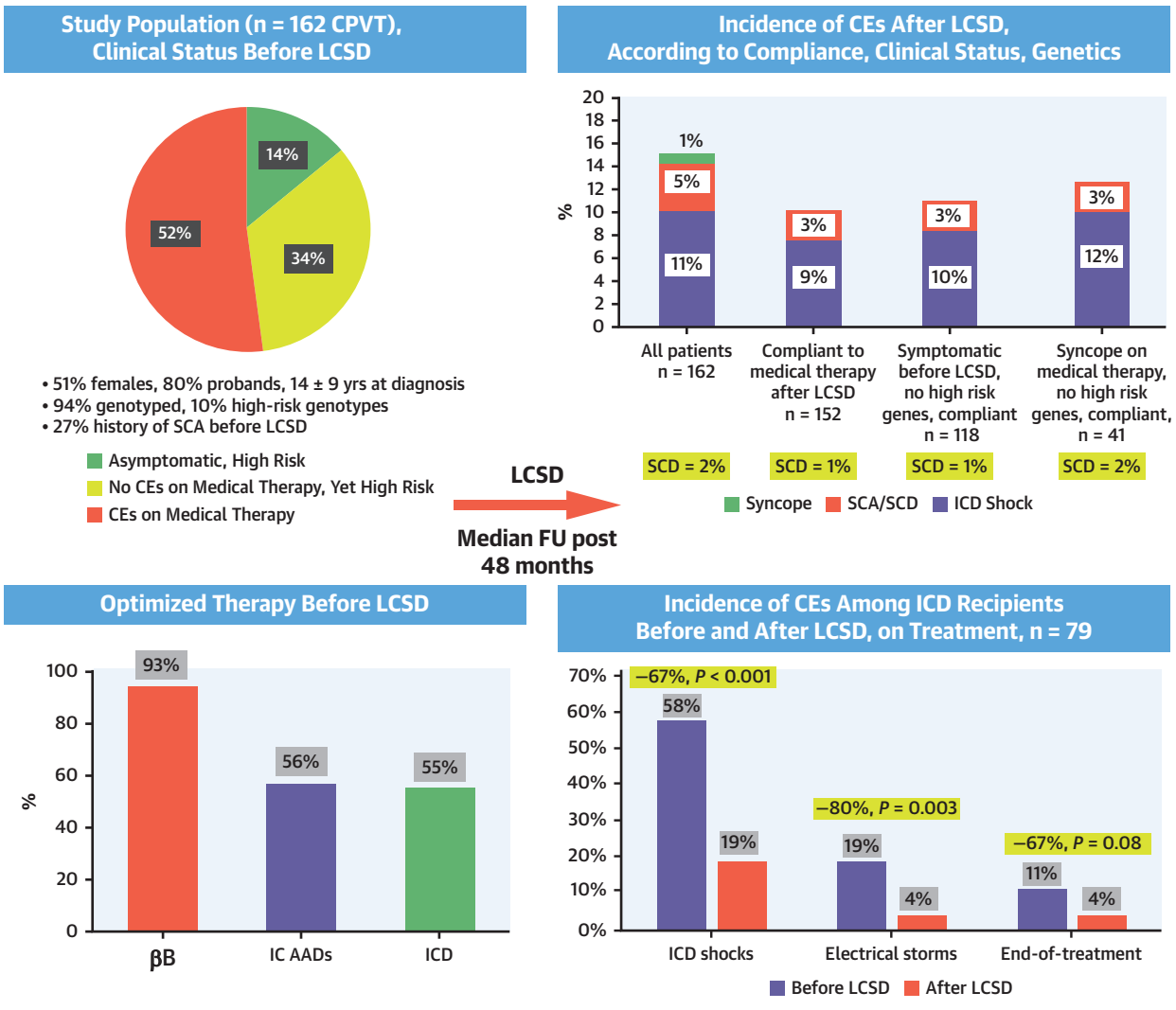
failures and subsequent SCAs/SCDs can still occur in up to two-thirds[3] of VT episodes due to nonuniform ICD efficacy according to the underlying rhythm (below 5% against bidirectional/polymorphic VT).[3,4,11]

ICD shocks, even when effective, induce a significant catecholamine release due to a combination of both central (perception of pain and fear) and peripheral mechanisms (the cardio-cardiac sympathetic reflex[25]) and thus increase the probability of immediate new and recurrent VTs, often exhausting the ICD capacity to deliver shocks. Several anecdotal reports exist of SCD in CPVT patients due to documented end-of-treatment.[26]

Our study includes 89 CPVT patients with an ICD at LCSD: 66% suffered recurrent ICD shocks before surgery, including 19% with electrical storms and 12% with end-of-treatment leading to SCAs. Beyond the impact on quality of life, this suggests that ≥10% of high-risk ICD recipients might have died without prompt resuscitation. LCSD significantly reduced appropriate ICD shocks and, in compliant patients, electrical storms. The latter effect has a major impact on the quality of life of patients and of families. Notably, SCD/SCA incidence was similar in patients with and without ICDs, even after adjusting for medical therapy compliance. Three of 4 of the SCD/SCA events after LCSD despite adherence to medical therapy and lack of a high-risk genotype were confined to patients with an ICD experiencing end-of-treatment. Furthermore, ICD presence remained an independent predictor of clinical events (primarily ICD shocks) after LCSD (HR: ~3), whereas compliance to medical therapy was protective. ICD shocks are not equivalent to SCAs/SCDs,[27] and we recently showed in almost 3,000 LQTS patients that ICD patients have an incidence of CEs approximately 10 times higher than patients without an ICD.[28] The differential LCSD efficacy in CPVT based on ICD presence likely stems from several factors including higher risk profile in some ICD recipients, a nonstandardized and noncontrolled ICD programming, and potential for undetected asymptomatic polymorphic/bidirectional VT episodes in CPVT patients without ICDs, particularly post-LCSD.

LCSD OUTCOMES. Secondary prevention. In our previous study,[14] we reported a post-LCSD recurrence rate varying from 6% in patients without CEs on medical therapy to 32% in those with CEs, with only 1 case (2%) of SCD. Mostly due to small numbers, we had not systematically considered therapeutic compliance[6] nor corrected for genotype,[8] 2 factors strongly associated with arrhythmic risk. Here, we now provide solid data on the efficacy of LCSD in CPVT taking into account these important potential confounders. Many patients were on combination drug therapy before LCSD, reflecting the broader use of flecainide. In patients with prior drug-refractory CEs, without high-risk genotypes and compliant to therapy, the incidence of CEs after LCSD was 19%, including a 6% combined incidence of SCD/SCA and 1% incidence of SCD. Overall, <5% of symptomatic

CENTRAL ILLUSTRATION **Summary of Main Patient's Characteristics and Outcome**



Bos JM, et al. JACC Clin Electrophysiol. 2026;■(■):■–■.

(Left)The clinical status (top) and optimized treatment (bottom) of the study population prior to left cardiac sympathetic denervation (LCSD) are shown. (Right) The outcomes post-LCSD are shown. (Top right) Cardiac events (CEs) incidence after LCSD for the entire population (N = 162) stratified by compliance, clinical status, and genetics. Noncompliance significantly affected CEs occurrence, whereas recurrence rates were relatively low among 118 symptomatic patients without high-risk genetics on treatment. (Bottom right) The incidence of isolated and repetitive implantable cardioverter-defibrillator (ICD) shocks (electrical storm/end-of-treatment) before and after LCSD highlight the procedure's significant impact. AAD = antiarrhythmic drug; βB = beta-blocker; CPVT = catecholaminergic polymorphic ventricular tachycardia; FU = follow-up; IC = class I; SCA = sudden cardiac arrest; SCD = sudden cardiac death.

patients compliant with medical therapy experienced life-threatening CEs (SCDs/SCAs) after LCSD. Most patients with CEs after LCSD suffered only isolated ICD shocks that should never be considered equivalent to SCA/SCD.

PATIENTS WITH SYNCOPE DESPITE MEDICAL THERAPY. This is the group of CPVT patients that, in the absence of high-risk genotypes and of prior SCA, elicits the greatest controversy between the ICD and LCSD indication.[10,11] Our data show that none of these patients had CEs after sole LCSD. When we considered also the patients with an ICD implanted before LCSD, only 15% experienced CEs post-LCSD, and all these CEs were ICD shocks, including 1 SCD due to ICD end-of-treatment following a βB switch. These findings support LCSD as the preferable initial treatment for these patients.

Primary prevention. Twenty-three patients, including 1 with a high-risk genotype, underwent LCSD despite being asymptomatic, due to NSVT on medical therapy. Notably, only 13% had been implanted with an ICD, whereas one-third were on combination drug therapy. These data highlight that experienced LCSD centers, fully supported by expert opinion,[17] are confident in pursuing LCSD in these patients instead of implanting an ICD.

The shorter median follow-up in this group compared to the other 2 reflects the evolving and expanding indications for LCSD. Importantly, no patient compliant with medical therapy experienced CEs during follow-up, supporting this management strategy. The single lethal event occurred in a noncompliant patient, further validating the selection of LCSD for this effectively high-risk, yet asymptomatic, population.

LCSD in high-risk genotypes. Another small but still very informative subgroup of patients is represented by those harboring a high-risk genotype, mostly represented (60% of cases) by *CASQ2* homozygosity. Indeed, 93% of them were symptomatic before LCSD (with the first symptom in their childhood), and 67% had suffered CEs on medical therapy before LCSD. These patients showed a trend for a higher incidence of CEs after LCSD, compared to the rest of the population, which did not reach statistical significance even when correcting for adherence to medical therapy. Also, there was only 1 case of SCD, and it was in the setting of noncompliance. Overall, as already demonstrated for LQTS,[18] these data support LCSD to reduce the arrhythmic burden even in the setting of high-risk genotypes.

RATIONALE FOR LCSD AND RCSD. The rationale for LCSD in LQTS and CPVT has been repeatedly presented[7,12,17,29] and rests on 3 main effects: 1) major reduction in norepinephrine release given the quantitatively dominant role of left cardiac sympathetic nerves; 2) increase in the threshold for ventricular fibrillation;[30] and 3) a reflex increase of cardiac vagal efferent activity.[31] The latter effect is particularly important for CPVT patients because it contributes to prevent or limit major increases in heart rate, which is among the main triggers for the CPVT arrhythmias. The addition of RCSD extends further these effects because the sympathetic control of heart rate is primarily under control of the right-sided cardiac nerves.[32] Most recently, the evidence has been provided that coculturing neurons from CPVT patients with healthy cardiac myocytes induces arrhythmogenic activity thus increasing, as Li et al[33] specify, the rationale for surgically interrupting cardiac sympathetic nerves.

We started using RCSD, following incomplete protection after LCSD, in the mid-1980s.[34] Our view is based on this long-term experience. As RCSD further reduces norepinephrine release in the ventricles and prevents rapid heart rate increases, a protective effect specifically relevant to CPVT, we believe that whenever LCSD provides no or incomplete protection, it is reasonable to equally consider RCSD or an ICD implant. The choice between the 2 should be a shared decision with patients/families, fully disclosing their benefits and drawbacks. We now envisage, and recommend, a wider use of RCSD for CPVT. Nonetheless, we stand by our view that, barring exceptional cases or circumstances, it is inappropriate to perform a bilateral CSD without having first assessed the efficacy of unilateral LCSD. We see no justification to violate the time-honored concept of using the least effective dose of any therapy. There is no reason to deprive the heart of its adrenergic support, if not necessary, while doubling the risk of surgery-related adverse events. A possible exception, based on our present data, might be represented by patients with high-risk genotypes where LCSD failures are more likely to occur.

STUDY LIMITATIONS. Due to the retrospective design and long study period, evolving drug therapies, including selective βB use in some patients, and evolving concepts of medical therapy (with or without flecainide) were present. The efficacy of LCSD would be even higher if we had only considered patients on nonselective βBs. The lack of detailed ICD data prevents us from determining the effective length of the arrhythmic episodes prior to ICD interventions and from comparing the efficacy of ICD shocks before and after LCSD. The fact that class I antiarrhythmic drugs were often added to βBs in the absence of a breakthrough events has limited the possibility of assessing their contribution; indeed, our data do not allow us to confirm or deny their protective effect[13] in this high-risk population.

CONCLUSIONS

The present study provides new data necessary for an updated management of CPVT patients that takes into account their need for safety and for a good quality of life. We show with adequate numbers that LCSD, sometimes complemented by RCSD, in patients compliant to the medical therapy, is highly protective against life-threatening arrhythmias and

greatly limits the need for ICDs. Indeed, our data suggest that, following LCSD, probably <5% of symptomatic CPVT patients compliant to medical therapy need an ICD. Furthermore, they show that ICDs do not reliably prevent SCD in adrenergic channelopathies,[22] highlighting the need for optimized medical therapy complemented by LCSD prior to implanting an ICD. Conversely, our data support LCSD as the first invasive treatment for patients with syncope and/or NSVT despite compliance to medical therapy and no history of SCA. Transparent information given in expert centers where all therapeutic options are available is necessary for an ethical approach to a shared decision between the patients with their families and the responsible physicians.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our data strongly add to the previous body of evidence supporting LCSD usage in CPVT patients. We show that <5% of symptomatic patients compliant to medical therapy suffered life-threatening CEs (SCD or SCA) after surgery, including only 1% of those with syncope on treatment. LCSD significantly reduced not only isolated ICD shocks but also electrical storms and end-of-treatment conditions, which could have been otherwise lethal despite the ICD. Noncompliance to medical therapy is a major clinical issue and should prompt LCSD together with ICD to prevent sudden death.

TRANSLATIONAL OUTLOOK: Despite its proven efficacy and significant impact on the quality of life, LCSD is still underused, with too many patients being directed to ICD implantation without the possibility of benefiting from its antiarrhythmic protection, including the reduction of life-threatening situations even among ICD recipients on medical therapy. The present data are expected to drive significant updates to guidelines and treatment pathways.

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KEY WORDS **beta-blockers, catecholamines, implantable cardioverter-defibrillators, sudden cardiac death, sympathetic nervous system, ventricular arrhythmias**

APPENDIX **For supplemental text, figures, and tables, please see the online version of this paper.**