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CAAD-PVC

Catheter Ablation versus Anti-arrhythmic Drugs for Premature Ventricular Complexes (CAAD-PVC): A Randomised Controlled Trial

STATISTICAL ANALYSIS PLAN

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Abbreviations

SD – Standard Deviation

IQR – Interquartile range

CI – Confidence Interval

ITT – Intention to treat

PVC – Premature ventricular complex

AAD – Anti-arrhythmic drug

VT – Ventricular tachycardia

1. Synopsis

Catheter Ablation versus Anti-arrhythmic Drugs for Premature Ventricular Complexes (CAAD-PVC) is a randomised controlled trial of patients with high burden premature ventricular complexes (PVCs) designed to compare treatment with medications to PVC ablation. The interventions will be compared based on their effect on PVC burden as well as quality of life and health service utilisation.

1.1 Primary objective

To assess in patients with PVCs if catheter ablation is more efficacious than medical therapy to reduce PVC burden measured by ≥24 hour heart rhythm monitoring at 12 weeks.

1.2 Secondary objectives

To compare catheter ablation with medical therapy on the following outcomes

1. Change in PVC burden at 12 weeks as measured by ≥24-hour heart rhythm monitoring
2. Reduction in PVC burden by at least 99% at 12 weeks.
3. Quality of Life score at 6 and 12 weeks as measured by questionnaires (ASTA, SF-36, DASS21 and EQ-5D-5L) compared to baseline. The ASTA will be the primary quality of life measure.
4. Tolerability of medical therapy (adherence, adverse events)
5. Tolerability of catheter ablation (complications, adverse events)
6. Health service utilization (hospital admissions)

1.3 Trial Design

A randomised, open label-controlled trial of patients with PVCs who will be randomised in a 1:1 manner to receive either catheter ablation or medical therapy and followed up for 12 weeks.

1.4 Interventions

All participants who meet the eligibility criteria for the study will be randomised to:

a. Catheter ablation for PVC within 2 weeks of randomisation

OR

b. Anti-arrhythmic drug (AADs) at maximally tolerated dose. These could include beta blocker, calcium channel blocker, sotalol or Class 1C agents (if structural heart disease ruled out). Choice of AADs will be up to treating physician, if no preference, trial will suggest sotalol or class 1 AADs.

1.5 Subgroups

The following subgroups will be used: sex, age (above or below the median), ejection fraction (above or below the median), beta blocker (not sotalol) only arrhythmic or not, PVC morphology (only suspected outflow tract or elsewhere) and presence of multiple PVC morphologies on heart rhythm monitoring. Subgroup analysis will be exploratory and be interpreted cautiously.

1.6 Power and sample size

This trial is powered for the primary endpoint which will be assessed for statistical significance according to the χ^2 test. Fifty patients will have 90% power to detect an absolute difference of about 32% (from 43% to 85%) between anti-arrhythmic drugs and PVC ablation assuming a success rate of 43% in the anti-arrhythmic arm (Gulletta et al., 2022, Kojić et al., 2023), using a two-side alpha of 0.05 and an expectation of no drop out.

1.7 Missing data

If there are more than 10% missing data, then missing data will be handled with the multiple imputation method using chained equations using a missing at random assumption.

2 Patient Population

Patients with high burden PVCs.

2.1 Inclusion criterion

1. PVC burden of ≥10% as determined by ≥24 hour heart rhythm monitoring
2. Normal left ventricular ejection fraction (ejection fraction ≥ 50%)
3. Aged ≥18 years.
4. Symptoms due to PVCs according to the judgement of the treating physician.

2.2 Exclusion criterion

1. Unable or unwilling to provide informed consent or comply with study requirements including study investigations and follow-up, medical adherence, completion of intervention.
2. Women who are pregnant or breastfeeding.
3. Life expectancy ≤ 12 months.
4. Ventricular tachycardia (VT) defined as inducible VT, spontaneous VT lasting ≥30 seconds, haemodynamically unstable VT, or ≥10 episodes of non-sustained ventricular tachycardia (defined as >5 consecutive beats but ≤ 30 seconds) within 24 hours during heart rhythm monitoring.
5. Previous catheter ablation for ventricular arrhythmia.
6. Clinically significant coronary artery disease
7. Structural heart disease including valvular disease or cardiomyopathy.
8. Known cardiac channelopathies (e.g. Catecholaminergic polymorphic ventricular tachycardia (CPVT), long- or short QT syndrome, Brugada syndrome).
9. Responsible primary care or other responsible physician believes it is not appropriate to participate in the study or unable to complete the study procedures, e.g. concomitant illness, physical impairment or mental condition which could interfere with the conduct of the study including outcome assessments

3. ANALYSIS

3.1 Analysis Principles

The intention to treat (ITT) populations will consist of all randomised patients. Primary and secondary endpoints will be measured at 6 and 12 weeks and will be required to occur within 14 days of the scheduled date. If they are outside this window they will be deemed missing, although they will be included in a sensitivity analysis.

A per protocol analysis will also be performed as a sensitivity analysis. This per-protocol analysis will include patients in the CA cohort if they received ablation within two weeks and in the AAD cohort if they received AADs within two weeks.

All p-values of less than 0.05 will be considered statistically significant. There will be no adjustments for multiple comparisons as secondary outcomes will be interpreted as exploratory.

3.2 Patient Flow Chart

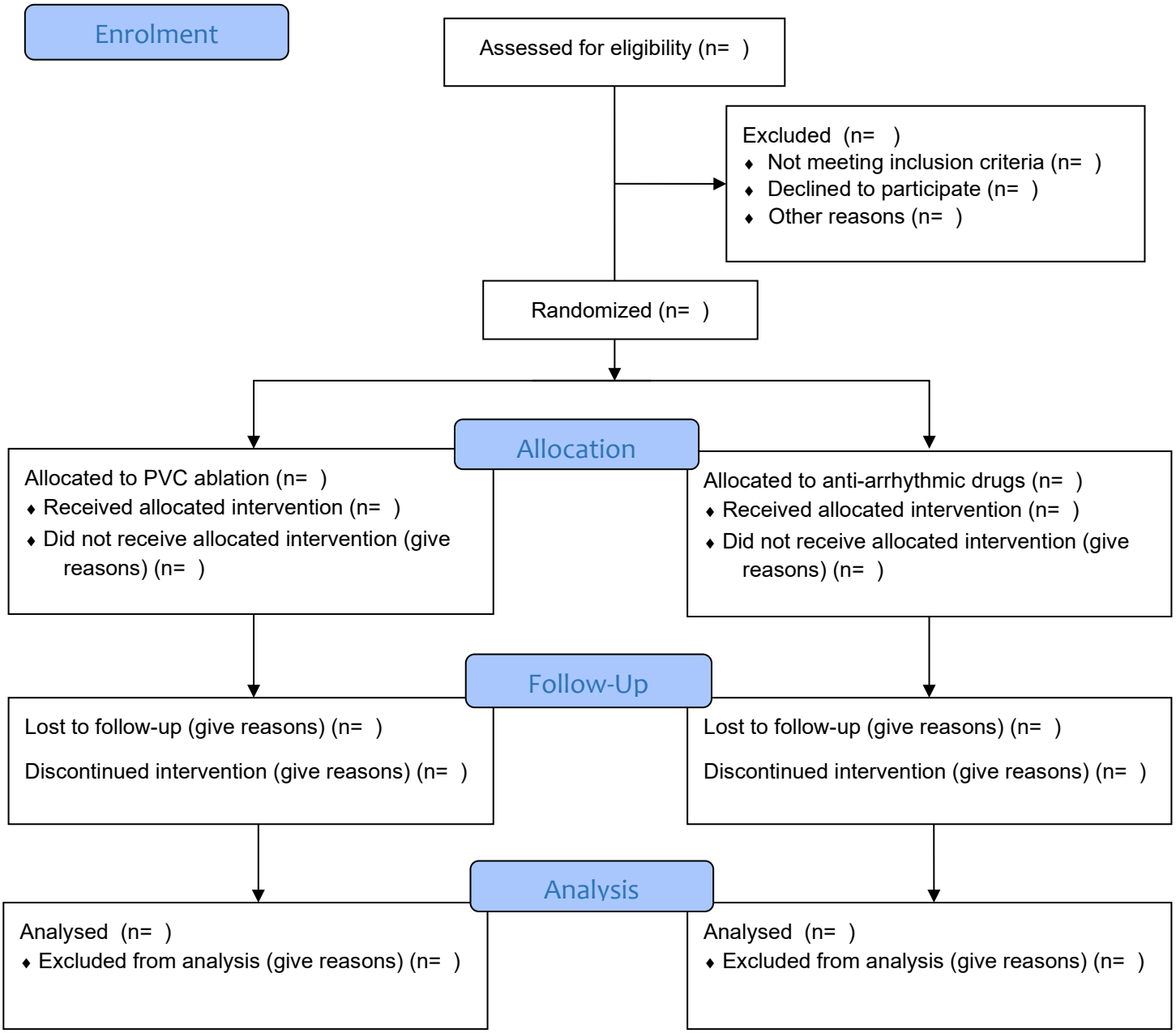


Figure 1: Consort Diagram for the Study

3.3 Baseline Characteristics

Variables that belong to demographic and clinical history information can be divided into categorical and numerical variables. Categorical variables will be summarised by their frequency distribution. Continuous variables will be summarised by descriptive statistics: mean, standard deviation, minimum, median and maximum. Parametric or non-parametric summary statistics will be preferred as appropriate.

Demographic and clinical features include age, sex, BMI, diabetes mellitus, hypertension, hypercholesterolaemia, chronic kidney disease, smoking history, alcohol use, implantable cardioverter defibrillator, atrial fibrillation or flutter, previous electrophysiology study. All current medications including their dose and frequency will be recorded and based on this the current use of the following medications will be listed as binary variables: HMG CoA reductase-inhibitors, ACEI inhibitors, neprilysin inhibitors, angiotensin receptor blockers, SGLT-2 inhibitors, aldosterone antagonists, beta blockers (excluding sotalol), sotalol, flecainide, mexiletine, amiodarone, non-dihydropyridine calcium channel blockers and anticoagulants.

Table 1 Baseline Characteristics by Intervention

Baseline Characteristics	PVC ablation	Anti-arrhythmic drugs
age	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
sex	n/N (%)	n/N (%)
BMI	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Race - white	n/N (%)	n/N (%)
Race – Asian	n/N (%)	n/N (%)
Race – Middle Eastern	n/N (%)	n/N (%)
Race - Indigenous	n/N (%)	n/N (%)
Race - other	n/N (%)	n/N (%)
diabetes mellitus	n/N (%)	n/N (%)
hypertension	n/N (%)	n/N (%)
hypercholesterolaemia	n/N (%)	n/N (%)
chronic kidney disease	n/N (%)	n/N (%)
smoking history (prior or current)	n/N (%)	n/N (%)
alcohol use (prior or current)	n/N (%)	n/N (%)
PVC burden before intervention	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
ASTA quality-of-life score before intervention	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
SF-36 quality-of-life score before intervention	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
DASS-21 quality-of-life score before intervention	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)

EQ-5D-5L quality-of-life score before intervention	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Symptomatic PVCs?	n/N (%)	n/N (%)
Medications at baseline:		
HMG CoA reductase-inhibitors*	n/N (%)	n/N (%)
ACEI inhibitors	n/N (%)	n/N (%)
neprolysin inhibitors	n/N (%)	n/N (%)
angiotensin receptor blockers	n/N (%)	n/N (%)
SGLT-2 inhibitors	n/N (%)	n/N (%)
aldosterone antagonists	n/N (%)	n/N (%)
beta blockers (excluding sotalol)	n/N (%)	n/N (%)
sotalol	n/N (%)	n/N (%)
flecainide	n/N (%)	n/N (%)
mexiletine	n/N (%)	n/N (%)
amiodarone	n/N (%)	n/N (%)
non-dihydropyridine calcium channel blockers	n/N (%)	n/N (%)
anticoagulants	n/N (%)	n/N (%)
Baseline PVC count/24 h	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Baseline PVC burden (%)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Duration of heart rhythm monitoring	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
PVC morphology suggestive of outflow tract source	n/N (%)	n/N (%)
Baseline left ventricular ejection fraction	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Baseline global longitudinal strain	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)

3.4 Summary of Treatment

Procedural data from the CA arm will be described. The same statistical methods will be used as for demographics and clinical history: categorical variables will be summarised by their frequency distribution. Continuous variables will be summarised by descriptive statistics: mean, standard deviation, minimum, median and maximum.

Procedural details include the following: anaesthesia type (sedation/general/TIVA/inhalational), location of PVC by pace mapping, by activation mapping and by site of ablation, inducibility of VT, acute success of ablation, duration of ablation and number of PFA lesions). Where required, these variables are defined in the study protocol.

Table 2 Procedural characteristics in the PVC ablation arm

Variable	Value
General anaesthesia?	n/N (%)
Right ventricular outflow tract ablation alone?*	n/N (%)
Left ventricular outflow tract ablation alone?*	n/N (%)
Intracavitary structure ablation*	n/N (%)
Papillary muscle ablation?*	n/N (%)
Summit ablation (LV/RV/GCV/endocardial LV, epicardial LV)?*	n/N (%)
VT inducible?	n/N (%)
VT cycle length	Mean (SD) Median (IQR) (missing=xx)
Use of isoprenaline?	n/N (%)
Abnormal substrate map?	n/N (%)
RF Ablation duration	Mean (SD) Median (IQR) (missing=xx)
Number of RFA lesions[#]	Mean (SD) Median (IQR) (missing=xx)
Number of sites of ablation	Mean (SD) Median (IQR) (missing=xx)
Acute success of ablation? (elimination of PVCs during the procedure)	n/N (%)

* Based on information from site of ablation, if this is not available then activation map, if this is not available then pace map and if this is not available then 12-lead electrocardiogram.
[#] If pulse field ablation is also used, the number of these lesions will also be counted.

Medication data from the AADs arm will be described. The frequency of each medication used at 12 weeks will be counted (see Table 3). A similar table will be generate for the CA arm, although it is expected that drug use will be very low at 6 and 12 weeks because the trial protocol suggests ceasing medications after CA.

Table 3 Medication use over time in anti-arrhythmic drug arm

Medication	Baseline	6 weeks	12 weeks
beta blockers (excluding sotalol)	n/N (%)	n/N (%)	n/N (%)
sotalol	n/N (%)	n/N (%)	n/N (%)
flecainide	n/N (%)	n/N (%)	n/N (%)
mexiletine	n/N (%)	n/N (%)	n/N (%)
amiodarone	n/N (%)	n/N (%)	n/N (%)

non-dihydropyridine calcium channel blockers	n/N (%)	n/N (%)	n/N (%)

3.5 Primary Outcome

3.5.1 Primary Outcome Determination

The primary endpoint is a binary variable that is reached on a per patient basis if the PVC burden reduces by at least 80% at 12 weeks compared to baseline. The reduction in PVC burden will be calculated as:

$$1 - \frac{\text{post intervention PVC burden}}{\text{baseline PVC burden}}$$

The primary outcome will be 1 if the reduction in PVC burden is ≥ 0.8 and will otherwise be 0. The 12 week heart rhythm monitors will need to be performed within 14 days of their planned date to be included.

3.5.2 Primary Outcome Analysis

The difference between groups will be quoted as percentages in each arm that achieve the primary endpoint. A risk difference with a 95% confidence interval will be calculated with the Wald method and statistical significance will be calculated with the Chi-squared test. If observed cell counts are small (<5), then the Fisher's exact test will be used instead of the Chi-squared test and the Newcombe Wilson method will be used instead of the Wald method.

Table 4 Primary analysis comparing PVC burden between ablation and anti-arrhythmic drugs

	PVC ablation	Anti-arrhythmic drugs	p-value
Percentage of reaching primary outcome of ≥ 80% PVC burden reduction	n/N (%) 95% CI	n/N (%) 95% CI	x.xxx

3.6 Secondary Outcomes

3.6.1 Alternative PVC burden measures

A reduction in PVC burden by at least 99% at 12 weeks as measured by heart rhythm monitoring will be assessed. These will be analysed with the same statistical techniques as the primary outcome using the Wald method and Chi-squared test (or Newcombe Wilson method and Fisher's exact test).

Table 5 Alternative definitions of PVC burden improvement comparing PVC burden between ablation and anti-arrhythmic drugs

	PVC ablation	Anti-arrhythmic drugs	p-value
≥ 99% PVC burden at 12 weeks	n/N (%)	n/N (%)	x.xxx

A secondary analysis to compare PVC-burden at follow up between CA and AADs will be performed using an appropriate regression model. Beta regression will be considered, or inflated beta

regression if boundary values occur. PVC burden at follow-up will be analysed with adjustment for baseline PVC burden. Adjustment will also be performed for outflow tract origin and multiple PVC morphologies by including a categorical covariate with three levels: (1) single morphology outflow tract PVC, (2) single morphology non-outflow tract PVC or (3) PVCs of multiple morphology. Adjustment variables will be limited to these listed pre-specified clinically relevant variables to avoid overfitting. Whether the PVC is from the outflow tract will be judged by clinician expert interpretation of a 12-lead electrocardiogram. Whether there are multiple PVC morphologies will be judged by heart-rhythm monitoring where a single morphology indicates that at least 90% of all PVCs are of a single morphology. Results will be presented as mean treatment differences with 95% confidence intervals and corresponding p values.

The average duration of Holter monitoring will also be reported.

Table 6 PVC burden as a continuous outcome between ablation and anti-arrhythmic drugs

Percentage of PVC burden	PVC ablation	Anti-arrhythmic drugs	Mean difference (95% CI)	P value
Baseline	Raw Mean (SD) Raw Median (IQR) (missing=xx)	Raw Mean (SD) Raw Median (IQR) (missing=xx)	difference (95% CI)	
12 weeks	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Difference (95% CI)	
Raw difference between 12 weeks and baseline	raw mean difference (SD)	raw mean difference (SD)	difference (95% CI)	
Adjusted analysis using regression at 12 weeks	model mean (SD)	model mean (SD)	adjusted mean difference (95% CI)	x.xxx

3.6.2 Quality of life

Self-reported quality of Life score at 6 and 12 weeks as measured by questionnaires (ASTA, SF-36, DASS21 and EQ-5D-5L) will be compared to baseline. The ASTA will be the primary quality of life measure. Confidence intervals and statistical significance of between group differences will be determined by ANCOVA adjusting for baseline value and PVC morphology as above. Table 7 will be presented for scores from ASTA, SF-36, DASS21 and EQ-5D-5L. If the normal distribution assumption is not valid other distributions will be considered.

Table 7 Quality of life compared between ablation and anti-arrhythmic drugs

Score from ASTA, SF-36, DASS21 and EQ-5D-5L	PVC ablation	Anti-arrhythmic drugs	Mean difference (95% CI)	P value
Baseline	Raw Mean (SD) Raw Median (IQR) (missing=xx)	Raw Mean (SD) Raw Median (IQR) (missing=xx)	difference (95% CI)	
6 weeks	Raw Mean (SD) Raw Median (IQR) (missing=xx)	Raw Mean (SD) Raw Median (IQR) (missing=xx)	difference (95% CI)	
12 weeks	Mean (SD)	Mean (SD)	Difference	

	Median (IQR) (missing=xx)	Median (IQR) (missing=xx)	(95% CI)	
Raw difference between 6 weeks and baseline	raw mean difference (SD)	raw mean difference (SD)	difference (95% CI)	
Adjusted analysis using regression at 6 weeks	model mean (SD)	model mean (SD)	adjusted mean difference (95% CI)	x.xxx
Raw difference between 12 weeks and baseline	raw mean difference (SD)	raw mean difference (SD)	difference (95% CI)	
Adjusted analysis using regression at 12 weeks	model mean (SD)	model mean (SD)	adjusted mean difference (95% CI)	x.xxx

This table will be replicated for each composite score from the ASTA, SF-36, DASS21 and EQ-5D-5L: ASTA quality-of-life score, ASTA symptom score, SF-36 aggregated physical component score, SF-36 aggregated mental component score, DASS-21 quality-of-life score, DASS-21 anxiety score, DASS-21 depression score, utility measured by EQ-5D-5L.

3.6.3 Healthcare utilisation

Healthcare utilisation will be quantified by counting hospital admissions and secondly cardiovascular hospital admissions. Statistical significance will be reported using Poisson regression or negative binomial regression depending on whether there is overdispersion.

Table 8 Secondary analysis of healthcare utilisation – hospital admissions

Hospital admissions	PVC ablation	Anti-arrhythmic drugs	RR (95% CI)	p-value
Had a hospital admission†	n/N (%)	n/N (%)	x.x (x.x,x.x)	x.xxx
Cardiovascular hospitalisation*	n, m (SD)	n, m (SD)	x.x (x.x,x.x)	x.xxx
Non cardiovascular hospitalisation*	n, m (SD)	n, m (SD)	x.x (x.x,x.x)	x.xxx
All hospitalisations*	n, m (SD)	n, m (SD)	x.x (x.x,x.x)	x.xxx

†represents the number of participants rather than events

*n, m (SD), where n is the number of events across all patients, and m is the mean number of events per patient within 12 weeks of follow up

3.7 Subgroup Analysis

Heterogeneity of treatment effect between the following groups will be assessed: sex, age (above or below the median), ejection fraction (above or below the median), beta blocker (not sotalol) only arrhythmic or not, PVC morphology (only suspected outflow tract or elsewhere) and presence of multiple PVC morphologies on heart rhythm monitoring. This will be done by fitting a logistic regression on the primary outcome with treatment as a fixed effect and the interaction of treatment and each covariate of interest. Subgroup analysis will be exploratory and be interpreted cautiously due to the small sample size.

Table 9 Interaction analysis

Covariate	PVC ablation	Anti-arrhythmic drugs	Treatment effect OR (95% CI)	Interaction p-value
Gender				x.xx
Male	n/N (%)	n/N (%)	x.xx (x.xx, x.xx)	
Female	n/N (%)	n/N (%)	x.xx (x.xx, x.xx)	
Ejection fraction				x.xx
Below	n/N (%)	n/N (%)	x.xx (x.xx, x.xx)	
Above	n/N (%)	n/N (%)	x.xx (x.xx, x.xx)	
Beta blocker				x.xx
Yes	n/N (%)	n/N (%)	x.xx (x.xx, x.xx)	
No	n/N (%)	n/N (%)	x.xx (x.xx, x.xx)	
PVC morphology				x.xx
Yes	n/N (%)	n/N (%)	x.xx (x.xx, x.xx)	
No	n/N (%)	n/N (%)	x.xx (x.xx, x.xx)	
Multiple PVC morphologies				x.xx
Yes	n/N (%)	n/N (%)	x.xx (x.xx, x.xx)	
No	n/N (%)	n/N (%)	x.xx (x.xx, x.xx)	

3.8 Safety Analysis

Adverse events and complications that occur at any point during the study in the CA and AADs arm will be counted. Depending on what adverse events are recorded, they will be grouped for easy interpretation. The full list of adverse events and side effects will be included in the supplementary information.

Serious adverse events will be defined as any untoward medical occurrence that results in any of the following

1. Death
2. Is life threatening in the opinion of the attending clinician
3. Requires inpatient hospitalisation or prolongation of existing hospitalisation
4. Results in persistent or significant disability or incapacity.
5. Is an important medical event in the opinion of the attending clinician that is not immediately life-threatening and does not result in death or hospitalisation, but which may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above.

The following events are not considered to be SAEs:

1. Planned hospitalisations for pre-existing condition.
2. Hospital admission for interventions or procedures required by the study protocol.
3. Emergency department presentation, without admission, for non-cardiovascular events.

Table 10 Primary and secondary outcomes

Adverse event	CA arm	AADs arm
Death	n/N (%)	n/N (%)
Failure of adherence to medical therapy	n/N (%)	n/N (%)
Medication side effects		
Visual symptoms (decreased vision, blurring, halos, visual changes)	n/N (%)	n/N (%)
Hypothyroidism	n/N (%)	n/N (%)
Hyperthyroidism	n/N (%)	n/N (%)
Hepatic dysfunction / hepatotoxicity	n/N (%)	n/N (%)
Symptomatic bradycardia / bradycardia	n/N (%)	n/N (%)
Torsades de pointes	n/N (%)	n/N (%)
Skin adverse event / rash	n/N (%)	n/N (%)
Photosensitivity	n/N (%)	n/N (%)
Skin discoloration	n/N (%)	n/N (%)
Tremor	n/N (%)	n/N (%)
Ataxia	n/N (%)	n/N (%)
Insomnia / sleep changes	n/N (%)	n/N (%)
Peripheral neuropathy	n/N (%)	n/N (%)
Heart failure	n/N (%)	n/N (%)
Fatigue	n/N (%)	n/N (%)
Gastrointestinal disturbances (nausea, vomiting, indigestion, flatulence, cramps, diarrhoea, constipation, ulceration)	n/N (%)	n/N (%)
Sensory disturbances (paraesthesia, taste abnormalities, hearing abnormalities)	n/N (%)	n/N (%)
Central nervous system effects (depression, mood changes, anxiety, confusion, delirium)	n/N (%)	n/N (%)
Sexual dysfunction (reduced libido or impotence)	n/N (%)	n/N (%)
Light-headedness / dizziness / faintness on standing	n/N (%)	n/N (%)
Involuntary muscle movements / neurological abnormality	n/N (%)	n/N (%)
Physical weakness or lack of energy	n/N (%)	n/N (%)
Shortness of breath / wheezing / laboured breathing	n/N (%)	n/N (%)
Burning, crawling, itching, numbness, prickling, pins and needles or tingling sensations	n/N (%)	n/N (%)
Cardiac arrhythmias	n/N (%)	n/N (%)
Hypotension	n/N (%)	n/N (%)
Interstitial pneumonitis	n/N (%)	n/N (%)
Severe cutaneous adverse reactions	n/N (%)	n/N (%)
QT prolongation	n/N (%)	n/N (%)
Optic neuropathy / optic neuritis	n/N (%)	n/N (%)
Vortex keratopathy	n/N (%)	n/N (%)
Transaminitis	n/N (%)	n/N (%)
Vertigo	n/N (%)	n/N (%)
Headache	n/N (%)	n/N (%)
Catheter ablation complications		
Procedure-related death (30-day mortality)	n/N (%)	n/N (%)
Retroperitoneal haemorrhage	n/N (%)	n/N (%)

Other major vascular injury (requiring surgical repair or a blood transfusion >1 unit of packed red cells)	n/N (%)	n/N (%)
Sepsis or bloodstream infection	n/N (%)	n/N (%)
Access-site infection	n/N (%)	n/N (%)
Pneumothorax	n/N (%)	n/N (%)
Anaesthesia-related complications	n/N (%)	n/N (%)
Acute kidney injury	n/N (%)	n/N (%)
Thromboembolism	n/N (%)	n/N (%)
Stroke	n/N (%)	n/N (%)
Transient ischaemic attack	n/N (%)	n/N (%)
Deep vein thrombosis	n/N (%)	n/N (%)
Embolism to limb or peripheral organs	n/N (%)	n/N (%)
Cardiac bleeding	n/N (%)	n/N (%)
Cardiac tamponade requiring percutaneous or surgical drainage	n/N (%)	n/N (%)
Valve injury	n/N (%)	n/N (%)
New-onset valvular regurgitation on follow-up	n/N (%)	n/N (%)
Temporary complete heart block	n/N (%)	n/N (%)
Permanent complete heart block	n/N (%)	n/N (%)
Myocardial ischaemia or infarction (defined by rise and fall of cardiac biomarkers with symptoms of ischaemia)	n/N (%)	n/N (%)
Myocardial ischaemia or infarction (defined by rise and fall of cardiac biomarkers with new ST changes or new left bundle branch block)	n/N (%)	n/N (%)
Myocardial ischaemia or infarction (defined by rise and fall of cardiac biomarkers with development of Q waves)	n/N (%)	n/N (%)
Myocardial ischaemia or infarction (defined by rise and fall of cardiac biomarkers with imaging evidence of new loss of viable myocardium or new regional wall motion abnormality)	n/N (%)	n/N (%)
Acute heart failure occurring within 48 hours of catheter ablation	n/N (%)	n/N (%)
Complications of epicardial access and/or ablation	n/N (%)	n/N (%)
Pericardial bleeding	n/N (%)	n/N (%)
Injury to subdiaphragmatic vessels or organs	n/N (%)	n/N (%)
Coronary artery injury	n/N (%)	n/N (%)
Phrenic nerve injury	n/N (%)	n/N (%)
Severe pericarditis or pleuritic pain requiring hospitalisation >72 hours	n/N (%)	n/N (%)