



HAL
open science

Implantable Cardioverter Defibrillator Therapy in Hypertrophic Cardiomyopathy: A SIMPLE Substudy Authors

Mate Vamos, Jeff S Healey, Jia Wang, Stuart Connolly, Philippe Mabo, Lieselot van Erven, Josef Kautzner, Michael Glikson, Jorg Neuzner, Gilles O'Hara, et al.

► **To cite this version:**

Mate Vamos, Jeff S Healey, Jia Wang, Stuart Connolly, Philippe Mabo, et al.. Implantable Cardioverter Defibrillator Therapy in Hypertrophic Cardiomyopathy: A SIMPLE Substudy Authors. Heart Rhythm, 2018, 15 (3), pp.386-392. 10.1016/j.hrthm.2017.11.020 . hal-01817900

HAL Id: hal-01817900

<https://hal-univ-rennes1.archives-ouvertes.fr/hal-01817900>

Submitted on 18 Jun 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1
2 **Implantable Cardioverter Defibrillator Therapy in Hypertrophic**
3 **Cardiomyopathy: A SIMPLE Substudy**
4

5 Authors: Mate Vamos, MD¹, Jeff S. Healey, MD^{2,3}, Jia Wang, MSc³, Stuart
6 J. Connolly, MD², Philippe Mabo, MD⁴, Lieselot VanErven, MD⁵,
7 Josef Kautzner, MD⁶, Michael Glikson, MD⁷, Jorg Neuzner, MD⁸,
8 Gilles O'Hara, MD⁹, Xavier Vinolas, MD¹⁰, Frederik Gadler, MD¹¹,
9 Stefan H. Hohnloser, MD¹

10
11 Affiliations: (1) University Hospital Frankfurt, Goethe University, Frankfurt, Germany (2)
12 McMaster University, Hamilton, Canada (3) Population Health Research
13 Institute, Hamilton, Canada (4) Centre Hospitalier Universitaire, Rennes,
14 France (5) Leiden University Medical Center, Leiden, the Netherlands (6)
15 Institute for Clinical and Experimental Medicine, Prague, Czech Republic (7)
16 Leviev Heart Center, Sheba Medical Center, Tel Hashomer, Israel (8)
17 Klinikum Kassel, Kassel, Germany (9) Institut Universitaire de Cardiologie et
18 de Pneumologie de Québec, QC, Canada (10) Hospital de Santa Creu i Sant
19 Pau, Barcelona, Spain (11) Karolinska Institute, Stockholm, Sweden

20 Short title: ICD in HCM patients

21 Word count: 4668

22 Conflicts of int.: The SIMPLE trial (NCT00800384) was funded by Boston Scientific.

23
24
25
26 Address for correspondence:

27 Stefan H. Hohnloser, MD, FHRS, FACC, FESC,

28 Department of Cardiology, Division of Clinical Electrophysiology

29 University Hospital Frankfurt - Goethe University

30 Theodor-Stern-Kai 7, D-60590 Frankfurt am Main, Germany

31 Tel. +49-69-6301-7404; Fax. +49-69-6301-7017

32 hohnloser@em.uni-frankfurt.de

1 **Abstract**

2 **Background:** Patients with hypertrophic cardiomyopathy (HCM) are considered to
3 be at high risk for elevated defibrillation thresholds, peri-procedural complications,
4 and failed appropriate shocks.

5 **Objective:** To determine the value of defibrillation testing in HCM patients
6 undergoing ICD implantation.

7 **Methods:** Defibrillation thresholds, perioperative complications, and long-term
8 outcomes were compared between patients with HCM, and those with ischemic or
9 dilated cardiomyopathy (ICM/DCM) enrolled in the SIMPLE trial. In patients with
10 HCM, outcomes were also compared between those randomized to DT versus no
11 DT.

12 **Results:** Adequate defibrillation safety margin without system change was achieved
13 in 46/52 (88.5%) HCM and in 948/1047 (90.5%) ICM/DCM patients ($p=0.63$).
14 Perioperative complications occurred in 1/52 (1.9%) HCM patients with DT, in
15 comparison to 67/1047 (6.4%) ICM/DCM patients with DT ($p=0.37$) or to 3/42 (7.1%)
16 HCM patients without DT ($p=0.32$). During follow-up, there was no significant
17 difference between HCM vs. ICM/DCM patients in terms of all-cause mortality
18 (adjusted-HR 1.02, 95% CI 0.45-2.34), composite of arrhythmic death or failed
19 appropriate shock (adjusted-HR 0.33, 95% CI 0.04-2.42), inappropriate shocks
20 (adjusted-HR 1.64, 95% CI 0.69-3.89) or system complications (adjusted-HR 1.93,
21 95% CI 0.88-4.27). All-cause mortality (HR 0.26, 95% CI 0.03-2.20), appropriate (HR
22 0.24, 95% CI 0.03-2.05) and inappropriate shocks (HR 2.13, 95% CI 0.51-8.94) were
23 similar in HCM patients without or with DT.

24 **Conclusion:** We did not find any difference in intraoperative defibrillation efficacy,
25 perioperative complications, and long-term outcomes between patients with HCM

1 and with ICM/DCM. DT did not improve intraoperative or clinical shock efficacy in
2 HCM patients.

3 **Keywords:** hypertrophic cardiomyopathy, HCM, implantable cardioverter defibrillator,
4 ICD, defibrillation testing, SIMPLE

5

6

7

ACCEPTED MANUSCRIPT

1 Introduction

2 Implantable cardioverter defibrillators (ICDs) are indicated for selected patients with
3 hypertrophic cardiomyopathy (HCM), either for primary or secondary prevention of
4 sudden cardiac death [1,2]. The majority of HCM patients undergoes ICD
5 implantation for primary prevention [2,3] with American and European guidelines
6 recommending individual sudden cardiac death risk stratification [1,2,4]. At the time
7 of ICD insertion, patients with HCM are considered to be prone to have elevated
8 defibrillation thresholds necessitating additional measures such as re-programming,
9 lead re-positioning, or insertion of additional ICD leads [5-8]. Previous studies also
10 indicate that HCM patients have an increased risk of peri-procedural complications
11 [3, 9-11], and that their clinical course may be complicated by a higher incidence of
12 failed appropriate ICD therapy [10,12] or inappropriate shocks [6,10,13].

13 SIMPLE was the largest randomized trial demonstrating that routine defibrillation
14 testing (DT) at the time of ICD insertion does not improve shock efficacy or reduce
15 mortality [14,15]. Moreover, elevation in postoperative troponin levels in patients
16 undergoing DT were associated with worse long-term outcomes [16]. Based on the
17 results of the SIMPLE trial, ICDs are implanted without DT in the majority of patients;
18 however, the necessity of DT specifically for HCM patients is still under debate. The
19 2015 HRS/EHRA/APHRS/SOLAECE consensus statement on optimal ICD
20 programming and testing did not provide clear guidelines or recommendations
21 regarding defibrillation testing in patients with HCM [17].

22 The database of the SIMPLE trial provides a unique opportunity to evaluate the
23 aforementioned clinical issues associated with ICD therapy in patients with HCM.

24

25

1 **Methods**

2 This is a secondary analysis from the SIMPLE trial (Shockless IMPLant Evaluation,
3 ClinicalTrials.gov number: NCT00800384). A detailed description of study design [14]
4 and results have been published previously [15]. Briefly, SIMPLE was a single-
5 blinded, randomized, multicentre, non-inferiority clinical trial enrolling 2,500 patients
6 who were receiving their first ICD either for primary or secondary prevention, with or
7 without cardiac resynchronization therapy. Patients were randomized to have either
8 defibrillation testing (testing group) or not (no-testing group). Implanters were
9 expected to position the ICD left-hand side and to provide a sensed R-wave of at
10 least 5.0 mV and acceptable high-voltage impedance. In the defibrillation testing (DT)
11 group, the protocol required induction of ventricular fibrillation in order to demonstrate
12 either one successful arrhythmia termination at 17J or two successful terminations at
13 21J. In case the initial system configuration did not achieve the predefined
14 defibrillation safety margin, the ICD had to be re-configured and DT repeated.

15 The primary efficacy endpoint of SIMPLE was the composite of arrhythmic death or
16 failed appropriate shock (i.e., a shock that did not terminate a spontaneous episode
17 of ventricular tachycardia or fibrillation). All-cause mortality was the most important
18 secondary outcome. The primary safety composite was assessed at 30 days after
19 ICD implantation to evaluate the safety of defibrillation testing, and it included death,
20 myocardial infarction, stroke, systematic or pulmonary embolism, heart failure, need
21 for chest compressions or an aortic ballon pump during implantation, use of intra-
22 operative vasoconstrictors, non-elective intubation, arterial-line complications,
23 unplanned stay in the ICU, other anoxic brain injury, pneumothorax, cardiac
24 perforation, ICD infection, or aspiration pneumonia.

1 The study protocol was approved by the institutional review boards of all participating
2 centres.

3 **Categorization of patients by the underlying cardiac disease.** Patients were
4 categorized by the investigator according to their underlying cardiac disease as
5 having coronary artery disease, hypertrophic (HCM) or dilated cardiomyopathy
6 (DCM), primary electrical disorder (Brugada syndrome, Long-QT syndrome,
7 catecholaminergic polymorphic ventricular tachycardia), and/or arrhythmogenic RV
8 cardiomyopathy. Clinical indication for ICD implantation was also recorded (i.e.
9 primary vs. secondary prevention). The population of interest of the current analysis
10 comprised patients with HCM. If patients had HCM and another diagnosis (i.e.
11 ICM), they were still classified as HCM. The control group consisted of a pooled
12 cohort of patients with ischemic cardiomyopathy or dilated cardiomyopathy
13 (ICM/DCM) who were randomized to undergo DT.

14 **Clinical endpoints.** In the current analysis we compared peri-operative
15 complications (as the primary safety endpoint of the original study) and defibrillation
16 thresholds between HCM patients and patients with ICM/DCM within the DT arm,
17 and between HCM patients with and without DT. Long-term clinical outcomes such
18 as all-cause mortality, composite of arrhythmic death or failed appropriate shock,
19 appropriate shock, inappropriate shock, and system revision between HCM patients
20 and ICM/DCM patients and in HCM patients with and without DT were also
21 compared.

22 **Statistical analysis.** All analyses were based on the intention-to-treat principle
23 unless otherwise specified. Endpoint events including deaths, shocks, and safety
24 outcomes were adjudicated by an adjudication committee that was unaware of
25 treatment allocation. All data were entered in a central database kept at the

1 Population Health Research Institute, Hamilton, Canada. Categorical variables were
2 compared using Chi-square test or Fisher's exact test and continuous variables using
3 two-sample t-test. To assess the risk of clinical outcomes between patient groups the
4 Cox proportional hazards regression model was used. The models were unadjusted
5 and adjusted for potential confounders including age, gender, primary prevention ICD
6 indication, NYHA class, LVEF, atrial fibrillation, hypertension, stroke/TIA, diabetes
7 and impaired renal function. Survival curves were constructed according to the
8 Kaplan-Meier method. Statistical analyses were performed with SAS version 9.4
9 software (SAS Institute, Inc., Cary, NC, USA). Two-sided p values <0.05 were
10 considered statistically significant.

11

12 **Results**

13 **Patient characteristics.** From the total of 2,500 randomized ICD recipients of the
14 SIMPLE trial, 95 (3.8%) patients had a diagnosis of HCM. A total of 2177 (87.1%)
15 patients with ICM/DCM constituted the control group (Table 1). As expected, patients
16 in the ICM/DCM cohort were generally older and had more often symptomatic heart
17 failure or other relevant comorbidities, such as hypertension, diabetes or chronic
18 kidney disease, compared to HCM patients. HCM patients received more often dual
19 chamber devices while more ICM/DCM patients were implanted with single chamber
20 or CRT-D systems. The mean value of the sensed R-wave at implantation was
21 16.7 ± 6.8 mV for HCM patients compared to 15.0 ± 6.2 mV in ICM/DCM cohort
22 ($p=0.023$).

23 There were no statistically significant differences in the baseline characteristics of
24 HCM patients with (N=53) and without defibrillation testing (N=42)(Supplementary
25 Table 1).

1 **Defibrillation thresholds.** An adequate defibrillation safety margin without system
2 change was achieved in comparable proportions of HCM and ICM/DCM patients
3 (88.5% vs. 90.5%, $p=0.626$)(Table 2). The success rate for achieving the predefined
4 safety margin without system change or with additional surgical (i.e. the RV lead
5 reposition, addition or removal of a coil, addition of a subcutaneous array) or
6 programming efforts (i.e. SVC coil off, can off, reversed polarity) was also similar
7 between patients in the HCM and control groups (92.3% vs. 93.4%, $p=0.772$).

8 **Perioperative complications.** The rate of perioperative complications (primary
9 safety outcome) assessed at 30 days post implant did not significantly differ between
10 patients with HCM and ICM/DCM who underwent DT (1/52 vs. 67/1047,
11 $p=0.367$)(Table 3).

12 Comparing perioperative complications between HCM patients with and without DT,
13 no significant difference was observed (primary safety outcome: 1/52 vs. 3/42,
14 $p=0.321$; secondary safety outcome: 0/52 vs. 3/42, $p=0.086$)(Supplementary Table
15 2).

16 **Long-term outcomes.** The mean follow-up duration in SIMPLE was 3.1 ± 1.0 years.
17 Crude Kaplan-Meier analysis demonstrated lower all-cause mortality (HR 0.32, 95%
18 CI 0.14-0.72), lower incidence of arrhythmic death or failed appropriate shock (HR
19 0.23, 95% CI 0.06-0.93), and lower rate of appropriate shocks (HR 0.38, 95% CI
20 0.17-0.86) in HCM patients compared to patients with ICM/DCM (Table 4A;
21 Supplementary Figure 1A-B; Figure 1A). There was no significant difference in the
22 crude rate of inappropriate shocks (HR 1.14, 95% CI 0.56-2.32) or system revision
23 (HR 0.78, 95% CI 0.39-1.58)(Table 4A; Figure 1B). The comparison of HCM and
24 ICM/DCM patients adjusted for confounding factors revealed no significant difference
25 in all-cause mortality (adjusted HR 1.02, 95% CI 0.45-2.34), composite of arrhythmic

1 death or failed appropriate shock (adjusted HR 0.33, 95% CI 0.04-2.42), rate of
2 inappropriate shocks (adjusted HR 1.64, 95% CI 0.69-3.89) or system complications
3 (adjusted HR 1.93, 95% CI 0.88-4.27)(Table 4A; Supplementary Figure 1A-B; Figure
4 1B). However, there was a trend towards less appropriate ICD therapies in HCM
5 patients compared to the ICM/DCM cohort (adjusted HR 0.44, 0.17-1.12,
6 $p=0.08$)(Table 3A; Figure 1A).

7 There was no significant difference between the HCM patients without versus with
8 DT in terms of all-cause mortality (HR 0.26, 95% CI 0.03-2.20), appropriate (HR 0.24,
9 95% CI 0.03-2.05) or inappropriate ICD shocks (HR 2.13, 95% CI 0.51-8.94)(Table
10 4B). The composite of arrhythmic death or failed appropriate shock occurred in two
11 HCM patients with DT versus none in the non DT group (Table 4B).

12

13 **Discussion**

14 **Main findings.** In this pre-specified secondary analysis of the SIMPLE trial, we did
15 not find any difference in outcomes for patients with HCM compared to patients with
16 ICM or DCM. We also confirmed the overall results of SIMPLE in the sub-group of
17 patients with HCM; specifically, there was no significant difference between HCM
18 patients with and without DT in terms of perioperative complications, clinical shock-
19 efficacy, or all-cause mortality. Therefore, the results of the main SIMPLE trial apply
20 to patients with HCM in whom it appears safe to conduct ICD implantation without
21 DT.

22 **Defibrillation thresholds.** High risk for elevated defibrillation thresholds
23 necessitating additional measures such as re-programming, re-positioning or
24 implanting additional ICD leads have been reported for patients with HCM in several

1 previous observational studies [5-8]. A weak correlation with LV wall thickness
2 [5,8,11] or QRS duration and defibrillation threshold [7] was also described.

3 These results are in contrast with more recent, single-center observations from Quin
4 et al. [18] and Francia et al. [19] who did not find a difference in defibrillation
5 thresholds between HCM and control groups; left ventricular hypertrophy or QRS
6 duration were not associated with elevated defibrillation thresholds.

7 Our study is the first to describe clinical outcomes in patients enrolled in a large,
8 multicenter, controlled, randomized trial and supports the findings of the latter two
9 studies. An adequate defibrillation safety margin without ICD system change was
10 achieved in the similar proportion of HCM patients as in the control group of patients
11 with ICM/DCM.

12 **ICD-related complications.** The incidence of perioperative complications ranges
13 from 2-18% [5,6,9-11] and depends largely on the definition used. For instance,
14 Schinkel et al. reported in a meta-analysis of ICD studies in HCM patients a system-
15 related complication rate of 15% (3.4%/year), which included perioperative
16 complications and complications during follow-up [3].

17 The perioperative complication rate for HCM and ICM/DCM patients in the present
18 analysis were 1.9% and 6.4%, respectively ($p=n.s.$). Need for system revision in
19 HCM patients during long-term follow-up was low at 2.8%/year.

20 **Long-term outcomes.** For HCM patients implanted with an ICD, all-cause mortality
21 rate ranged from 0.5% up to 2.25% per year [3,5,6,10,20,21]. We found an
22 annualized all-cause mortality rate of 1.9% in HCM patients, not significantly different
23 from that in ICM/DCM patients.

24 The evaluation of shock efficacy by determining failed appropriate shock incidence
25 seems to be particularly relevant in the HCM population. There is only one prior study

1 comparing shock efficacy for spontaneous VT/VF in HCM patients with and without
2 DT [19]. This study compromised 66 patients in whom ICD shock efficacy was 75%
3 at first attempt and 12 out of 12 VT/VF in 7 patients were successfully converted with
4 ≥ 1 shocks. The present analysis confirms this finding with a very low rate of
5 arrhythmic death or failed appropriate shock (0.6%/year). Our study expands these
6 observations by comparing HCM patients with ICM/DCM patients where again no
7 significant differences between the two patient groups after adjusting for confounders
8 were found.

9 Previous studies have reported incidences of appropriate ICD discharges of 2.3-
10 11%/year [5,6,9-11,20,22]. In our patient population, appropriate ICD discharges
11 occurred at an annual incidence of 2.0% with a trend towards less appropriate ICD
12 therapies in HCM patients compared to the ICM/DCM cohort.

13 Prior studies have reported relatively high rates of inappropriate ICD therapies in
14 HCM patients, predominantly due to supraventricular arrhythmias or T-wave
15 oversensing [3,6,10,13,20]. For instance, in a recently published report from the
16 Swedish ICD registry, inappropriate ICD shock occurred in 14.3%, which was mainly
17 triggered by atrial fibrillation/flutter or ectopic tachycardia (56.5%) [13]. However, this
18 study reports an outcome of registry patients recruited between 1995 and 2012.
19 Therefore, programming of the devices was probably different from current standards
20 focused on minimization of inappropriate therapy. In our study, there was a low
21 incidence of 2.8% per year, not significantly different from the one observed in
22 patients with ICM/DCM.

23 Whether newer ICD technologies such as the subcutaneous ICD will further improve
24 device efficacy and safety in HCM patients remains to be determined [23,24].

1 **Limitations.** Classification of the underlying cardiac disease within the SIMPLE trial
2 relied on the judgement of the investigator with no pre-specified definitions applied.
3 The typical clinical variables used for risk stratification in HCM guidelines [1,2,4] were
4 not collected in a systematic fashion. The relatively small number of patients with
5 HCM in the SIMPLE trial resulted in low statistical power to detect differences in
6 outcomes; however, this is the largest report based on a randomized patient
7 population with prospectively collected data and blinded endpoint adjudication to
8 evaluate DT in patients with HCM.

10 **Conclusions**

11 In this retrospective analysis of the SIMPLE trial, the rate of ICD-related
12 complications and long-term outcomes in HCM patients were not significantly
13 different from those observed in patients with ICM/DCM. Moreover, routine
14 defibrillation testing did not seem to be associated with beneficial clinical effects in
15 HCM patients.

17 **Disclosures**

18 The Shockless IMPLant Evaluation (SIMPLE) trial (NCT00800384) was funded by
19 BostonScientific.

20 M.V. reports lecture/consulting fees from Bayer, Minimal Invasive Technology Ltd.,
21 Pfizer and Spectranetics and support attending scientific meetings from Bayer,
22 Boston Scientific, Daiichi Sankyo, Egis, Pfizer, and SJM, outside the submitted work.

23 J.S.H. has received grants from Boston Scientific and Medtronic and have founding
24 from the Heart and Stroke Foundation, Ontario Provincial office and from the
25 Population Health Research Insitute Chair in Cardiology Research. S.H.H has

1 received consulting fees from Boston Scientific, the sponsor of the SIMPLE trial,
2 during the conduct of the study, and consulting fees from Bayer, BI, Boston Scientific,
3 BMS, Gilead, J&J, Medtronic, Pfizer, SJM, sanofi-aventis, and Cardiome, outside the
4 submitted work. J.K. has received consulting fees from Bayer, Biosense Webster,
5 Boehringer Ingelheim, Boston Scientific, Liva Nova, Medtronic, MSD and St Jude
6 Medical, outside of the submitted work. J.W., S.J.C., P.M., L.V.E., M.G., J.N., G.O.,
7 X.V., and F.G. have nothing to disclose.

8

1 References

2

3 1 Gersh BJ, Maron BJ, Bonow RO, et al. American College of Cardiology
4 Foundation/American Heart Association Task Force on Practice Guidelines. 2011
5 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic
6 Cardiomyopathy: a report of the American College of Cardiology
7 Foundation/American Heart Association Task Force on Practice Guidelines.
8 Developed in collaboration with the American Association for Thoracic Surgery,
9 American Society of Echocardiography, American Society of Nuclear Cardiology,
10 Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular
11 Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol.*
12 2011;58:e212-60.

13

14 2 Elliott PM, Anastakis A, Borger MA, et al. 2014 ESC Guidelines on diagnosis and
15 management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and
16 Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology
17 (ESC). *Eur Heart J.* 2014;35:2733-79.

18

19 3 Schinkel AF, Vriesendorp PA, Sijbrands EJ, Jordaens LJ, ten Cate FJ, Michels M.
20 Outcome and complications after implantable cardioverter defibrillator therapy in
21 hypertrophic cardiomyopathy: systematic review and meta-analysis. *Circ Heart Fail.*
22 2012;5(5):552-9.

23

- 1 4 O'Mahony C, Jichi F, Pavlou M, et al. A novel clinical risk prediction model for
2 sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Hypertrophic
3 Cardiomyopathy Outcomes Investigators. Eur Heart J. 2014;35:2010-20.
4
- 5 5 Almquist AK, Montgomery JV, Haas TS, Maron BJ. Cardioverter-defibrillator
6 implantation in high-risk patients with hypertrophic cardiomyopathy. Heart Rhythm.
7 2005;2:814-9.
8
- 9 6 Lin G, Nishimura RA, Gersh BJ, Phil D, Ommen SR, Ackerman MJ, Brady PA.
10 Device complications and inappropriate implantable cardioverter defibrillator shocks
11 in patients with hypertrophic cardiomyopathy. Heart. 2009;95:709-14
12
- 13 7 Nagai T, Kurita T, Satomi K, Noda T, Okamura H, Shimizu W, Suyama K, Aihara N,
14 Kobayashi J, Kamakura S. QRS prolongation is associated with high defibrillation
15 thresholds during cardioverter-defibrillator implantations in patients with hypertrophic
16 cardiomyopathy. Circ J. 2009;73:1028-32.
17
- 18 8 Roberts BD, Hood RE, Saba MM, Dickfeld TM, Saliaris AP, Shorofsky SR.
19 Defibrillation threshold testing in patients with hypertrophic cardiomyopathy. Pacing
20 Clin Electrophysiol. 2010;33:1342-6.
21
- 22 9 Syska P, Przybylski A, Chojnowska L, Lewandowski M, Sterliński M, Maciag A,
23 Gepner K, Pytkowski M, Kowalik I, Maczyńska-Mazuruk R, Rużyło W, Szwed H.
24 Implantable cardioverter-defibrillator in patients with hypertrophic cardiomyopathy:

1 efficacy and complications of the therapy in long-term follow-up. *J Cardiovasc*
2 *Electrophysiol.* 2010;21:883-9.

3

4 10 O'Mahony C, Lambiase PD, Quarta G, Cardona M, Calcagnino M, Tsovolas K, Al-
5 Shaikh S, Rahman SM, Arnous S, Jones S, McKenna W, Elliott P. The long-term
6 survival and the risks and benefits of implantable cardioverter defibrillators in patients
7 with hypertrophic cardiomyopathy. *Heart.* 2012;98:116-25.

8

9 11 Maeda R, Minami Y, Haruki S, Kanbayashi K, Itani R, Suzuki A, Ejima K, Shiga T,
10 Shoda M, Hagiwara N. Implantable cardioverter defibrillator therapy and sudden
11 death risk stratification in hypertrophic cardiomyopathy patients with midventricular
12 obstruction: A single-center experience. *Int J Cardiol.* 2016;214:419-22.

13

14 12 Maron BJ, Spirito P, Shen WK, et al. Implantable cardioverter-defibrillators and
15 prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA.*
16 2007;298:405-12.

17

18 13 Magnusson P, Gadler F, Liv P, Mörner S. Hypertrophic Cardiomyopathy and
19 Implantable Defibrillators in Sweden: Inappropriate Shocks and Complications
20 Requiring Surgery. *J Cardiovasc Electrophysiol.* 2015;26:1088-94.

21

22 14 Healey JS, Hohnloser SH, Glikson M, Neuzner J, Viñolas X, Mabo P, Kautzner J,
23 O'Hara G, Van Erven L, Gadler F, Appl U, Connolly SJ. The rationale and design of
24 the Shockless IMPLant Evaluation (SIMPLE) trial: a randomized, controlled trial of

1 defibrillation testing at the time of defibrillator implantation. Am Heart J.
2 2012;164:146-52.

3

4 15 Healey JS, Hohnloser SH, Glikson M, et al. Shockless IMPLant Evaluation
5 [SIMPLE] investigators. Cardioverter defibrillator implantation without induction of
6 ventricular fibrillation: a single-blind, non-inferiority, randomised controlled trial
7 (SIMPLE). Lancet 2015;385:785-91.

8

9 16 Vamos M, Healey JS, Wang J, Duray GZ, Connolly SJ, van Erven L, Vinolas X,
10 Neuzner J, Glikson M, Hohnloser SH. Troponin levels after ICD implantation with and
11 without defibrillation testing and their predictive value for outcomes: Insights from the
12 SIMPLE trial. Heart Rhythm. 2016;13:504-10.

13

14 17 Wilkoff BL, Fauchier L, Stiles MK, et al. 2015 HRS/EHRA/APHS/SOLAECE
15 expert consensus statement on optimal implantable cardioverter-defibrillator
16 programming and testing. Heart Rhythm. 2016;13:e50-86.

17

18 18 Quin EM, Cuoco FA, Forcina MS, Coker JB, Yoe RH, Spencer WH 3rd,
19 Fernandes VL, Nielsen CD, Sturdivant JL, Lemane RB, Wharton JM, Gold MR.
20 Defibrillation thresholds in hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol.
21 2011;22:569-72.

22

23 19 Francia P, Adduci C, Semprini L, Palano F, Santini D, Musumeci B, Santolamazza
24 C, Volpe M, Autore C. Prognostic Implications of Defibrillation Threshold Testing in

1 Patients With Hypertrophic Cardiomyopathy. *J Cardiovasc Electrophysiol.*
2 2017;28:103-108.

3

4 20 Begley DA, Mohiddin SA, Tripodi D, Winkler JB, Fananapazir L. Efficacy of
5 implantable cardioverter defibrillator therapy for primary and secondary prevention of
6 sudden cardiac death in hypertrophic cardiomyopathy. *Pacing Clin Electrophysiol.*
7 2003;26:1887-96.

8

9 21 Blazsó P, Kákonyi K, Forster T, Sepp R. Cardiomyopathy and ion channel
10 diseases registry: the Szeged CardioGen Registry. *Orv Hetil.* 2017;158:101-105

11

12 22 Jayatilleke I, Doolan A, Ingles J, McGuire M, Booth V, Richmond DR, Semsarian
13 C. Long-term follow-up of implantable cardioverter defibrillator therapy for
14 hypertrophic cardiomyopathy. *Am J Cardiol.* 2004;93:1192-4.

15

16 23 Francia P, Adduci C, Palano F, Semprini L, Serdoz A, Montesanti D, Santini D,
17 Musumeci B, Salvati A, Volpe M, Autore C. Eligibility for the Subcutaneous
18 Implantable Cardioverter-Defibrillator in Patients With Hypertrophic Cardiomyopathy.
19 *J Cardiovasc Electrophysiol.* 2015;26:893-9.

20

21 24 Lambiase PD, Gold MR2, Hood M, Boersma L, Theuns DA, Burke MC, Weiss R,
22 Russo AM, Käab S, Knight BP. Evaluation of subcutaneous ICD early performance in
23 hypertrophic cardiomyopathy from the pooled EFFORTLESS and IDE cohorts. *Heart*
24 *Rhythm.* 2016;13:1066-74.

25

1 **Tables**2 **Table 1** Baseline characteristics of patients with HCM and with ICM/DCM

	All (N=2272)	HCM (N=95)	ICM/DCM (N=2177)	P Value
Age, mean±SD	63.6±10.8	57.0±14.0	63.9±10.5	<0.001
Gender (Male), n(%)	1864 (82.0)	63 (66.3)	1801 (82.7)	<0.001
BMI, mean±SD	28.0±4.9	28.3±4.7	28.0±4.9	0.524
ICD implanted for primary prevention, n(%)	1708 (75.2)	76 (80.0)	1632 (75.0)	0.266
NYHA class				<0.001
I/II, n(%)	935 (41.2)	21 (22.1)	914 (42.0)	
III/IV, n(%)	754 (33.2)	7 (7.4)	747 (34.3)	
LVEF, mean±SD	30.5±11.4	56.6±17.8	29.5±9.7	<0.001
Atrial fibrillation, n(%)	526 (23.2)	25 (26.3)	501 (23.0)	0.455
Hypertension, n(%)	1481 (65.2)	42 (44.2)	1439 (66.1)	<0.001
Previous stroke/TIA, n(%)	245 (10.8)	6 (6.3)	239 (11.0)	0.152
Diabetes, n(%)	703 (30.9)	17 (17.9)	686 (31.5)	0.005
Impaired renal function, n(%)	454 (20.0)	6 (6.3)	448 (20.6)	<0.001
Amiodarone use, n(%)	347 (15.3)	9 (9.5)	338 (15.5)	0.108
ACE inhibitor, n(%)	1665 (73.3)	28 (29.5)	1637 (75.2)	<0.001
ARB, n(%)	390 (17.2)	17 (17.9)	373 (17.1)	0.847
Beta-blocker, n(%)	2041 (89.8)	72 (75.8)	1969 (90.4)	<0.001
Aldosterone antagonist, n(%)	897 (39.5)	10 (10.5)	887 (40.7)	<0.001
Oral anticoagulant, n(%)	468 (20.6)	13 (13.7)	455 (20.9)	0.089
Digitalis, n(%)	282 (12.4)	5 (5.3)	277 (12.7)	0.031
Type of ICD				<0.001
VVI-ICD, n(%)	1005 (44.2)	32 (33.7)	973 (44.7)	
DDD-ICD, n(%)	575 (25.3)	56 (58.9)	519 (23.8)	
CRT-ICD, n(%)	676 (29.8)	6 (6.3)	670 (30.8)	
Dual coil ICD lead, n(%)	1322 (58.2)	54 (56.8)	1268 (58.2)	0.786
Implant R-wave, mean±SD	15.1±6.3	16.7±6.8	15.0±6.2	0.023

3 *ACE = angiotensin-converting-enzyme, ARB = angiotensin II receptor antagonist, BMI = body mass index, DCM = dilated*
4 *cardiomyopathy, DT = defibrillation testing, HCM = hypertrophic cardiomyopathy, ICD = implantable cardioverter defibrillator, ICM =*
5 *ischaemic cardiomyopathy, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association functional classification, SD*
6 *= Standard deviation, TIA = transient ischemic attack*

7

8

1 **Table 2** Comparison of defibrillation testing between HCM patients and ICM/DCM
 2 patients

3

	All (N=1099*)	HCM (N=52*)	ICM/DCM (N=1047*)	P Value
Adequate defibrillation safety margin achieved without any change	994 (90.4)	46 (88.5)	948 (90.5)	0.626
Achieved with additional efforts				
RV lead reposition/Add or remove of coil/Add subcutaneous array	8 (0.7)	0 (0.0)	8 (0.8)	>0.999
SVC coil programmed out/Can programmed off/Polarity reversed	24 (2.2)	2 (3.8)	22 (2.1)	0.315
Not achieved with additional efforts				
RV lead reposition/Add or remove of coil/Add subcutaneous array	18 (1.6)	1 (1.9)	17 (1.6)	0.585
SVC coil programmed out/Can programmed off/Polarity reversed	16 (1.5)	1 (1.9)	15 (1.4)	0.542

4 * Included only patients who underwent defibrillation testing as per study protocol. One HCM patient randomized to DT did not receive
 5 DT. Two patients with HCM did not achieve adequate defibrillation safety margin and no additional efforts were made (protocol
 6 deviation).

7 DCM = dilated cardiomyopathy, HCM = hypertrophic cardiomyopathy, ICM = ischaemic cardiomyopathy, RV = right ventricular, SVC =
 8 superior vena cava
 9

10

11

1 **Table 3** Comparison of perioperative complications between HCM patients and
 2 ICM/DCM patients (subjects undergoing DT)

3

	All (N=1099†)	HCM (N=52†)	ICM/DCM (N=1047†)	P Value
Primary safety Composite*, n(%)	68 (6.2)	1 (1.9)	67 (6.4)	0.367
Secondary safety Composite**, n(%)	47 (4.3)	0 (0.0)	47 (4.5)	0.164
Death, n(%)	5 (0.5)	0 (0.0)	5 (0.5)	>0.999
Stroke, n(%)	3 (0.3)	0 (0.0)	3 (0.3)	>0.999
Non-CNS systemic embolism, n(%)	2 (0.2)	0 (0.0)	2 (0.2)	>0.999
Pulmonary embolism, n(%)	1 (0.1)	0 (0.0)	1 (0.1)	>0.999
Myocardial infarction, n(%)	1 (0.1)	0 (0.0)	1 (0.1)	>0.999
Heart failure needing inotropes or diuretics, n(%)	23 (2.1)	0 (0.0)	23 (2.2)	0.622
Intraoperative hypotension, n(%)	7 (0.6)	0 (0.0)	7 (0.7)	>0.999
Need for chest compression, n(%)	4 (0.4)	0 (0.0)	4 (0.4)	>0.999
Non-elective intubation, n(%)	5 (0.5)	0 (0.0)	5 (0.5)	>0.999
Aspiration pneumonia, n(%)	1 (0.1)	0 (0.0)	1 (0.1)	>0.999
Unplanned stay in ICU, n(%)	1 (0.1)	0 (0.0)	1 (0.1)	>0.999
Pneumothorax, n(%)	12 (1.1)	0 (0.0)	12 (1.1)	>0.999
Pericarditis, cardiac perforation or tamponade, n(%)	9 (0.8)	1 (1.9)	8 (0.8)	0.355
Device infection, n(%)	3 (0.3)	0 (0.0)	3 (0.3)	>0.999
Arterial-line complication, n(%)	1 (0.1)	0 (0.0)	1 (0.1)	>0.999
Anoxic brain injury, n(%)	0 (0.0)	0 (0.0)	0 (0.0)	-

4 * Included all complications

5 ** Included all complications from table except for aspiration pneumonia, pneumothorax, Pericarditis/cardiac perforation/cardiac
 6 tamponade, device infection and anoxic brain injury

7 † Included only patients who had an ICD implanted. 1 HCM patient did not receive ICD.

8 CNS = central nervous system, DCM = dilated cardiomyopathy, DT = defibrillation testing, HCM = hypertrophic cardiomyopathy, ICM =
 9 ischaemic cardiomyopathy

10

11

1 **Table 4A** Risk of clinical outcomes in patients with HCM and with ICM/DCM

2

Clinical outcomes	Overall		HCM		ICM/DCM		Unadjusted		Adjusted*	
	n/N	Rate (%/yr)	n/N	Rate (%/yr)	n/N	Rate (%/yr)	HR (95% CI)	P value	HR (95% CI)	P value
All-cause mortality	406/2272	5.8	6/95	1.9	400/2177	5.9	0.32 (0.14-0.72)	0.006	1.02 (0.45-2.34)	0.959
Arrhythmic Death or Failed appropriate shock	186/2272	2.7	2/95	0.6	184/2177	2.8	0.23 (0.06-0.93)	0.04	0.33 (0.04-2.42)	0.275
Appropriate shock	337/2272	5.3	6/95	2.0	331/2177	5.4	0.38 (0.17-0.86)	0.02	0.44 (0.17-1.12)	0.084
Inappropriate shock	165/2272	2.5	8/95	2.8	157/2177	2.5	1.14 (0.56-2.32)	0.72	1.64 (0.69-3.89)	0.261
System revision	234/2272	3.6	8/95	2.8	226/2177	3.6	0.78 (0.39-1.58)	0.493	1.93 (0.88-4.27)	0.102

3 * Adjusted for age, gender, primary prevention, NYHA class, LVEF, atrial fibrillation, Hypertension, stroke/TIA, diabetes and impaired renal function

4 DCM = dilated cardiomyopathy, HCM = hypertrophic cardiomyopathy, ICM = ischaemic cardiomyopathy

5

6

7 **Table 4B** Risk of clinical outcomes in HCM patients with and without DT

8

Clinical outcomes	Overall		No DT		DT		No DT vs. DT	
	n/N	Rate (%/yr)	n/N	Rate (%/yr)	n/N	Rate (%/yr)	HR (95% CI)	P value
All-cause mortality	6/95	1.9	1/42	0.7	5/53	2.9	0.26 (0.03-2.20)	0.215
Arrhythmic Death or Failed appropriate shock	2/95	0.6	0/42	0.0	2/53	1.2	-	-
Appropriate shock	6/95	2.0	1/42	0.7	5/53	3.1	0.24 (0.03-2.05)	0.192
Inappropriate shock	8/95	2.8	5/42	4.0	3/53	1.8	2.13 (0.51-8.94)	0.300

9 DT = defibrillation testing, HCM = hypertrophic cardiomyopathy

10

11

12

1 **Figure legends**

2

3 **Figure 1A** Kaplan-Meier curves of appropriate shock by HCM vs. ICM/DCM

4 **Figure 1B** Kaplan-Meier curves of inappropriate shock by HCM vs. ICM/DCM

ACCEPTED MANUSCRIPT



