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EHRA SURVEY

Investigation on Sudden Unexpected Death in the Young (SUDY) in Europe: results of the European Heart Rhythm Association Survey

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Abstract

The aims of this centre-based survey, promoted and disseminated by the European Heart Rhythm Association (EHRA) was to investigate the current practice for the investigation of Sudden Unexplained Death in the Young (SUDY) amongst European countries. An online questionnaire composed of 21 questions was submitted to the EHRA Research Network, European Cardiac Arrhythmia Genetics (ECGen) Focus Group members, and European Reference Network GUARD-Heart healthcare partners. There were 81 respondents from 24 European countries. The majority (78%) worked in a dedicated clinic focusing on families with inherited cardiac conditions and/or SUDY or had easy access to a nearby one. On average, an autopsy was performed in 43% of SUDY cases. Macroscopic examination of the body and all organs were completed in 71% of cases undergoing autopsy, and expert cardiac examination in 32%. Post-mortem genetic testing was requested on average in 37% of Sudden Arrhythmic Death Syndrome (SADS) cases, but not at all by 20% of survey respondents. Psychological support and bereavement counselling for SADS/SUDY families were available for ≤50% of participants. Whilst electrocardiogram (ECG) and echocardiography were largely employed to investigate SADS relatives, there was an inconsistent approach to the use of provocative testing with exercise ECG, sodium channel blocking drugs, and/or epinephrine and genetic testing. The survey highlighted a significant heterogeneity of service provision and variable adherence to current recommendations for the investigation of SUDY, partly attributable to the availability of dedicated units and specialist tests, genetic evaluation, and post-mortem examination.

Keywords Sudden death • Sudden Unexplained Death in the Young • Sudden Arrhythmic Death Syndrome • Inherited cardiac conditions • Provocation testing • Autopsy • Genetic testing • European Heart Rhythm Association survey

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Introduction

Sudden death (SD) can be defined as a witnessed, non-traumatic, and unexpected fatal event occurring within 1 h of the onset of symptoms in an apparently healthy individual or an unwitnessed death that occurred in the 12–24 h prior to the individual last being seen in good health.[1,2] Sudden Unexpected Death in the Young (SUDY) aged 1–40 years, is a rare occurrence,[3–5] affecting around 2–3 in every 100 000 young people every year in Europe.[6] This amounts to several thousand deaths per annum with a greater impact than when older people die suddenly. There is also a high likelihood of underlying genetic heart disease as the cause of death,[6–8] and therefore genetic risk to other family members that requires identification in order to prevent further mortality. Historical studies have indicated, however, that there is an extreme heterogeneity in provision for investigation of genetic heart disease in SUDY and Sudden Arrhythmic Death Syndrome (SADS—autopsy negative SD) victims and their families across Europe despite several position statements and guidelines.[6,9,10]

Recently, a survey was initiated by the European Cardiac Arrhythmia Genetics (ECGen) Focus Group of the European Heart Rhythm Association (EHRA), with the aim to gain an understanding of the current provision and heterogeneity across Europe of the following:

a. autopsy practice and post-mortem genetic studies;
b. referrals for clinical and genetics services for families of decedents with SUDY;
c. SADS family investigation protocols and the role for diagnostic provocation tests and; and
d. family psychological services and support.

Methods

This centre-based survey was promoted and disseminated by EHRA in a collaboration between the Scientific Initiatives Committee (SIC), the ECGen Focus Group of EHRA, and the European Reference Network for rare cardiac diseases, Guard-HEART. An online questionnaire, consisting of 21 questions, was developed and circulated to the EHRA Research Network, ECGen members, and GUARD-Heart healthcare partners. Resulting anonymized data about participants, their institutions, and services and procedures to investigate SUDY, including the use of post-mortem genetic testing and family assessment, were collected complying with the European General Data Protection Regulation (GDPR) 2016/679.

Survey results are expressed as categorical data (numbers and proportions). Comparisons between groups were carried out using the Fisher's exact test.

Results

Survey participants

From 26 January to 13 February 2021, 81 respondents participated to the questionnaire although 9 failed to respond to most questions. The survey results were therefore drafted from answers from the 72 participants (89%) who replied to the majority of questions, unless otherwise stated.

Twenty-four out of the 57 (42%) European Society of Cardiology (ESC) National Cardiac Societies were represented in the survey: Algeria, Austria, Belgium, Czechia, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Lithuania, Malta, Netherlands, Poland, Portugal, Serbia, Slovak Republic, Spain, Sweden, Switzerland, Turkey, and United Kingdom (*Figure 1*). The vast majority of participants worked in university hospitals (83%), followed by non-university public hospitals (7%), private hospitals/practices (6%), and other institutions (4%).

Most of the survey respondents were cardiac electrophysiologists (72%), followed by general cardiologists (36%), clinical geneticists (12%), paediatric cardiologists (11%), cardiac imaging experts (10%), genetic counsellors (7%), and cardiologists specialized in inherited cardiac conditions (ICCs)/genetics (4%). Other healthcare providers accounted for 11% of the survey respondents.

Investigation of SUDY

The investigation of SUDY was mainly based on the 2015 ESC Guidelines on Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death,[1] with 60/72 (83%) of practitioners referring to this document. The 2013 Heart Rhythm Society (HRS)/EHRA/Asia Pacific Heart Rhythm Society (APHRS) Expert Consensus Statement on the Diagnosis and Management of Arrhythmia Syndromes[11] and the 2020 APHRS/HRS Expert Consensus Statement on the Investigation of Decedents with Sudden Unexplained Death and Patients with Sudden Cardiac Arrest, and of their Families[2] were utilized by 61% and 47% of the survey participants, respectively. In two cases other documents were utilized, while two participants did not use any specific guideline for the investigation of SUDY.

Investigation of SUDY cases comprised collection of medical history (97%), personal history, and prior investigation of the decedent (93%), automatic external defibrillator or electrocardiogram (ECG) data from the time around SD (92%) medical history of family members (90%), witness accounts (73%), medical history of family members (69%) (data from 71 answers).

Post-mortem studies

On average, an autopsy was performed in 43% of SUDY cases: 28 respondents (39%) stated that the autopsy rate ranged between 50% and 100%; 16 (23%) reported a rate between 25% and 49%, while 22 (31%) a rate from 1% to 24%. Five respondents stated that no autopsy is usually undertaken (7%) (*Figure 2A*). The major factors hindering autopsy practice for the 27 survey takers who reported an autopsy rate <25% were that: autopsy was not mandatory in the respondent's country (85%), logistic factors (41%), and costs (19%).

Participants from centres in which autopsy is undertaken to investigate SUDY cases (66/71, 93%) specified that this was usually requested by a coroner or medical examiner equivalent (41%), while the police, the medical resuscitation team and the primary care physician were less frequently involved (26%, 15% and 3%, respectively).

Routine examinations at the time of autopsy included macroscopic examination of the body and all organs (71%), histology of the heart (71%), histology of the brain (40%), photography (32%); expert cardiac examination was routinely performed in only 32% of cases (data from 66 answers).

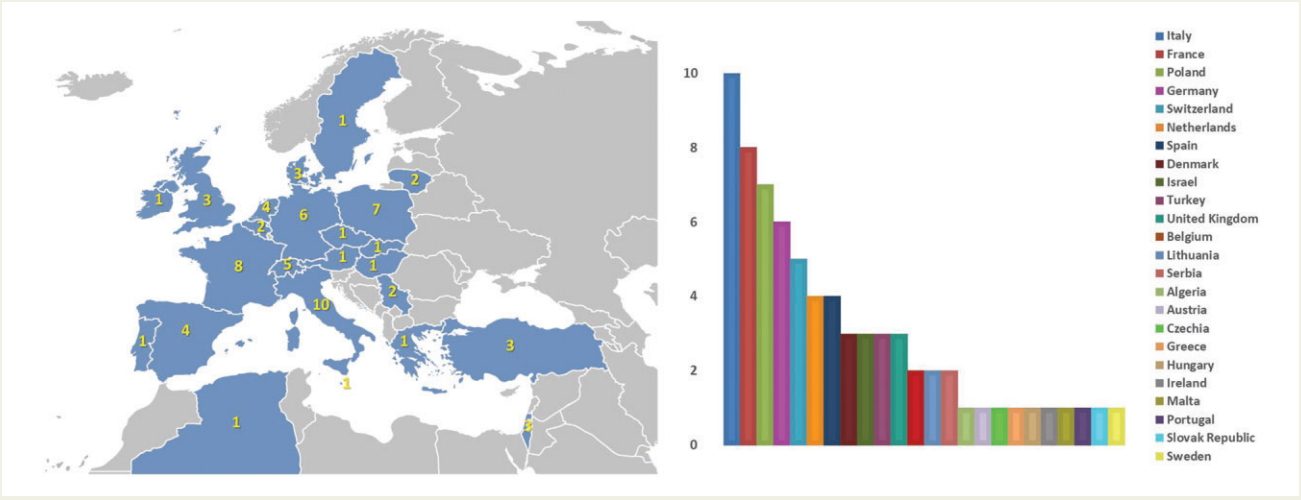

Figure 1 Country of origin of survey participants.

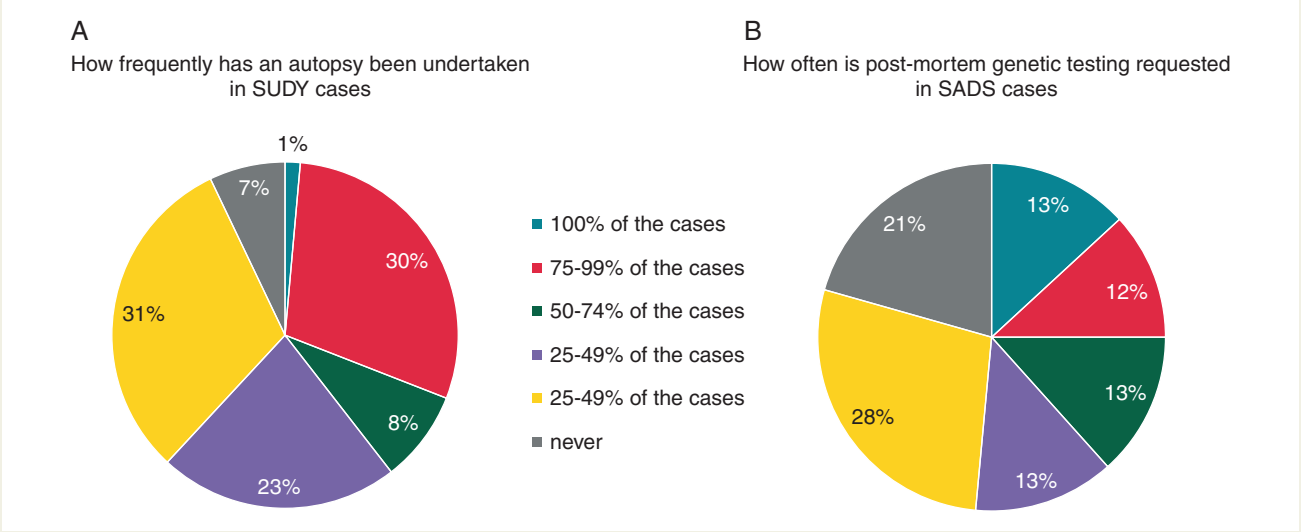

Figure 2 Proportion of post-mortem autopsy (data from 71 answers) (*A*) and genetic testing (data from 59 answers) (*B*) performed for the evaluation of Sudden Unexplained Death in the Young (SUDY) and Sudden Arrhythmic Death Syndrome (SADS).

Post-mortem genetic testing

On average, material suitable for DNA/RNA extraction was retained in 48% of SUDY cases; 30 respondents declared a proportion ≥50% and 21 a proportion ranging from 1% to 49%. Five subjects declared that no samples are routinely collected (data from 71 answers).

The collected samples were mainly frozen blood (EDTA) (48%), frozen liver or spleen (29%) or cardiac tissue (23%), with tissue culture or collection in RNAlater solution being less common (9%) (data from 65 answers).

Post-mortem genetic testing (molecular autopsy) was requested on average in only 37% of SADS cases. Nine survey participants (13%) declared that post-mortem genetic testing was performed routinely, 17 (25%) that this was done in over half of cases, and 28 (41%) in less than half of cases molecular autopsy was not routinely utilized by one-fifth of the survey respondents (data from 68 answers) (*Figure 2B*). In most cases, post-mortem genetic testing was requested by a cardiologist, either after (28%) or before (10%) family evaluation; less frequently by the coroner at the time of autopsy (24%) or the clinical geneticist (19%). Nine percent of the respondents declared that genetic evaluation was performed only after a complete series of cardiac investigations in relatives, while 10% could not provide any information regarding this (data from 58 answers).

Genetic counselling was routinely offered before testing by 24 (41%) participants, and sporadically by 18 (31%). Six (10%) declared

that no counselling was available prior to testing, while 11 did not provide details (data from 59 answers).

Where genetic testing took place, gene panel sequencing was offered by 69% of respondents, while whole-exome sequencing and single-gene testing were much less common (8% and 1%, respectively). Whole-genome sequencing was not utilized, and 20% of respondents gave no information on the type of genetic test performed. A wide arrhythmia *and* cardiomyopathy panel was usually utilized by 61% of participants, while 12% only focused on the genes most frequently involved with primary arrhythmia syndromes (*KCNQ1, KCNH2, SCN5A*, and *RYR2*); wider arrhythmia *or* cardiomyopathy panels were used by 7% and 2% of participants, respectively (data from 59 answers).

Family evaluation

The number of SUDY families investigated each year at each respondent's institution was variable. High-volume centres were a minority, with seven participants claiming ≥100 referrals each year and five examining between 51 and 100 families (*Figure 3*). The multidisciplinary assessment of SUDY families relied mostly on specialist EP assessment (96%), cardiac imaging (93%), and specialist adult genetic cardiology (83%). Genetic counselling and clinical genetics were available for 73% and 72% respondents, respectively, although genetic nursing was only employed by 22% of them. Access to paediatric services, including paediatric cardiology and specialist paediatric genetic cardiology, was offered by a lower proportion of respondents compared to adult cardiology (69% and 44%, respectively). Less than half (34/72, 47%) declared that a specialist pathology assessment for SUDY cases was offered. Psychological support from clinical psychology specialists and bereavement counselling were available for 50% and 15% of survey participants, respectively (*Figure 4*).

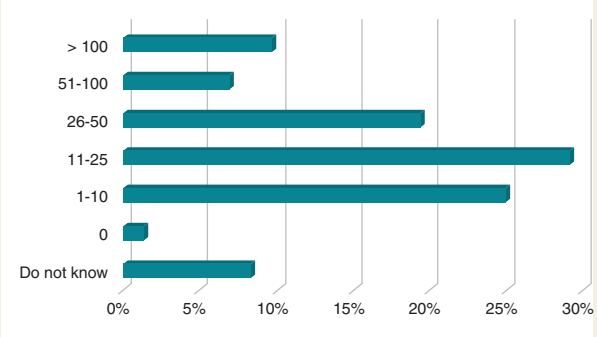

Figure 3 Number of SUDY families evaluated every year. SUDY, Sudden Unexplained Death in the Young.

Following a SUDY, the referral of family members was recommended by 78% of survey participants when a genetic cause of death was suspected at autopsy. Both familial screening and genetic testing were recommended by 64% in cases of unexplained death, and by half if the aetiology of the death was equivocal. In SUDY cases in which no post-mortem had been performed, 47% of the respondents referred all families for screening and genetic testing, while 28% only did so in selected cases.

The proportion of first and second-line tests recommended for first degree relatives of SADS decedents is shown in *Figure 5*. Standard 12-lead electrocardiography and echocardiography were the first-line tests most utilized (used by 95% and 94% of survey respondents, respectively), followed by exercise ECG testing (68%), standard 3-lead ambulatory ECG monitoring (56%), and high precordial lead ECG (55%). Other first-line examinations included signal-averaged ECG, 12-lead ambulatory ECG monitoring, provocative testing with sodium-channel blockers (SCBs) and/or epinephrine and cardiac magnetic resonance imaging (MRI) (*Figure 5, top panel*). In case first-line tests were inconclusive, cardiac MRI was more routinely considered (58%), as well as provocative tests,

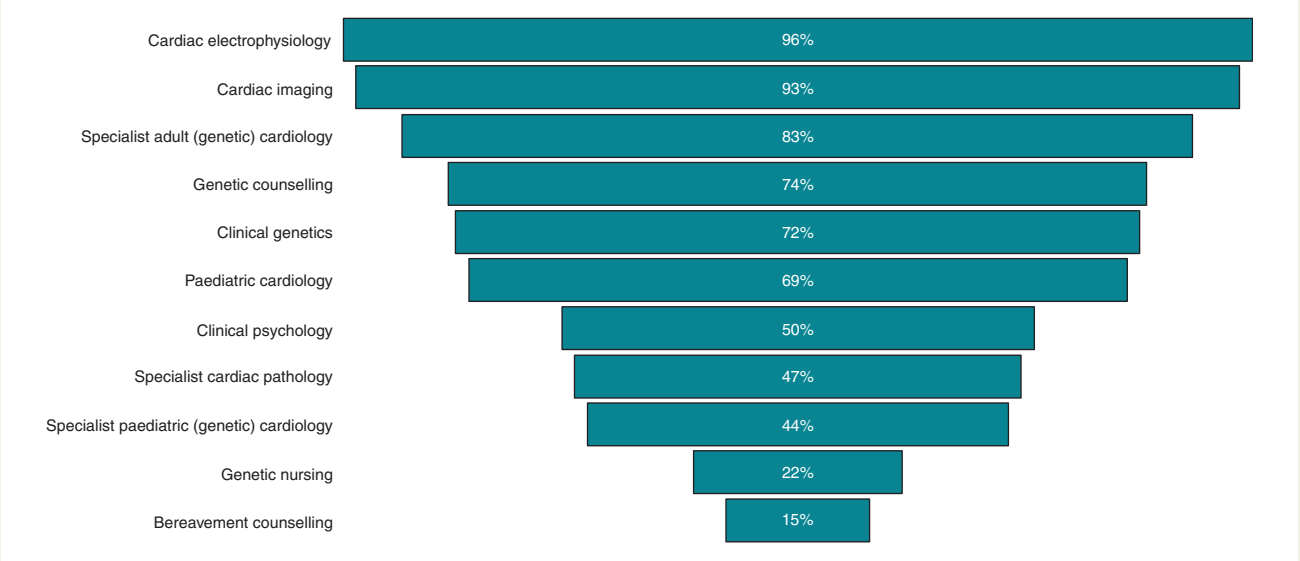

Figure 4 Services for multidisciplinary assessment of SUDY families. SUDY, Sudden Unexplained Death in the Young.

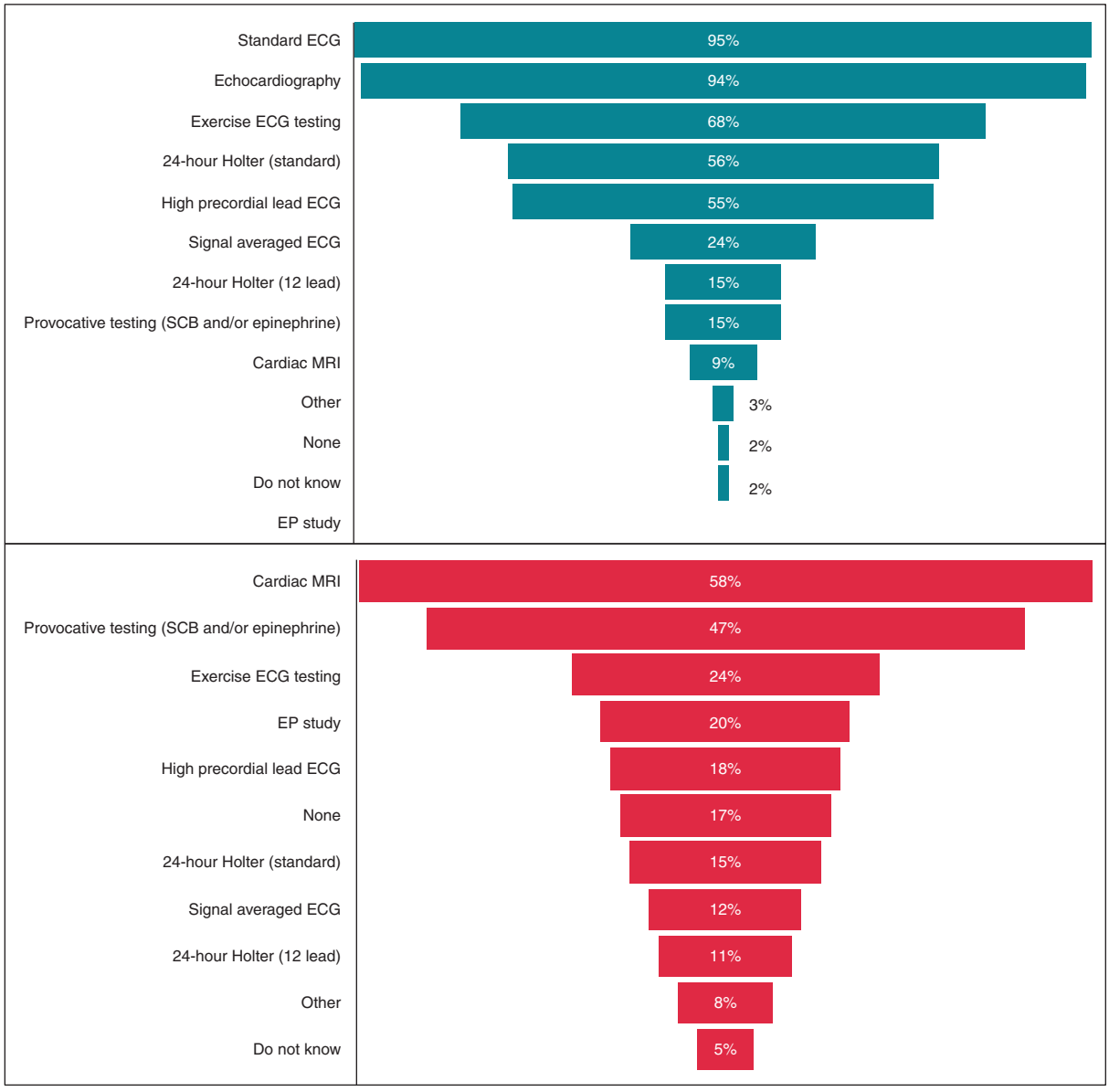

Figure 5 First (top panel) and second-line (bottom panel) tests for first-degree relatives of SADS decedent (data from 66 answers). SADS, Sudden Arrhythmic Death Syndrome; SCB, sodium channel blockers; EP study, electrophysiological study

if not performed previously as a first line test (47%) (*Figure 5, bottom panel*). Almost one quarter (24%) of the survey cohort offered provocative testing with SCB agents to selected SADS relatives showing type 2 Brugada pattern; 18% only recommended the test in selected post-pubertal patients with a type 2 Brugada pattern and whose deceased relative with SADS was male and died at rest or asleep. SCB challenge was offered without reference to the resting ECG pattern by 18% of respondents if first-line tests were negative, by 9% if both first-line and second-line tests were negative; and by 15% if the SADS victim had died at sleep or at rest; 8% of survey participants did not offer the test at all (*Figure 6, top panel*). Epinephrine challenge was used by less than half of participants, mainly in selected relatives whose SADS decedent died during exertion with negative first and second line tests (27%) (*Figure 6*, bottom panel) (data from 66 answers).

Genetic testing for SADS relatives was offered mainly where a post-mortem test in the decedent had showed a pathogenic or likely pathogenic variant i.e. predictive testing (62% of participants), or in relatives with a specific phenotype, and targeted to that phenotype (42% of participants). Genetic testing was offered to all relatives, regardless of phenotype by 16 (24%) survey takers.

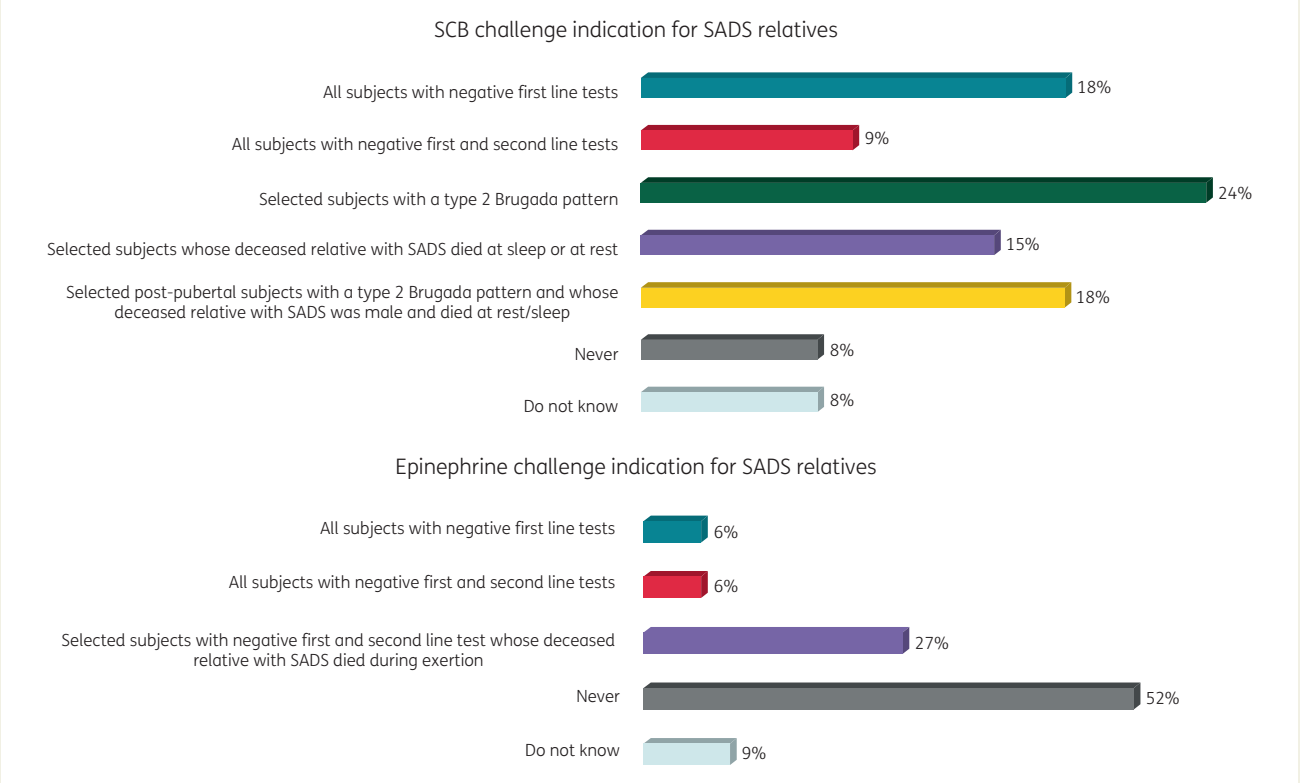

Figure 6 Pharmacological provocation tests (data from 66 answers). SADS, Sudden Arrhythmic Death Syndrome. SCB, sodium channel blockers.

Psychosocial support for SADS relatives was offered mainly on request (56%), while 15% of respondents performed it routinely and 6% never (data from 66 answers).

Variation between specialist centres and non-specialist centres

In total, 56/72 (78%) survey respondents worked in a dedicated clinic focusing on families with ICCs and/or SUDY, or had easy access to a dedicated clinic in another centre; 16 participants (22%) instead worked in a non-specialist setting. *Table 1* summarizes the main differences between the two groups. Overall, specialist dedicated clinics saw more cases and families (25 participants from ICC clinics vs. 0 from the non-specialist setting declared ≥26 families per annum, $P < 0.001$), and were more likely to offer genetic testing, genetic counselling and genetic nursing, as well as bereavement counselling and/or clinical psychology service. Although specialist cardiac pathology availability was not different amongst the two groups, expert cardiac examination was performed more often in the specialist setting (38% vs. 8%, $P = 0.02$). Moreover, post-mortem genetic testing was offered more frequently in dedicated clinics.

Discussion

This survey provided important insights on the investigation on SUDY across Europe, highlighting a substantial heterogeneity of available services, and a suboptimal adherence to the current guidelines and expert consensus documents recommendations (*Table 2*), especially regarding post-mortem examination, genetic testing of victims, use of provocative testing in relatives, and psychological support of families.

Salient findings

Three-quarters of healthcare providers investigating and managing SUDY families work in or have easy access to a dedicated multidisciplinary unit. However, specialist genetic paediatric and clinical psychology/bereavement counselling services are underrepresented, being available for less than half of practitioners. The 2020 HRS/APHRS guidelines were the first to stress the importance of psychological support, so these may not have been in place yet.

Nonetheless, current clinical practice is frequently not in line with the recommendations in a substantial proportion of institutions despite respondents indicating that international guidelines and expert consensus documents are in use. Dedicated ICC/SUDY units generally performed better than non-specialist ones in terms of adherence to guidelines and availability of specialist healthcare providers and tests.

Post-mortem evaluation

Post-mortem examination, together with details on the circumstances of death is considered a critical element to the investigation of SUDY.[1,2,11] The results of this survey showed that, on average, less than half of SUDY cases are investigated with autopsy, with only 38% of institutions requesting it in more than half of cases. In addition, when the post-mortem evaluation is performed, it is not always

Table 1 Comparison between dedicated ICC/SUDY and non-dedicated units

Dedicated ICC/SUDY clinic ($n = 56$)		Non specialist clinic ($n = 16$)	*P*-value
	Services available for the investigation of SUDY		
51	Specialist adult genetic cardiology	9	0.003
51	Cardiac imaging	15	NS
54	Cardiac electrophysiology	14	NS
42	Paediatric cardiology/specialist paediatric (genetic) cardiology	10	NS
51	Clinical genetics/genetic counselling	8	0.0008
16	Genetic nursing	0	0.01
25	Specialist cardiac pathology	8	NS
34	Bereavement counselling/clinical psychology	3	0.004
	Number of families investigated each year		
26	1–25	13	NS
25	≥26	0	<0.001
	Post-mortem evaluation		
45%	Proportion of SUDY cases evaluated with autopsy	35%	–
18/56 (32%)	Centres not performing autopsy or performing autopsy in ≤ 25% of the cases	9/15 (60%)	NS
20/53 (38%)		1/13 (8%)	0.02
	Expert cardiac examination		
51%	Proportion of SUDY cases in which cardiac samples for DNA/RNA extraction are collected	33%	–
	How often is post-mortem genetic testing requested in SADS cases		
10/56 (18%)	Never	4/12 (33%)	NS
13/56 (23%)	1–25%	6/12 (50%)	NS
8/56 (14%)	25–49%	1/12 (8%)	NS
25/56 (45%)	≥50%	1/12 (8%)	0.02

ICC, inherited cardiac condition; SUDY, Sudden Unexplained Death in the Young.

Table 2 Summary of Guidelines and Expert consensus documents class of recommendations and level of evidence for the investigation of SCD/SUDY and family evaluation

	HRS/EHRA/APHRS expert consensus 2013 (ref [11])	ESC guidelines 2015 (ref [1])	APHRS/HRS expert consensus 2020 (ref [2])
Dedicated clinic with appropriately trained staff to evaluate potential SCD/SUDY cases and first-degree relatives with a diagnosed or suspected ICC	I		I B
Collection of personal/family history and circumstances of the sudden death for all SUDS victims	I		I B
Autopsy with at least histological examination of the heart to investigate the causes of sudden death	I	I C	I B
Expert cardiac pathology examination	I		I B
Collection of suitable tissue for toxicology and molecular pathology	I	I C	I B
Molecular autopsy/post-mortem genetic testing	IIa	IIa C	I B
Referral of family members in SCD/SUDY cases with a diagnosed or suspected ICC	I		I B

Class I: strong evidence in favour of the strategy.
Class IIa: moderate evidence in favour of the strategy.
Class IIb: weak evidence in favour of the strategy.
Class III: no benefit or harm from the strategy.
Level of evidence A: high-quality evidence from 1 or more randomized trial or meta-analysis of randomized trials.
Level of evidence B: moderate-quality evidence from single randomized trial or large non-randomized studies.
Level of evidence C: expert consensus and/or small studies, retrospective studies or registries.
APHRS, Asia Pacific Heart Rhythm Society; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; ICC, inherited cardiac condition; SCD, sudden cardiac death; SUDY, Sudden Unexplained Death in the Young.

comprehensive, contrary to current recommendations; macroscopic examination of body and organs, brain histology assessment, and expert cardiac pathology examination are not always performed and can vary significantly within countries.[12]

Genetic testing

Current guidelines and consensus documents recommend retaining samples and perform post-mortem genetic testing in SUDY cases with a normal autopsy or when an inheritable cardiac condition is suspected.[2,11] Furthermore, cascade genetic screening of first-degree blood relatives is advised where a pathogenic variant has been identified in the index case. This survey shows that, instead, DNA/RNA is extracted from only approximately half of SUDY cases, and post-mortem genetic testing (molecular autopsy) is performed in less than 40% of SADS decedents. Of note, molecular autopsy is not utilized routinely by one-fifth of healthcare providers dealing with SUDY families, despite clear recommendations to do so.

The availability of genetic counselling is also variable and is offered only occasionally in one-third of cases, and not at all in 10% of cases. Predictive genetic testing for SADS/SUDY relatives is still underutilized (by less than two-thirds of caregivers), and targeted genetic testing is advised in less than half of cases.

In order to avoid difficulties in the interpretation of variants in the absence of an associated phenotype, current recommendations *do not recommend* the use of genetic testing in the absence of a suspected ICC. Despite this clear principle, genetic testing is offered to all relatives without a phenotype by approximately one-quarter of healthcare providers.

Family investigation protocols

Following a SUDY, family evaluation is encouraged in the majority of cases in which an ICC is suspected at post-mortem. First-line testing with ECG and echocardiography is near ubiquitous but then protocols appear to diverge, despite successive consensus statements recommending the exercise ECG[2,11] and data supporting the greater sensitivity of high precordial lead ECGs for the Brugada type 1 ECG pattern.[13,14]

Provocative pharmacological testing is usually considered for the diagnosis of primary arrhythmia syndromes such as Brugada syndrome (BrS) (SCB challenge), long QT syndrome (LQTS), or catecholaminergic polymorphic ventricular tachycardia (epinephrine challenge).[1,2,11] The use of epinephrine challenge has been suggested as an alternative to exercise testing in SUDY families.[2] However, the reliability and reproducibility of epinephrine challenge in LQTS have been questioned,[15] as has the accuracy of SCB testing in controls[16] and SUDY families.[17] Nonetheless, systematic ajmaline provocation testing in SADS families where an autopsy has been performed and other tests are negative does increase the yield of BrS diagnoses substantially.[18]

This survey illustrates this dilemma. Use of SCB challenge is heterogeneous and is more commonly employed when the presence of ECG findings is suspicious for BrS and the circumstances of death of the decedent compatible with BrS. Systematic testing after negative initial evaluation is less commonly employed. Epinephrine challenge is still offered by half of practitioners, although mainly in families with negative investigations whose deceased relative died during exertion.

Genetic testing for SADS family members is mainly offered when a specific variant has been detected in the deceased or when a specific phenotype is identified at cardiac investigations.

Implications

These results suggest a substantial heterogeneity of the investigation of SUDY and management of SUDY families across Europe, in particular regarding the rate and thoroughness of autopsies performed, the availability and use of post-mortem and cascade genetic testing, and psychological support for SADS/SUDY families. This may result in misdiagnosis of SADS and/or underreporting of cases attributable to ICCs, potentially putting family members at increased risk.

A clinical or public health initiative?

There are clear opportunities for improving access to comprehensive genetics, paediatric, clinical, and psychological services for relatives of SUDY decedents that would align better with current recommendations. However, the largest obstacle across Europe to equal access to care is accurate diagnosis of the cause of death at autopsy, which has also been identified by a recent predominantly non-European survey.[19] This is not usually an issue for health services but is under the jurisdiction of national departments of justice. Lobbying of European governments and raising of public awareness by professional societies,[20] such as the ESC, in collaboration with patient groups will be necessary to promote change that will address heterogeneity. For example, this approach has led to successful legislation in Denmark for mandatory notification of all unexpected SD to law enforcement and the autopsy can be requested by law (the 'Health Act').

Conclusions

Scientific societies and experts' consensus documents provide thorough recommendations to investigate the causes of SUDY and help identify relatives at risk of sudden cardiac death from SUDY families. However, adherence to guidelines is still suboptimal in many European countries, especially where no dedicated SUDY/ICC units are in place. Improvement and expansion of existing specialist structures and access to autopsy in SUDY is needed to provide a better understanding of the causes and improve prevention strategies.

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Conflict of interest: none declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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