Sedation Strategies for Defibrillation Threshold Testing: Safety Outcomes with Anesthesiologist Compared to Proceduralist-Directed Sedation. An Analysis from the Shockless Implant Evaluation (SIMPLE) Study

By

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A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

in

Translational Medicine

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ABSTRACT

Implantable cardioverter defibrillator (ICD) therapy has been shown to reduce morbidity and mortality in patients at risk for sudden cardiac death. Defibrillation threshold (DT) testing is performed to assess device detection and termination of ventricular fibrillation. The patient's defibrillation threshold is amount of energy (Joules) needed to terminate VF. Traditionally, DT has been performed under general anesthesia.

Anesthesiologist-directed sedation (ADS) may increase procedural time, increase use of unnecessary procedures such as arterial lines, have higher cardiorespiratory complications and be more costly. Given this, DT testing is now occurring under the direction of proceduralists. However, data regarding safety of proceduralist directed sedation (PDS) is sparse. At present there is no standard practice exists with respect to ADS versus PDS for DT testing. We therefore aimed to determine predictors for ADS and evaluate adverse events and safety outcomes with ADS versus PDS for DT testing.

We conducted a post-hoc analysis of the Shockless Implant Evaluation (SIMPLE) trial. SIMPLE trial was a single-blind, randomised, multicentre, non-inferiority trial designed to compare the efficacy and safety of ICD implantation without DT testing versus the standard of ICD implantation with DT testing. We performed an analysis on the 1242 patients who underwent DT testing (624 ADS and 618 PDS). We determined independent predictors of ADS at DT testing and evaluated intra-operative and in-hospital adverse composite events and two safety composite outcomes at 30-days as done in the SIMPLE trial. Propensity score adjusted models were used to compute odds ratio (OR) and 95% CI to evaluate the association between

adverse and safety outcomes with method of sedation and independent predictors for use of ADS.

In our analysis we found that compared to PDS, patients who received ADS were younger (62±12 years vs. 64±12 years, p=0.01), had lower ejection fraction (LVEF 0.31±13 vs. 0.33±13, p=0.03), were more likely to receive inhalational anesthesia, propofol or narcotics (p<.001, respectively) and receive an arterial line (43% vs.8%, p= <.0001). Independent predictors for ADS sedation were presence of coronary artery disease (OR 1.69, 95% CI 1.0-2.72, p=0.03) and hypertrophic cardiomyopathy (OR 2.64, 95% CI 1.19- 5.85, p=0.02). ADS had higher intra-operative adverse events (2.2% vs 0.5%; OR 4.70, 95% CI 1.35-16.5, p=0.02) and higher primary safety outcomes at 30 days (8.2% vs 4.9%; OR 1.70 95% CI 1.10-2.78, p=0.02) and no difference in other outcomes compared to PDS.

Our data suggests that proceduralist directed sedation is safe and a higher incidence of intra-operative adverse events and primary safety outcomes at 30 days with ADS were noted. However further confirmatory research is needed.

PREFACE

This thesis is the original work by Kenneth Quadros. The research project, of which this thesis is a part, received research ethics approval from the Research Ethics Board at McMaster University and Population Health Research Institute (PHRI) and was registered on ClinicalTrials.gov NCT00800384 on Dec 2 2008. Ethics committee approval was received for all sites, and all patients gave written informed consent. The data collection and analysis are my original work.

This thesis has been submitted as a manuscript to a peer review journal for review. I have included this manuscript on the following pages as formatted for the peer review journal.

I was responsible for interpretation of analysis and manuscript preparation. RK Sandhu conceived the research question, supervised analysis and was involved in manuscript preparation. JS Healey was involved in supervising analysis and manuscript preparation. YY Liu performed the statistical analysis. SJ Connolly, V Kutyifa, P Mabo, S Hohnloser, G O'Hara, L VanErven, J Neuzner, J Kautzner, F Gadler, X Vinolas, U Appl and YY Liu contributed to, discussed and commented on the manuscript.

ACKNOWLEDGEMENTS

This project would not have been possible without the support of many people. Many thanks to my supervisor Dr Roopinder K Sandhu who read my numerous revisions and helped me work through problems when they presented themselves and find solutions. I would also like to thank the SIMPLE investigators for enrolling patients in the SIMPLE trial as well as the statistician Yan Yun Liu. The SIMLPE trial received funding from Boston Scientific and the Heart and Stroke Foundation (Ontario Provincial office).

Table of Contents

List of Tables

List of Figures

List of Abbreviations.

ICD – Implantable cardioverter defibrillator.

DT – Defibrillation threshold.

ADS – Anesthesiologist directed sedation.

PDS – Proceduralist directed sedation.

LVEF – Left ventricular ejection fraction.

CHAPTER 1

STRUCTURED ABSTRACT

Aims: No standard practice exists with respect to anesthesiologist directed sedation (ADS) versus sedation by proceduralist (PDS) for defibrillation threshold (DT) testing. We aimed to evaluate adverse events and safety outcomes with ADS versus PDS for DT testing.

Methods: A post-hoc analysis of the Shockless Implant Evaluation (SIMPLE) study was performed among the 1242 patients who had DT testing (624 ADS and 618 PDS). We evaluated both intra-operative and in-hospital adverse composite events and two safety composite outcomes at 30-days of the main trial. Propensity score adjusted models were used to compute odds ratio (OR) and 95% CI to evaluate the association between adverse and safety outcomes with method of sedation and independent predictors for use of ADS.

Results: Compared to PDS, patients who received ADS were younger (62±12 years vs. 64±12 years, p=0.01), had lower ejection fraction (LVEF 0.31±13 vs. 0.33±13, p=0.03), were more likely to receive inhalational anesthesia, propofol or narcotics (p<.001, respectively) and receive an arterial line (43% vs.8%, p= <.0001). Independent predictors for ADS sedation were presence of coronary artery disease (OR 1.69, 95% CI 1.0-2.72, p=0.03) and hypertrophic cardiomyopathy (OR 2.64, 95% CI 1.19- 5.85, p=0.02). ADS had higher intra-operative adverse events (2.2% vs 0.5%; OR 4.47, 95% CI 1.25-16.0, p=0.02) and higher primary safety outcomes at 30 days (8.2% vs 4.9%; OR 1.72 95% CI 1.06-2.80, p=0.03) and no difference in other outcomes compared to PDS.

Conclusion: Proceduralist directed sedation is safe, however, this could be result of selection bias. Further research is needed.

Key Words – implantable cardioverter defibrillator, defibrillation threshold testing, sedation, adverse events, safety outcomes

CONDENSED ABSTRACT

Among 1242 patients who underwent defibrillation testing at time of device implant in the SIMPLE trial, anesthesiologist directed sedation was associated with significantly higher intra-operative composite adverse events and safety events at 30 days compared to proceduralist directed sedation. Proceduralist directed sedation is safe but requires further confirmatory studies.

CHAPTER 2

WHAT'S NEW

- This is the first study that compares adverse events and safety outcomes with anesthesiologist directed sedation (ADS) to proceduralist directed sedation (PDS) in a large population of patients undergoing DT testing at implantable cardioverter defibrillator (ICD) implant.
- In our analysis from Shockless Implant Evaluation (SIMPLE) trial, we found that presence of coronary artery disease and hypertrophic cardiomyopathy were independent predictors for anesthesiologist directed sedation whereas; reduced left ventricular ejection fraction and New York Heart Association (NYHA) heart failure class did not predict use of ADS.
- Anesthesiologist directed sedation was associated with higher incidence of intra-operative adverse events and higher primary safety outcomes at 30 days. There was no difference in in-hospital adverse events and secondary safety outcomes between ADS and PDS. Higher incidence of adverse events with ADS was due to intraoperative hypotension requiring intravenous vasoconstrictors. PDS appeared safe in our study, however further research is needed in this area.

CHAPTER 3

INTRODUCTION

The implantable cardioverter-defibrillator (ICD) is a well-established therapy for patients who have suffered a life-threatening ventricular arrhythmia or are at high risk for sudden cardiac death (1-3). Traditionally defibrillation threshold (DT) testing, which is performed to assess device detection and termination of ventricular fibrillation has been done under general anesthesia (4). While the use of general anesthesia provides ideal sedation for patient comfort, as DT testing can be painful and traumatic; a dedicated anesthesiologist can also manage airway and hemodynamic issues that may occur among this patient population, with a high prevalence of comorbidities. However, anesthesiologist-directed sedation (ADS) may increase procedural time, increase use of procedures such as arterial lines, have higher cardiorespiratory complications and be more costly (5-7). Given this, DT testing is now occurring under the direction of implant operators using moderate sedation and analgesia.

However, data regarding the safety of proceduralist-directed sedation (PDS) for DT testing is sparse (8-11). In two retrospective, single-center studies, PDS using midazolam was related to respiratory depression leading to acute hypoxia in 5.9% of patients, all successfully treated with head and chin tilt and manual ventilation (10) while 10% of patients undergoing PDS with propofol for DT testing had a serious adverse event and 38.7% experienced a non-serious adverse event (8). A single observational study comparing ADS with PDS found the use of intravenous etomidate to induce deep sedation for DT testing in the absence of an anesthesiologist or the use of propofol in the presence an anesthesiologist evoked no difference in episodes of arterial hypotension, hypoxia or in-hospital mortality (11).

At present, no standard practice exists with regards to who should perform sedation at the time of DT testing. Therefore, we evaluated adverse and safety outcomes among 1242 patients undergoing DT testing with either ADS or PDS in the Shockless Implant Evaluation (SIMPLE) trial.

CHAPTER 4

METHODS

Study Population:

The SIMPLE trial design and results have been previously published (12). Briefly, this is a single-blind, randomized, clinical trial comparing the efficacy and safety of ICD implantation with and without DT testing at 85 hospitals in 18 countries worldwide. A total of 2500 patients were included in this study and followed for a mean of 3.1 years. For our analysis, we included the 1253 patients who were randomized to DT testing. Data on intra-procedural sedation at time of DT was present for 1242 patients. The DT protocol required induction of ventricular fibrillation to show either one successful arrhythmia cessation at 17 J or two successful cessations at 21 J with reconfiguration and retesting if initial DT testing was unsuccessful. Among the 85 enrolling centers there were 46 sites where DT was performed with PDS and 39 who performed DT with anesthesia support.

Outcomes:

We assessed two adverse composite outcomes (intra-operative and in-hospital) and two 30-day safety composite outcomes from the main trial with use of ADS versus PDS (12). Intra-operative adverse events included need for chest compressions or an aortic balloon pump during the ICD implantation procedure, non-elective intubation, complications from arterial line insertion and intraoperative hypotension necessitating use of vasoconstrictors for more than 15 min. In-hospital adverse events included death, myocardial infarction (MI), stroke (CVA), transient ischemic attack (TIA), systemic or pulmonary embolism and heart failure requiring intravenous diuretics or inotropes.

The primary composite safety endpoint included death, MI, CVA, systemic or pulmonary embolism, heart failure requiring intravenous diuretics or inotropes, the need for chest compressions or an aortic balloon pump during the ICD implantation procedure, use of intraoperative vasoconstrictors for more than 15 min, non-elective intubation, arterial-line complications, an unplanned stay in the ICU, other anoxic brain injury, pneumothorax, cardiac perforation, ICD infection, or aspiration pneumonia. A secondary composite safety endpoint excluded pneumothorax, tamponade including cardiac perforation, ICD infection, and an unplanned ICU stay, was pre-specified to examine complications thought to be more directly related to induction of ventricular fibrillation. All adverse and safety outcomes were adjudicated by a committee blinded to randomization group.

Statistical Analysis:

Baseline and implant characteristics of patients according to sedation provider were summarized as mean $\pm$ standard deviation for continuous variables, and frequency/percentage for categorical variables. To test baseline differences in patient demographic and clinical characteristics, a two sample T test was used for continuous variables and Chi-square or Fisher exact test was used for categorical variables. Logistic regression was used for baseline characteristics to determine predictors associated with ADS with forward selection and a significant p value of 0.1 was needed for entry into the model. The association between sedation approach and risk of clinical outcomes were investigated using logistic regression and odds ratios were calculated (OR, 95%CI) for the relative chance of an event (non 0) happening with ADS compared to PDS.

We also performed non-parsimonious logistic regression analyses and propensity score adjusted analyses for the primary and secondary safety composite endpoints and the intra-

operative composite safety outcome. The models were adjusted according to variables that were clinically important and variables that were significant in univariate analysis. The non-parsimonious logistic regression models were adjusted for age, sex, left ventricular ejection fraction, systolic blood pressure, New York Heart Association class, underlying coronary artery disease, history of cardiac arrest and impaired renal function. The propensity score analysis adjusted for age, sex, left ventricular ejection fraction, systolic and diastolic blood pressure, New York Heart Association class, underlying coronary artery disease, Beta blocker use, history of cardiac arrest and impaired renal function. Additional analyses were not performed for in-hospital adverse composite endpoint because of the small number of events. All tests were 2-sided and conducted at the 0.05 level. Analyses were conducted in SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

CHAPTER 5

RESULTS

Baseline characteristics:

The baseline and implant characteristics for DT testing according to ADS and PDS are shown in Table 1. Compared to DT testing performed by PDS, patients who had undergone DT with ADS were younger (62 ± 12 years vs. 64 ± 12 years, p=0.01), had lower blood pressure (systolic blood pressure 122 ±18 mm Hg vs. 126 ± 20 mm Hg, p=0.001 and diastolic blood pressure 72 ±11mm Hg vs. 74±12 mm Hg, p=0.003), received an ICD for a primary prevention indication (78.4% v 69.2%, p=0.0002), had a lower ejection fraction (33% ± 13% vs. 31% ± 12%, p=0.03), and received more arterial lines for invasive hemodynamic monitoring (43% vs. 8%, p = <0.0001). In the ADS group, the intraoperative sedation was more likely inhaled anesthetics (15% vs. 0%, p= < 0.0001), systemic narcotics (62% vs. 31%, p= <0.001) and propofol (72% vs. 33%, p= <0.001).

Independent predictors for Anesthesiologist Directed Sedation:

Independent predictors for use of ADS for DT testing included the presence of coronary artery disease (OR 1.60, 95% CI, 1.05-2.72, p 0.03) and hypertrophic cardiomyopathy (OR 2.64, 95% CI 1.19-5.85, p=0.02, Table 2). A reduced left ventricular ejection fraction, history of ventricular tachycardia (VT), history of cardiac arrest or New York Heart Association (NYHA) III or IV heart failure symptoms were not significantly associated with use of ADS.

Adverse and Safety Outcomes:

Overall, there were 14 intra-operative adverse events in ADS group (2.2%) compared to 3 (0.5%) with the PDS approach (p=0.01, Table 3). Intra-operative composite adverse events were significantly higher in the ADS group compared to DT testing performed by PDS (OR

4.70, 95% CI 1.35-16.5, p=0.02). This was primarily driven by higher rate of intraoperative hypotension necessitating use of vasoconstrictors for more than 15 min (OR 8.01, 95% CI 1.00 – 64.2, p=0.05, Supplement). Six patients required non-elective intubation during DT testing in the ADS group, versus 1 patient in the PDS group and two patients experienced arterial line complications in the ADS group and none with a PDS approach (Supplementary table 1). There was no significant association between in in-hospital adverse events and approach to sedation (p=0.41). No in-hospital deaths occurred for either ADS or PDS but there were higher heart failure events requiring intravenous diuretics or inotropes in the ADS group (1.3% versus 0.5%, p=0.22).

At 30-days, there were 51 (8.2%) primary safety outcomes in ADS group compared to 30 primary safety outcomes in PDS (4.9%, p=0.02). The primary safety composite outcome was higher in ADS compared to PDS (OR 1.74, 95%CI 1.10-2.78, p=0.02; multivariable-adjusted: OR 1.72, 95% CI 1.06-2.81, p=0.03; propensity score adjusted: OR 1.72, 95% CI 1.06-2.80, p=0.03) however there was no significant difference in the secondary safety composite outcome (p=0.11). In the ADS group 5 patients died and no patient died with PDS (Supplementary table 2).

Table 1. Baseline characteristics of Patients Undergoing Defibrillation Threshold Testing According to Anesthesiologist or Proceduralist Directed Sedation.

Characteristics	Anesthesiologist directed sedation (N=624)	Proceduralist directed sedation (N=618)	P value
	N (%)	N (%)	
Age (years) mean (SD)	62.1 (11.7)	63.8 (11.6)	0.01
Male	507 (81.3)	502 (79.8)	0.5
Blood pressure (mm Hg) mean (SD)			
Systolic	122 (18)	126 (20)	0.001
Diastolic	71 (11)	74 (12)	0.003
LV Ejection fraction mean (SD)	31% (13%)	33% (13%)	0.03
Indication			
Underlying CAD	489 (78.4%)	435 (65.2%)	0.0002
Dilated cardiomyopathy	220 (35.3%)	194 (30.8%)	0.10
Long QT and Brugada	13 (2.1%)	16 (2.5%)	0.59
Hypertrophic cardiomyopathy	31 (5.0%)	22 (3.5%)	0.20
Comorbidities			
Coronary heart disease	399 (63.9%)	400 (63.6%)	0.90
Hypertension	380 (60.9%)	398 (63.3%)	0.39
Diabetes	174 (27.9%)	186 (29.6%)	0.51
Previous myocardial infarction	315 (50.5%)	329 (52.3%)	0.51
History of Atrial Fibrillation	144 (23.1%)	155 (24.6%)	0.52
Heart Failure, New York Heart Association (NYHA) class			
I	42 (6.7%)	46 (7.3%)	0.69
II	200 (32.1%)	210 (33.4%)	0.61
III	195 (31.3%)	192 (30.5%)	0.78
Impaired Renal Function	105 (16.8%)	129 (20.5%)	0.09
Baseline Medications			
Amiodarone	98 (15.7%)	92 (14.6%)	0.59
ACE Inhibitor	444 (71.2%)	444 (70.6%)	0.82
Aldosterone antagonist	198 (31.7%)	247 (39.3%)	0.005
Beta blocker	552 (88.5%)	532 (84.6%)	0.04
Type of Device			
Single chamber ICD implanted	275 (44.1%)	277 (44.0%)	1
Dual chamber ICD implanted	168 (26.9%)	156 (24.8%)	0.39
Resynchronization ICD implanted	181 (29.0%)	185 (29.4%)	0.87
Type of Anesthetic Agent			
Inhalational	91 (14.6%)	0 (0.0%)	<.0001
Benzodiazepine	278 (44.6%)	376 (59.8%)	<.0001
Narcotic	389 (62.3%)	195 (31.0%)	<.0001

Propofol	446 (71.5%)	206 (32.8%)	<.0001
Etomidate	95 (15.2%)	158 (25.1%)	<.0001
Local Anesthesia	431 (69.1%)	481 (76.5%)	0.003
Arterial line inserted	266 (42.6%)	52 (8.3%)	<.0001

Table 2. Predictors for Anesthesiologist Directed Sedation

Risk factor	Odds ratio (95% CI)	P-value
Age (years)	0.99 (0.98-1.00)	0.05
Male Sex	1.09 (0.81-1.48)	0.56
Indication		
Underlying CAD	1.69 (1.05-2.72)	0.03
Dilated cardiomyopathy	1.32 (0.90-1.93)	0.15
Long QT and Brugada	1.04 (0.38-2.79)	0.94
HCM	2.64 (1.19-5.85)	0.01
ARVC	0.21 (0.02-1.93)	0.16
Other	0.81 (0.49-1.34)	0.41
Comorbidities		
Hypertension	0.98 (0.76-1.26)	0.85
Diabetes	0.99 (0.76-1.30)	0.96
Previous Stroke or TIA	0.83 (0.56-1.23)	0.35
Previous MI	0.85 (0.61-1.18)	0.33
History of previous PCI or CABG	0.82 (0.59-1.14)	0.24
History of Sustained VT	1.51 (0.75-3.06)	0.25
History of Atrial Fibrillation	1.03 (0.78-1.37)	0.82
Heart Failure NYHA Class	1.13 (0.34-3.70)	0.84
I	0.67 (0.20-2.23)	0.51
II	0.65 (0.20-2.15)	0.48
III	0.69 (0.21-2.29)	0.54
IV	0.24 (0.04-1.43)	0.11
Impaired Renal Function	0.83 (0.61-1.14)	0.24
Left ventricular ejection fraction	0.98 (0.96-1.00)	0.09
LVEF < 20% vs. > 50%	0.94 (0.26-3.42)	0.74

Risk factor	Odds ratio (95% CI)	P-value
LVEF 20% – 35% vs. > 50%	1.07 (0.41-2.80)	0.89
LVEF 35% – 50% vs. > 50%	1.20 (0.58-2.50)	0.43

Abbreviations: HCM=hypertrophic cardiomyopathy; ARVC=arrhythmogenic right ventricular cardiomyopathy; TIA=transient ischemic attack; VT=ventricular tachycardia; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; LVEF=left ventricular ejection fraction

Table 3. Adverse events and 30-day Safety Outcomes of Anesthesiologist Compared to Proceduralist Directed Sedation for Defibrillation Threshold Testing.

Outcomes	Overall (n=1242)	ADS (n=624)	PDS (n=629)	OR (95% CI) unadjusted	p value	OR (95% CI) Multivariable adjusted	p value	OR (95% CI) Propensity score adjusted	p value
	N (%)	N (%)	N (%)						
Adverse events									
Intra-operative adverse events*	17 (0.01%)	14 (2.2%)	3 (0.5%)	4.70 (1.35 – 16.5)	0.02	4.60 (1.29 – 16.5)	0.02	4.47 (1.25 – 16.0)	0.02
In-hospital adverse events§	13 (0.01%)	8 (1.3%)	5 (0.8%)	1.59 (0.52 – 4.89)	0.41	-		-	
Safety events									
	N (%)	N (%)	N (%)						
Primary safety composite†	81 (6.5%)	51 (8.2%)	30 (4.9%)	1.74 (1.10 – 2.78)	0.02	1.72 (1.06 – 2.81)	0.03	1.72 (1.06 – 2.80)	0.03
Secondary safety composite‡	56 (4.5%)	34 (5.4%)	22 (3.6%)	1.56 (0.90 – 2.70)	0.11	1.59 (0.90 – 2.79)	0.11	1.61 (0.92 – 2.83)	0.09

p value for Fisher exact test for comparison between two groups.

*Includes need for chest compressions, non-elective intubation, complications from arterial line insertion and intraoperative hypotension necessitating use of vasoconstrictors for more than 15 min and intra-aortic balloon pump during the ICD implantation procedure.

§Includes death, myocardial infarction, stroke, transient ischemic attack, systemic or pulmonary embolism and heart failure requiring intravenous diuretics or inotropes.

† Includes death, stroke, non-CNS embolus, pulmonary embolism, anoxic brain damage, myocardial infarction, heart failure, intra-operative hypotension requiring IV inotropes, need for CPR and IABP, non-elective intubation, aspiration pneumonia, unplanned ICU stay, pneumothorax, pericarditis/pericardial tamponade from cardiac perforation, device infection, arterial line complication.

‡Includes all adverse events listed in primary safety composite apart from anoxic brain injury, aspiration pneumonia, pneumothorax, pericarditis or cardiac tamponade, and device infection. This related to complications thought to be more directly related to induction of ventricular fibrillation.

Supplementary Table 1. Intraoperative and In-hospital Adverse Events According to Approach to Sedation.

Outcomes	Overall (n=1242)	ADS (N 624)	PDS (N 618)	p value (based on Fisher)	Odds ratio (95% CI)	P value
	N (%)	N (%)	N (%)			
Composite Intra-operative adverse events*	17 (0.1%)	14 (2.2%)	3 (0.5%)	0.01	4.70 (1.35 - 16.5)	0.01
Need for chest compressions	5 (0.0%)	4 (0.6%)	1 (0.2%)	0.37	3.98 (0.44 - 35.7)	0.37
Non-elective intubation	7 (0.0%)	6 (1.0%)	1 (0.2%)	0.12	5.99 (0.72 - 49.9)	0.12
Arterial line complication	2 (0.0%)	2 (0.3%)	0 (0.0%)	0.50	--	--
Intraoperative hypotension	9 (0.0%)	8 (1.3%)	1 (0.2%)	0.03	8.01 (1.00 - 64.2)	0.05
Need for Intra-aortic balloon pump	0 (0.0%)	0 (0.0%)	0 (0.0%)	--	--	--
Composite In-hospital adverse events§	13 (0.0%)	8 (1.3%)	5 (0.8%)	0.58	1.59 (0.52 - 4.89)	0.41
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	--	--	--
MI	1 (0.0%)	0 (0.0%)	1 (0.2%)	0.50	--	--
Stroke	1 (0.0%)	0 (0.0%)	1 (0.2%)	0.50	--	--
TIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	--	--	--
Non-CNS embolus	0 (0.0%)	0 (0.0%)	0 (0.0%)	--	--	--
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)	--	--	--
Heart failure	11 (0.0%)	8 (1.3%)	3 (0.5%)	0.22	2.66 (0.70 - 10.1)	0.22

p value for Fisher exact test for comparison between two groups.

* Includes need for chest compressions, non-elective intubation, complications from arterial line insertion and intraoperative hypotension necessitating use of vasoconstrictors for more than 15 min and intra-aortic balloon pump during the ICD implantation procedure.

§ Includes death, myocardial infarction (MI), stroke (CVA), transient ischemic attack (TIA), systemic or pulmonary embolism and heart failure requiring intravenous diuretics or inotropes.

Supplementary Table 2. 30-day Safety Composite Outcomes According to Approach to Sedation

Outcomes	Total	ADS	PDS	p value (based on Fisher)	Odds ratio (95% CI)	P-value
	N (%)	N (%)	N (%)			
Primary safety composite [Ω]	81 (6.5%)	51 (8.2%)	30 (4.9%)	0.02	1.74 (1.10 - 2.78)	0.02
Secondary safety composite [¥]	56 (4.5%)	34 (5.4%)	22 (3.6%)	0.13	1.56 (0.90 - 2.70)	0.11
Death	5 (0.4%)	5 (0.8%)	0 (0.0%)	0.06	--	--
Stroke	3 (0.2%)	1 (0.2%)	2 (0.3%)	0.62	0.49 (0.04 - 5.47)	0.57
Non-CNS embolus	2 (0.2%)	1 (0.2%)	1 (0.2%)	1.00	0.99 (0.06 - 15.9)	1.00
Pulmonary embolism	2 (0.2%)	1 (0.2%)	1 (0.2%)	1.00	0.9 9(0.06 - 15.9)	1.00
Anoxic brain injury	0 (0.0%)	0 (0.0%)	0 (0.0%)	--	--	--
Myocardial infarction	1 (0.1%)	0 (0.0%)	1 (0.2%)	0.50	--	--
Heart failure needing intropes or diuretics	28 (2.3%)	14 (2.2%)	14 (2.3%)	1.00	0.99 (0.47 - 2.09)	0.98
Intraoperative hypotension	9 (0.7%)	8 (1.3%)	1 (0.2%)	0.03	--	--
Need for chest compressions	5 (0.4%)	4 (0.6%)	1 (0.2%)	0.37	3.98 (0.44 - 35.7)	0.21
Non-elective intubation	7 (0.6%)	6 (1.0%)	1 (0.2%)	0.12	5.99 (0.72 - 49.9)	0.09
Aspiration pneumonia	1 (0.1%)	1 (0.2%)	0 (0.0%)	1.00	--	--
Unplanned ICU stay	1 (0.1%)	1 (0.2%)	0 (0.0%)	1.00	--	--
Pneumothorax	16 (1.3%)	10 (1.6%)	6 (1.0%)	0.45	1.66 (0.60 - 4.60)	0.32
Pericarditis, cardiac tamponade or cardiac perforation	11 (0.9%)	8 (1.3%)	3 (0.5%)	0.22	2.66 (0.70 - 9.97)	0.14

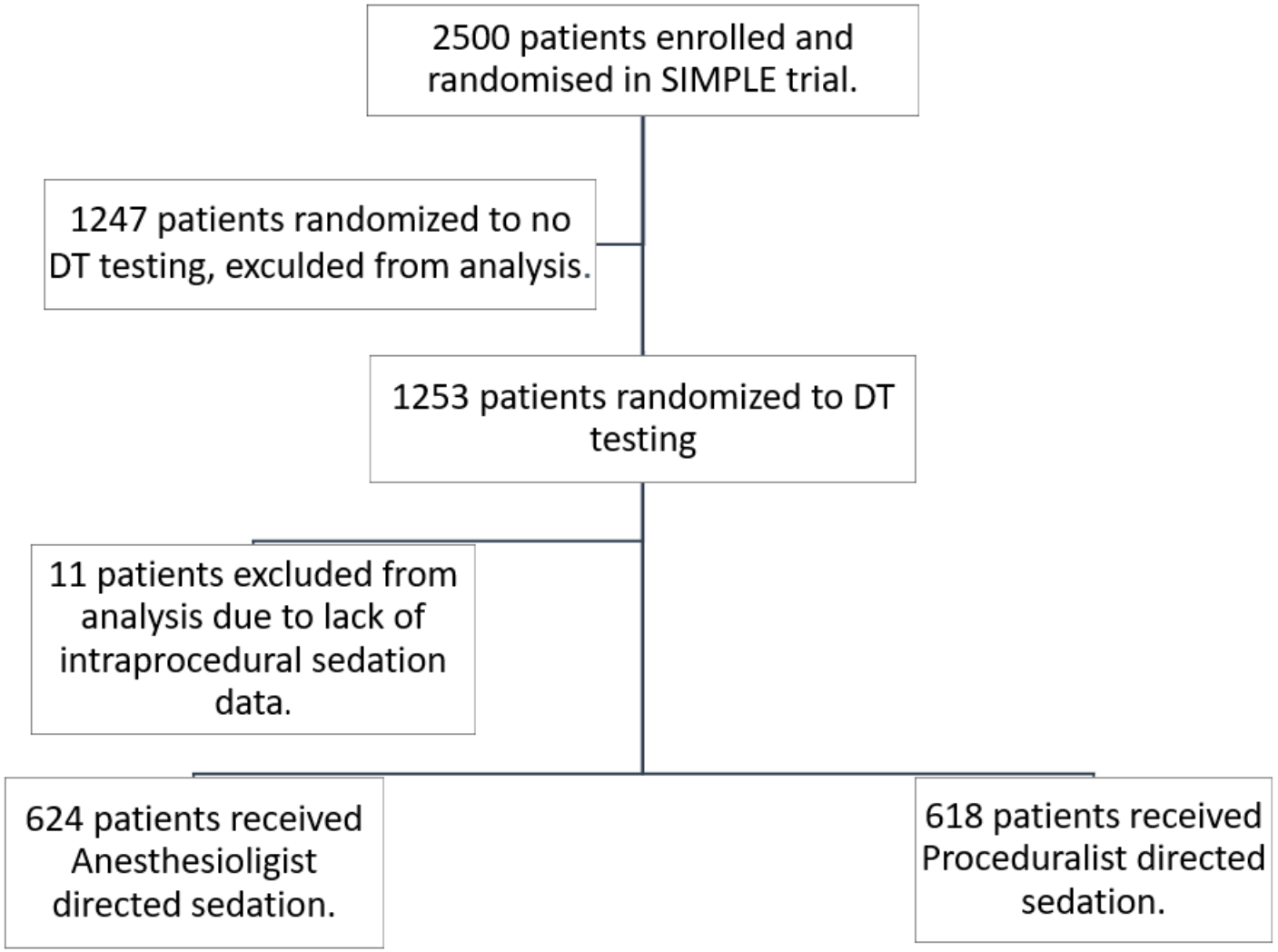
Outcomes	Total	ADS	PDS	p value (based on Fisher)	Odds ratio (95% CI)	P-value
Device infection	3 (0.2%)	3 (0.5%)	0 (0.0%)	0.25	--	--
Arterial-line complication	2 (0.2%)	2 (0.3%)	0 (0.0%)	0.50	--	--

p value for Fisher exact test for comparison between two groups.

Ω Includes death, stroke, non-CNS embolus, pulmonary embolism, anoxic brain damage, myocardial infarction, heart failure, intra-operative hypotension requiring IV inotropes, need for CPR and IABP, non-elective intubation, aspiration pneumonia, unplanned ICU stay, pneumothorax, pericarditis/pericardial tamponade from cardiac perforation, device infection, arterial line complication..

¥ Includes all adverse events listed in primary safety composite apart from anoxic brain injury, aspiration pneumonia, pneumothorax, pericarditis or cardiac tamponade, and device infection. This related to complications thought to be more directly related to induction of ventricular fibrillation.

Figure 1


2500 patients enrolled and randomised in SIMPLE trial.
1247 patients randomized to no DT testing, exculded from analysis.
1253 patients randomized to DT testing
11 patients excluded from analysis due to lack of intraprocedural sedation data.
624 patients received Anesthesioligist directed sedation.
618 patients received Proceduralist directed sedation.

CHAPTER 6

DISCUSSION

To the best of our knowledge, this is the first study evaluating adverse and safety outcomes with ADS compared to PDS in a large cohort of patients who had undergone DT testing at the time of ICD implant. Intraoperative and in-hospital adverse events occurred in <1% of patients undergoing PDS for DT testing. In the ADS group, there was a 4.7 times higher odds associated with intraoperative adverse events and 1.7 times higher odds of the primary safety composite outcome at 30-days compared to PDS group. Although, higher rates of in-hospital adverse events and secondary 30-day safety composite events also occurred with ADS, no significant differences were observed between these two approaches.

The safety of PDS for DT testing at ICD implant has been investigated with few single-center, retrospective studies(8-10). Only a single study from the late 1990's has compared ADS and PDS approaches(11). We found an intraoperative adverse event rate of 0.5% in patients undergoing DT testing using PDS with a variety of anesthetic agents, which is lower than prior studies that reported adverse event rates ranging between 5.9% and 9.2% using midazolam (9,10) and 10% for serious adverse events and 38.7% for non-serious adverse events when using propofol(8). However, the definition of adverse events differed among studies. When comparing similar adverse events i.e. hypotension requiring inotropic support, we found a rate of 0.2% compared to 4.6% and 8.1% from two retrospective analyses using midazolam or propofol, respectively (8,9). Respiratory depression requiring intubation rarely occurred in our study and others with a PDS approach and there were no documented intraoperative deaths (8-11). When comparing PDS to ADS, we found higher rates of both intraoperative hypotension requiring inotropic support and need for intubation with ADS for DT testing. Our study is novel in

assessing in-hospital adverse events and 30-day safety outcomes for both ADS and PDS approaches for DT testing. We found higher event rates with ADS compared to PDS for each of these additional outcomes and there were 5 deaths at 30-days with ADS.

The higher adverse event rates found in the ADS group compared to the PDS group in our study and other work with a PDS only approach (8,13) may, in part, be explained by the use of propofol. This anesthetic agent was used in 71.5% of our patients undergoing DT testing using ADS but only 32.8% using a PDS approach. Propofol is known negative inotrope and has been associated with cardiovascular complications in patients with advanced stages of heart failure and diminished cardiac reserve capacity (14). Although, there was no difference in NYHA class between patients in the ADS and PDS groups, LVEF and blood pressure were both lower in the ADS group. In the study using PDS with propofol, patients had more severe heart failure and reduced ejection fraction than our study population regardless of whether patients were in the ADS or PDS group (8). Worsening NYHA class and use of propofol infusion were independent predictors of the high non-serious adverse event rate. We found the most common type of anesthetic agent used in the PDS group was Benzodiazepines (e.g. midazolam). Prior studies have found fewer intraoperative adverse events with use of midazolam for PDS of DT testing compared to propofol and shown to be safe for a cardiologist-only approach to sedation for electrical cardioversion of atrial fibrillation (15,16). Although we didn't specifically obtain data regarding amnesia related to sedation, this has been documented with a PDS approach to DT testing using etomidate, propofol and midazolam (10,11).

Clinical Implications

The safety regarding approach to sedation for DT testing is important despite increasing evidence that DT testing does not improve mortality or ICD efficacy and may not be necessary

for de novo implants (12,17,18) because there are considerable populations where the lack of DT testing is unclear such as device replacement, secondary prevention indication, hypertrophic cardiomyopathy, channelopathies, and subcutaneous implants. In addition, DT testing is still being performed at first implant in many centers, ranging anywhere from 20%-71% (5,19) and likely reflects physician preference to ensure systemic integrity, reliable sensing and to allow for immediate system revision for DT failures. PDS for DT testing is appealing because it eliminates challenges related to scheduling of anesthesiology, particularly a cardiac anesthetist, may reduce procedure and staff time, have fewer cardiorespiratory complications and lower costs (5-7). This approach should require an EP lab that is well equipped to deal with emergencies; nurses appropriately trained with sedation and experienced operators.

There are several limitations of our study. Firstly, this is a retrospective post-hoc analysis of a randomized control trial that was conducted to answer a different question, namely the utility of DT testing at ICD implant. Secondly participants in this study were not randomized to PDS or ADS, thus potentially resulting in a selection bias. Sedation strategies were decided based on the site practices and operator preference. Third, because event rates were low, we were unable to evaluate whether the type of sedation used was associated with adverse and safety outcomes. Finally, the cost-effectiveness of PDS was not studied however, prior work has demonstrated that PDS results in lower costs (5-7).

CHAPTER 7

CONCLUSION

This large study of complex cardiac patients undergoing ICD implant demonstrates that PDS is safe for DT testing and compared to ADS has significantly fewer intra-operative adverse events and safety outcomes at 30-days. There were no differences in the in-hospital adverse events between the two approaches to sedation although event rates were higher with ADS. This is the first study that we are aware of that compares adverse events and safety outcomes with ADS to PDS. The higher incidence of intra-operative adverse events and safety outcomes at 30 days was primarily driven by higher rate of intraoperative hypotension necessitating use of vasoconstrictors for more than 15 min. We hypothesize that the increased rate of hypotension could be due to the more frequent use of propofol for sedation in the ADS group. Propofol is known to have a negative inotropic effect and can precipitate heart failure in vulnerable patients with advanced heart failure and reduced left ventricular ejection fraction.

Another salient finding of this project is that in the participants who underwent DT testing as part of the SIMPLE trial, the independent predictors of ADS were the presence of coronary artery disease and hypertrophic cardiomyopathy. What was interesting to note was that traditional risk factors such as advanced NYHA class (III and IV), a reduced left ventricular ejection fraction, history of ventricular tachycardia were not independent predictors of ADS.

We also noted an intra-operative and in-hospital adverse event rate of < 1 % in the PDS group. This is lower than previous reported incidence of adverse events with PDS for DT testing. Our study is the first to assess safety outcomes of DT testing at 30 days.

Our work does have limitations. This is a post hoc analysis of participants who were part of a study designed to answer a different question, namely the utility of DT testing for new ICD implants. Participants were randomized to DT testing versus no DT testing. The decision for ADS or PDS was at the discretion of the operator or site preferences. Due to the low number of events, were unable to determine if any particular sedation agent was associated with higher incidence of adverse events.

In summary, PDS for DT testing is becoming more prevalent and appears safe however further confirmatory research is needed to help develop practice standards regarding sedation approach for DT testing. A better understanding of this may help direct future practise.

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