Received: 25 April 2024 | Revised: 16 November 2024 | Accepted: 9 December 2024

DOI: 10.1002/joa3.13204

ORIGINAL ARTICLE

Journal of Arrhythmia Open Access WILEY

Management of patients following implantable cardioverter-defibrillator therapy—The importance of a multifaceted approach

Karshana Selvarajah MSc[1] | Parisha Khan MSc[1] | Nishat Jahagirdar Pgdip[1] | Antonio Cannatà MD[1,2] | Rahul Mukherjee MBBS, PhD[1] | Daniel I. Bromage MBChB, PhD[1,2] | Theresa McDonagh MD[1,2] | Francis Murgatroyd MA, FRCP[1] | Paul A. Scott DM, FRCP[1]

[1]Department of Cardiology, King's College Hospital NHS Foundation Trust, London, UK

[2]School of Cardiovascular Medicine and Sciences, King's College London, London, UK

Correspondence
Parisha Khan, Department of Cardiology, King's College Hospital, Suite 6, Golden Jubilee Wing, Denmark Hill, London SE5 9RS, UK.
Email: khan_parisha81@hotmail.co.uk

Funding information
Abbott Fund

Abstract

Background: The most effective way to treat patients following a first ICD therapy is unclear. We hypothesised that following first ICD therapy, combining different treatment strategies would be associated with a reduction in the risk of subsequent therapy compared to single strategies alone.

Methods: Data was collected from consecutive patients undergoing ICD implantation at King's College Hospital between January 2009 and December 2019. We assessed the use of 7 specific treatment strategies, introduced after the 1st therapy—start/increase the dose of beta-blockers, prognostic heart failure medications, antiarrhythmic drugs as well as ICD reprogramming, ablation, ICD upgrade/revision and coronary revascularisation. We evaluated the association between these treatment strategies and the risk of a subsequent ICD therapy.

Results: During a mean 50 months follow-up, 267 patients experienced 1st ICD therapy (212 appropriate and 55 inappropriate). Combining treatment strategies was associated with a significant reduction in the risk of subsequent therapy for appropriate therapy compared to 0/7 strategies (1st appropriate ICD therapy, 1/7 treatment strategy ($n=80$), 43% lower risk and ≥2/7 treatment strategies ($n=73$) 58% reduction, $p=<.001$). This was also true for inappropriate therapy (1st inappropriate therapy, 1 treatment strategy ($n=22$) 86% lower risk and ≥2/7 treatment strategies ($n=25$), 94% reduction, $p<0.001$) compared to patients with 0/7 treatment strategies ($n=8$).

Conclusion: An approach combining treatment strategies may be more effective than using single strategies alone to prevent subsequent therapy in patients presenting following a 1st ICD therapy.

KEYWORDS
anti-tachycardia pacing, implantable cardioverter-defibrillator, supra, ventricular fibrillation, ventricular tachycardia

1 | INTRODUCTION

Implantable cardioverter defibrillators (ICDs) prevent sudden cardiac death (SCD) by delivering either anti-tachycardia pacing (ATP) or shock therapy. However, although often lifesaving, this ICD therapy can have a range of detrimental effects.[1,2] When a patient presents following their first ICD therapy, the risk of a subsequent ICD therapy is elevated. Therefore, one of the critical aspects of managing these patients is preventing future ICD therapy, especially shocks. A range of different treatment options may reduce the risk of subsequent ICD therapy, including optimisation of ICD programming, anti-arrhythmic drug therapy, treatment of the underlying substrate and ablation.[3] These treatment strategies are relatively diverse, reflecting the complex pathophysiology underlying arrhythmogenesis in ICD recipients.

We hypothesised that in patients presenting following their first ICD therapy, combining different treatment strategies would be associated with a reduction in the risk of subsequent therapy compared to using single strategies alone.

2 | METHODS

2.1 | Study population

This was a single-centre, retrospective cohort study. Details of the study population have been published previously.[4] We included consecutive patients who received a first transvenous ICD or Cardiac Resynchronisation Therapy—Defibrillator (CRT-D) for any indication between January 2009 and December 2019 at King's College Hospital (KCH), London, a regional cardiothoracic centre.

The study was approved by the institutional review board at our centre. All patients received devices based on national guidelines at the time of implant. The choice of device/lead manufacturer and device type was at the discretion of the implanting physician.

2.2 | Device programming

Standardised implant programming guidelines were introduced in our centre in October 2013. Although guideline compliance was encouraged, it was not mandated, and the final programming decisions were at the discretion of the implanting physician. Prior to this, programming was at the discretion of the implanting physician.

Our programming guidelines have been published in detail previously.[4] The guidelines were based on generic programming and incorporated the use of high detection rates, long detection times and ATP programmed "on" for all ventricular tachyarrhythmia detection zones where available.

2.3 | Study follow up and data collection

Our institution adopted the national British Heart Rhythm Society (BHRS) guideline recommendation for ICD follow-up.[5] Following implantation, there was an acute follow-up phase at 6 weeks and 3 months. Thereafter, to ensure patients were followed up at regular intervals, automatic transmissions were scheduled via remote monitoring every 3 months in conjunction with an annual clinic visit.

Data collection was performed by retrospective review of medical and device records for baseline characteristics and follow-up data. Evaluation of arrhythmia was based on stored device electrograms as assessed by two highly specialised Cardiac Physiologists.

2.4 | Patient management following ICD therapy

After the implant, patients were educated to seek acute medical advice following a shock by either calling emergency services, presenting to the hospital emergency department, or contacting the clinic via a dedicated emergency contact number. In addition, patients were contacted if ICD therapy was noted on a remote transmission.

Following the occurrence of ICD therapy, patients were reviewed. The timing and location of this review depended on the clinical scenario. Patients presenting with a shock were usually reviewed by a cardiologist within 24 h of notification of the shock, whereas patients receiving ATP alone were not necessarily reviewed so rapidly. Patients experiencing multiple shocks were usually managed as an inpatient, whereas patients presenting with single shocks or ATP alone were often managed in the outpatient setting.

At the clinical review management changes were made, including device reprogramming and medication changes, and the option of a procedure discussed. During the study period, there were no departmental guidelines for the management of patients post ICD therapy and management was at the discretion of the clinical team.

We assessed the treatment of patients following their first ICD therapy. We evaluated 7 specific treatment strategies. These were chosen based on published data demonstrating their association with a reduction in SCD or ventricular arrhythmias:

1. Start/increase the dose of beta-blocker[6]
2. Start/increase the dose of non-betablocker prognostic heart failure (HF) medication (angiotensin-converting enzyme inhibitor

(ACE-I), angiotensin receptor blocker (ARB), sacubitril/valsartan or mineralocorticoid receptor antagonist (MRA))[6]
3. Start/increase the dose of antiarrhythmic drugs (AAD; sotalol or amiodarone)[7]
4. ICD reprogramming[8]
5. Ablation (ventricular ablation following appropriate therapy and atrial/AV node ablation after inappropriate therapy)[9]
6. ICD upgrade/revision (new atrial, RV or LV lead)[10]
7. Coronary revascularisation[11]

For the purposes of this analysis, 1st ICD therapy refers to any device therapy occurring prior to the clinical review. This includes patients that received multiple treatments for the same arrhythmia episode (e.g., multiple rounds of ATP and then a shock) or multiple arrhythmia episodes (e.g., multiple episodes of an arrhythmia treated with ATP or a shock). A subsequent ICD therapy refers to any device therapy occurring after the clinical review.

2.5 | End points

The study endpoint was the occurrence of a subsequent ICD therapy following the occurrence of the 1st ICD therapy. We performed separate analyses for appropriate therapy and inappropriate therapy. For patients whose 1st ICD therapy was appropriate, the primary endpoint was a subsequent appropriate ICD therapy. For patients whose 1st ICD therapy was inappropriate, the primary endpoint was a subsequent inappropriate ICD therapy.

2.6 | Statistical analysis

Categorical variables are expressed as percentages (numbers) and continuous variables that are not normally distributed are expressed as median (lower quartile to upper quartile).

We evaluated the association between the 7 different treatment strategies introduced following the occurrence of the 1st ICD therapy and the risk of a subsequent ICD therapy in Cox proportional hazard regression models. We performed separate analyses for appropriate and inappropriate therapy.

For appropriate therapy, we performed both univariable and multivariable analyses. For the multivariable analysis, we adjusted for baseline variables associated with the occurrence of a 1st appropriate ICD therapy and variables likely to influence treatment (age, indication, aetiology, type of device and pre or post programming). The number of variables in the multivariable analysis was limited given the number of patients reaching the end-point for this analysis ($n=113$).

For inappropriate therapy, given the small number of patients experiencing the endpoint of a subsequent inappropriate therapy ($n=18$), we performed only univariable analyses.

To evaluate the benefit of combining different treatment strategies, we divided the patients into 3 groups based on how many of the 7 treatment strategies were introduced following their 1st ICD therapy: 0/7 treatments, 1/7 treatments or ≥2/7 treatments. We performed separate analyses for appropriate and inappropriate therapy. We also performed separate analyses for the endpoints of any therapy (ATP or shock) and shock only. We evaluated the relationship between these groups and the occurrence of a subsequent ICD therapy in univariable Cox proportional hazard regression models. We then performed adjusted analyses, with adjustments as per the previous analyses.

Kaplan–Meier curves were created for the study endpoints with patients grouped by treatment group. Separate analyses were performed for appropriate and inappropriate therapy. Groups were compared using the log-rank test.

We also evaluated the association between combining different treatment strategies and the risk of a subsequent mortality in Cox proportional hazard regression models. For this analysis, we combined appropriate and inappropriate therapy and performed unadjusted and adjusted analysis (for baseline variables likely to be associated with mortality).

In all analyses with the end-point of ICD therapy, cases were censored following the occurrence of any ICD therapy other than the therapy of interest for that analysis, as treatment received for one therapy type may influence the risk of other therapy types (i.e., in the appropriate ICD therapy analysis, patient were censored if they experienced inappropriate therapy). In addition, the occurrence of death, device explant and transfer to another institution were considered censoring events. Assumptions of proportional-hazards modelling were evaluated and were found to be valid. All tests were two-tailed and a p-value <0.05 was considered significant. The SPSS 27.0 software package was used to conduct the statistical analysis.

3 | RESULTS

3.1 | Patient characteristics

There were 1230 new ICD/CRTD patients registered at KCH during the study period. After the exclusion of patients where the original ICD was implanted at another institution ($n=122$), implanted pre-2009 ($n=86$) or was a S-ICD ($n=19$), 1003 patients were left for analysis (Figure 1 and Table 1).

3.2 | Details of first ICD therapy

During a mean follow-up of 50 +/−35 months, 276 (27.5%) patients experienced device therapy. Using survival analysis, the rates of appropriate ICD therapy at 1, 3 and 5 years were 12.7%, 21.8% and 29.3%, and appropriate shock 6.3%, 12.6% and 17.0%. The rates of inappropriate ICD therapy at 1, 3 and 5 years were 3.9%, 7.2% and 9.8%, and inappropriate shock 3.1%, 4.8% and 5.9%.

In 9/276 (3.3%) patients, the notes relating to their clinical review post first ICD therapy were not available (1 appropriate and 8 inappropriate therapy), and they were excluded from the analysis (Figure 1). This left 267 patients who experienced ICD therapy

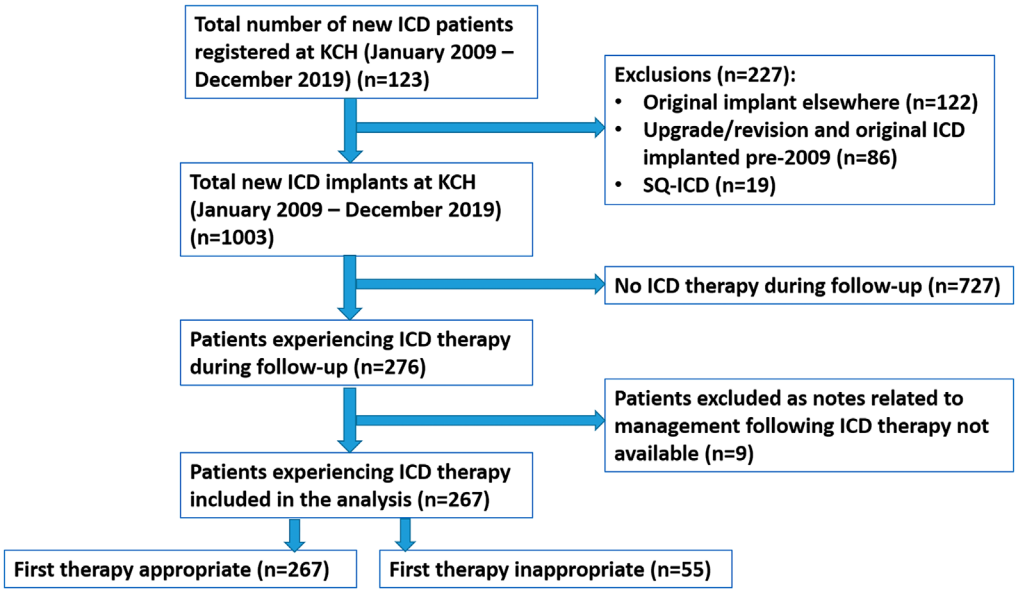

FIGURE 1 Derivation of the study population.

included in the analysis, 212 whose first therapy was appropriate and 55 whose first therapy was inappropriate (Table 1).

3.3 | Risk of subsequent ICD therapy follow first ICD therapy

3.3.1 | Appropriate therapy

During a mean follow-up of 37+/−36 months following the first appropriate therapy, 113/212 patients had a subsequent appropriate ICD therapy, of which 66 had an appropriate shock. Using survival analysis, the rates of a subsequent appropriate ICD therapy at 1, 3 and 5 years following the first appropriate therapy were 26.4%, 43.1% and 54.6% and a subsequent shock 13.6%, 20.0% and 28.5%. The rate of appropriate therapy was significantly higher following a first appropriate ICD therapy that at initial implant (113/212, 53.3% vs. 212/1003, 21.1%; $p = <.001$). This was also true for the rate of inappropriate therapy (18/55, 32.7% vs. 55/1003, 5.5%, $p = <.001$).

Of patients whose first appropriate therapy was successfully treated with ATP alone ($n = 111$), the risk of a subsequent appropriate shock at 1, 3 and 5 years was 13.0%, 19.2% and 24.2%. Using Kaplan–Meier analysis, there was no difference in the risk of a subsequent shock between patients whose initial therapy was ATP alone compared to those that received a shock (1-year risk of appropriate shock 13.0% vs. 14.3% respectively, $p = .14$).

3.3.2 | Inappropriate therapy

During a mean follow-up of 44+/−43 months following the first inappropriate therapy, 18/55 patients had a subsequent inappropriate ICD therapy, of which 15 had an inappropriate shock. Using survival analysis, the rates of subsequent inappropriate ICD therapy at 1, 3 and 5 years following a first inappropriate therapy were 21.5%, 30.9% and 35.0% and subsequent shock 19.8%, 25.1% and 29.3%.

Using Kaplan–Meier analysis, there was no difference in the risk of a subsequent shock between patients whose initial therapy was ATP alone ($n = 14$) compared to those that received an inappropriate shock ($n = 41$) (15.6% vs. 21.0% respectively, $p = .93$).

3.4 | Management of patients following first icd therapy

3.4.1 | Appropriate therapy

Of the 212 patients whose first ICD therapy was appropriate, 59 (27.8%) had none of the 7 therapeutic interventions we evaluated, 80 (37.7%) had one and 73 (34.4%) had two or more (Table 4). Patients whose first appropriate ICD therapy was treated with a shock ($n = 101$) were more likely to have a greater number of interventions introduced than patients whose first ICD therapy was treated with ATP alone ($n = 111$) (<0.001) (Table 2).

In uni- and multivariable analyses, individually none of the 7 therapeutic interventions was associated with a significant reduction in the risk of a subsequent appropriate ICD therapy (ATP or shock) (Table 3). Analysing ICD and CRT-D devices separately gave similar results. Furthermore, when we excluded patients with hypertrophic cardiomyopathy (HCM) or channelopathy, the results were similar.

3.4.2 | Inappropriate therapy

Of the 55 patients whose first ICD therapy was inappropriate, 8 (14.5%) had none of the 7 therapeutic interventions we evaluated introduced, 22 (40.0%) had one and 25 (45.5%) had two or more. Patients whose first inappropriate ICD therapy was treated with a

TABLE 1 Baseline Characteristics of patients included in the study. Patients are grouped by type of 1st ICD therapy.

		Any device therapy ($n = 267$)	
Variable, *n* (%)	**Total ($n = 1003$)**	**1st therapy appropriate ($n = 212$)**	**1st therapy inappropriate ($n = 55$)**
Age, yrs.	66.0 (59.0–76.0)	67.0 (58.0–75.0)	65.0 (55.0–74.0)
Gender, Male	788 (78.6)	182 (85.8)	43 (78.2)
Indication			
Primary	583 (58.1)	81 (38.2)	27 (49.1)
Secondary	420 (41.9)	131 (61.8)	28 (50.9)
Aetiology			
IHD	606 (60.4)	129 (60.8)	35 (63.6)
NIDCM	231 (23.0)	50 (23.6)	15 (27.3)
HCM	40 (4.0)	6 (2.8)	2 (3.6)
Channelopathies	33 (3.3)	8 (3.8)	2 (3.6)
Other	93 (9.3)	19 (9.0)	1 (1.8)
LVEF			
<35	695 (69.3)	129 (60.8)	30 (54.5)
35–50	172 (17.1)	55 (25.9)	15 (27.3)
>50	136 (13.6)	28 (13.2)	10 (18.2)
QRS duration, ms			
<120	526 (52.4)	114 (53.8)	25 (45.5)
121–149	261 (26.0)	60 (28.3)	17 (30.9)
>150	216 (21.5)	38 (17.9)	13 (23.6)
Co-morbidities			
COPD	57 (5.7)	10 (4.7)	6 (10.9)
CKD	79 (7.9)	14 (6.6)	5 (9.1)
Diabetes	237 (23.6)	51 (24.1)	15 (27.3)
Hypertension	264 (26.3)	70 (33.0)	16 (29.1)
PVD	21 (2.1)	5 (2.4)	0 (0.0)
History of atrial arrhythmias	329 (32.8)	70 (33.0)	29 (52.7)
Discharge medication			
ACE or ARB	744 (74.2)	151 (71.2)	38 (69.1)
Amiodarone	111 (11.1)	32 (15.1)	7 (12.7)
Beta blockers	867 (86.4)	192 (90.6)	48 (87.3)
Diuretics	573 (57.1)	104 (49.1)	21 (38.2)
Mineralocorticoid Receptor	217 (21.6)	35 (16.5)	10 (18.2)
Device type			
VR ICD	323 (32.2)	66 (31.1)	18 (32.7)
DR ICD	270 (26.9)	84 (39.6)	25 (45.5)
CRT	410 (40.9)	62 (29.2)	12 (21.8)
Pre or post programming[a]			
Pre	504 (50.2)	147 (69.3)	40 (72.7)
Post	499 (49.8)	65 (30.7)	15 (27.3)

Note: Data are presented as median (Q1-Q3) or *n* (%).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, Cardiac resynchronisation therapy; DR, Dual chamber; HCM, Hypertrophic cardiomyopathy; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; NIDCM, non-ischaemic dilated cardiomyopathy; PVD, peripheral vascular disease; VR, Single chamber.

[a]Post, device implanted following introduction of standardised ICD programming guidelines in Oct 2013; pre, device implanted prior to introduction of standardised ICD programming guidelines.

TABLE 2 Treatment of patients following the occurrence of 1st ICD therapy. Patients are grouped by whether 1st therapy was appropriate or inappropriate, and whether it was treated by ATP only or a shock.

	Treatment following 1st appropriate therapy				Treatment following 1st inappropriate therapy			
Treatment strategy, *n* (%)	Any therapy (*n* = 212)	ATP only (*n* = 111)	Shock (*n* = 101)	*p* value ATP vs. shock	Any therapy (*n* = 55)	ATP only (*n* = 14)	Shock (*n* = 41)	*p* value ATP vs. shock
Betablocker started/increased	71 (33.5)	34 (30.6)	37 (36.6)	.384	26 (47.3)	4 (28.6)	22 (53.7)	.130
Prognostic HF medication started/increased	44 (20.8)	18 (16.2)	26 (25.7)	.093	15 (27.3)	3 (21.4)	12 (29.3)	.734
AADs started/increased	64 (30.2)	19 (17.1)	45 (44.6)	<.001	11 (20.0)	1 (7.1)	10 (24.4)	.255
ICD Reprogramming	52 (24.5)	23 (20.7)	29 (28.7)	.202	22 (40.0)	4 (28.6)	18 (43.9)	361
PCI	6 (2.8)	3 (2.7)	3 (3.0)	1.000	0 (0.0)	0 (0.0)	0 (0.0)	–
Device upgrade	3 (1.4)	2 (1.8)	1 (1.0)	1.000	0 (0.0)	0 (0.0)	0 (0.0)	–
VT ablation	14 (6.6)	1 (0.9)	13 (12.9)	<.001	–	–	–	–
Atrial/AV node ablation	–	–	–	–	3 (5.5)	0 (0.0)	3 (7.3)	0.562

Abbreviations: AV node, atrioventricular node; AAD, anti-arrhythmic drugs; HF, heart failure; PCI, percutaneous coronary intervention; VT, ventricular tachycardia.

TABLE 3 Cox-regression models evaluating the association between the management of patients following 1st ICD therapy and the risk of a subsequent ICD therapy. Separate analyses are performed for appropriate and inappropriate therapy. For the appropriate therapy analysis, the end-point is any appropriate therapy (ATP or shock). For the inappropriate therapy analysis, the end-point is any inappropriate therapy (ATP or shock). For the inappropriate therapy analysis, only univariable analyses was performed given the small number of patients reaching the end-point (*n* = 18).

	Appropriate therapy (*n* = 212)				Inappropriate therapy (*n* = 55)	
	Unadjusted		Adjusted[a]		Unadjusted	
Treatment strategy	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Beta-blocker started/increased (*n* = 71)	0.80 (0.54–1.19)	0.267	0.78 (0.51–1.21)	.269	0.40 (0.15–1.06)	.065
HF medication started/increased (*n* = 44)	0.66 (0.40–1.08)	0.100	0.59 (0.35–1.02)	.051	0.43 (0.14–1.31)	.138
AADs started/increased (*n* = 63)	0.75 (0.50–1.14)	0.175	0.72 (0.46–1.13)	.151	0.42 (0.10–1.83)	.248
ICD Reprogramming (*n* = 52)	1.11 (0.72–1.71)	0.640	1.11 (0.70–1.76)	.644	1.24 (0.50–3.07)	.638
PCI (*n* = 6)	0.42 (0.10–1.71)	0.227	0.34 (0.08–1.46)	.146	–	–
Device upgrade (*n* = 3)	0.05 (0.00–26.71)	0.347	0.00 (0.00–7.784E)	.969	–	–
Ablation[b] (*n* = 16)	0.47 (0.19–1.15)	0.098	0.46 (0.18–1.16)	.100	0.04 (0.00–73.25)	.408

Abbreviations: AAD, anti-arrhythmic drugs; CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention; VT, ventricular tachycardia.

[a]Additional adjusted for age, indication for device implantation, aetiology, device type and pre or post programming.

[b]VT ablation for appropriate therapy analysis and atrial/AV node ablation for inappropriate therapy analysis.

shock (*n* = 41) were more likely to have a greater number of interventions introduced than patients whose first ICD therapy was treated with ATP alone (*n* = 14) (*p* = .005) (Table 2).

In univariable analyses, individually none of the therapeutic interventions was associated with a significant reduction in the risk of a subsequent inappropriate ICD therapy (ATP or shock) (Table 3). Multivariable analysis was not performed given the small number of patients reaching the endpoint (*n* = 18). Analysing ICD and CRT-D devices separately gave similar results. Furthermore, when we excluded patients with HCM or channelopathy, the results were similar.

TABLE 4 Cox-regression models evaluating the association between the management of patients following 1st appropriate therapy ($n=212$) and the risk of a subsequent appropriate therapy. Patients are grouped by how many therapy-reducing treatment strategies were introduced following the 1st appropriate therapy. Data are also presented for the different individual treatment strategies and combinations of treatment strategies. Separate analyses are performed for the end-points of any appropriate therapy (ATP or shock) and appropriate shock.

End-point	Subsequent appropriate ATP or shock therapy ($n=113$)				Subsequent appropriate shock therapy ($n=66$)			
	Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]	
Treatment groups	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Group 1–0/7 treatment strategy ($n=59$)	Ref	–	Ref	–	Ref	–	Ref	–
Group 2–1/7 treatment strategy ($n=80$)	0.57 (0.37–0.88)	0.011	0.54 (0.34–0.85)	0.008	0.61 (0.35–1.10)	0.092	0.57 (0.32–1.04)	0.063
Beta blocker started/increased ($n=27$)	0.62 (0.35–1.09)	0.096	0.62 (0.33–1.14)	0.121	0.62 (0.29–1.33)	0.217	0.70 (0.32–1.54)	0.378
Heart failure medication started/increased ($n=11$)	0.59 (0.25–1.40)	0.228	0.43 (0.16–1.16)	0.096	0.64 (0.22–1.90)	0.425	0.49 (0.14–1.79)	0.283
AAD medication started / increased ($n=24$)	0.45 (0.23–0.87)	0.017	0.36 (0.18–0.72)	0.004	0.48 (0.20–1.14)	0.095	0.42 (0.17–1.04)	0.061
ICD reprogramming ($n=14$)	0.73 (0.33–1.65)	0.453	0.82 (0.35–1.95)	0.660	1.03 (0.34–2.76)	0.950	0.99 (0.36–2.75)	0.999
Ablation—VT ablation ($n=3$)	0.67 (0.16–2.80)	0.585	0.37 (0.59–2.28)	0.282	0.62 (0.83–4.60)	0.638	0.39 (0.39–3.89)	0.424
Group 3–2/7 or more treatment strategies ($n=73$)	0.42 (0.26–0.68)	<0.001	0.36 (0.22–0.59)	<0.001	0.40 (0.21–0.76)	0.005	0.33 (0.17–0.63)	0.001
BB start/increase + ICD reprogramming ($n=13$)	0.35 (0.14–0.90)	0.029	0.36 (0.16–1.01)	0.052	0.25 (0.06–1.05)	0.058	0.25 (0.05–1.21)	0.084
BB start/increase + HF start/increase ($n=9$)	0.41 (0.15–1.15)	0.091	0.33 (0.10–1.07)	0.065	0.52 (0.15–1.75)	0.292	0.51 (0.12–2.18)	0.367
AAD start/increase + BB start/increase+ HF start/increase ($n=6$)	0.31 (0.08–1.30)	0.111	0.20 (0.05–0.85)	0.030	0.40 (0.00–10.45)	0.256	-	-
AAD start/increase + BB start/increase + HF start/increase + ICD programming ($n=3$)	2.22 (0.29–16.88)	0.443	2.17 (0.26–18.01)	0.472	0.05 (0.00–417281.86)	0.708	-	-

Abbreviations: AAD, anti-arrhythmic drugs; CI, confidence interval; HR, hazard ratio; PCI, Percutaneous Coronary Intervention; VT, ventricular tachycardia.

[a]Adjusted for age, indication for device implantation, aetiology, history of atrial arrhythmias, device type, pre or post ICD programming.

3.5 | Combining treatment strategies following first ICD therapy

3.5.1 | Appropriate therapy

Combining treatment strategies following the 1st appropriate ICD therapy was associated with a significant reduction in the risk of a subsequent appropriate therapy (Table 4). Compared to patients where 0/7 treatment strategies were used ($n=59$), patients where 1 treatment strategy was introduced ($n=80$) had a 43% lower risk of a subsequent appropriate therapy (HR 0.57, $p=.01$), and the introduction of 2 or more treatment strategies ($n=73$) was associated with a 58% reduction in the risk of a subsequent appropriate therapy (HR 0.42, $p=<.001$). When the endpoint was a subsequent appropriate shock, the findings were statistically significant in the 2 or more treatment strategy group (HR 0.40, $p=.005$). The results were similar in analyses adjusted for baseline variables.

Patients receiving subsequent appropriate therapy following the first therapy ($n=113/212$) had significantly fewer treatments compared to those who received no subsequent therapies ($n=99/212$) (Group 1 0/7 treatments $n=39$ vs. $n=20$ and Group 3 2/7 treatments $n=32$ vs. $n=41$ respectively, $p=.034$).

Analysing ICD and CRT-D devices separately gave similar results. Furthermore, when we excluded patients with HCM or a channelopathy, the results were similar.

The single individual treatment strategy associated with the lowest risk of a subsequent appropriate therapy was AAD being started/increased (HR 0.45, $p=.02$) (Table 4). All the combination of 2 treatment strategies were associated with similar reductions in risk compared to no treatment strategies.

Using Kaplan–Meier analysis there was increased freedom from ICD therapy in patients with more therapeutic strategies introduced ($p=.001$) (Figure 2).

3.5.2 | Inappropriate therapy

Combining treatment strategies following the 1st inappropriate ICD therapy was associated with a significant reduction in the risk of subsequent inappropriate therapy (Table 5). Compared to patients where 0/7 treatment strategies were used ($n=8$), patients where 1 treatment strategy was introduced ($n=22$) had an 86% lower risk of a subsequent inappropriate therapy (HR 0.14, $p=.002$), and the introduction of 2 or more treatment strategies ($n=25$) was associated with a 94% reduction in the risk of a subsequent inappropriate therapy (HR 0.06, $p<0.001$). The introduction of 1 or more treatment strategies was also associated with a significant reduction in the risk of subsequent inappropriate shocks (HR 0.14, $p=.008$ [1 strategy] and HR 0.09, $p=.001$ [2 or more strategies]). The findings were similar but of less statistical significance. The results were similar in adjusted analyses.

Patients receiving subsequent inappropriate therapy following the first therapy ($n=18/55$) had fewer treatments compared to those who received no subsequent therapies ($n=37/55$) (Group 1 0/7 treatments $n=5$ vs. $n=3$ and Group 3 2/7 treatments $n=4$ vs. $n=21$ respectively, $p=.064$).

Analysing ICD and CRT-D devices separately gave similar results. Furthermore, when we excluded patients with HCM or a channelopathy, the results were similar.

Individually, none of the single treatment strategies were associated with a reduction in subsequent therapy. However, the

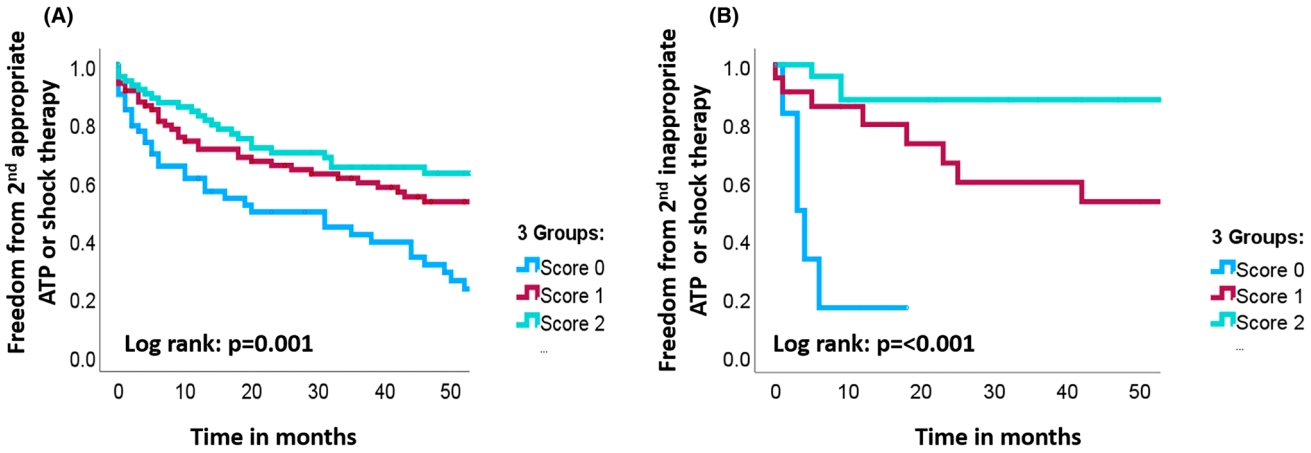

FIGURE 2 Kaplan–Meier survival curves for the occurrence of a subsequent ICD therapy following the occurrence of a 1st ICD therapy. Patients are grouped by the number of therapeutic strategies introduced following the occurrence of a 1st ICD therapy. Separate analyses are performed for appropriate therapy (A) and inappropriate therapy (B).

TABLE 5 Cox-regression models evaluating the association between the management of patients following 1st inappropriate therapy ($n=55$) and the risk of a subsequent inappropriate therapy. Patients are grouped by how many therapy-reducing treatment strategies were introduced following the 1st inappropriate therapy. Data are also presented for the different individual treatment strategies and combinations of treatments strategies. Separate analyses are performed for the end-points of any inappropriate therapy (ATP or shock) and inappropriate shock.

End-point	Subsequent inappropriate ATP or shock therapy ($n=18$)				Subsequent inappropriate shock therapy ($n=14$)			
	Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]	
Treatment groups	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Group 1–0/7 treatment strategy ($n=8$)	Ref	-	Ref	-	Ref	-	Ref	-
Group 2–1/7 treatment strategy ($n=22$)	0.14 (0.04–0.50)	.002	0.11 (0.03–0.44)	.002	0.14 (0.03–0.60)	.008	0.10 (0.02–0.47)	.003
Beta blocker started/increased ($n=6$)	0.16 (0.02–1.43)	.101	0.12 (0.01–1.30)	.081	0.19 (0.02–1.74)	.142	0.10 (0.01–1.60)	.103
Heart failure medication started/increased ($n=2$)	0.03 (0.00–307.38)	.463	-	-	0.03 (0.00–699.04)	.498	-	-
AAD medication started / increased ($n=4$)	0.01 (0.00–18.74)	.242	-	-	0.01 (0.00–42.28)	.288	-	-
ICD reprogramming ($n=8$)	0.34 (0.08–1.49)	.150	0.26 (0.05–1.29)	.099	0.32 (0.06–1.82)	.200	0.26 (0.04–1.66)	.155
Ablation—AT/AV nodal ablation ($n=2$)	0.03 (0.00–307.38)	.463	-	-	0.03 (0.00–699.04)	.498	-	-
Group 3–2/7 or more treatment strategies ($n=25$)	0.06 (0.01–0.22)	<.001	0.05 (0.01–0.21)	<.001	0.09 (0.02–0.39)	.001	0.07 (0.02–0.32)	<.001
BB start/increase + ICD programming ($n=7$)	0.09 (0.01–0.82)	.032	0.00 (0.00–9.57E)	.972	0.11 (0.01–1.00)	.050	0.00 (0.00–6.300E)	.935
BB start/increase + HF start/increase ($n=7$)	0.01 (0.00–17.54)	.210	-	-	0.01 (0.00–51.20)	.264	-	-
BB start/increase + HF start/increase + ICD programming ($n=2$)	0.27 (0.03–2.42)	.240	0.44 (0.04–5.13)	.512	0.30 (0.03–2.91)	.300	0.44 (0.04–5.13)	.512

Abreviations: AAD, anti-arrhythmic drugs; AT, atrial tachycardia, AV node, atrioventricular node; CI, confidence interval, HF, Heart failure; HR, hazard ratio; PCI, percutaneous coronary intervention; VT, ventricular tachycardia.

[a]Adjusted for history of atrial arrhythmias.

number of patients receiving each individual treatment strategy was small.

Using Kaplan–Meier analysis there was an increase in freedom from ICD therapy in patients with a greater number of therapeutic strategies introduced ($p<0.001$) (Figure 2).

3.5.3 | Management of patients following first ICD therapy and mortality

In univariable analyses, the only individual treatment strategies that were associated with a reduction in mortality were ICD reprogrammed (HR 0.58, $p=.037$) and device upgrade (HR 3.98, $p=.021$). Only ICD reprogramming remained significant in a multivariable analysis (Table 6).

Combining treatment strategies following the 1st ICD therapy was not significantly associated with a reduction in the risk of mortality. The results were similar in adjusted analyses (Table 7).

4 | DISCUSSION

We evaluated the management of patients presenting with a 1st ICD therapy in over 1000 consecutive new ICD recipients. There are several findings of note. First, following the 1st ICD therapy, the risk of a subsequent therapy is statistically higher compared to after the initial implant. Second, for both appropriate and inappropriate therapy, the risk of a subsequent shock is similar whether the initial therapy was ATP alone or a shock. However, patients experiencing initial ATP alone were likely to have fewer therapy-reducing treatment strategies introduced than patients treated following a shock. Third, combining treatment strategies was associated with a greater reduction in the risk of a subsequent therapy following the 1st ICD therapy, compared to single treatment strategies alone.

Although ICD therapy can reduce SCD, it has a range of downsides. These include increases in mortality and healthcare utilization, and a reduction in quality of life.[1,2] It is therefore important to attempt to safely minimise it by preventing the delivery of unnecessary

TABLE 6 Cox-regression analyses evaluation the association between the management of patients following 1st ICD therapy and the risk of subsequent mortality.

	All-cause mortality ($n=136$)			
	Univariable		Multivariable[a]	
Treatment strategy	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Beta-blocker started/increased ($n=71$)	1.17 (0.78–1.76)	.443	1.18 (0.77–1.83)	.434
HF medication started/ increased ($n=59$)	1.24 (0.78–1.95)	.361	0.80 (0.48–1.34)	.392
AADs started/increased ($n=75$)	1.05 (0.68–1.64)	.818	1.19 (0.74–1.91)	.467
ICD Reprogramming ($n=74$)	0.58 (0.35–0.97)	.037	0.55 (0.32–0.94)	.030
PCI (n=6)	1.63 (0.52–5.17)	.404	1.19 (0.35–3.97)	.783
Device upgrade (n=3)	3.93 (1.23–12.59)	.021	3.39 (0.91–12.61)	.069
Ablation ($n=17$)	1.20 (0.53–2.75)	.662	1.16 (0.46–2.89)	.754

Abbreviations: AAD, anti-arrhythmic drugs; CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention; VT, ventricular tachycardia.

[a]Additional adjusted for age, indication for device implantation, aetiology, device type and pre or post programming.

TABLE 7 Cox-regression analyses evaluating the association between the management of patients following 1st appropriate or inappropriate (ATP or shock, $n=267$) and the risk of a subsequent mortality. Patients are grouped by how many therapy-reducing treatment strategies were introduced following the 1st therapy.

End-point	All-cause mortality ($n=136$)			
	Unadjusted		Adjusted[a]	
Treatment groups	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Group 1 ($n=67$) (0/7 treatment strategies)	Ref	0.824	Ref	0.511
Group 2 ($n=100$) (1/7 treatment strategy)	1.08 (0.65–1.80)	0.775	1.09 (0.64–1.83)	0.756
Group 3 ($n=98$) (≥2/7 or more treatment strategies)	0.93 (0.55–1.59)	0.794	0.82 (0.47–1.43)	0.475

[a]Adjusted for age, indication for device implantation, aetiology, device type and pre or post programming.

or inappropriate ICD therapy and reducing the incidence of the arrhythmias that lead to appropriate device therapy. Most data concerning strategies to reduce ICD therapy relate to initial implant and, other than ICD programming, predominantly focus on reducing appropriate therapy. At this time point, strategic ICD programming, antiarrhythmic drugs and ventricular tachycardia (VT) ablation have all been shown to reduce the burden of ICD therapy, though only strategic programming has been found to reduce mortality.[7–9]

As demonstrated by our analysis, compared to the initial implant, patients are at greater risk of ICD therapy once they have already received therapy. The occurrence of a 1st ICD therapy is, therefore, an important opportunity to institute treatment strategies to prevent further device therapy. Despite this, there is little data to guide the management of patients following device therapy. The therapeutic option that has been evaluated in most detail in patients following appropriate ICD therapy is VT ablation, which reduces the risk of a subsequent ICD therapy but not mortality.[9]

We found that combining different treatment strategies was associated with a more significant reduction in the risk of subsequent ICD therapy compared to single therapeutic strategies used alone. This underlines the potential complexity of arrhythmogenesis in ICD patients. It also emphasises the importance of a more systematic approach to treating arrhythmic triggers, cardiac substrate and underlying cardiac comorbidity in patients following ICD therapy.[12]

Although we evaluated 7 specific therapeutic interventions, there will be other aspects of clinical management that are important in preventing device therapy that we did not assess. Furthermore, although some treatment approaches are likely to be possible in most patients (e.g., device reprogramming or changing anti-arrhythmic drug therapy), the potential to institute others will depend on the patient.

We did not find that combining treatment strategies was associated with a reduction in mortality. Although given the well-recognised association between ICD shocks and mortality this may be counterintuitive, there are a number of potential explanations. The number of patients in our analysis was small, giving us limited power to detect any changes in mortality. We used the end-point of all-cause mortality, which will likely dilute any impact of the treatment strategies on cardiac mortality. Furthermore, due to the observational nature of our analysis, there are likely to be unmeasured confounding factors that influence mortality that we have not been able to adjust for. Lastly, the therapeutic interventions proven to reduce ICD therapy that we evaluated in our analysis have not been universally shown to improve mortality. Anti-arrhythmic drugs and VT ablation, both effective treatments to reduce ICD therapy and two of the interventions included in our analysis, have not been shown to improve mortality.

5 | LIMITATIONS

As a retrospective study of prospectively collected data, we recognize several important limitations that may have influenced our results.

Data on the management of patients following ICD therapy were retrospectively identified by medical record review. Consequently, it is possible that some treatment was missed or misclassified.

We have demonstrated an association between the treatment of patients following ICD therapy and the risk of recurrent ICD therapy, but not proven causation. The treatment of patients following ICD therapy may have been influenced by patient factors not captured in our analysis. It may be that these patient factors influence outcomes rather than the treatment itself. Furthermore, the treatment of patients and the potential to increase or start new medication will be heavily influenced by the medication they are already on and their clinical status. For example, patients with advanced heart failure may be unable to tolerate an increase in medication due to hypotension or be unsuitable for an interventional procedure but also have an elevated arrhythmic risk due to their advanced cardiac disease.

Moreover, it is possible that the use of a multifaceted management approach in patients presenting with ICD therapy is purely an indicator of higher quality patient care. This high-quality care, rather than the treatment strategies themselves, may be associated with improved outcomes.

The occurrence of ICD therapy, especially ATP, is heavily influenced by implant programming, which varied during the study. Although we attempted to adjust for this in our analyses by including the implant programming, this may have influenced our results.

6 | CONCLUSION

For both appropriate and inappropriate therapy, the risk of a subsequent ICD therapy is significantly elevated following the 1st therapy. An approach combining treatment strategies may be more effective than using single strategies alone to prevent subsequent therapy in patients presenting following a 1st ICD therapy.

FUNDING INFORMATION

This work was supported by an unrestricted educational grant from Abbott Medical funding the salary of Karshana Selvarajah.

CONFLICT OF INTEREST STATEMENT

The authors have nothing to report.

DATA AVAILABILITY STATEMENT

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

ORCID

Karshana Selvarajah https://orcid.org/0009-0009-7753-6827

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How to cite this article: Selvarajah K, Khan P, Jahagirdar N, Cannatà A, Mukherjee R, Bromage DI, et al. Management of patients following implantable cardioverter-defibrillator therapy—The importance of a multifaceted approach. J Arrhythmia. 2025;41:e13204. https://doi.org/10.1002/joa3.13204