Journal Pre-proof

Age-related differences and associated mid-term outcomes of subcutaneous implantable cardioverter defibrillators: a propensity-matched analysis from a multicenter European registry

Simone Gulletta, MD, Alessio Gasperetti, MD, Marco Schiavone, MD, Julia Vogler, MD, Fabian Fastenrath, MD, Alexander Breitenstein, MD, Mikael Laredo, MD, Pietro Palmisano, MD, Gianfranco Mitacchione, MD, PhD, Paolo Compagnucci, MD, Lukas Kaiser, MD, Samer Hakmi, MD, Andrea Angeletti, MD, Silvana De Bonis, MD, Francesco Picarelli, MD, Roberto Arosio, MD, Michela Casella, MD, PhD, Jan Steffel, MD, Nicolai Fierro, MD, Fabrizio Guarracini, MD, Luca Santini, MD, Carlo Pignalberi, MD, Agostino Piro, MD, Carlo Lavalle, MD, PhD, Ennio Pisanò, MD, Maurizio Viecca, MD, Antonio Curnis, MD, Nicolas Badenco, MD, Danilo Ricciardi, MD, Antonio Dello Russo, MD, PhD, Claudio Tondo, MD, PhD, Jürgen Kuschyk, MD, Paolo Dello Bella, MD, Mauro Biffi, MD, Giovanni B. Forleo, MD, PhD, Roland Tilz, MD

PII: S1547-5271(22)00214-4

DOI: https://doi.org/10.1016/j.hrthm.2022.02.029

Reference: HRTHM 9171

To appear in: *Heart Rhythm*

Received Date: 15 January 2022

Revised Date: 22 February 2022

Accepted Date: 23 February 2022

Please cite this article as: Gulletta S, Gasperetti A, Schiavone M, Vogler J, Fastenrath F, Breitenstein A, Laredo M, Palmisano P, Mitacchione G, Compagnucci P, Kaiser L, Hakmi S, Angeletti A, De Bonis S, Picarelli F, Arosio R, Casella M, Steffel J, Fierro N, Guarracini F, Santini L, Pignalberi C, Piro A, Lavalle C, Pisanò E, Viecca M, Curnis A, Badenco N, Ricciardi D, Russo AD, Tondo C, Kuschyk J, Bella PD, Biffi M, Forleo GB, Tilz R, Age-related differences and associated mid-term outcomes of subcutaneous implantable cardioverter defibrillators: a propensity-matched analysis from a multicenter European registry, *Heart Rhythm* (2022), doi: https://doi.org/10.1016/j.hrthm.2022.02.029.

Age-related differences and associated mid-term outcomes of subcutaneous implantable cardioverter defibrillators: a propensity-matched analysis from a multicenter European registry

Running title: Age-related differences in S-ICD

Simone Gulletta[†1], MD; Alessio Gasperetti[†2], MD; Marco Schiavone[2], MD; Julia Vogler[3], MD; Fabian Fastenrath[4], MD; Alexander Breitenstein[5], MD; Mikael Laredo[6], MD; Pietro Palmisano[7], MD; Gianfranco Mitacchione[8], MD, PhD; Paolo Compagnucci[9], MD; Lukas Kaiser[10], MD; Samer Hakmi[10], MD; Andrea Angeletti[11], MD; Silvana De Bonis[12], MD; Francesco Picarelli[13], MD; Roberto Arosio[14], MD; Michela Casella[15], MD, PhD; Jan Steffel[5], MD; Nicolai Fierro[1], MD; Fabrizio Guarracini[16], MD; Luca Santini[17], MD; Carlo Pignalberi[18], MD; Agostino Piro[19], MD; Carlo Lavalle[19], MD, PhD; Ennio Pisanò[20], MD; Maurizio Viecca[2], MD; Antonio Curnis[8], MD; Nicolas Badenco[6], MD; Danilo Ricciardi[13], MD; Antonio Dello Russo[15], MD, PhD; Claudio Tondo[21], MD, PhD; Jürgen Kuschyk[4], MD; Paolo Dello Bella[1], MD; Mauro Biffi[11], MD; Giovanni B. Forleo*[2,14], MD, PhD; Roland Tilz*[3], MD

Affiliations:

[1]Arrhythmology and Electrophysiology Unit, San Raffaele Hospital, IRCCS, Milan, Italy (IT)
[2]Cardiology Unit, Luigi Sacco University Hospital, Milan, Italy (IT)
[3]Herzzentrum Lubeck, Lubeck, Germany (GE)
[4]Cardiology Unit, University Medical Centre Mannheim, Manheim, Germany (GE)
[5]University Hospital Zurich, Zurich, Switzerland (CH)
[6]APHP, Hôpital Pitié Salpêtrière, Paris, France (FR)
[7]Cardiology Unit, "Card. G. Panico" Hospital, Tricase, Italy (IT)
[8]Cardiology Unit, Spedali Civili Brescia, Brescia, Italy (IT)
[9]Università Politecnica delle Marche, Ancona, Italy (IT)
[10]St. George Klinik Asklepios, Hamburg, Germany (GE)
[11]Cardiology Unit, IRCCS, Department of Experimental, Diagnostic and Specialty Medicine, Sant'Orsola Hospital, University of Bologna, Bologna (IT)
[12]Department of Cardiology, Castrovillari Hospital, Cosenza (IT)
[13]Department of Cardiology, Campus Biomedico, Rome (IT)
[14]University of Milan, Milan, Italy (IT)
[15]Cardiology and Arrhythmology Clinic, University Hospital "Umberto I-Salesi-Lancisi", Ancona, Italy (IT)
[16]Department of Cardiology, S. Chiara Hospital, Trento, Italy (IT)
[17]Cardiology Unit, Ospedale G.B. Grassi, Ostia, Italy (IT)
[18]Cardiology Unit, Ospedale San Filippo Neri, Rome, Italy (IT)
[19]Cardiology Unit, Policlinico Umberto I, Rome, Italy (IT)
[20]Cardiology Unit, Vito Fazzi Hospital, Lecce, Italy (IT)
[21]Heart Rhythm Center, Monzino Cardiology Center, IRCCS, Milan, Italy (IT)

[†]Shared first co-authorship
*Shared last co-authorship

Corresponding Author:

Marco Schiavone, MD

Luigi Sacco University Hospital - Via G.B. Grassi, 74 - 20157 Milan (IT)

email: marco.schiavone11@gmail.com

Word count: 4727

DISCLOSURES: Dr. LS is a consultant/speaker for Boston Scientific. Prof. CT is a member of Boston Scientific advisory board. Dr. JS has received consultant and/or speaker fees Boston Scientific and has received grant support through his institution from Boston Scientific. Other authors report no disclosures.

FUNDING SOURCES: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ClinicalTrials.gov Identifier: NCT0473876.

ABSTRACT

Background. A few limited case series have shown that the S-ICD system is safe in teenagers and young adults, but a large-scale analysis is currently lacking.

Objectives. To compare mid-term device-associated outcomes in a large real-world cohort of S-ICD patients, stratified by age at implantation.

Methods. Two propensity-matched cohorts of teenagers + young adults (≤ 30-year-old) and adults (> 30-year-old) were retrieved from the ELISIR registry. The primary outcome was the comparison of the inappropriate shock rate; complications, freedom from sustained ventricular arrhythmias, overall and cardiovascular mortality were deemed secondary outcomes.

Results. Teenagers + young adults represented 11.0% of the entire cohort. Two propensity-matched groups of 161 patients each were used for the analysis; median follow-up was 23.1 [13.2–40.5] months. 15.2% patients experienced inappropriate shocks and 9.3% device related complications were observed, with no age-related differences in inappropriate shocks (16.1% vs 14.3%; p=0.642) and complication rates (9.9% vs 8.7%; p=0.701). At univariate analysis, young age was not associated with increased rates of inappropriate shocks (HR 1.204 [0.675–2.148]: p=0.529). At multivariate analysis, the use of SMART pass algorithm was associated to a strong reduction in inappropriate shocks (aHR 0.292 [0.161–0.525]; p<0.001), while ARVC was associated with higher rates of inappropriate shocks (aHR 2.380 [1.205–4.697]; p=0.012).

Conclusion. In a large multicentered registry of propensity-matched patients, the use of S-ICD in teenagers/young adults resulted safe and effective. The rates of inappropriate shocks and complications between cohorts were not significantly different. The only predictor of increased inappropriate shocks was a diagnosis of ARVC.

Keywords: S-ICD; young adults; teenagers; devices; complications.

INTRODUCTION

In the last decade, the subcutaneous implantable cardioverter-defibrillator (S-ICD) has become a cornerstone in sudden cardiac death (SCD) prevention, as an established alternative to the transvenous (TV) ICD among patients not needing pacing or cardiac resynchronization therapy (CRT) (1). SCD prevention with ICD therapy has also been demonstrated to be safe and effective in young patients with ventricular arrhythmias, arrhythmogenic cardiomyopathies and congenital heart diseases (2). Young patients often represent the most suitable candidates for an entirely S-ICD system, since they have to face a lifetime of device therapy and they rarely have a pre-existing or concurrent pacing or CRT indication. Indeed, TV-ICD bear the risk of significant lead related complications as well as potential venous access issues, that pose significant concerns on their mid-term use in young patients. On the other side, S-ICD offers lower rate and a safer management of lead and major procedure-related complications, as well as an easier management of these events, especially regarding lead extraction (3–5).

To date, a few limited case series, and experiences with S-ICD in teenagers and young adults have shown that the S-ICD system is safe and feasible in this population, with a rate of IS comparable to TV-ICD (6,7), but a focused analysis on a large scale is currently lacking in this setting. Therefore, aim of this study was to evaluate the mid-term outcomes in the largest independent European S-ICD registry based on baseline patients' profile and age at implantation.

METHODS

Registry population

The ELISIR project (Experience from the Long-term Italian S-ICD registry) is a European, multi-center, open-label, independent, and physician-initiated observational registry, whose characteristics and preliminary composition have been previously described (8,9). At the time of this manuscript drafting, a total of twenty-one Public and Private Healthcare Institutions from 4 different countries in Europe were involved in the registry. All consecutive patients meeting current guideline indications for ICD implantation and undergoing implantation of a S-ICD device (*Boston Scientific, Marlborough, Massachusetts, USA*) enrolled in the registry were used for the current analysis.

Patients were classified into two cohorts, depending on the age at device implantations:

- Adults: defined as > 30 year of age;
- Teenagers + Young Adults: defined as follows: a) teenagers: ≤ 20 years old; b) young adults > 20 and ≤ 30 years old;

This manuscript has been drafted in accordance with the tenets of the Helsinki Declaration and has been approved by the local institutional review board. Data supporting this study are available upon reasonable request to the corresponding author.

Data collection

Data collection methods for the patients enrolled in this registry have been previously presented[13]. In brief, for each enrolled patient, baseline and procedural characteristics were collected in accordance with a centralized spreadsheet, clearly defining each research item. Follow-up strategy was left to each center's policy, with most patients being evaluated at 1-, 6-, 12- months, and every 6 months thereafter. All device therapy delivered over the entirety of follow-up, both appropriate and inappropriate, and/or arrhythmia recorded during in-hospital and/or remote follow-up and/or in-clinic device interrogation were collected, as well as cardiovascular and overall mortality. In case of

inappropriate shocks (IAS), the trigger of the IAS was collected as well.

Events definition

As per registry protocol, an appropriate shock was defined as a therapy delivered because of a correctly recognized shockable rhythm. An IAS was defined as shock delivered due to: 1) a supraventricular (SV) tachycardia; 2) oversensing of either cardiac or non-cardiac signals; 3) any other cause resulting in device shock in the absence of a clinical arrhythmia. Complications were defined as follows: major pocket hematoma requiring a transfusion or a pocket revision; pocket infection; lead displacement impacting device functioning and requiring reintervention; lead fracture; lead infection; device extraction; unexpected pneumothorax.

Aim of the study - Cohort and outcomes definition

The aim of the current study was to compare the mid-term device-associated outcomes in a large real-world cohort of S-ICD recipients based on age class and clinical profile at implantation. Two propensity matched cohorts of teenagers + young adults and adults were retrieved. Propensity matching was performed for the following baseline characteristics: sex; placement of the S-ICD in primary/secondary prevention; different arrhythmic substrates (namely: ischemic cardiomyopathy; dilatative cardiomyopathy (DCM); hypertrophic cardiomyopathy (HCM); arrhyhtmogenic right ventricular cardiomyopathy (ARVC); Brugada syndrome (BrS); idiopathic ventricular fibrillation (VF). **Figure 1** displays the flowchart that led to the two final cohorts. **Figure 2** and **Table S1** report standardized % of bias reduction achieved through propensity matching.

The primary outcome of the study was defined as the comparison of the IAS rate observed during the entirety of follow up in between the two age groups. Rate of complications, freedom from sustained ventricular arrhythmic events, overall and cardiovascular mortality were also assessed in the two cohorts and assessed as secondary outcomes.

Statistical analysis

Continuous variables were reported as mean±standard deviation (s.d.) or as median [inter-quartile range (1^{st}-3^{rd} quartile) (IQR)] if normally or non-normally distributed, respectively. Categorical variables were reported as count (%). Propensity matching for the pre-specified variables was performed using the nearest neighbor method without replacement, using common support and a caliber set at 0.005. Post-matching bias reduction have been reported, both numerically and graphically (**Figure 2** and **Table S1**). Comparisons have been performed using a X^2 test or a Fisher's Exact Test between categorical variables, and a Student's t test or a Mann-Whitney U test between numerical variables, as appropriate according to their distribution. Event-free survival was plotted using Kaplan Meier estimates and a log-rank test was used to compare them. A Cox regression was used to assess the associations between post-matching baseline and procedural characteristics and clinical outcomes. Time of censoring was set either as the time of the outcome or the time of last follow-up, whichever came first. Univariable analyses were performed at first, reporting unadjusted Hazard Ratios (HR); all variables reaching a threshold p value 0.10 were then fit into a multivariable model to adjust for confounders, from which adjusted Hazard Ratios (aHR) were retrieved. A two-sided p value < 0.05 was considered significant throughout the manuscript. All analysis were performed using STATA 14.0 (StataCorp LLC, College Station, TX).

RESULTS

Patient population

Teenagers and young adults represented 11.0% of the patients (n=51 teenagers; n=113 young adults) present in the registry. After extraction and propensity matching, two cohorts of 161 patients each were retrieved and used for the study. Considering not-matched variables, teenagers and young adults at the time of S-ICD implantations were more active (BMI:23.3±4.2 vs 26.0±4.2; p<0.001; sport practice rate: 21.3% vs 12.4%, p=0.026) and had lower rates of cardiovascular risk factors compared to the adult cohort (hypertension: 8.1% vs 28.0%, p<0.001; diabetes: 1.5% vs 7.1%, p=0.035; atrial fibrillation: 11.8% vs 18.9%, p=0.047). The whole characteristics of the study cohorts have been reported in **Table 1.** Comparison of baseline characteristics between Teenagers and Young Adults patients have been reported in **Table S2.**

Peri-procedural data

Periprocedural characteristics of the two cohorts are reported in **Table 2**. No differences in S-ICD implantation technique between the teenagers/young adult and the adult cohort were observed, with a two-incision technique (90.0% vs 92.5%, p=0.419) and an inter-muscular placement (82.0% vs 82.0%, p=1.000) resulting the most common. Defibrillation Testing was performed significantly more commonly in the TA&YA cohort (91.3% vs 84.5%; p <0.001). A higher shock zone was observed in the TA&YA cohort (250 [240–250] vs 240 [230–250]; p <0.001), while no differences in the use of the SMART Pass algorithm between the two cohorts were reported (82.6% vs 82.0%, p=0.884)

Mid-term outcomes and predictors

The complete follow-up data has been reported in **Table 2**. Patients were followed-up for a median of 23.1 [13.2–40.5] months of follow-up, without significant differences between the two groups (22.1 [12.9–36.2] vs 25.1 [14.7–41.4]; p=0.208). Overall, 49 (15.2%) patients experienced

inappropriate S-ICD shocks and 30 (9.3%) device related complications were observed. When assessed in the two different groups, no age-related differences in complication rates (9.9% vs 8.7%; p=0.701) or IAS (16.1% vs 14.3%; p=0.642) were observed. When triggers of IAS events were analyzed, a significantly higher rate of inappropriate interventions due to AF/AT (0.6% vs 5.6%, p=0.010) was observed in the adults cohort, while a trend towards significance in higher rates of IAS trigger by T wave oversensing was observed in the teenager and young adult cohort (11.2% vs 5.6%; p=0.070).

As **Figure 3** shows, no difference in overall freedom from sustained ventricular arrhythmias between the two cohorts were observed (16.1% vs 12.4%, p = 0.339). Specific outcome comparison between the Teenagers and the Young Adult sub-cohorts have been reported in **Table S3.**

At univariate analysis, young age was not associated with increased rates of IAS (HR 1.204 [0.675–2.148]: p=0.529). The use of SMART pass algorithm was instead associated to a strong reduction in IAS (aHR 0.292 [0.161–0.525]; p<0.001), while a diagnosis of ARVC was associated with higher rates of IAS (aHR 2.380 [1.205–4.697]; p=0.012). **Figure 4** reports Kaplan Meier curves for the occurrence of IAS in the two groups. **Table 3** reports univariate and multivariate assessment of the predictors of IAS in the study.

DISCUSSION

The aim of this manuscript was to summarize the mid-term outcomes among the recipients of an S-ICD in a large, multicenter, European registry based on age-related differences in patients' baseline clinical profile. The main points of this study are hereby summarized:

1) First, in a large, multicenter, real-world registry encompassing a broad population, teenagers (<20 years old) and young adults (20-30 years old) represented 11.0% of S-ICD recipients. Teenagers and young adults received an S-ICD more frequently for inherited cardiomyopathies, while adults S-ICDs had more frequently a structural acquired cardiomyopathy.
2) Second, after propensity matching for sex, primary prevention rate, and arrhythmic substrate, the overall rate of device-related complications and the rate of inappropriate shocks were comparable between age groups.
3) Finally, a diagnosis of ARVC was strongly associated to higher IAS rates, while the use of a SMART Pass algorithm was consistently associated with a strong reduction in IAS, across age groups.

Teenagers, young adults and S-ICD

Many of the S-ICD characteristics contribute to make this device very appealing for the management of cardiac arrhythmias in teenagers and young adults. A European Heart Rhythm Association (EHRA) survey showed that its complete extravascular design, the very low rates of lead malfunctions reported, the better aesthetic result perceived by the recipients, and the possibility of an active lifestyle after implantation are major determinants in choosing this device instead of a transvenous one, when treating patients with a long life expectancy (10,11). Although being actively marketed as a device for young, active individuals, all currently available analysis assessing its effectiveness and safety in teenager and young adults resulted fairly limited in sample size (7,12,13). Changes in body size due to physical growth, as well as complex anatomy in patients with congenital

heart diseases are perceived as important factors that may limit the implant of S-ICDs. Some concerns have also been raised in smaller patients due to the relatively large S-ICD generator that may appear particularly prominent, but as for Bettin *et al*. (7), in our cohort no generator was replaced due to patient discomfort.

Moreover, the S-ICD system may represent a reliable alternative in reducing the TV-ICD complications. Indeed, a multicenter study evaluating TV lead electrode performance in children and young adults, have shown that younger age at insertion is an independent predictor of lead failure (14). The S-ICD is able to minimize the morbidity and mortality risks associated with early endocardial ICD lead failure, especially in patients requiring lifelong ICD therapy, offering a safer option when dealing this complication. In our cohort, young age was not associated with higher rates of lead failure and consequent lead extraction, due to a very small number of this events being observed in the overall cohort.

Another crucial aspect regarding S-ICD implantation is the role of defibrillation testing (DT) to assess the appropriate sensing of ventricular arrhythmias and testing system integrity at implant. Forleo *et al.* (15) have recently demonstrated that DT performance was not associated with significant differences in cardiovascular mortality and ineffective shocks. Interestingly, in our cohort, young patients were more likely to undergo DT at implant. This finding may reflect a specific physician choice, more inclined to seek a confirmation of the device function in this specific patient population.

Inappropriate shock predictors

One of the main concerns associated with the use of S-ICD devices in teenagers and young adults are IAS. Multiple studies, indeed, have reported elevated rates of inappropriate therapies in this specific subset of patients. In a very small sample size cohort, Silvetti *et al.* (12) reported a 7% of IAS rate, while Lewandoski *et al.* (13) reported a significantly higher rate of IAS (31.2%), although over a much longer follow-up. Finally, Bettin *et al.* (7) observed a 16.1% rate of IAS in teenagers and young adults, with younger age resulting an independent predictor of IAS in S-ICD recipients. The main

triggers for these IAS among all three of these cohorts were TWO and non-cardiac (muscular) signal interference.

Our data at first glance seem to be confirming these findings in a much larger population. Over almost two years of follow-up in fact, 16.1% of patients in the teenager and young adult group in our registry experienced an IAS, with TWO and muscular signal interference representing the most common triggers. Compared to a propensity-matched cohort of adult patients, however, no significant difference in IAS was observed and substrate, more specifically a diagnosis of ARVC that implies an evolving myocardial substrate, resulted the only predictor of increased IAS risk. This finding points towards a much greater relative importance of the arrhythmic substrate compared to the age bracket as a risk factor for higher rates of IAS. Younger patients are in fact more commonly recipients of S-ICDs due to genetic cardiomyopathies and channelopathies and the reported increased prevalence of IAS due to age may then have been mirroring this difference in substrates.

Importance of substrate and SMART Pass algorithm

Among the tested predictors for IAS, the implant of an S-ICD due to ARVC was strongly associated with an increased risk of IAS. Data regarding the use of S-ICD devices specifically in patients with ARVC are limited to two patient cohorts, both reporting an elevated rate of IS. Indeed, Migliore *et al.* (16) observed a 14% rate of IAS in a cohort of 44 patients with ARVC, while Orgeron *et al.* (17) reported a 21% of IAS among patients with this specific cardiomyopathy. The most common reason for IS in these reports was TWO, which may reflect the finding of our study.

ARVC is a disease characterized by an important loss of myocardiocytes due to fibro-fatty replacement. This myocardial loss is often associated to a progressive lowering of the amplitude of QRS complexes of these patients. This low amplitude in QRS complexes may cause the device to read T waves as QRS complexes, causing TWO, double counting, and IAS. SMART Pass algorithm have proven exceedingly effective in reducing rates of IAS in the setting of multiple cardiomyopathies among young adults. Nazer *et al*. (18), in fact, reported good S-ICD performances

in patients with HCM, with low rates of IAS, while the use of SMART Pass algorithms reduced IAS due to TWO in a cohort of patients with Brugada syndrome, as reported by Shinohara *et al.* (19). This algorithm, however, may be insufficient to avoid IAS in infiltrative diseases (i.e. cardiac sarcoidosis) or diseases with great loss of myocardiocytes (i.e. laminopathies) presenting over time with low QRS signals. Still, most of these conditions present alongside advanced conduction disturbances and do not represent prime candidate for S-ICD devices. The only disease in which this problem may actually bear clinical relevance seems to be ARVC. However, as showed by Orgeron *et al.* (17) ARVC patients with TV-ICDs are noted to have considerable risk of inappropriate therapy as well. In comparison, a significant minority of S-ICD patients has experienced IAS at a similar rate than TV-ICD patients in this setting. Further study characterizing IAS triggers and dynamic changes of the cardiac signal over time in patients with ARVC are needed.

Limitations

A limitation of this study is the non-randomized, observational nature inherently associated with nature of the European, real-world, multicentered registry of unselected patients undergoing S-ICD implantation from which this data has been extracted. Furthermore, many of the centers involved in this project are third level referral centers in their region and a certain degree of selection bias among the enrolled patients cannot be excluded.

CONCLUSION

In a large multicentered European registry of patients with S-ICD, 11.0% of all recipients were teenagers or young adults. The use of S-ICD in teenagers/young adults resulted safe and effective, and the rates of complications and IAS between teenagers/young adults and adults were not significantly different. The only predictor of increased IAS was a diagnosis of ARVC.

REFERENCES

1. Wilkoff BL., Fauchier L., Stiles MK., et al. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. Europace 2016;18(2):159–83. Doi: 10.1093/europace/euv411.
2. Berul CI., Van Hare GF., Kertesz NJ., et al. Results of a Multicenter Retrospective Implantable Cardioverter-Defibrillator Registry of Pediatric and Congenital Heart Disease Patients. J Am Coll Cardiol 2008;51(17):1685–91. Doi: 10.1016/j.jacc.2008.01.033.
3. Basu-Ray I., Liu J., Jia X., et al. Subcutaneous Versus Transvenous Implantable Defibrillator Therapy: A Meta-Analysis of Case-Control Studies. JACC Clin Electrophysiol 2017;3(13):1475–83. Doi: 10.1016/j.jacep.2017.07.017.
4. Gasperetti A., Schiavone M., Ziacchi M., et al. Long-term complications in patients implanted with subcutaneous implantable cardioverter-defibrillators: Real-world data from the extended ELISIR experience. Heart Rhythm 2021. Doi: 10.1016/j.hrthm.2021.07.008.
5. Mitacchione G., Schiavone M., Gasperetti A., Viecca M., Curnis A., Forleo GB. Neglected lead tip erosion: An unusual case of S-ICD inappropriate shock. J Cardiovasc Electrophysiol 2020;31(12):3322–5. Doi: 10.1111/jce.14746.
6. Griksaitis MJ., Rosengarten JA., Gnanapragasam JP., Haw MP., Morgan JM. Implantable cardioverter defibrillator therapy in paediatric practice: A single-centre UK experience with focus on subcutaneous defibrillation. Europace 2013;15(4):523–30. Doi: 10.1093/europace/eus388.
7. Bettin M., Larbig R., Rath B., et al. Long-Term Experience With the Subcutaneous Implantable Cardioverter-Defibrillator in Teenagers and Young Adults. JACC Clin Electrophysiol 2017;3(13):1499–506. Doi: 10.1016/J.JACEP.2017.08.017.
8. Ricciardi D., Ziacchi M., Gasperetti A., et al. Clinical impact of defibrillation testing in a real-world S-ICD population: Data from the ELISIR registry. J Cardiovasc Electrophysiol 2021;32(2):468–76. Doi: 10.1111/jce.14833.

9. Gasperetti A., Schiavone M., Biffi M., et al. Intraprocedural PRAETORIAN score for early assessment of S-ICD implantation: a proof-of-concept study. J Cardiovasc Electrophysiol 2021. Doi: 10.1111/jce.15254.

10. Boveda S., Lenarczyk R., Fumagalli S., et al. Factors influencing the use of subcutaneous or transvenous implantable cardioverter-defibrillators: results of the European Heart Rhythm Association prospective survey. Europace 2018;20(5):887–92. Doi: 10.1093/EUROPACE/EUY009.

11. Botto GL., Forleo GB., Capucci A., et al. The Italian subcutaneous implantable cardioverter-defibrillator survey: S-ICD, why not? Europace 2017;19(11):1826–32. Doi: 10.1093/europace/euw337.

12. Silvetti MS., Pazzano V., Verticelli L., et al. Subcutaneous implantable cardioverter-defibrillator: is it ready for use in children and young adults? A single-centre study. Europace 2018;20(12):1966–73. Doi: 10.1093/EUROPACE/EUY139.

13. Lewandowski M., Syska P., Kowalik I. Children and young adults treated with transvenous and subcutaneous implantable cardioverter-defibrillators: A 22-year single-center experience and new perspectives. Kardiol Pol 2020;78(9):869–74. Doi: 10.33963/KP.15469.

14. Atallah J., Erickson CC., Cecchin F., et al. Multi-institutional study of implantable defibrillator lead performance in children and young adults results of the Pediatric Lead Extractability and Survival Evaluation (PLEASE) Study. Circulation 2013;127(24):2393–402. Doi: 10.1161/CIRCULATIONAHA.112.001120.

15. Forleo GB., Gasperetti A., Breitenstein A., et al. Subcutaneous implantable cardioverter-defibrillator and defibrillation testing: A propensity-matched pilot study. Hearr Rhythm 2021. Doi: 10.1016/j.hrthm.2021.06.1201.

16. Migliore F., Viani S., Bongiorni MG., et al. Subcutaneous implantable cardioverter defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy: Results from an Italian multicenter registry. Int J Cardiol 2019;280:74–9. Doi:

10.1016/j.ijcard.2019.01.041.

17. Orgeron GM., Bhonsale A., Migliore F., et al. Subcutaneous implantable cardioverter-defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia: A transatlantic experience. J Am Heart Assoc 2018;7(21). Doi: 10.1161/JAHA.118.008782.

18. Nazer B., Dale Z., Carrassa G., et al. Appropriate and inappropriate shocks in hypertrophic cardiomyopathy patients with subcutaneous implantable cardioverter-defibrillators: An international multicenter study. Heart Rhythm 2020;17(7):1107–14. Doi: 10.1016/j.hrthm.2020.02.008.

19. Shinohara T., Abe I., Hirota K., et al. Usefulness of subcutaneous implantable cardioverter-defibrillator therapy in patients with Brugada syndrome. Heart Vessels 2021;36(2):260–6. Doi: 10.1007/s00380-020-01683-0.

FIGURE LEGENDS

Figure 1. Workflow chart showing the selection process for the study population. **Abbreviations:** pts: patients.

Figure 2. Standardized percentage of bias reduction achieved through propensity matching. **Abbreviations:** ARVC: arrhythmogenic right ventricular cardiomyopathy; BrS: Brugada syndrome; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; ICM: ischemic cardiomyopathy.

Figure 3. Kaplan Meier showing overall freedom from sustained ventricular arrhythmias in the teen-ager/young adult cohort (in red) and in the adult cohort (in blue). **Abbreviations**: m.o.: months; TA: teen-agers; YA: young adults.

Figure 4. Kaplan Meier showing survival from inappropriate shocks in the teen-ager/young adult cohort (in red) and in the adult cohort (in blue). **Abbreviations:** IAS: inappropriate shocks; m.o.: months; TA: teen-agers; YA: young adults.

Table 1

Baseline characteristics of the study cohort			
	Teenagers + Young Adults (n=161)	Adults (n=161)	p
Age (years), median[IQR]	22.1±4.6	49.7±11.7	**<0.001**
Male, n(%)	111 (68.9)	111 (68.9)	1.000
BMI, median[IQR]	23.3±4.2	26.0±4.2	**<0.001**
Diabetes, n(%)	2 (1.5)	10 (7.1)	**0.035**
Hypertension, n(%)	13 (8.1)	45 (28.0)	**<0.001**
Sport Practice, n(%)	35 (21.7)	20 (12.4)	**0.026**
CKD, n(%)	5 (3.1)	14 (8.7)	*0.056*
LVEF (%), mean±d.s	54.4±13.3	51.9±13.9	0.101
Primary Prevention Implant, n(%)	82 (50.9)	82 (50.9)	1.000
Underlying Cardiac Disease			
Ischemic cardiomyopathy, n(%)	*10 (6.2)*	*10 (6.2)*	1.000
Dilatative cardiomyopathy, n(%)	*17 (10.6)*	*17 (10.6)*	1.000
Hypertrophic cardiomyopathy, n(%)	*33 (20.5)*	*33 (20.5)*	1.000
Arrhythmogenic right ventricular cardiomyopathy, n(%)	*21 (13.0)*	*21 (13.0)*	1.000
Brugada syndrome, n(%)	*25 (15.5)*	*25 (15.5)*	1.000
Idiopathic VF, n(%)	*24 (14.9)*	*24 (14.9)*	1.000
Other, n(%)	*19 (11.8)*	*19 (11.8)*	1.000
Atrial Fibrillation, n(%)	19 (11.8)	32 (18.9)	**0.047**
Paroxysmal, n(%)	*17 (10.6)*	*20 (12.4)*	
Persistent, n(%)	*2 (1.2)*	*7 (4.4)*	*0.029*
Permanent, n(%)	*0*	*5 (3.1)*	
Removal of previous TV device, n(%)	11 (6.8)	15 (9.4)	0.413

Abbreviations: BMI=body mass index; CKD=chronic kidney disease; LVEF=left ventricular ejection fraction; TV=transvenous, VF=ventricular fibrillation.

Table 2

	Teenagers + Young Adults (n=161)	Adults (n=161)	p
Peri-procedural Characteristics			
Two incision technique, n(%)	144 (90.0)	149 (92.5)	0.419
Inter-muscular device placement, n(%)	132 (82.0)	132 (82.0)	1.000
DT, n(%)	147 (91.3)	136 (84.5)	**<0.001**
Shock Zone (bpm), median [IQR]	250 [240–250]	240 [230–250]	**<0.001**
Standard shock polarity, n(%)	152 (95.0)	148 (91.9)	0.265
SMART Pass algorithm on, n(%)	133 (82.6)	132 (82.0)	0.884
Follow-up data			
Length of follow-up (months), median [IQR]	22.1 [12.9–36.2]	25.1 [14.7–41.1]	0.208
Patients experiencing appropriate shocks, n(%)	26 (16.1)	20 (12.4)	0.339
Patients experiencing inappropriate shocks, n(%)	26 (16.1)	23 (14.3)	0.642
Due to AF/AT, n(%)	*1 (0.6)*	*9 (5.6)*	***0.010***
Due to TWO, n(%)	*18 (11.2)*	*9 (5.6)*	*0.070*
Due to Myopotentials, n(%)	*5 (3.1)*	*1 (0.6)*	*0.090*
Other, n (%)	*2 (1.2)*	*4 (2.5)*	*0.491*
Overall complications, n (%)	16 (9.9)	14 (8.7)	*0.701*
Infective, n (%)	2 (1.2)	5 (3.1)	*0.252*
Lead Infection, n (%)	1 (0.6)	1 (0.6)	*1.000*
Pocket Infection, n (%)	1 (0.6)	4 (2.5)	*0.173*
Non infective, n (%)	14 (8.7)	9 (5.6)	*0.279*
Lead Displacement, n (%)	3 (1.9)	1 (0.6)	0.314
Pocket Hematoma, n (%)	11 (6.8)	7 (4.3)	0.332
Lead Fracture, n (%)	0	1 (0.6)	0.317
Death, n (%)	4 (2.5)	3 (1.9)	1.000

Abbreviations: AF=atrial fibrillation; AT=atrial tachycardia; DT=defibrillation testing; TWO=T-wave oversensing; VF=ventricular fibrillation; VT=ventricular tachycardia.

Table 3

	Inappropriate Shocks					
	HR	C.I.	p	aHR	C.I.	p
Age < 30	1.204	[0.675–2.148]	0.529			
Male sex	0.739	[0.402–1.356]	0.326			
Sport	1.345	[0.667–2.711]	0.407			
Hypertension	0.790	[0.353–1.767]	0.566			
BMI	1.010	[0.942–1.081]	0.784			
Diabetes	1.417	[0.339–5.917]	0.633			
Primary Prevention	0.667	[0.371–1.199]	0.179			
Dilatative Cardiomyopathy	1.159	[0.491–2.735]	0.737			
Ischemic Cardiomyopathy	1.748	[0.626–4.885]	0.287			
Brugada Syndrome	0.647	[0.338–1.239]	0.189			
Hypertrophic Cardiomyopathy	0.475	[0.170–1.326]	0.155			
ARVC	2.248	[1.141–4.431]	**0.019**	2.380	[1.205–4.697]	**0.012**
Idiopathic VF	1.752	[0.842–3.643]	0.133			
AF	0.986	[0.460–2.119]	0.971			
CKD	0.720	[0.175–2.972]	0.650			
LVEF	0.986	[0.967–1.005]	0.155			
Inter-muscular Placement	0.797	[0.410–1.547]	0.503			
Two incision technique	0.884	[0.373–2.091]	0.779			
SMART Pass algorithm	0.300	[0.167–0.540]	**<0.001**	0.292	[0.161–0.525]	**<0.001**

Abbreviations: AF=atrial fibrillation; ARVC=arrhythmogenic right ventricular cardiomyopathy; BMI=body mass index; CKD=chronic kidney disease; LVEF=left ventricular ejection fraction; LQTS: long QT syndrome; VF=ventricular fibrillation.