

Effectiveness of a simple medication adjustment protocol for optimizing peri-cardioversion rate control: A derivation and validation cohort study



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BACKGROUND Rate control medications are foundational in the management of persistent atrial fibrillation (AF). There are no guidelines for adjusting these medications prior to elective direct-current cardioversion (DCCV).

OBJECTIVE To derive and validate a preprocedural medication adjustment protocol that maintains peri-DCCV rate control and minimizes risk of postconversion bradycardia, pauses, need for pacing, and cardiopulmonary resuscitation (CPR).

METHODS Consecutive patients with persistent AF awaiting elective DCCV across 2 hospitals were screened for inclusion into derivation, validation, and control cohorts. In the derivation cohort, each patient taking an atrioventricular (AV) nodal blocker had medications adjusted based on heart rate (HR) 2 days before DCCV, and the magnitude of dose adjustment was compared with peri-DCCV HR. The adjustment protocol that achieved the highest percentage of optimal peri-DCCV rate control was tested prospectively in the validation cohort and compared to a standard-of-care control group.

RESULTS The optimal protocol from the derivation cohort (n = 71), based on the 2-day pre-DCCV HR, was to (1) CONTINUE AV nodal blocker for HR \geq 100 beats per minute (bpm), (2) reduce dose by ONE increment when 80–99 bpm, (3) reduce dose by TWO increments when 60–79 bpm, and (4) HOLD when $<$ 60 bpm. In the prospective validation cohort (n = 106), this protocol improved peri-DCCV rate control (82% vs 62%, $P < .001$) compared to current standard of care (n = 107). There were no conversion pauses \geq 5 seconds, need for pacing, or CPR post-DCCV.

CONCLUSION This simple preprocedural medication adjustment protocol provides an effective strategy of optimizing peri-DCCV rate control in patients with AF.

KEYWORDS Atrial fibrillation; AV nodal blockers; Bradycardia; Cardioversion; Rate control

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Introduction

Contemporary guidelines recommend targeting a ventricular response of less than 100 or 110 beats per minute (bpm) in patients with atrial fibrillation (AF).^{1,2} Atrioventricular (AV) nodal blocking medications are the cornerstone of this treatment. Bradycardia and bradycardia-associated complications are common (0.4%–18% of patients) following direct-current cardioversion (DCCV), attributed to the association between sinus node dysfunction and AF,³ faster ventricular rates in AF

than sinus rates, and medication-related sinus node suppression.^{4–6}

There are currently no established recommendations or systematic datasets to guide the adjustment of AV nodal blockers prior to DCCV. We sought to derive and validate a preprocedural medication adjustment protocol that maintains optimal rate control before DCCV and minimizes bradycardia after DCCV.

Methods

Study population and overview

This multisite cohort study included 3 groups of patients (derivation, validation, and control cohorts) \geq 19 years old with persistent AF undergoing elective DCCV across 2 tertiary care hospitals in Canada. This study was approved by the institutional review board of the University of British

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KEY FINDINGS

- Postconversion bradycardia from direct-current cardioversion (DCCV) may in part be owing to rate control medication-related sinus node suppression, yet there are no established recommendations to guide adjustment of these medications prior to DCCV. Our study reveals that approximately one-third of patients with atrial fibrillation (AF) undergoing elective DCCV do not have optimal peri-procedural rate control despite expert care from multidisciplinary AF clinics.
- We have derived and validated a simple medication adjustment protocol that improves peri-DCCV rate control and minimizes postconversion bradycardia compared to current standard of care, thereby effectively preventing its potential complications.
- Our medication adjustment protocol is effective and applicable for different atrioventricular nodal blockers, including diltiazem, and is not altered by the concurrent use of antiarrhythmics. The protocol is also safe in patients where DCCV fails to restore sinus rhythm.

Columbia and complied with the guidelines set forth in the Declaration of Helsinki. All participants provided written informed consent for collection of their health data. Patients with a pacemaker or implantable cardioverter-defibrillator and patients with atrial flutter or in whom DCCV did not restore sinus rhythm were excluded from the study.

In the derivation cohort, we retrospectively evaluated the effectiveness of all medication management strategies used in consecutive patients undergoing elective DCCV between September 2015 and April 2017. Patients were assessed at a multidisciplinary AF clinic prior to DCCV, where the clinical pharmacist adjusted each patient's rate control medications (continue, hold, or reduce dose) upon review of their medications and the electrocardiogram (ECG)-based heart rate (HR) 2 days before DCCV. To avoid contributing to postconversion bradycardia, medication doses were not increased. Patients on diltiazem were instructed to either continue or hold their last dose, as the formulation was a capsule that was physically impractical to divide into doses. Patients taking antiarrhythmic medications or digoxin continued these medications without adjustment prior to DCCV.

We compared rate control medication dose adjustment, stratified by HR 2 days before DCCV, to both the ECG-based HRs within 30 minutes before and 5 minutes after DCCV. To allow comparison between medications, rate control medication doses were standardized using a dose equivalency table (Table 1). All HRs were recorded by 12-lead ECG. The strategy with the highest proportion of patients who achieved optimal rate control, defined as a HR between 50 and 100 bpm at both 30 minutes before and 5 minutes after DCCV, was evaluated prospectively in a validation cohort and compared to a standard-of-care control

group of patients undergoing DCCV during a similar timeframe (May 2017 to May 2019). The validation cohort consisted of consecutive patients subsequent to the derivation cohort from the same multidisciplinary AF clinic. The control cohort consisted of consecutive patients at a second multidisciplinary AF clinic, where rate control medications were adjusted based on the current standard of care. The same aforementioned inclusion and exclusion criteria were applied to all cohorts.

Synchronized DCCV was performed as per standard practice.¹ Patients consented to the procedure and received propofol as the preferred general anesthetic. A single 200 J biphasic shock was delivered with pads in anteroposterior position and continuous ECG monitoring. DCCV was considered acutely successful if sinus rhythm was restored and the patient was discharged following DCCV in sinus rhythm. For patients with multiple DCCVs during the study period, only the first successful attempt was included to avoid bias of previous medication adjustments affecting subsequent medication adjustment.

Outcome measures

The primary outcome was the proportion of patients with optimal peri-DCCV rate control (HR between 50 and 100 bpm) measured by ECG at both 30 minutes pre-DCCV and 5 minutes post-DCCV. Secondary outcomes were time to first return beat after DCCV and adverse events including the need for cardiopulmonary resuscitation (CPR) or external pacing, and conversion pauses. The first return beat was defined as the first identifiable QRS complex indicating ventricular contraction following DCCV on ECG rhythm strip.

Statistical analysis

Continuous variables are reported as the mean \pm one standard deviation and were compared using two-tailed Student's t-tests or Wilcoxon rank-sum tests, and Analysis of Variance where applicable. Categorical variables are reported as frequency (and percentage) and were compared by the Pearson's Chi-Squared test. All analyses were conducted using SPSS 20.0 (IBM, Armonk, NY). The authors had full access to the data and have all read and agreed with the contents of the manuscript as written.

Results

Retrospective derivation cohort – review of all medication adjustment strategies

The derivation cohort included 71 patients with AF undergoing DCCV (Figure 1; Table 2) with a mean ventricular response of 80.7 ± 18.4 bpm 2 days prior to DCCV, with only 69% achieving optimal peri-DCCV rate control (Table 3). There were equal numbers of patients with inadequate and excessive rate control (11% of each), that prompted AV node blocking adjustment. There were no conversion pauses ≥ 5 seconds or bradycardia-associated complications requiring CPR or external pacing. Figure 2 shows the effect

Table 1 Dose equivalency and increment system for rate control medications

Medication	Increments [†]				
	0.5	1	2	3	4
Beta-blocker[‡]					
Bisoprolol	1.25 mg daily	2.5 mg daily	5 mg daily	7.5 mg daily	10 mg daily
Metoprolol	12.5 mg BID	25 mg BID	50 mg BID	75 mg BID	100 mg BID
Atenolol	12.5 mg daily	25 mg daily	50 mg daily	75 mg daily	100 mg daily
Carvedilol	3.125 mg BID	6.25 mg BID	12.5 mg BID	18.75 mg BID	25 mg BID
Sotalol	20 mg BID	40 mg BID	80 mg BID	120 mg BID	160 mg BID
Non-DHP CCB[§]					
Diltiazem	-	120 mg daily	240 mg daily	360 mg daily	480 mg daily
Verapamil	-	120 mg daily	240 mg daily	360 mg daily	480 mg daily
Digitalis[§]					
Digoxin	-	62.5 mcg daily	125 mcg daily	-	250 mcg daily

BID = twice daily; CCB = calcium channel blocker; DHP = dihydropyridine.

[†]Magnitude of medication dose reduction was measured in increments. For example, adjusting bisoprolol 5 mg daily to 2.5 mg daily would be described as reducing the dose by 1 increment.

[‡]Dose equivalency for beta-blockers has been established in literature.^{7,8}

[§]Dose equivalencies for non-DHP CCBs and digitalis have not been established in literature and are generated based on clinical practice at the AF Clinic in Vancouver, Canada.

^{||}Note that sotalol is not strictly a rate control medication. However, among the 13 patients taking sotalol in the validation cohort, 10 patients had sotalol doses reduced using this table.

of medication adjustment on peri-DCCV rate control stratified by the HR 2 days before DCCV.

In the 9 patients taking diltiazem monotherapy, the adjustment strategy with the highest proportion of optimal peri-DCCV rate control was to (1) CONTINUE diltiazem when HR \geq 80 bpm and (2) HOLD their last dose of diltiazem when HR < 80 bpm based on the 2-day pre-DCCV HR. This strategy of diltiazem adjustment, termed CONTINUE-HOLD-80, was prospectively evaluated in the validation cohort.

For patients not taking diltiazem monotherapy, the adjustment strategy with the highest proportion of

optimal peri-DCCV rate control was to (1) CONTINUE AV nodal blocker for HR \geq 100 bpm, (2) reduce dose by ONE increment for HR between 80 and 99 bpm, (3) reduce dose by TWO increments for HR between 60 and 79 bpm, and (4) HOLD for HR < 60 bpm based on the 2-day pre-DCCV HR (Figure 3) and using the dose equivalency Table 1. The adjusted medication dose pertained to the last scheduled dose prior to DCCV. This adjustment strategy, termed CONTINUE-ONE-TWO-HOLD, was evaluated in the prospective validation cohort.

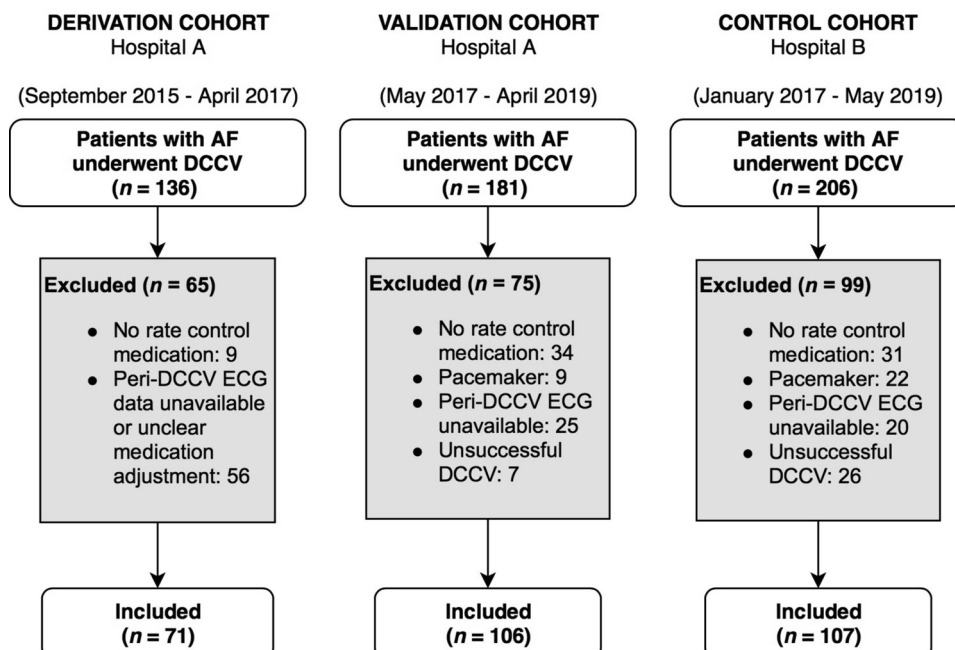


Figure 1 Overview of patient cohorts. AF = atrial fibrillation; DCCV = direct-current cardioversion; ECG = electrocardiogram.

Table 2 Clinical characteristics of the patient cohorts

Characteristic	Cohort			P
	Derivation n = 71	Validation n = 106	Control n = 107	
Age at time of DCCV				
Mean years ± SD	65.5 ± 10.3	64.3 ± 9.80	66.9 ± 10.3	.177
Sex				
Male, %	52 (73)	80 (75)	77 (72)	.84
Heart rate 2 days prior to DCCV				
Mean bpm ± SD	80.7 ± 18.4	80.7 ± 14.6	88.3 ± 17.5 [†]	.001
<60 bpm	9 (13)	3 (3)	4 (4) [†]	
60–79 bpm	25 (35)	48 (45)	30 (28) [†]	
80–99 bpm	26 (37)	42 (40)	47 (44) [†]	
≥100 bpm	11 (15)	13 (12)	26 (24) [†]	
Rate control medication, %				
Beta-blocker	64 (90)	86 (81)	77 (72)	.48
Bisoprolol	29 (41)	41 (39)	27 (25)	
Metoprolol	14 (20)	20 (19)	28 (26)	
Sotalol	10 (14)	13 (12)	1 (1)	
Atenolol	7 (10)	6 (6)	5 (5)	
Carvedilol	4 (6)	4 (4)	14 (13)	
Nadolol	0 (0)	2 (2)	0 (0)	
Nebivolol	0 (0)	0 (0)	1 (1)	
Propranolol	0 (0)	0 (0)	1 (1)	
Non-DHP CCB	12 (17)	23 (22)	26 (24)	
Diltiazem	9 (13)	22 (21)	23 (22)	
Verapamil	3 (4)	1 (1)	3 (3)	
Digoxin	3 (4)	3 (3)	9 (8)	
Antiarrhythmic medication, %				
Amiodarone	11 (15)	12 (11)	11 (10)	.47
Flecainide	3 (4)	1 (1)	2 (2)	
Propafenone	0 (0)	4 (4)	5 (5)	

bpm = beats per minute; CCB = calcium channel blocker; DCCV = direct-current cardioversion; DHP = dihydropyridine.

Data presented as n (%) unless otherwise indicated.

[†]Heart rate measured 1 week prior to DCCV.

Prospective evaluation of the CONTINUE-ONE-TWO-HOLD/CONTINUE-HOLD-80 protocol—Validation vs control cohort

The validation cohort consisting of 106 consecutive patients was compared with a control group of 107 consecutive patients (Figure 1). Both cohorts were similar with respect to

age, sex, and distribution of the use of rate control and antiarrhythmic medications (Table 2).

The CONTINUE-ONE-TWO-HOLD/CONTINUE-HOLD-80 protocol (Figure 3) significantly improved peri-DCCV rate control in the validation cohort compared to the control cohort overall (82% vs 62%, $P < .001$) (Table 3).

Table 3 Primary outcome: Distribution of peri-DCCV heart rates

Heart rate	Cohort			P [†]
	Derivation n = 71	Validation n = 106	Control n = 107	
30-minute pre-DCCV				
Mean bpm ± SD	81.5 ± 20.4	81.2 ± 13.6	84.0 ± 20.4	.23
<50 bpm	2 (3)	0 (0)	1 (1)	
50–100 bpm	58 (82)	96 (91)	87 (81)	
>100 bpm	11 (15)	10 (9)	19 (18)	
5-minute post-DCCV				
Mean bpm ± SD	57.9 ± 11.0	61.1 ± 10.1	59.1 ± 12.0	.187
<50 bpm	11 (15)	9 (8)	22 (21)	
50–100 bpm	60 (85)	97 (92)	85 (79)	
>100 bpm	0 (0)	0 (0)	0 (0)	
Optimal peri-DCCV rate control (50–100 bpm)	49 (69)	87 (82)	66 (62)	<.001
Post-DCCV bradycardia (<50 bpm)	11 (15)	9 (8)	22 (21)	.012

bpm = beats per minute; CCB = calcium channel blocker; DCCV = direct-current cardioversion.

Data presented as n (%) unless otherwise indicated.

[†]P represents the P value between the validation and control cohorts.

		Type of medication adjustment					HOLD
		CONTINUE	REDUCTION (magnitude)				
			1	2	3	4	
Heart rate 2 days pre-DCCV (bpm)	<60	50%			0%		100%
	60 to 79	73%	80%	100%			60%
	80 to 99	79%	100%	50%	100%	100%	40%
	≥100	100%	33%	50%			0%

100% of patients were optimal
 0-99% of patients were optimal
 No data

Figure 2 Percentage of patients in the derivation cohort achieving optimal peri-cardioversion rate control following medication adjustment in relation to heart rate 2 days before cardioversion. bpm = beats per minute; DCCV = direct-current cardioversion.

There were no conversion pauses ≥ 5 seconds or bradycardia-associated complications requiring CPR or external pacing in either the validation or control group. Concurrent use of antiarrhythmic medications did not adversely alter peri-DCCV rate control (Supplemental Table 1).

CONTINUE-ONE-TWO-HOLD subgroup

In the non-diltiazem subgroup of patients, the CONTINUE-ONE-TWO-HOLD protocol had significant improvement in peri-DCCV rate control in the validation cohort compared to the control cohort (81% vs 62%, $P = .006$) (Supplemental Table 2).

CONTINUE-HOLD-80 subgroup

In the subgroup of patients with diltiazem monotherapy, the CONTINUE-HOLD-80 protocol significantly improved peri-DCCV rate control in the validation cohort compared to the control cohort (89% vs 61%, $P = .044$) (Supplemental Table 2).

Discussion

There are 2 primary findings of our study. The first is that a significant percentage of patients undergoing cardioversion do not have optimal peri-DCCV rate control (31% in the derivation cohort and 38% in the control group) despite expert care from multidisciplinary, dedicated AF clinics. Second, this simple and easily implementable CONTINUE-ONE-TWO-HOLD/CONTINUE-HOLD-80 protocol (Figure 3) significantly improves peri-DCCV rate control and reduces postcardioversion bradycardia. We are not aware of any published guidelines or studies to guide peri-DCCV medication adjustment. Our protocol is effective, simple, easily implementable, and generalizable to the majority of patients undergoing elective DCCV.

Overall, the derived protocol was very effective at improving peri-DCCV rate control. Of the 19 patients in

the validation cohort that did not achieve optimal peri-DCCV rate control, 7 did not have optimal rate control (HR < 50 bpm or > 100 bpm) at the 2-day pre-DCCV ECG, which likely suggests a failure of the long-term AF rate control strategy and not of the preprocedural medication adjustment strategy itself. When these patients with poor AF rate control 2 days before DCCV were excluded from the analysis, the efficacy of the derived protocol increased from 82% to 88%.

In contemporary practice, it is common to add loading doses of antiarrhythmic medications prior to DCCV to prevent recurrence of AF following conversion to sinus rhythm.⁹ In the validation cohort, antiarrhythmic medication doses were not adjusted around the time of DCCV. The concurrent use of these medications did not adversely affect peri-DCCV rate control in our study (Supplemental Table 1). Therefore, antiarrhythmic medications, when started, should be continued for the purposes of maintaining rhythm control.

Although the patients evaluated were those who had acutely successful DCCV, we also assessed the CONTINUE-ONE-TWO-HOLD/CONTINUE-HOLD-80 protocol, where DCCV was not successful. Of the 7 patients in whom DCCV was not successful, 2 had suboptimal peri-DCCV rate control (Supplemental Table 3). Both of these patients had suboptimal rate control at the 2-day pre-DCCV ECG as well, which again suggests a failure of the long-term AF rate control strategy and not of the medication adjustment strategy itself. The ventricular response of the remaining 5 patients was between 61 and 86 bpm, indicating that the validated protocol is also safe in patients where DCCV does not restore sinus rhythm.

We routinely confirm the presence of AF by 12-lead ECG 2 days before DCCV, which was the impetus for using this time point and method to guide medication adjustment in the CONTINUE-ONE-TWO-HOLD/CONTINUE-HOLD-80 protocol. Although the 12-lead ECG is the gold standard for AF rate assessment,^{10,11} alternative methods of measurement such as non-12-lead ECGs and HR by blood pressure monitors, pulse oximeters, and smart devices that utilize photoplethysmography have comparable accuracy and could likely be used for AF rate assessment in conjunction with our algorithm.¹² Furthermore, although we used the HR 2 days before DCCV in this algorithm, it is likely that other time points could be equally as valid upon which to base medication adjustment recommendations, assuming the absence of factors that may alter HR, such as other medication adjustments or concurrent illnesses.¹³

Limitations

Different AV nodal blockers have different half-lives and thus variable steady-state pharmacokinetics.¹⁴ To increase the generalizability of our results, our protocol used an equivalency table to compare between AV nodal blockers. We acknowledge that specific recommendations for each

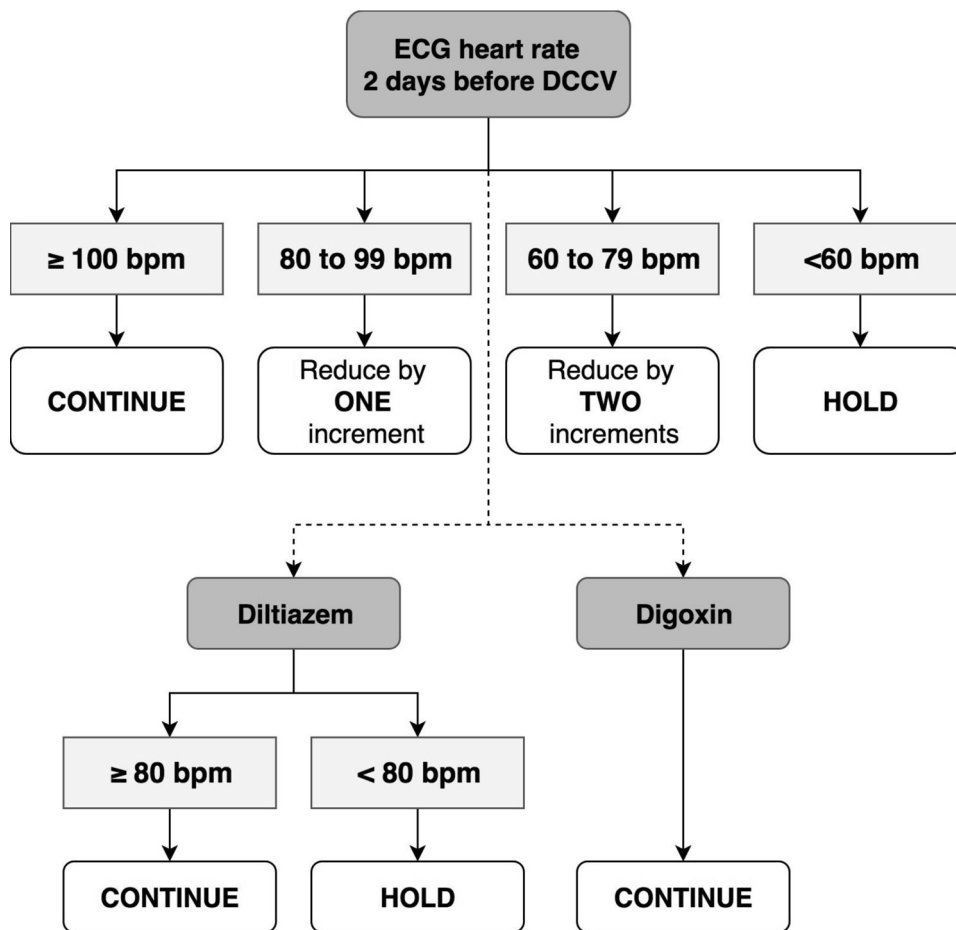


Figure 3 The CONTINUE-ONE-TWO-HOLD/CONTINUE-HOLD-80 protocol for medication adjustment. bpm = beats per minute; DCCV = direct-current cardioversion; ECG = electrocardiogram.

AV nodal blocker may provide further improvements in peri-DCCV rate control compared to the class-based recommendations used in our protocol. However, the derived protocol demonstrated similar efficacy when applied to each AV nodal blocker (Table 2). In addition, we only evaluated the effect of adjusting the last scheduled dose of AV nodal blocker prior to DCCV. We expect that reducing more consecutive preceding doses could result in further improvements in post-DCCV bradycardia, but the benefits would likely be offset by an increase in pre-DCCV tachycardia.

In our analysis, we did not further stratify the efficacy of this protocol in patients with comorbidities that may affect drug elimination, such as kidney or liver dysfunction.¹⁵ Patients screened for the study were not excluded for these reasons and, as such, we expect our results to be generalizable to these patients. Previous literature has also identified advanced age and female sex as major independent predictors of bradycardic complications following DCCV.⁶ However, our cohorts were similar in terms of distribution of age and sex and these predictors were unlikely to account for differences.

In the validation cohort, there were 3 patients taking digoxin in addition to other AV nodal blockers and there

were also 4 patients taking both calcium channel blockers (CCB) and beta blockers (BB). In the digoxin cohort, digoxin was continued with no dose adjustment. In the CCB/BB cohort, the CCB was continued while only the BB dose was adjusted. The sample size of these patients does not allow for a rigorous analysis to determine whether a different strategy would be better at optimizing peri-DCCV rate control in these particular situations. We did not identify an increased incidence of peri-DCCV bradycardia or tachycardia when compared to the rest of the cohort.

Lastly, we have considered the potential effect of procedural anesthesia on HR and controlled for this by ensuring that general anesthesia was performed as per standard practice in elective DCCV and that postconversion HRs were measured at the same time points in all patients. Propofol was most commonly used owing to its safety profile in elective DCCV.¹⁶ Its rapid onset and offset is unlikely to contribute to profound sustained bradycardia.

Conclusion

The CONTINUE-ONE-TWO-HOLD/CONTINUE-HOLD-80 protocol is a simple, safe, and generalizable preprocedural

strategy of adjusting peri-DCCV rate-controlling medications in patients with AF. This strategy significantly improves peri-DCCV rate control compared to standard of care delivered by multidisciplinary, dedicated AF clinics.

Acknowledgment

We thank the AF Clinic staff for their important contributions and the patients for their participation in the study.

Funding Sources

The authors have no funding sources to disclose.

Disclosures

The authors have no conflicts to disclose.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent

All participants provided written informed consent for collection of their health data.

Ethics Statement

This study complied with the guidelines set forth in the Declaration of Helsinki. This study was approved by the institutional review board of the University of British Columbia.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hroo.2021.01.002>.

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