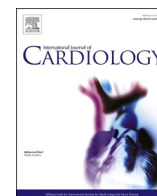




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## Atrial flutter and fibrillation in patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension in the ASPIRE registry: Comparison of rate versus rhythm control approaches

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## ABSTRACT

**Background:** The development of atrial flutter and fibrillation (AFL/AF) in patients with pre-capillary pulmonary hypertension has been associated with an increased risk of morbidity and mortality. Rate and rhythm control strategies have not been directly compared.

**Methods:** Eighty-four patients with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) with new-onset AFL/AF were identified in the ASPIRE registry. First, baseline characteristics and rates of sinus rhythm (SR) restoration of 3 arrhythmia management strategies (rate control, medical rhythm control and DC cardioversion, DCCV) in an early (2009–13) and later (2014–19) cohort were compared. Longer-term outcomes in patients who achieved SR versus those who did not were then explored.

**Results:** Sixty (71%) patients had AFL and 24 (29%) AF. Eighteen (22%) patients underwent rate control, 22 (26%) medical rhythm control and 44 (52%) DCCV. SR was restored in 33% treated by rate control, 59% medical rhythm control and 95% DCCV ( $p < 0.001$ ). Restoration of SR was associated with greater improvement in functional class (FC) and Incremental Shuttle Walk Distance ( $p$  both  $< 0.05$ ). It also independently predicted superior survival (3-year survival 62% vs 23% in those remaining in AFL/AF,  $p < 0.0001$ ). In addition, FC III/IV independently predicted higher mortality (HR 2.86,  $p = 0.007$ ). Right atrial area independently predicted AFL/AF recurrence (OR 1.08,  $p = 0.01$ ). DCCV was generally well tolerated with no immediate major complications. **Conclusions:** Restoration of SR is associated with superior functional improvement and survival in PAH/CTEPH compared with rate control. DCCV is generally safe and is more effective than medical therapy at achieving SR.

### 1. Introduction

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are clinical syndromes characterised by increased right ventricular afterload due to elevated pulmonary vascular resistance (PVR) and pressure resulting from pulmonary artery remodelling and obstruction [1]. Subsequent progressive

right ventricular dysfunction results in functional tricuspid regurgitation, an increase in right atrial pressure and right atrial dilatation [2].

Atrial arrhythmias such as atrial flutter (AFL) and atrial fibrillation (AF) are common in patients with PAH and CTEPH with a cumulative incidence ranging from 10 to 33% [3–11]. Possible mechanisms for atrial arrhythmias in pulmonary hypertension (PH) include electrical remodelling subsequent to right atrial stretch/fibrosis [12–15] and

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sympathetic overdrive [16–19]. The loss of atrial contraction at end-diastole leads to reduced right ventricular filling, a decrease in cardiac output and subsequent clinical worsening with symptoms and signs of heart failure [5–9]. Restoration of sinus rhythm with electrical cardioversion (DCCV), antiarrhythmic drugs or catheter ablation seems to reverse cardiac decompensation [7]. Atrial arrhythmias in PAH/CTEPH have been correlated with an increased risk of mortality, highlighting the importance of restoring and maintaining sinus rhythm [3–6,10].

Although current international guidelines recommend a rhythm control strategy in PAH/CTEPH [1], there are no data directly comparing rate versus rhythm control. In addition, electrical and pharmacological methods to restore sinus rhythm have not been compared. We have therefore performed a retrospective observational study firstly to compare rates of sinus rhythm restoration following medical rate control, medical rhythm control and DCCV. We hypothesised that electrical cardioversion is safe and more likely to restore normal rhythm than a purely pharmacological approach. Secondly, we also hypothesised that successful rhythm control will result in improved functional status and survival.

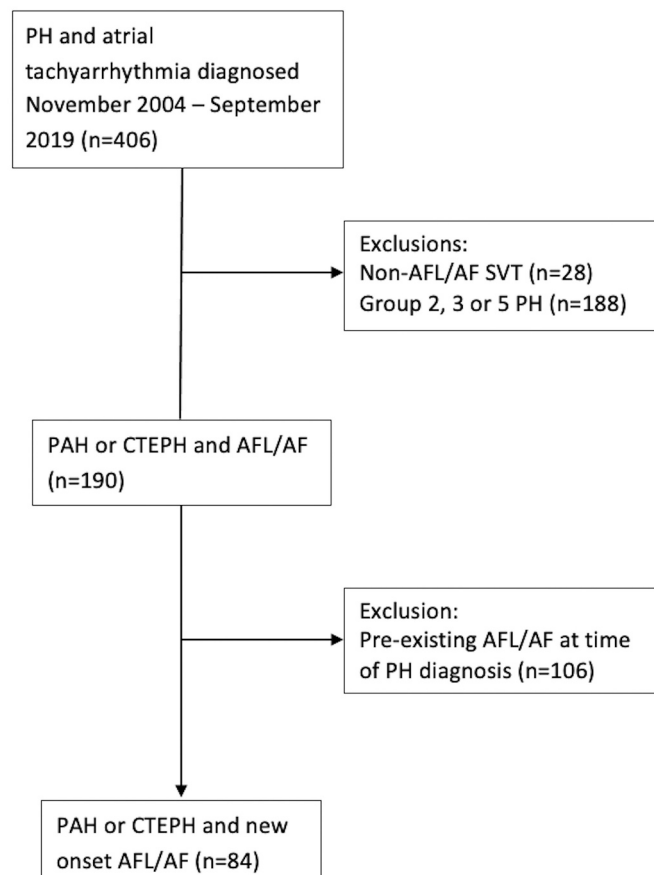
## 2. Methods

### 2.1. Enrolment

We interrogated the ASPIRE (Assessing the Spectrum of Pulmonary

hypertension Identified at a REferral centre) registry to identify all patients with PAH and CTEPH (both inoperable and operable) noted to have new-onset AFL or AF diagnosed in our centre between November 2004 and September 2019 (Fig. 1). Patients with previously diagnosed AFL/AF at the time of referral were not included. Patients with significant parenchymal lung disease or spirometric abnormality were defined as having group 3 disease and were excluded as previously described [20]. Censoring was performed on 1st April 2021. Clinical practice in attempting to restore sinus rhythm in our centre changed, due to availability of expertise and resources, from a medication-based approach (early cohort) to a predominantly DCCV-based approach from 2014 (later cohort). For the later cohort our approach was a rhythm control strategy with DCCV (often preceded by anticoagulation, if not already anticoagulated, and beta blockers +/- digoxin for initial rate control). In some patients we also commenced anti-arrhythmic medication following successful DCCV to maintain sinus rhythm. For the early cohort our approach was purely medical consisting of amiodarone for AFL and rate control alone for AF. Eligibility was determined based on a right heart catheterisation demonstrating both a mean pulmonary arterial pressure  $\geq 25$  mmHg and pulmonary arterial wedge pressure  $\leq 15$  mmHg and AFL or AF confirmed on a 12-lead ECG. The definition of AF was based on irregularly irregular R-R intervals, absence of distinct repeating P waves and presence of irregular atrial activations [21]. Typical AFL was defined as an arrhythmia with an atrial rate between 250 and 330 beats/min and a sawtooth pattern in leads II, III and

### Consort Diagram



Abbreviations: PH, pulmonary hypertension; AFL, atrial flutter; AF, atrial fibrillation; SVT, supraventricular tachycardia; PAH, pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension

Fig. 1. Consort diagram of the study.

aVF, whilst other atypical forms of AFL were also considered if they had a similar atrial waveform appearance [22]. Patients with other forms of PH, other supraventricular arrhythmias, perioperative arrhythmias around the time of pulmonary endarterectomy or pre-existing AF or AFL were excluded from the study.

## 2.2. Data retrieval

Data were retrieved from outpatient clinic visits or inpatient admissions related to patients' first presentation with AFL/AF or arrhythmia recurrence. The management strategy of the arrhythmia (rate versus rhythm control) and the method of rhythm control (medications, DCCV or catheter ablation) was recorded. We retrieved pulmonary haemodynamics prior to arrhythmia onset (mean interval 26 months). Atrial size measurements were performed retrospectively by 2 investigators (MAS and AC), blinded to clinical details, using the computer tomography (CT) chest scan nearest to arrhythmia onset (mean 11 months). WHO Functional Class (FC) and Incremental Shuttle Walk Distance (ISWD) were recorded at the time of arrhythmia diagnosis, at the clinic visit before onset (mean 6 months) and at the first visit after arrhythmia treatment initiation (mean 5 months). An improvement in ISWD was defined as a  $\geq 15\%$  increase between arrhythmia onset and the first available follow-up visit [23].

## 2.3. Arrhythmia management

Patients were assigned a management strategy: rate control (strategy 1), rhythm control with medications only (strategy 2) and rhythm control with DCCV with or without medications (strategy 3). Strategy 1 patients were treated with digoxin monotherapy, a non-dihydropyridine calcium channel blocker (CCB) or a combination of digoxin and a cardioselective beta blocker. Strategy 2 patients were treated with amiodarone as monotherapy or in combination with a rate control agent. Strategy 3 patients underwent DCCV with or without rate or rhythm control medications. DCCV was performed when patients had been adequately anticoagulated for at least 3 weeks. Successful cardioversion was documented instantly (in case of DCCV) or at a subsequent follow up visit if patients were treated by medications only.

## 2.4. Statistics

Most parameters did not exhibit normal distribution and are presented as median (interquartile range). Continuous variables between the 3 different groups were compared using the Kruskal-Wallis test. The Mann-Whitney  $U$  test was used when comparing continuous variables between cardioverted and non-cardioverted patients. Categorical variables were compared using  $\chi^2$  test. Wilcoxon signed rank test was used to compare ISWD at different time periods related to arrhythmia onset. Binary logistic regression was performed to identify predictors of arrhythmia recurrence following cardioversion. If a patient had multiple cardioversions and recurrences, only the first event was considered for the purposes of this regression analysis. Forward likelihood ratio Cox regression analysis was performed to identify risk factors for mortality with parameters having a  $p$ -value  $< 0.2$  being entered into multivariate analysis. Kaplan-Meier survival analysis was performed to compare survival from arrhythmia therapy onset in cardioverted and non-cardioverted patients. Further analysis was performed on cardioverted patients to compare survival with or without arrhythmia recurrence.  $P$ -values  $< 0.05$  were considered statistically significant. All calculations were performed using IBM SPSS Statistics 26 (SPSS Statistics for Macintosh, Version 26.0. Armonk, NY, USA: IBM Corp) and GraphPad Prism 9 (GraphPad Prism version 9.3.1 for Macintosh. San Diego, CA, USA).

## 2.5. Ethics

This study was conducted using data extracted from the ASPIRE registry (research database REC ref. 22/EE/0011). This study was approved by the ASPIRE data management committee and data was extracted and anonymised as per ASPIRE standard operating policy.

## 3. Results

### 3.1. Baseline characteristics and arrhythmia treatment

Eighty-four patients were included in the study including 40 patients treated by a purely medical approach and 44 patients who underwent DCCV (Table 1). Sixty percent, 29%, 9% and 2% of patients had 0, 1, 2 and 3 cardiac comorbidities respectively (defined as systemic hypertension, diabetes, ischaemic heart disease or valve replacement). There was no significant difference in number of comorbidities between those in strategy 1 group compared with strategies 2 and 3 ( $p = 0.5$ ). Of the 66 patients treated with rhythm control, 22 (33%) received medication only while 44 (67%) received DCCV with or without medications. Sixty patients (71%) had AFL. A higher percentage of patients with AF rather than AFL were treated by rate control. There was no significant difference in atrial size or pulmonary haemodynamics between patients with AFL and AF (Supplementary Table 1). Thirty-one percent of patients had evidence of thyroid disease, defined as treated or untreated hyper- or hypothyroidism at the time of arrhythmia onset.

Seventy-one patients (84%) were receiving PAH therapies at arrhythmia onset; 42 monotherapy (26 on phosphodiesterase-5 inhibitors, 14 on endothelin receptor antagonists and 2 on prostanoids) and 29 combination therapy, including 9 patients treated with prostanoids. PAH therapies were intensified in 40% of patients at the time or within 3 months following arrhythmia onset. Forty-four percent of patients in whom SR was restored had PAH therapy escalated compared with 30% of patients who remained in AF/AFL ( $p = 0.25$ ).

In strategy group 1 (rate control), 10 patients (56%) received digoxin monotherapy, 1 (6%) CCB monotherapy, 4 (22%) a combination of digoxin and bisoprolol while 3 patients (17%) were not treated with rate-limiting medication. In strategy group 2 (medical rhythm control), 9 patients (41%) received amiodarone monotherapy, 11 (50%) digoxin and amiodarone, and 2 (9%) CCB and amiodarone. In strategy group 3 (DCCV), 36 patients (82%) received rate-limiting or anti-arrhythmic monotherapy (9 (20%) beta blockers, 1 (2%) digoxin, 21 (48%) amiodarone, 4 (9%) flecainide, 1 (2%) CCB) and 1 patient (2%) a combination of amiodarone and digoxin. The vast majority of amiodarone was commenced following DCCV. Beta blocker therapy was instituted cautiously, especially in patients with pre-existing severe right ventricular dysfunction.

Eleven patients treated with DCCV subsequently underwent catheter ablation for AFL with no significant procedure-related adverse events. Four patients underwent ablation soon after DCCV while 7 patients underwent the procedure following 1 or more arrhythmia recurrences. None of the patients with AF received catheter ablation treatment.

Sixty-nine percent of patients were receiving anticoagulation with warfarin or a direct oral anticoagulant at arrhythmia onset. A further 19% of patients were commenced on anticoagulation following diagnosis of arrhythmia. Ten patients were not anticoagulated due to significant iron deficiency anaemia and/or recent bleeding and the presence of hereditary haemorrhagic telangiectasia with significant epistaxis. Overall, 73% of patients who were anticoagulated received a vitamin K antagonist and 23% a direct oral anticoagulant.

### 3.2. Sinus rhythm restoration

In total, 61 patients (73%) achieved restoration of sinus rhythm. Baseline characteristics were compared between those who reverted to sinus rhythm versus those who remained in AFL/AF (Table 2). Patients

**Table 1**  
Baseline characteristics.

	All patients (n = 84)	Strategy 1: Rate control (n = 18)	Strategy 2: Rhythm control with medication only (n = 22)	Strategy 3: Rhythm control with DCCV +/- medication (n = 44)	P-value
Years of enrolment		2009–14 (Early Cohort)		2014–19 (Later Cohort)	
Age at time of diagnosis (years)	66 (57–73)	69 (64–76)	61 (54–69)	66 (57–73)	0.11
Female (%)	46	67	45	39	0.13
Diagnosis					0.28
IPAH, n (%)	26 (31)	3 (16.7)	6 (27.3)	17 (38.6)	
PAH-CTD, n (%)	18 (21.4)	7 (38.9)	5 (22.7)	6 (13.6)	
PAH-CHD, n (%)	7 (8.3)	3 (16.7)	2 (9.1)	2 (4.5)	
PoPH, n (%)	1 (1.1)	0 (0)	0 (0)	1 (2.3)	
CTEPH, n (%)	32 (38.1)	5 (27.8)	9 (40.9)	18 (40.9)	
Haemodynamics*					
mRAP (mmHg)	10 (8–14)	10.5 (3–14)	10 (8–16)	9 (7–14)	0.66
mPAP (mmHg)	48 (41–58)	41 (39–51)	49 (45–60)	52.5 (42–60)	0.07
PAWP (mmHg)	11 (8–14)	7 (5–13)	11 (9–13)	11 (8–15)	0.22
CO (L/min)	4.6 (3.3–5.3)	4.1 (3.7–5.1)	4.7 (3.4–5.2)	4.6 (3.1–5.7)	0.93
CI (L/min/m <sup>2</sup> )	2.4 (1.9–2.7)	2.4 (2.1–2.7)	2.2 (1.8–2.9)	2.3(1.7–2.7)	0.53
PVR (dyn/s/cm <sup>5</sup> )	688 (491–1124)	647 (436–775)	778 (489–1165)	710 (478–1131)	0.67
Arrhythmia					0.02
Atrial fibrillation (%)	29	50	36	16	
Atrial flutter (%)	71	50	64	84	
WHO FC*					0.58
I (%)	1	0	5	0	
II (%)	19	22	18	18	
III (%)	73	78	68	73	
IV (%)	7	0	9	9	
ISWD (m)*	180 (75–270)	100 (40–270)	225 (60–310)	185 (103–268)	0.46

Data expressed as median (interquartile range). \*Refers to most recent assessment prior to arrhythmia onset. Abbreviations: DCCV, DC Cardioversion; PAH, pulmonary arterial hypertension; IPAH, idiopathic PAH; CTD, connective tissue disease; CHD, congenital heart disease; PoPH, portopulmonary hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; mRAP, mean right atrial pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; WHO FC, world health organisation functional class; ISWD, incremental shuttle walking distance.

**Table 2**  
Baseline characteristics for patients who reverted to sinus rhythm versus remained in AFL/AF.

	Sinus rhythm restored (n = 61)	Remained in AFL/AF (n = 23)	P-value
Age at time of diagnosis (years)	65 (56–72)	67 (59–73)	0.46
Female (%)	41	61	0.14
Haemodynamics*			
mRAP (mmHg)	10 (7–3)	10 (8–15)	0.58
mPAP (mmHg)	48 (41–58)	49.5 (41–59)	0.70
PAWP (mmHg)	11 (8–14)	9 (6–14)	0.51
CO (L/min)	4.6 (3.2–5.4)	4.6 (3.5–5.1)	0.66
CI (L/min/m <sup>2</sup> )	2.3 (1.9–2.7)	2.5 (1.8–2.9)	0.54
PVR (dyn/s/cm <sup>5</sup> )	655 (456–1124)	785 (527–1097)	0.44
Arrhythmia			0.02
Atrial fibrillation (%)	21	48	
Atrial flutter (%)	79	52	
WHO FC*			0.17
I (%)	0	5	
II (%)	20	17	
III (%)	70	78	
IV (%)	10	0	
ISWD (m)*	190 (90–265)	110 (42–333)	0.63

Data expressed as median (interquartile range). \*Refers to most recent assessment prior to arrhythmia onset. Abbreviations: mRAP, mean right atrial pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; WHO FC, World Health Organisation functional class; ISWD, incremental shuttle walking distance.

with AFL were more likely to cardiovert than patients with AF (80% vs 54%). Similar proportions of patients with CTEPH and idiopathic PAH achieved sinus rhythm (81% versus 76%,  $p > 0.05$ ). Sinus rhythm was restored in 6/18 (33%) patients treated by rate control, 13/22 (59%) by

medical rhythm control and 42/44 (95%) by DCCV,  $p < 0.05$ . DCCV was more likely to restore sinus rhythm than pharmacological cardioversion ( $p < 0.001$ ) (Fig. 2a).

### 3.3. Functional improvement

Data on functional status at arrhythmia onset and at first follow-up visit were available and analysed in 68 patients (81%) for FC and 52 (62%) for ISWD. Twenty-eight out of 68 patients (41%) demonstrated an improvement in FC after arrhythmia treatment. Patients who were in sinus rhythm at their follow-up visit were more likely to have improved in FC than those who remained in AFL/AF (49% vs 8%,  $p = 0.006$ , Fig. 2b). Patients achieving sinus rhythm were more likely to experience improvement in ISWD  $\geq 15\%$  than those who remained in AFL/AF (78% vs 42%,  $p = 0.018$ , Fig. 2c).

### 3.4. Arrhythmia recurrence

28/61 patients (46%) who achieved sinus rhythm experienced one or more recurrences of arrhythmia during the study period. The median time from arrhythmia to recurrence was 8 (3,25) months. Right atrial (RA) size measured on CT was the only significant predictor of arrhythmia recurrence at binary logistical regression (OR 1.08, CI 1.02–1.14;  $p = 0.01$ , Table 3). Recurrence rates between the three management strategies were not compared due to the heterogeneity of long-term antiarrhythmic medications in the DCCV group following initial treatment. However, patients receiving amiodarone did demonstrate a non-significant trend towards lower recurrence rates (OR 0.43, CI 0.13–1.45;  $p = 0.17$ ).

### 3.5. Survival

The mortality rate during the study period was 64% with a median

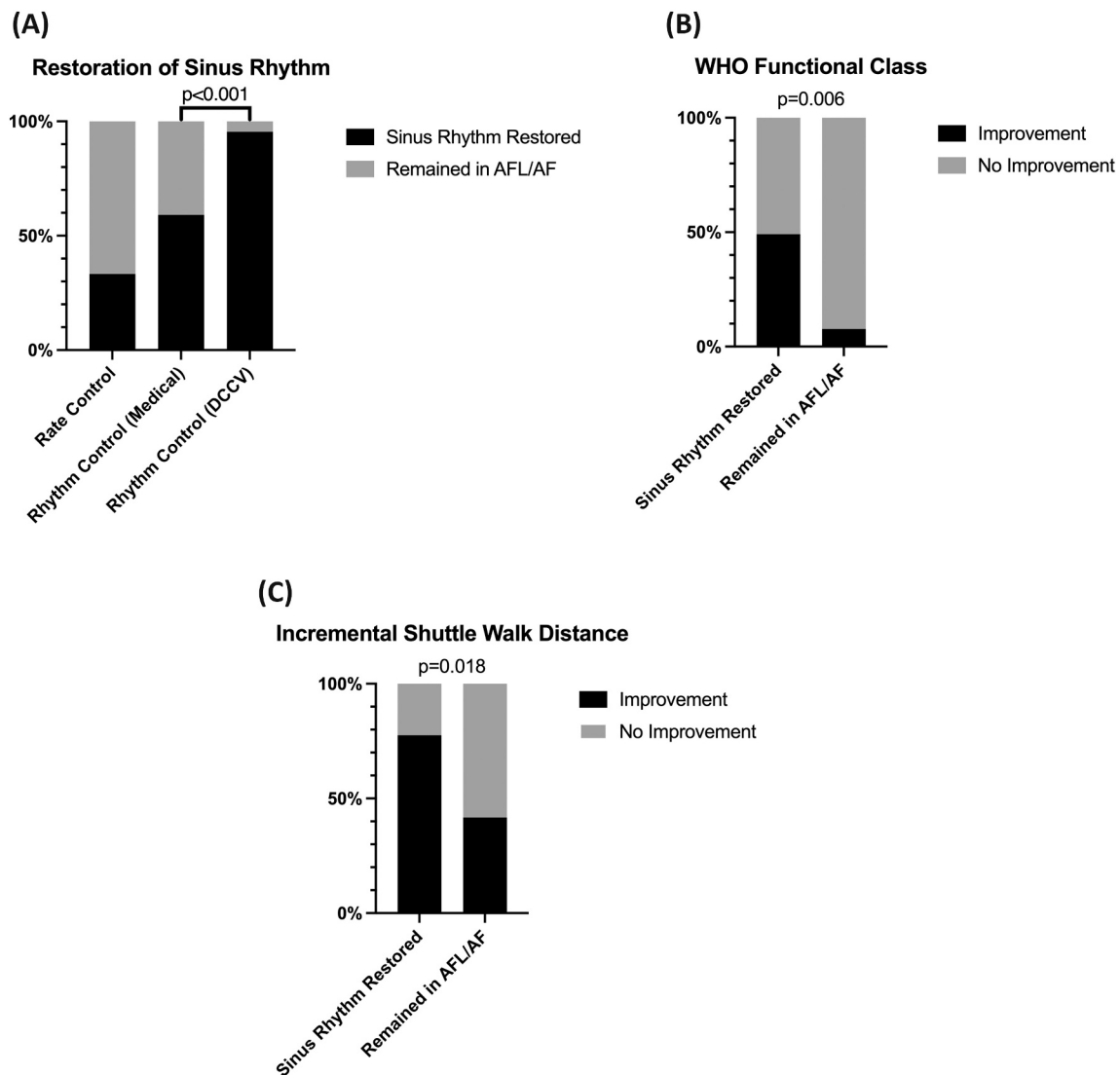


Fig. 2. Chance of restoration of sinus rhythm with different treatment strategies and its impact on functional status.

**Table 3**

Binary logistical regression for recurrence of atrial arrhythmia following cardioversion.

	OR (95% CI)	P-value
Age at arrhythmia onset (yrs)	0.99 (0.95, 1.03)	0.57
mRAP (mmHg)	0.95 (0.86, 1.06)	0.39
RA area (cm <sup>2</sup> )	1.08 (1.02, 1.14)	0.01
Long-term Amiodarone	0.43 (0.13, 1.45)	0.17

Abbreviations: OR, odds ratio; mRAP, mean right atrial pressure; RA, right atrial.

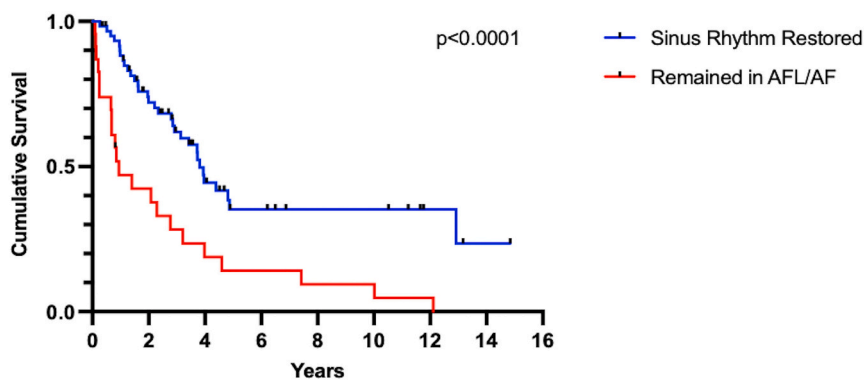
time from arrhythmia onset to death of 22 months. Survival in patients who achieved sinus rhythm was superior to those who remained in AFL/AF (3-year survival of 62% versus 23%;  $p < 0.001$ , Fig. 3). Multivariate analysis demonstrated a lower risk of mortality following restoration of sinus rhythm (HR 0.28, CI 0.15 to 0.53;  $p < 0.001$ , Table 4). Conversely, FC III/IV at most recent assessment before arrhythmia treatment was a risk factor for mortality (HR 2.86, CI 1.33 to 6.13;  $p = 0.007$ ). We did not demonstrate a significant difference in survival between patients who achieved sinus rhythm and then maintained it and those who experienced one or more arrhythmia recurrences ( $p = 0.42$ , log rank analysis). If the 18 CTEPH patients who underwent pulmonary endarterectomy were excluded from analysis, then similar results were observed with 3-

year survival of 60% in those who had sinus rhythm restored compared with 23% in those who did not ( $p < 0.001$ ). Similarly, sinus rhythm restoration and lower FC at most recent assessment prior to arrhythmia onset remained independent predictors of survival at Cox regression. In addition, higher age at arrhythmia onset was also an independent predictor of mortality (HR 1.04, CI 1.01 to 1.07;  $p = 0.01$ ).

### 3.6. Complications of arrhythmia treatment

Three patients treated with amiodarone (7%) developed abnormal thyroid function tests requiring cessation. Two other patients developed an isolated modest rise in T4 levels that did not require amiodarone cessation. No patients required complex treatments such as radioactive iodine or thyroidectomy. Following DCCV, 3/44 (7%) developed transient bradycardia and 5/44 (11%) transient hypotension. Propofol with midazolam were the most frequently used anaesthetic agents for sedation with a smaller number receiving etomidate. Low or high flow oxygen was prophylactically used to avoid desaturation during DCCV. There were no major complications or deaths immediately following DCCV apart from in a single patient with end-stage PAH who needed vasopressor support on intensive care unit post-DCCV and sadly died 3 days later. Although a contribution of DCCV and anaesthesia to this outcome cannot be excluded, the patient had a very poor functional

## Survival from arrhythmia therapy



Patients at risk

Years	0	2	4	6	8	10	12	14	16
Sinus rhythm restored	61	38	17	10	7	7	3	1	0
Remained in AFL/AF	23	9	4	3	2	2	1	0	0

Abbreviations: AFL, atrial flutter; AF, atrial fibrillation

Fig. 3. Survival in patients with restored sinus rhythm and those who remained in atrial arrhythmia.

Table 4

Cox regression mortality analysis.

	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at arrhythmia onset (yrs)	1.03 (1.01, 1.06)	0.005		
mRAP (mmHg)*	1.02 (0.98, 1.07)	0.367		
PVR (dyn/s/cm <sup>5</sup> )*	1.0 (1.0, 1.001)	0.221		
Restoration of sinus rhythm	0.35 (0.199, 0.60)	<0.001	0.28 (0.15, 0.53)	<0.001
WHO FC (ref = I/II)*	2.1 (1.02, 4.31)	0.044	2.86 (1.33, 6.13)	0.007
ISWD (m)*	0.995 (0.993, 0.999)	0.042		

\* Refers to most recent assessment prior to arrhythmia onset. Abbreviations: mRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; WHO FC, World Health Organisation functional class; ISWD, incremental shuttle walking distance.

status and cardiac output prior to DCCV with an exceedingly poor prognosis.

#### 4. Discussion

In this study we have compared different approaches to rate and rhythm control in patients with AFL/AF and PAH or CTEPH. We have observed that restoration of sinus rhythm was associated with superior survival and functional improvement. We also observed that DCCV was superior to medical attempts at achieving sinus rhythm and is safe in the majority of patients. Caution should be exercised in fragile patients, with careful consideration of the risks and perceived clinical benefit. Lastly, the risk of recurrence of AFL/AF is related to right atrial area.

We found DCCV to be extremely effective at achieving restoration of sinus rhythm with an efficacy of 95%, including success in 6 out of 7 patients with AF. DCCV has previously been demonstrated to be

effective in PAH patients with AFL; Olsson et al [7] attempted DCCV in 9/24 AFL patients (38%) with 100% success, whilst in patients with AF, 61% of DCCV attempts led to stable sinus rhythm. Importantly, in the current study we have been able to compare DCCV with medical attempts at cardioversion and found that medical rhythm therapy was less effective with an efficacy of 59%. We also found DCCV to be a generally well-tolerated procedure with a single patient requiring critical care management following the procedure. Transient bradycardia and hypotension were the commonest adverse events and the risk-benefit ratio of DCCV should be assessed on a patient-by-patient approach.

In patients with PH, passive RA emptying in diastole is decreased and active emptying increased compared to normal subjects due to significant right ventricular (RV) diastolic dysfunction [24]. Moreover, RA contraction at end-diastole serves to increase the distance between the RV base and apex, thereby increasing the potential contraction length of the RV once systole begins, which is measured by tricuspid annular plane systolic excursion (TAPSE) on echo. It has been shown that in PAH, RA contraction accounts for 51% of TAPSE against 32% in normal subjects [25]. All of the above suggest that in PH, RV filling is more dependent on the atrial 'kick' at the end of diastole than in normal individuals. We therefore hypothesised that its loss in AFL/AF would be associated with adverse clinical outcomes and its restoration with clinical benefits.

Consistent with this hypothesis, we observed that failure to restore sinus rhythm was associated with significantly worse survival, independent of age or most recent ISWD or haemodynamics. Restoration of sinus rhythm was associated with improvement in ISWD in 78% and in FC in 41% of patients. These data are consistent with previous reports [3–10]. For example, in the study of Olsson et al [7], mean 6-min walk test distance dropped from 362 to 258 m with the onset of arrhythmia and increased back up to 345 m after cardioversion, whilst in Wen et al [8] atrial arrhythmias were associated with clinical worsening in 97.5% of the patients, whilst all of them improved after sinus rhythm was restored.

We observed AFL more commonly than AF which is in contrast to a number of previous studies which reported higher [5,8,9] or equal

proportions [7] of AF compared with AFL. A possible explanation for this discrepancy might be inclusion of patients with covert left heart disease in other studies. For example, Cannillo et al [5] observed left atrial dilatation on echocardiography in 53% of patients while Smith et al [10] studied 79 patients and found LA volume index to be an independent predictor of developing AFL/AF. In contrast, we found no difference in left atrial area or PAWP between those patients with AFL or AF.

The recurrence rate for atrial arrhythmias in our cohort was 46%, compared with rates reported in other studies of 15–64% [3–11]. Olsson et al [7] observed a lower recurrence rate at 27%. Of note, 67% of their patients with AFL eventually underwent catheter ablation compared with only 18% in our cohort. Catheter ablation is considered to be more effective at maintaining sinus rhythm than anti-arrhythmic drugs in AFL [26–28]. These data suggest that after initial restoration of sinus rhythm, catheter ablation therapy in suitable candidates should be performed.

There are a number of limitations to the current study. This was a retrospective study and there was therefore heterogeneity of arrhythmia types between the groups. Furthermore, it is possible that some patients with AFL/AF were missed and so robust estimates of AFL/AF incidence have not been possible. We were unable to perform risk stratification since, due to the long period of study enrolment, NT-proBNP levels were not available in the majority. Various factors such as lead-time and confounder biases may have impacted on outcomes in addition to the management strategy employed. Due to the study size, a limited number of parameters could be assessed in survival analyses. CT, rather than echocardiography, was used to assess atrial areas since echocardiographic images were no longer available for a number of patients enrolled in the early cohort. CT-derived atrial area has, however, previously been demonstrated to be prognostically significant with high levels of reproducibility [29,30]. A relatively low proportion of patients were receiving combination therapy at the time of arrhythmia onset. This likely reflects the lack of evidence for combination therapy in CTEPH and the historical nature of many of the PAH patients, prior to more recent randomised controlled trial data. Finally, we did not include catheter ablation data in regression analysis as only a small number of our patients underwent this procedure, and it was performed at different time points.

In conclusion, our study suggests that a heart rhythm control strategy is superior to a rate control strategy in patients with PAH/CTEPH, with sinus rhythm restoration being associated with superior survival and functional improvement. Furthermore, DCCV is generally safe and more effective at restoring sinus rhythm than pharmacological therapy in this patient group.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2022.09.031>.

#### Author contributions

MAS, RC and AC take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

CE, AH, RL, DGK, AK, JTM, A Rothman and RT contributed to Investigation and Writing – Review and Editing.

A Raitthatha contributed to Conceptualisation, Methodology, Investigation and Writing – Review and Editing.

AART contributed to Investigation, Data Curation and Writing – Review and Editing.

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