MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

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Extravascular Implantable Cardioverter-Defibrillator

Keyword: Extravascular Implantable Cardioverter-Defibrillator, arrythmia, ventricular fibrillation, sudden cardiac death

SUMMARY OF TECHNOLOGY

An implantable cardioverter-defibrillator (ICD) is a battery-powered device that monitors heart rhythm and can deliver an electric shock to restore normal sinus rhythm when arrhythmias are detected, for patients with fatal ventricular arrhythmia at risk of sudden cardiac death (SCD).[1] Currently there are several types of ICD available in the market including transvenous (TV ICDs) and subcutaneous (SQ ICD) implantable cardioverter-defibrillators. Issues such as vascular injury, lead fracture, and vessel occlusions as the result of TV ICD usage, have created demand for an extravascular ICD system.

A novel extravascular implantable cardioverter-defibrillator (EV ICD) device, EV ICD™ System by Medtronic is an investigational single-chamber, MR-conditional, EV ICD (volume = 33 cm3) with ICD generator positioning in a subcutaneous or an intermuscular tissue pocket along the left mid-axillary line.[1] It is a multiprogrammable cardiac device that monitors and regulates the patient's heart rate, also providing diagnostic and monitoring features to assist with system evaluation and patient care (Figure 1). The EV ICD lead is an 8.7-Fr epsilon-shaped passive fixation lead with two pace-sense rings and two defibrillation coils. The EV ICD system can deliver up to 40 J for defibrillation and provide antitachycardia pacing (ATP), post-shock pacing, and asystole support pacing.[1] It offers graded responses to a sensed ventricular arrhythmia - on detection of a minor arrhythmia, a built-in conventional pacemaker is activated to restabilize cardiac rhythm. If that fails, low energy synchronized cardioversion and high-energy defibrillation shocks can be delivered by a single trans-venous lead.[1]

Implantations were performed in cardiac catheterization laboratories or hybrid operating rooms by cardiologists who underwent a structured hands-on training.[1] As opposed to TV ICD, the EV ICD lead is implanted in the substernal space (anterior mediastinum), which is an intriguing area due to proximity to the heart via a minimally invasive subxiphoid (Figure 2).[1] The lead is connected to a device that is implanted below the left armpit (in the left mid-axillary region).

Medtronic has received US FDA approval for a Continued Access Study while the agency reviews the company's EV ICD pre-market application.[2] Worldwide, the EV ICD system is still investigational and not yet approved for sale or distribution.

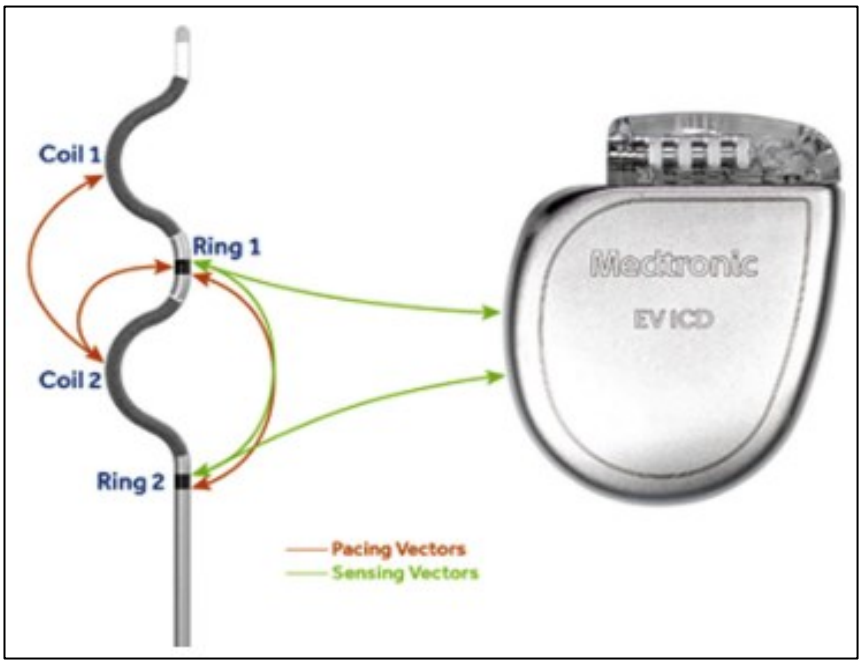

Figure 1: Extravascular ICD leads & device[1]

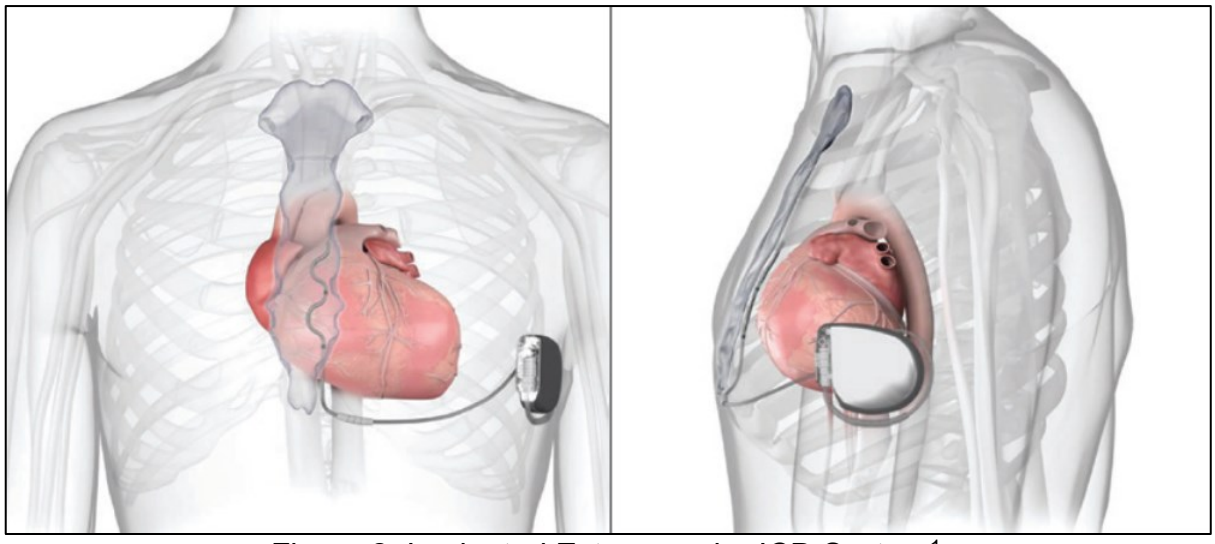

Figure 2: Implanted Extravascular ICD System[1]

INNOVATIVENESS

Novel, completely new	
Incremental improvement of the existing technology	/
New indication of an existing technology	

DISEASE BURDEN

Sudden cardiac death (SCD) is defined as sudden natural death presumed to be of cardiac cause that occurs within 1 h of onset of symptoms in witnessed cases, and within 24 hours of last being seen alive when it is unwitnessed.[3] The condition is most often due to either sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) although sometimes it may be due to a bradyarrhythmia or electromechanical dissociation.[4]

Ventricular fibrillation (VF) is a chaotic rhythm with undulations that are irregular in timing and morphology, without discrete QRS complexes on the surface ECG.[3] Ventricular tachycardia (VT) is defined as ≥3 consecutive beats with a rate >100 b.p.m. originating from the ventricles, independent from atrial and atrioventricular (AV) nodal conduction.[3]

Sudden cardiac death (SCD) continues to be a major health issues globally as well as in Malaysia as it accounts for approximately 50% of all cardiovascular deaths, with up to 50% being the first manifestation of cardiac disease. The incidence of SCD increases markedly with age. With a very low incidence during infancy and childhood (1 per 100 000 person- years), the incidence is approximately 50 per 100 000 person-years in middle-aged individuals (in the fifth to sixth decades of life). At any age, males have higher SCD rates compared with females, even after adjustment for risk factors of coronary artery disease (CAD). It is estimated that 10–20% of all deaths in Europe are SCD. In Malaysia, data collected among 545 sudden death cases in University of Malaya Medical Centre, Kuala Lumpur over period of 5 years showed that sudden cardiac deaths accounted for 65% of all sudden natural deaths. Majority of cases were males and was in age group 41-50 years old.[5]

CURRENT OPTIONS FOR PATIENTS

Essential step in the management of ventricular arrhythmia is to identify and treat reversible causes such as electrolyte disturbances, ischaemia and drugs. Reversible causes may account for up to 50% of SCA. However, most of the time it is difficult to determine the exact underlying cause of SCA and whether it is reversible.

Current available treatment options for patients with ventricular arrythmia include pharmacotherapy and device therapy.

Pharmacotherapy

Anti-arrhythmic medications that have been shown to reduce the incidence of SCD include β-blockers, mineralocorticoid receptor antagonist (MRA), angiotensin converting enzyme inhibitors (ACE-I), angiotensin-receptor blocker - neprilysin inhibitor (ARNI), statins and amiodarone.[4]

Synchronised Electrical Cardioversion

In the acute management of irregular pre-excited tachycardias associated with haemodynamic instability, synchronised electrical cardioversion delivered in time (synchronised) with the QRS complex becomes the treatment of choice.[3] It is also recommended in haemodynamically stable patients who are unresponsive or with

contraindications to pharmacological therapy as well as unstable conditions of SVT due to pre-excitation, reentry (AVNRT, AVRT), focal atrial tachycardia, atrial fibrillation, atrial flutter, SVT in adults with congenital heart disease, regular/sustained VT, in the acute management of narrow and persistent wide QRS tachycardia of unknown aetiology, or SVT in pregnancy.[3]

Radiofrequency Ablation

In the event of VT storms, radiofrequency ablation may be considered.[4]

Implantable cardioverter-defibrillator

Malignant ventricular tachyarrhythmia termination via an automated implantable defibrillator was first described in 1970, and via the transvenous implantable cardioverter-defibrillator (TV ICD) in the 1990s.[1] One important advancement in modern TV ICD technology was the introduction of antitachycardia pacing (ATP) for ventricular tachycardia (VT) to reduce appropriate but painful and often unnecessary shocks.

An implantable cardioverter-defibrillator ICD is an integral part of treating patients surviving a cardiac arrest due to a ventricular arrhythmia or those deemed to be at high risk thereof.[4] According to recent Clinical Practice Guidelines in Management of Heart Failure, it can be implanted as secondary prevention in patients with documented sustained ventricular arrhythmias.[4] Antiarrhythmics drug therapy with amiodarone can be considered as adjunctive therapy in patients with ICD to reduce the number of shocks and in patients who are not candidates for ICD.[4]

The ICD should be considered in patients who fulfil the eligibility criteria, who otherwise have good clinical function and prognosis (life expectancy of more than 1 year) to improve their survival.

Criteria of patients who should be considered for ICD include[4];

- Patients resuscitated from SCD due to ventricular fibrillation or haemodynamically unstable sustained ventricular tachycardia. These cardiac arrest survivors have a high risk of recurrent events and implantation of an ICD has been shown to reduce mortality
- Patients with chronic heart failure and left ventricular ejection fraction (LVEF) ≤ 35% who experience syncope of unclear origin have a high risk of subsequent SCD.
- Patients who had prior MI and LVEF ≤ 40% with non-sustained VT and inducible sustained patients VT or VF during an electrophysiological (EP) study.

The overview of different types of ICD systems is illustrated in Figure 3[1].

	Transvenous ICD[a]	Subcutaneous ICD[b]	Extravascular ICD[c]
Lead location	Endovascular/endocardial	Parasternal (subcutaneous)	Anterior mediastinum (substernal)
Potential for cardiac injury/ perforation	Present	Absent	Present
ICD generator location	Pectoral	Left midaxillary region	Left midaxillary region
Maximum delivered energy	40 J	80 J	40 J
ATP	Available	Not available	Available
Chronic pacing therapy	Available as chronic pacing therapy	Not available	Available as short-duration pause prevention pacing
Postshock pacing	Available	Available	Available
Generator volume	33 cc	60 cc	33 cc
Generator mass	79 g	130 g	77 g

Abbreviations: ATP, antitachycardia pacing; EV ICD, extravascular implantable cardioverter-defibrillator; MRI, magnetic resonance imaging; S-ICD, subcutaneous ICD.

Figure 3: Overview of different types of ICD systems[1]

Transvenous ICD implantation may be complicated by vascular injury, cardiac perforation, pneumothorax, haemothorax, and venous obstruction as well as mechanical failure and serious infection resulting in lead extraction.[6]

The subcutaneous ICD was developed to avoid the vascular risks of transvenous ICDs. In a recent comparison with transvenous ICDs, the subcutaneous ICD (SQ ICD) effectively prevented sudden arrhythmic death with fewer complications. However, the distance of the SQ lead from the heart has resulted in an SQ ICD that does not offer antitachycardia pacing (ATP).[7] In addition, higher defibrillation energy requirements necessitate a larger generator than transvenous ICDs (60 cm^3 vs. 30 cm^3), with compromised longevity (projected life span, 7.3 years vs. 13.6 years) and potential patient comfort issues.[7]

Compared to existing commercially available subcutaneous ICDs, the EV ICD system includes a smaller device that uses lower defibrillation energy owing to its juxtaposition to the heart, which may result in longer battery life, and is able to deliver pacing therapies such as ATP and backup asystole pacing from a single device.[8]

POTENTIAL IMPACT

Systematic search was conducted from scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed and from the general search engines such as Google Scholar and US Food and Drug Administration (US FDA) on the effectiveness and safety of extravascular ICD in managing fatal arrythmia and retrieved two studies. Last evidence search was conducted on 4 October 2022.

Efficacy/effectiveness

Molnar et al conducted a multicenter, non-randomised, retrospective analysis of 45 patient CT scans quantitatively and qualitatively and results assessing bony, cardiac, vascular, and other organ structures from two human clinical studies with substernal lead placement.[8] Substernal implantation was attempted or completed in 45 patients. Defibrillation testing was successful in 37 of 41 subjects (90%) using ≥10 J safety margin. There were two intra-procedural adverse events in one patient, including

reaction to anaesthesia and an episode of transient atrial fibrillation during ventricular fibrillation induction. Anatomical factors associated with defibrillation failure included large rib cage width, myocardium extending very posteriorly, and a low heart position in the chest ($p<0.05$), though not significant adjusting for multiple comparisons. Retrospective analysis demonstrates the ability to implant within the substernal space with low intra-procedural adverse events and high defibrillation efficacy despite a wide range of anatomical variability.[8]

A recently published Extravascular ICD Pivotal Study was a prospective, global, multicenter, single-group, non-randomised, premarket approval study designed to enroll up to 400 patients at up to 60 sites.[9] After implantation, patients were followed up at 2 weeks, 3 months, 6 months, and every 6 months until study closure. Patients with a class I or IIa indication for an ICD for primary or secondary prevention according to international guidelines were recruited. Patients who required bradycardia pacing or cardiac resynchronization therapy or who had undergone sternotomy were excluded. The primary efficacy end point was successful defibrillation at implantation, defined as termination of an induced sustained shockable ventricular arrhythmia either with one 20-J shock or with 30 J on two consecutive episodes. The efficacy objective would be met if the lower boundary of the one-sided 97.5% confidence interval for the percentage of patients with successful defibrillation was greater than 88% when testing was performed with a safety margin of 10 J or more. The primary safety end point was freedom from major system- or procedure-related complications at 6 months. The safety objective would be met if the lower boundary of the one-sided 97.5% confidence interval for the percentage of patients free from such complications was greater than 79%.[9]

Among 316 patients with an implantation attempt, the lead was placed in 315 (99.7%). Defibrillation testing was initiated in 307 patients, completed in 302, and successful in 298. One device remained implanted at the physician's discretion despite incomplete electrical testing. Thus, in 316 implantation attempts, 299 patients (94.6%) underwent complete implantation and proceeded to long-term follow up. The percentage of patients with successful defibrillation was 98.7% (one-sided 97.5% confidence interval [CI], 96.6%; $p<0.001$ for the comparison with the efficacy performance goal of 88%), with 72.5% successful at 20 J and 27.5% successful at 30 J (Figure 4).

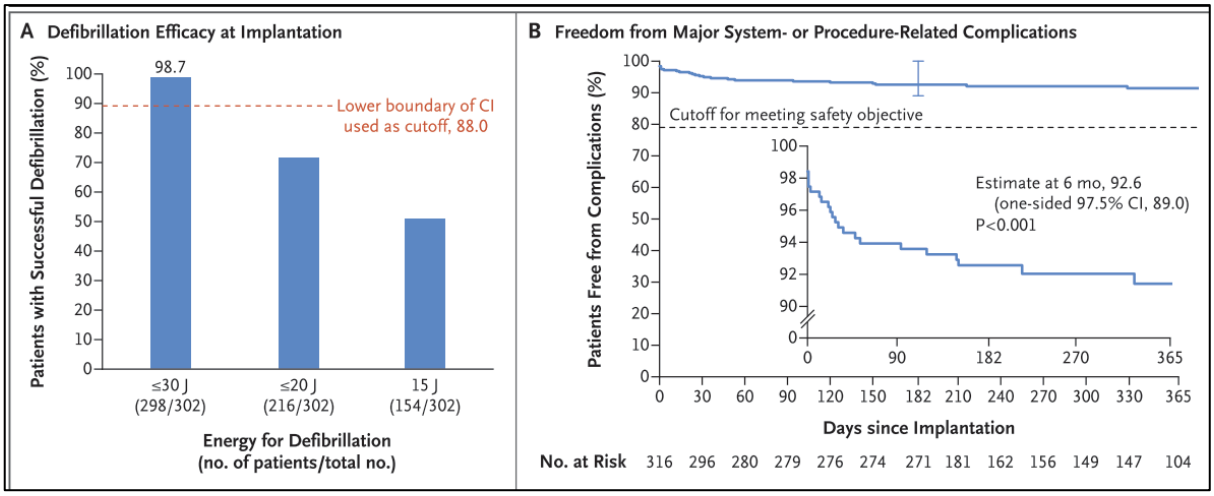

Figure 4: Defibrillation efficacy at implantation

Ventricular tachycardia or ventricular fibrillation was detected with the use of a programmed sensitivity of 0.2 mV or more (approximately 3 times the maximum sensitivity of 0.075 mV) in all 307 patients in whom defibrillation testing was initiated.[9]

Long-Term Defibrillation Testing

A total of 37 patients were enrolled in a prespecified 6-month defibrillation protocol distinct from implantation protocol.[9] Ventricular arrhythmia could not be induced in 1 patient. Among the 36 patients who completed testing, the testing was successful in all 36: 30 patients underwent defibrillation with 30 J, and 6 patients underwent defibrillation with 40 J. Additional defibrillation testing was conducted at the physician's discretion from 1 to 405 days after implantation in 18 patients, all of whom underwent defibrillation successfully with 40 J or less.[9]

Safety

Primary Safety End Point

In the same study, safety of EV ICD was also evaluated. [9] The Kaplan–Meier estimate of the percentage of patients free from major system- or procedure- related complications through 182 days was 92.6% (lower boundary of the one-sided 97.5% CI, 89.0%; $p<0.001$ for the comparison with the safety performance goal of 79%) (Figure 3b). No major intraprocedural complications were reported, and a single minor complication of muscle injury (inadvertent blunt dissection of the rectus fascia) resolved without sequelae. Through 6 months, 25 major complications were observed in 23 patients, most commonly lead dislodgement (10 events in 9 patients). No major complications had further clinical sequelae. No deaths from arrhythmia related to ineffective device therapy were reported. Through 6 months, the Kaplan–Meier estimates of the percentage of patients with major procedure-related and major system-related complications were 5.4% and 4.9%, respectively. There was one report of a device lock- up at implantation related to a software–hardware interaction that resulted in device replacement. Two lead fractures occurred, resulted from implantation below the xiphisternum and substantial unanticipated bending conditions, after more than 6 months. However, the fractures did not result in harm to patients other than the need to undergo repeat interventions.[9]

Inappropriate Therapies

Of 299 patients who underwent implantation, 29 (9.7%) received 118 inappropriate shocks for 81 arrhythmic episodes during the 10.6-month mean follow-up.[9] The median number of inappropriate shocks per patient was 2. The Kaplan– Meier estimated frequency of inappropriate shock was 8.5% at 6 months. Causes of inappropriate shocks were P-wave oversensing (34 episodes), lead noise (19), T-wave oversensing (11), atrial fibrillation or atrial flutter (10), electromagnetic interference (4), other supraventricular tachycardia or sinus tachycardia (2), and non-sustained ventricular tachycardia (1).[9]

Infection

A total of 13 system- or procedure-related infections were reported in 13 patients (4.1%) through the 10.6-month mean follow-up, 9 of which were addressed through medication with or without wound care.[9] Four infections resulted in system removal (1.3%; 26 to 188 days after implantation); all 4 infections were related to the lateral device pocket, with 2 also involving the xiphoid incision site.[9]

Cost/Cost-effectiveness

There was no retrievable evidence on cost-effectiveness of EV ICD.
However, according to an article in the National Heart Association website, the cost of the device in 2018 was between RM32,000 and RM80,000.[10]

Ethical/Societal Considerations

Ethical and legal issues have emerged related to the decision to deactivate and not performing a generator change at the end of life of a patient, where both patient and the supporting health team decide that the ICD is no longer performing a meaningful purpose for the patient. Expert consensus statements published in 2008 and 2010 by the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) stated that patients near the end of life are very likely to develop frequent arrhythmias owing to hypoxia, sepsis, heart failure, and electrolyte imbalance. The resultant ICD shocks become so frequent and uncomfortable that the harm derived from an ICD outweighs the benefits. Deactivation removes the direct therapeutic benefit of the ICD and neutralises the harm from the device. Hence, in a patient near the end of life, reprogramming or deactivating the ICD could be appropriate.

CONCLUSION

The study showed that the novel EV ICD system was safe and efficacious at 3 months for patients with life-threatening arrhythmias, with no major intraprocedural complications. The technology may offer advantages over transvenous and subcutaneous systems by avoiding placement in the heart and vasculature. However, complications at 6 months may pose safety issues. A larger scale clinical study to characterize the EV ICD system, longer duration study and in comparison, with other treatment options such antiarrhythmic drugs and other ICD systems is warranted. Furthermore, cost implication of the intervention on the health system needs to be ascertained.

EVIDENCE

Based on available evidence up to 4 October 2022

1. Molnár L, Crozier I, Haqqani H, et al. The extravascular implantable cardioverter-defibrillator: characterization of anatomical parameters impacting substernal implantation and defibrillation efficacy. EP Eur. 2022;24(5):762–73
2. Friedman P, Murgatroyd F, Boersma LVA, et al. Efficacy and Safety of an Extravascular Implantable Cardioverter–Defibrillator. N Engl J Med. 2022;387(14):1292–302. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2206485

REFERENCES

1. Thompson AE, Atwater B, Boersma L, et al. The development of the extravascular defibrillator with substernal lead placement: A new Frontier for device-based treatment of sudden cardiac arrest. J Cardiovasc Electrophysiol 2022;33(6):1085–95.
2. Medtronic Extravascular ICD meets global pivotal clinical trial's safety and

effectiveness endpoints. 28 August 2022. Available from: https://news.medtronic.com/2022-08-28-Medtronic-Extravascular-ICD-meets-global-pivotal-clinical-trials-safety-and-effectiveness-endpoints

3. Molnár L, Crozier I, Haqqani H, et al. The extravascular implantable cardioverter-defibrillator: characterization of anatomical parameters impacting substernal implantation and defibrillation efficacy. EP Eur. 2022;24(5):762–73.

4. Zeppenfeld K, Tfelt-Hansen J, Slade A, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022; Available from: https://academic.oup.com/eurheartj/advancearticle/doi/10.1093/eurheartj/ehac262/6675633

5. Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary heart disease. Circulation 2012;125:1043–1052.

6. Stecker EC, Reinier K, Marijon E, Narayanan K, Teodorescu C, Uy-Evanado A, et al. Public health burden of sudden cardiac death in the United States. Circ Arrhythm Electrophysiol 2014;7:212–217

7. Winkel BG, Holst AG, Theilade J, Kristensen IB, Thomsen JL, Ottesen GL, et al. Nationwide study of sudden cardiac death in persons aged 1–35 years. Eur Heart J 2011;32:983–990

8. Abd Rahim F, Yap Yee Guan. Sudden Cardiac Death. Malaysian J Med Heal Sci. 2008;4(2):1–10.

9. Ministry of Health Malaysia. Malaysian Clinical Practice Guidelines (CPG): Management of Heart Failure. Vol. 19. 2019. 1–158 p. Available from: https://www.malaysianheart.org/files/5d6f717e6d58e.pdf

10. Kirkfeldt RE, Johansen JB, Nohr EA, et al. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. Available from: https://academic.oup.com/eurheartj/article/35/18/1186/461882

11. Knops RE, Van Der Stuijt W, Delnoy PPHM, et al. Efficacy and Safety of Appropriate Shocks and Antitachycardia Pacing in Transvenous and Subcutaneous Implantable Defibrillators: Analysis of All Appropriate Therapy in the PRAETORIAN Trial. Circulation. 2022;145(5):321–9.

12. Friedman P, Murgatroyd F, Boersma LVA, et al. Efficacy and Safety of an Extravascular Implantable Cardioverter–Defibrillator. N Engl J Med. 2022;387(14):1292–302. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2206485

13. National Heart Association of Malaysia. Help available for those who seek it. 2008. Available from: https://malaysianheart.org/?p=highlights&a=81

14. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. Circulation 2008; 117:e350–e408.

15. Padeletti L, Arnar DO, Boncinelli L, et al. EHRA Expert Consensus Statement on the management of cardiovascular implantable electronic devices in patients nearing end of life or requesting withdrawal of therapy. Europace 2010; 12:1480–1489.

16. Wilkoff BL, Auricchio A, Brugada J, et al. HRS/EHRA Expert Consensus on the Monitoring of Cardiovascular Implantable Electronic Devices (CIEDs): description of techniques, indications, personnel, frequency and ethical considerations: developed in partnership with the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA); and in collaboration with the American College of Cardiology (ACC), the American Heart Association (AHA), the European Society of Cardiology (ESC), the Heart Failure Association of ESC (HFA), and the Heart Failure Society of America (HFSA). Endorsed by the Heart Rhythm Society, the European Heart Rhythm Association, the American College of Cardiology, the American Heart Association. Europace 2008; 10:707–725.

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