A Propensity matched case-control study comparing efficacy, safety and costs of the Subcutaneous vs. Transvenous Implantable Cardioverter Defibrillator

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ABSTRACT

Background- Subcutaneous implantable cardioverter defibrillators (S-ICD) have become more widely available. However, comparisons with conventional transvenous ICDs (TV-ICD) are scarce.

Methods and Results- We conducted a propensity matched case-control study including all patients that underwent S-ICD implantation over a five-year period in a single tertiary centre. Controls consisted of all TV-ICD implant patients over a contemporary time period excluding those with pacing indication, biventricular pacemakers and those with sustained monomorphic ventricular tachycardia requiring anti-tachycardia pacing. Data was collected on device-related complications and mortality rates. A cost efficacy analysis was performed. Sixty-nine S-ICD cases were propensity matched to 69 TV-ICD controls. During a mean follow-up of 31 ± 19 (S-ICD) and 38 ± 27 months (TV-ICD; p=0.11) there was a higher rate of device-related complications in the TV-ICD group predominantly accounted for by lead failures (n=20, 29% vs. n=6, 9%; p=0.004). S-ICD was associated with a relative risk reduction of device-related complications of 70%. The total mean cost for each group, including the complication-related costs was £9967 ± 4511 ($13,639 ± 6173) and £12601 ± 1786 ($17,243 ± 2444) in the TV-ICD and S-ICD groups respectively (p=0.0001). If the annual complication incidence rates remained constant in both groups, the cumulative cost would be balanced in five years.

Conclusions- TV-ICDs are associated with increased device-related complication rates compared to a propensity matched S-ICD group during a similar follow-up period. Despite the existing significant difference in unit cost of the S-ICD, overall S-ICD costs may not exceed TV-ICD over a longer follow-up period.

Keywords: Sudden cardiac death, Implantable cardioverter defibrillator, Lead, Device-related complications

INTRODUCTION

The implantable cardioverter defibrillator (ICD) is a well-established treatment for the prevention of sudden cardiac death (SCD) (1-3). Over 300, 000 Transvenous ICDs (TV-ICD) are implanted worldwide per annum (4). However, these devices have been associated with early and long-term complications (5-10). Device-related infection rates of between 0.67-1.49% have been reported over a three to 12 month follow-up period (5, 6, 8). Overall pooled complication rates secondary mainly to lead displacement, hematoma, pneumothorax (excluding inappropriate shocks) of 9%, are reported in randomized controlled trials (11). Long-term lead failure rates of up to 20% have been reported over a ten-year period (12). These complications are recognized to have a financial impact (13, 14).

Subcutaneous ICDs (S-ICDs) were introduced into clinical practice initially to treat those patients where venous access is not feasible due to their underlying anatomy, such as in congenital heart disease limiting the introduction of intracardiac leads, and young adults where lead longevity and the possible need of lead extraction in the future is a concern (15). Preliminary results suggest that these devices are safe and effective (16-18).

As of yet there is minimal data available directly comparing S-ICDs and TV-ICDs in terms of complication rates (19, 10). From a cost-efficacy perspective S-ICDs are initially more expensive than conventional TV-ICDs at implant. However, the impact of potential differences in long-term complication rates on the overall cost has not yet been addressed.

We conducted a propensity matched case (S-ICD)-control (TV-ICD) study with the aims to i) compare the safety and efficacy during a long-term follow-up between these two groups ii)

perform a cost efficacy analysis evaluating whether the initial implant costs are balanced by the long-term economic impact of device-related complications.

METHOD

Sample Characterization

We included all patients that underwent S-ICD implantation over a five-year period in a single tertiary center. These were defined as the cases. The controls used in the propensity match included all patients that underwent TV-ICD implantation over a contemporary period in the same centre. Patients who had a concomitant pacing indication, biventricular devices, documentation of sustained monomorphic ventricular tachycardia (VT) likely to require anti-tachycardia pacing (ATP), and advisory transvenous leads were excluded. Using electronic and paper records we collected data on baseline characteristics including age, gender, diabetes, hypertension, chronic kidney disease (defined as stage 4 or 5), and left ventricular ejection fraction (EF). Data was also collected on the underlying cardiac etiology and the indication of the ICD implant i.e. primary or secondary prevention. Propensity score matching employing the factors in table 1 and with a 1:1 ratio was used to obtain a control group of TV-ICDs and assure that S-ICDs and their contemporary controls were similar in all baseline variables. Probabilities in the S-ICD group were matched 1:1 to the best TV-ICD corresponding patient.

S-ICD procedure

Prior to S-ICD implantation all patients undergo electrocardiogram (ECG) screening to ensure suitability for a S-ICD through excluding those susceptible to T wave over-sensing. S-ICD implantation at our centre is performed under general anesthetic (GA).

Device Programming

TV-ICDs were programmed either with one or two therapy zones based on the patient's age, underlying cardiac etiology and the presence of previous ventricular arrhythmia events. ATP and shocks were programmed in the VT and ventricular fibrillation (VF) zone in TV-ICDs. Subsequent adjustments to therapies and detection zones were performed during follow-up, or following the occurrence of arrhythmic events. Supraventricular tachycardia discriminators were switched on and high-rate timeout turned off.

Follow-up and Outcomes

Data was collected on complication rates during follow-up. This included any early or late complications deemed to be related to the device. Early complications were implant-related complications i.e. those that occurred within 30 days of the first implant. Device-related infections were those necessitating removal of the ICD system and/or antibiotic treatment. Pocket hematoma were defined as those resulting in >2g/dl Haemoglobin loss and/or requiring evacuation. Lead failure was defined as those that resulted in inappropriate shocks secondary to lead noise and/or replacement of the lead. Once a patient experienced a device-related complication they were blanked from further analysis therefore follow-up was based on time to event.

Data from our local device clinic follow-up records and stored device electrograms (EGMs) during episodes of detected VT/VF, any therapy deliveries, and inappropriate shocks were analyzed by a cardiac physiologist specializing in Electrophysiology, Consultant Electrophysiologist or Senior Electrophysiology Fellow. Sustained VT episodes meeting criteria for appropriate ICD intervention were classified as either VT/VF, according to the rate and detection window where therapy was delivered. Non-sustained VT episodes that met detection

criteria and terminated before therapy was delivered were not classified as VT/VF. Patients were classified as having had appropriate shocks, if a shock was delivered during a VT or VF event. Effective ATP therapy (for TV-ICDs) was defined as overdrive ventricular pacing able to restore sinus rhythm following a VT or VF episode. An appropriate ICD intervention was classified as the presence of either an appropriate shock or an effective ATP.

The incidence of inappropriate shocks delivered due to misdetection of tachycardia (either supra-ventricular tachycardia, sinus tachycardia, atrial fibrillation, T-wave over-sensing, lead noise or artifact) was also compared between the two treatment groups.

Data regarding multiple arrhythmia episodes (either in the VT or VF zones), and appropriate ICD therapies (ATPs and appropriate shocks) in the same patient were collected, and the mean number was compared between the two groups. From 2011 onwards, home-monitoring systems (LATITUDE, CARELINK and MERLIN) became available in our Institution and were also used for follow-up purposes.

We also collected data on mortality rates in both groups particularly if any deaths were device-related.

Cost-Efficacy Analysis

A cost efficacy analysis was performed where the initial implant costs and the costs of device-related complications in each group were determined and compared. For the device-related complications we took into account the costs of repeat procedure(s) including catheterization (cath) lab usage, GA cost, procedure-related equipment costs, and the cost of the new implant and hospital stay. We also took on board the cost of the investigations performed pre and post

their repeat procedure i.e. ECGs, blood tests, blood cultures, chest x-ray, echocardiogram. As the mean procedure time and hospital stay for the initial TV-ICD and S-ICD procedure was not different in our cohort, the cost related directly to these were not taken into account when determining the cost difference between the two groups. As the S-ICDs were implanted under GA the cost related to GA was included in the implant cost. The UK Department of Health published costs for hospital stay are used by the centre in the costing of hospital stay for each patient and were thereby used in our cost calculations (20). The cost of the device and procedure-related equipment were based on the cost the centre paid directly to the manufacturer to purchase the products. The costs of the relevant investigations were obtained from the NICE guidelines on preoperative tests (21).

Statistical analysis

A propensity score was obtained for all eligible participants undergoing ICD implantation through binary logistic regression: ICD modality (TV-ICD or S-ICD) was the binary outcome and all baseline variables (table 1) were used as covariates for estimating a probability (the propensity score). Then, probabilities in the S-ICD group were matched 1:1 to the closest TV-ICD patient fulfilling inclusion criteria using the nearest neighbor matching approach. The propensity score was matched to 5 decimals whenever possible. If this was not possible, we subsequently attempted 4, 3 and then 2 decimal matching. If a S-ICD patient could not be matched to any TV-ICD subject on the second digit of the propensity score, then the S-ICD subject was discarded from the matched analysis.

Comparisons between S-ICD and TV-ICD were performed. Based on Stuart (22), analyses were performed using the groups as a whole, rather than using the individual matched pairs. Chi-square was used for the comparison of nominal variables. The student t-test, or its non-

parametric equivalent, Mann-Whitney when appropriate, was used for comparison of continuous variables; the Levene's test was used in order to check the homogeneity of variance. Cox proportional regression model was used to calculate hazard ratios for each individual device-related complication. Results with $p<0.05$ were regarded as significant.

Kaplan-Meier curves were traced for comparing survival free from device-related complications among the two treatment groups. For the purpose of time to event analysis only time to first event was considered, the patients were censored after their first event. SPSS (IBM SPSS Statistics, Version 20 IBM Corp, Armonk, NY, USA) was used for descriptive and inferential statistical analysis.

RESULTS

A total of 69 patients underwent S-ICD implantation between 2010-2015. A total of 429 patients underwent TV-ICD implantation over a contemporary time period. Following propensity matching 69 of these were matched to the S-ICD group. Baseline characteristics of these two groups are demonstrated in table 2.

Device programming

In the TV-ICD group 22 patients had a single VF zone programmed whilst the remaining 47 patients had an additional VT therapy zone. On average the VT therapy zone started at 176 ± 14 beats per min (bpm). S-ICDs were programmed with a SVT discriminator zone at 180-220bpm and a VF therapy zone at >220 bpm.

Device therapy

In the TV-ICD group five patients had an appropriate ICD therapy (n=4 ICD shocks for VT/VF and n=1 ATP for VT). In the TV-ICD group the device failed to cardiovert VT in one patient and as a result they were externally cardioverted, followed by having the generator changed to a high-energy generator. In the S-ICD group three patients had an appropriate shock for VT/VF. In one patient the S-ICD failed to cardiovert VT that then spontaneously terminated. The patient had the S-ICD device extracted and had a TV-ICD system implanted.

Device-related complications (table 3 and 4)

During a mean follow up of 38 ± 27 months there was a total of 20 device-related complications in 20 patients, including inappropriate shocks, in the TV-ICD group (29%). Figure 1 shows the distribution of the causes for the device-related complications in each group. When excluding inappropriate shocks there were a total of 14 device-related complications (20%). The most common device-related complications in the TV-ICD group were lead-related affecting six patients (9%). Lead-related complications were predominantly due to lead fractures or insulation defects (3/6, 50%). Lead-related complications resulted in the ICD lead being explanted and a new ICD lead being implanted in five out of the six cases. This was performed under GA in all five cases. In the TV-ICD group, one patient also experienced atrial lead displacement within two months of implant and required repositioning of the atrial lead. This was not included when comparing device-related complications between TV-ICD vs. S-ICDs. During a mean follow-up 31 ± 19 months there were a total of six device-related complications in the S-ICD group (10%) that was predominantly made up of inappropriate shocks (n=3, 4%).

There were two implant-related complications (<30 days) in the TV-ICD group whilst no implant-related complications were seen in the S-ICD group.

Device-related infections occurred in both groups that required generator and lead extraction and implantation of a new system (TV-ICD n=4 vs. S-ICD n=1; p=0.37). There were no associated complications from the device extraction.

A total of six inappropriate shocks occurred in the TV-ICD group versus three in the S-ICD group (9% vs. 3%; p=0.49). The reasons for the inappropriate shocks are demonstrated in table 3. Three out of the six inappropriate shocks in the TV-ICD group occurred in patients that had two therapy zones programmed (3/47 vs. 3/22; p=0.37). Inappropriate shocks in the S-ICD group were all due to T wave over-sensing in sinus rhythm and were effectively managed by changing the sensing vector.

One of the patients in the TV-ICD group underwent a S-ICD implant following transvenous system extraction due to device-related systemic infection. In the S-ICD group one patient had a TV-ICD implanted following S-ICD extraction as it failed to cardiovert haemodynamically tolerated VT.

When comparing the device-related complications between TV-ICD and S-ICD including inappropriate shocks, there were significantly more complications seen in the TV-ICD group (n=20, 29% vs. n=6, 9%; p=0.004). This was also the case when excluding all inappropriate shocks (n=14, 20% vs. 3, 4%; p=0.008) and excluding inappropriate shocks in those in the TV-ICD group with two-therapy zone programmed (n=17, 25% vs. n=6, 9%; p=0.021). The S-ICD group had a significantly lower risk of device-related complications compared to the TV-ICD group (HR 0.30, 95% CI 0.12-0.76; p=0.01). There was a 70% relative risk reduction (RRR) of device-related complications in the S-ICD group compared to the TV-ICD group. The Kaplan Meier curves show that in the S-ICD group, there was a higher rate of survival free from device-

related complications during follow-up (figure 2; HR=2.78; 95%CI 1.10-7.01, P=0.031). There were no deaths in either group.

Cost efficacy analysis

The initial implant costs and the costs related to device complications are demonstrated in table 5. The mean device-related complication cost was significantly higher in the TV-ICD group (£7281 ± 4972 ($9963 ± 6804) TV-ICD vs. £2896 ± 1833 ($3963 ± 2508) S-ICD; p=0.0027). The overall mean cost per patient including initial implant and complication costs was £12601 ± 1786 ($17,243 ± 2444) for S-ICD and £9967 ± 4511 ($13,639 ± 6173) for TV-ICD (p=0.0001). Assuming the annual complication incidence rates remained constant in both groups, the cumulative cost related to TV-ICDs would be balanced over the next five years (TV-ICD £91774 ($121,252) vs. S-ICD £903125 ($119,3213)) with a possible increased cost of £212 ($279) per patient in the TV-ICD group.

DISCUSSION

This is the first propensity-matched case-control study comparing both complication rates and cost between S-ICD and TV-ICD. We conclude that there was a significant increase in device-related complication in the TV-ICD group compared to the S-ICD group with S-ICDs being associated with a 70% RRR in device-related complications. Furthermore, despite the significant difference in unit cost of the S-ICD (i.e. the S-ICD is initially more expensive), the overall S-ICD costs tend to balance with those of the TV-ICD over a longer period of follow-up.

In the TV-ICD group the most common complication encountered was lead-related (n=6, 9%) and this resulted in the need for lead replacement and removal of the existing lead in majority of cases (5/7, 71%), suggesting the ICD lead is truly the Achilles' heel of the system (23). Further

to this, three patients had suspected lead fractures (4.3%). It has been demonstrated that lead failure rates are higher in younger patients (24, 25), which correlated with our findings as these patients were in the younger age group in our cohort.

The most frequent complication in the S-ICD group was inappropriate shocks due to T wave over-sensing in sinus tachycardia. The rates of inappropriate shocks in our cohort was lower than that reported in previous studies (4% vs. 7-13%) (17, 18). In all cases of inappropriate shocks we were able to prevent any further recurrence through altering the sensing vector. It has been shown that patients with TV-ICDs with two therapy zones programmed experience higher rates of inappropriate shocks (26-28). However, in our cohort there was no significant difference in inappropriate shock rates in those with single or two-therapy zones programmed (p=1.00). The inappropriate shock rates in those with single treatment zone programming were similar to that of already published data (27, 28). When excluding, from the TV-ICD group those with inappropriate shocks and two-therapy zone programming, the device-related complications were still significantly higher in the TV-ICD group compared to the S-ICD group (p=0.021).

Device-related complications add an extra £145,609 ($199, 251) to the total cost associated with TV-ICDs. Despite this there was an excess cost of £2,634 ($3604) per patient in the S-ICD group. However, it can be argued that paying this additional cost to achieve a 70% RRR in device-related complications and thereby minimizing patient morbidity is a justified investment. Furthermore, the risk of lead failure increases as the transvenous lead ages (24) and therefore it is likely that the costs related to complications will increase with time in the TV-ICD group (i.e. it is likely that our analysis was a best case scenario for TV-ICDs). If the incidence rate of device-related complications remains stable over the next five years we would not expect a cost difference between these two groups with the further caveat the S-ICD generator change pocket

complications such as infection are equivalent to TV-ICD and there are no long-term S-ICD lead complications.

In this study we excluded all patients that had any pacing requirement and those with sustained monomorphic VT requiring ATP. Further to this, one of the patients in the S-ICD group had their system extracted as it failed to terminate ventricular arrhythmia and went on to have a TV-ICD implanted. In the TV-ICD group one patient had their ICD system extracted due to systemic infection and went on to have a S-ICD implanted. This does emphasize the importance of careful patient selection in ICD device prescription.

Limitations

This is a propensity-matched study over a relatively short time frame of around 30 months and therefore additional unforeseen events may develop over a longer time frame that could influence these findings. The majority of the patients in this cohort had hypertrophic cardiomyopathy reflecting the S-ICD population at our centre in the early phases of S-ICD use, and therefore the findings may not be transferable to the general ICD population. Every attempt was made to match patients with single chamber ICDs, which was achieved in 72% of cases. Since only one patient had an atrial lead displacement, the utilization of a dual chamber ICD did not significantly affect the findings in terms of lead complications. Costs may vary between nations and reimbursement structures but this analysis provides an indication of the relative differences between the two devices and could be adjusted accordingly depending on individual local reimbursement structures.

CONCLUSION

We have demonstrated that the device-related complication rates associated with TV-ICDs are higher than that of S-ICDs. We have further shown that there is no significant difference in inappropriate shock rates between these two groups. Despite there being a significant difference in unit cost of the S-ICD, overall S-ICD costs may not exceed TV-ICD over a longer period of follow-up. This will need to be further evaluated in a randomized controlled study.

DISCLOSURES

Nothing to declare

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Table 1- Shows the factors that were used in the propensity match

Factors used in the propensity matching
Age
Gender
Diabetes
Hypertension
Chronic kidney disease
Left ventricular ejection fraction
Cardiac aetiology
Indication i.e. primary or secondary prevention

Table 2- Demonstrates the baseline characteristics of the patients in the S-ICD and TV-ICD group

Baseline characteristics used in propensity match	**S-ICD n=69**	**TV-ICD n=69**	**p- value**
Age mean ± SD	35 ±13	40 ±10	0.17
Male n (%)	52 (75)	52 (75)	1.00
DM n (%)	0	0	
Hypertension n (%)	6 (9)	4 (6)	0.74
CKD n (%)	1 (1)	1 (1)	1.00
Aetiology n (%)			
Ischaemic cardiomyopathy	6 (9)	5 (7)	1.00
Dilated cardiomyopathy	4 (6)	5 (7)	1.00
Hypertrophic cardiomyopathy	41 (59)	42 (61)	1.00
Arrhythmogenic right ventricular cardiomyopathy	7 (10)	6 (9)	0.79
Idiopathic ventricular fibrillation	6 (9)	6 (9)	1.00
Brugada Syndrome	4 (6)	4 (6)	1.00
Congenital heart disease	1 (1)	1 (1)	1.00
Indication n (%)			
Primary prevention	56 (81)	56 (81)	1.00
Secondary prevention	13 (19)	13 (19)	1.00
Left ventricular ejection fraction mean ± SD	57 (±15)	58 (±13)	0.80
EF ≤35 n (%)	12 (17)	7 (10)	0.32
EF 36-44 n (%)	1 (1)	5 (7)	0.21
EF 45-54 n (%)	4 (6)	3 (4)	1.00
EF ≥ 55 n (%)	51 (74)	54 (78)	0.69

Table 3- Shows the device-related complications in each group during follow-up

Device related complications during follow-up	**TV-ICD n=69**	**S-ICD n=69**	**p-value**
Mean follow up ± SD	32 ± 21	31 ± 19	.....
Total number of complications including inappropriate shocks n (%)	20 (29.0)	6 (8.7)	**0.004**
Total number of complication excluding inappropriate shocks n (%)	14 (20.2)	3 (4.3)	**0.008**
Total number of complication excluding inappropriate shocks in those with two therapy zones programmed n (%)	17 (23.2)	6 (8.7)	**0.021**
Implant-related complications (<30 days) n (%)	2 (2.9)	0	0.24
Right ventricular lead perforation resulting in tamponade	1 (1.4)	0	1.00
Right ventricular lead displacement	1 (1.4)	0	1.00
Device infection n (%)	4 (5.8)	1 (1.4)	0.37
Generator and leads explanted	4 (5.8)	1 (1.4)	0.37
ICD generator-related complications n (%)	1 (1.4)	1 (1.4)	1.00
Generator displacement requiring repositioning	0	1 (1.4)	1.00
Wound revision	1 (1.4)	0	1.00
ICD lead-related complications resulting in lead intervention n (%)	6 (8.7)	0	**0.028**
Drop in RV sensing +/-resulting in T wave oversensing	2 (2.9)	0	0.50
Raised RV threshold with suspected micro-displacement	1 (1.4)	0	1.00
Lead fracture or lead insulation defect	3 (4.3)	0	0.12
Device failed to cardiovert ventricular arrhythmia n (%)	1 (1.4)	1 (1.4)	1.00
Generator replaced to a high energy box	1 (1.4)	0	1.00
Inappropriate shocks n (%)	6 (8.7)	3 (4.3)	0.49
Sinus tachycardia	2 (2.9)	0	0.50
Atrial tachycardia	1 (1.4)	0	1.00
Atrial fibrillation	3 (4.3)	0	0.24
T wave-oversensing in context of sinus tachycardia	0	3 (4.3)	0.24

Table 4- Demonstrates the incidence rate per 100 person-year and hazard ratios in S-ICD and TV-ICD groups

	S-ICD n=69	TV-ICD n=69	HR	p-value
Total device-related complications excluding implant-related				
Incidence rate* (95% CI)	45.4 (22.8-70.1)	55.6 (38.8-71.2)	0.30 (0.12-0.76)	**0.01**
Device infection				
Incidence rate* (95% CI)	48.9 (9.2-90.0)	74.3 (34.3-94.2)	0.02 (0-220.24)	0.42
ICD generator-related complications				
Incidence rate* (95%CI)	45.5 (8.6-88.2)	44.1 (8.3-87.4)		0.61
ICD lead-related complications				
Incidence rate* (95% CI)	0	48.8 (24.7-73.5)		N/A
Device failed to cardiovert ventricular arrhythmia				
Incidence rate* (95% CI)	68.3 (13.3-97.0)	71.0 (13.9-97.4)		0.61
Inappropriate shock				
Incidence rate* (95% CI)	35.4 (12.5-66.0)	54.0 (27.7-78.3)	0.34 (0.07-1.71)	0.19

* Per 100 person-year

Table 5- Demonstrates the initial implant costs and the costs associated with the complications seen during follow up in each group

	TV-ICD n=69	**S-ICD n=69**	**p-value**
Median hospital stay, days (range)	1 (1-9)	1 (1-9)	1.00
Total initial implant cost including GA cost £ ($)	542, 085 (741,789)	852,150 (116,6082)	
Total device-related complication costs £ ($)	145,609 (199, 251)	17,381 (23, 784)	
Hospital stay	42,139 (57, 663)	2181 (2984)	
Procedure-related costs*	46,250 (63, 289)	3200 (4378)	
Generator and/or lead replacement	57,220 (78, 300)	12,000 (16,421)	
Total overall cost £ ($)	687, 694 (941, 040)	869, 531 (118,9866)	
Mean cost of a device-related complication £ ($)	7281 ± 4972 (9963 ± 6804)	2896 ± 1833 (3963 ± 2508)	**0.0027**
Mean cost per patient £ ($)	9967 ± 4511 (13,639 ± 6173)	12,601 ± 1786 (17,243 ± 2444)	**0.0001**

* Including pre and post procedural investigations, cath lab time, GA and equipment costs

FIGURE LEGEND

Figure 1- Pie charts demonstrating the device-related complications seen in the S-ICD and TV-ICD group during follow-up.

Figure 2- Kaplan Meier survival curves demonstrating the survival free from device-related complications in the S-ICD and TV-ICD group.