Management of Tachycardia-Mediated Cardiomyopathy: Experience from the Vancouver General Hospital Cardiac Function Clinic (TMC-EXPLOR Study)

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ABSTRACT

Background: Tachycardia-mediated cardiomyopathy (TMC) is a reversible form of heart failure with reduced ejection fraction (HFrEF), most commonly caused by atrial fibrillation or atrial flutter. Evidence for its management is scarce, and practice patterns are highly variable.

Objective: To describe management patterns for HFrEF and atrial arrhythmias in patients with TMC at a specialty heart failure clinic.

Methods: This retrospective cohort study involved adults with HFrEF and a physician-determined diagnosis of TMC, with an initial visit for this problem between October 2018 and October 2019. The 2 primary outcomes, evaluated at 1 year after the initial visit, were the proportion of patients receiving triple therapy (combination of angiotensin receptor–neprilysin inhibitor [or angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker if ejection fraction improved to > 40% by 1 year], β-blocker, and mineralocorticoid receptor antagonist at any dose) and the proportion receiving or with a plan to receive rhythm control.

Results: A total of 59 participants met the inclusion criteria. The mean age was 73 years, 39 patients (66%) were male, and 42 (71%) had hypertension. At 1-year follow-up, 42 (71%) were receiving triple therapy, and rhythm control was attempted or planned for 20 (34%). Among the 17 patients (29%) not receiving triple therapy, a mineralocorticoid receptor antagonist was the agent most commonly omitted.

Conclusions: In a specialty heart failure clinic, most patients with TMC were receiving triple therapy, with a mineralocorticoid receptor antagonist being the agent most commonly missing among those not receiving triple therapy. One-third of patients with TMC had received a rhythm-control strategy. These gaps in HFrEF therapy and rhythm control represent key areas for quality improvement initiatives in the management of patients with TMC.

Keywords: tachycardia-mediated cardiomyopathy, heart failure, atrial fibrillation, rhythm control, rate control, guideline-directed medical therapy

RÉSUMÉ

Contexte : La cardiomyopathie rythmique (CMR) est une forme réversible d’insuffisance cardiaque à fraction d’éjection réduite (HFrEF), le plus souvent causée par la fibrillation auriculaire ou le flutter auriculaire. Les données probantes relatives à sa prise en charge sont rares et les modèles de pratique sont très variables.

Objectif : Décrire les schémas de prise en charge de l’HFrEF et des arythmies auriculaires chez les patients atteints d’une CMR dans une clinique spécialisée en insuffisance cardiaque.

Méthodes : Cette étude de cohorte rétrospective impliquait des adultes atteints d’HFrEF et ayant reçu un diagnostic de CMR déterminé par un médecin, avec une première visite pour ce problème de santé entre octobre 2018 et octobre 2019. Les 2 résultats principaux, évalués 1 an après la première visite, étaient les suivants : 1) la proportion de patients recevant une trithérapie (association récepteur de l’angiotensine-néprilysine (ARNi) [ou inhibiteur de l’enzyme de conversion de l’angiotensine/antagoniste des récepteurs de l’angiotensine II si la fraction d’éjection s’est améliorée à > 40 % à 1 an], un traitement par β-bloquant et un antagoniste des récepteurs des minéralocorticoïdes à n’importe quelle dose); et 2) la proportion recevant ou prévoyant de recevoir un médicament antarythmique.

Résultats : Au total, 59 participants répondaient aux critères d’inclusion. L’âge moyen était de 73 ans; 39 patients (66 %) étaient des hommes et 42 (71 %) avaient de l’hypertension. Au marqueur d’un an, 42 (71 %) recevaient une trithérapie et un médicament antarythmique a été tenté ou était prévu pour 20 (34 %) patients. Parmi les 17 patients (29 %) ne recevant pas de trithérapie, l’agent le plus souvent omis était l’antagoniste des récepteurs des minéralocorticoïdes.

Conclusions : Dans une clinique spécialisée dans l’insuffisance cardiaque, la plupart des patients atteints d’une CMR recevaient une trithérapie, l’antagoniste des récepteurs minéralocorticoïdes étant l’agent le plus souvent absent chez ceux qui n’en recevaient pas. Un tiers des patients atteints d’une CMR avaient reçu un médicament antarythmique. Ces lacunes concernant la thérapie HFrEF et la gestion de l’arythmie représentent des domaines clés pour les initiatives d’amélioration de la qualité dans la prise en charge des patients atteints d’une CMR.

Mots-clés : cardiomyopathie rythmique, CMR, insuffisance cardiaque, fibrillation auriculaire, gestion de l’arythmie, contrôle de la fréquence, thérapie médicale guidée par des directives
INTRODUCTION

Tachycardia-mediated cardiomyopathy (TMC) is a form of reversible left ventricular dysfunction secondary to persistent atrial or ventricular tachyarrhythmias.1,2 Given their high incidence, atrial fibrillation (AF) and atrial flutter are the most common arrhythmias leading to TMC.3 A sustained rapid ventricular rate creates a cascade of adverse cellular, hemodynamic, and neurohormonal changes, which eventually lead to left ventricular dysfunction and presentation with heart failure with reduced ejection fraction (HFREF).4 It is difficult to distinguish TMC from co-existing HFREF and AF, and the diagnosis is often made in retrospect following rapid improvement in left ventricular ejection fraction (LVEF) after treatment of the underlying arrhythmia.

TMC is one of the most common forms of non-ischemic cardiomyopathy; however, because there have been few TMC-specific trials, not all guidelines include TMC-specific recommendations. For instance, the European 2016 heart failure (HF) guidelines5 and 2016 AF guidelines6 suggest that for patients who experience tachycardia-induced cardiomyopathy as a result of rapid AF, catheter ablation can improve symptoms and cardiac function. The Canadian Cardiovascular Society’s 2014 AF guidelines7 note that patients with arrhythmia-induced cardiomyopathy should be considered for early rhythm control, and the same organization’s 2017 HF guidelines8 recommend guideline-directed medical therapy and rhythm control for patients with HFREF and persistent symptomatic arrhythmia. The 2014 guideline of the American College of Cardiology and American Heart Association proposed rate control by ativoventricular nodal blockade or a rhythm-control strategy for patients with AF and rapid ventricular response causing or suspected of causing tachycardia-induced cardiomyopathy.9

The current approach to managing TMC is similar to that for managing coexisting HFREF and AF, consisting of guideline-directed medical therapy for HFREF and treatment of the underlying arrhythmia.10–14 Traditionally, rate control was considered the cornerstone of AF management because of its convenience and perceived safety relative to pharmacological rhythm control, which mainly relies on the use of amiodarone in patients with reduced LVEF.15,16 However, trials involving patients with coexisting HFREF and AF have shown a greater role for catheter ablation in improving LVEF and reducing mortality when compared with pharmacological rate- or rhythm-control strategies.17–22 More recently, the EAST-AFNET 4 trial demonstrated greater reduction in cardiovascular events with rhythm-control strategies compared with pharmacological rate control in patients with AF diagnosed within 1 year.23

The objective of this study was to characterize the management patterns for HF and atrial arrhythmias in patients with TMC in a specialty HF clinic. We hypothesized that contemporary management of TMC in a specialty HF clinic would include high use of target-dose, guideline-directed medical therapy for HFREF—consistent with utilization of this approach for HFREF from other causes—along with high use of a rhythm-control strategy for AF.

METHODS

Design and Setting

We conducted a retrospective single-centre cohort study at the Vancouver General Hospital’s cardiac function clinic, a multidisciplinary HF clinic serving patients in Metro Vancouver. The study was approved by the University of British Columbia Clinical Research Ethics Board (H20-03057).

Eligibility Criteria

We included patients aged 18 years or older who had HF and LVEF less than or equal to 40% secondary to TMC (determined by physician diagnosis), with an initial clinic visit between October 2018 and October 2019. Patients were excluded if a cause of HFREF other than TMC was documented in the electronic medical record.

Primary Outcomes

The 2 primary outcomes, evaluated at 1 year after the initial clinic visit, were the proportion of patients receiving triple therapy for HFREF (as defined below) and the proportion of patients receiving or with a plan to receive rhythm control (as defined below). Triple therapy was defined as the combination of an angiotensin receptor–neprilysin inhibitor (ARNI), a β-blocker, and a mineralocorticoid receptor antagonist (MRA) at any dose. In addition, patients receiving an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) instead of an ARNI were considered to be receiving triple therapy if their LVEF improved to greater than 40% within 1 year from the initial visit. The difference in criteria for the use of ACEI/ARB in patients with LVEF above 40% and ARNI in patients with LVEF of 40% or below was based on the recommendation in the 2017 Canadian Cardiovascular Society guidelines for management of HF8 to change ACEI/ARB to ARNI in those who remain symptomatic despite triple therapy, because ARNI was superior to ACEI/ARB in the PARADIGM-HF trial. The study period preceded the incorporation of sodium-glucose co-transporter 2 (SGLT2) inhibitors as part of guideline-directed medical therapy in the Canadian Cardiovascular Society guidelines,24 and this form of treatment was therefore excluded from this outcome. Rhythm control was defined in terms of individual rhythm-control interventions, including direct current cardioversion, pharmacological rhythm control with amiodarone, and catheter ablation for AF (pulmonary vein isolation) or atrial flutter (cavotricuspid isthmus ablation).
Secondary Outcomes

Secondary outcomes included the proportion of patients receiving each of ACEI/ARB, ARNI, β-blocker, MRA, digoxin, loop diuretics, SGLT2 inhibitors, or hydralazine–nitrate at any dose and at the target doses outlined in the 2017 Canadian Cardiovascular Society HF guidelines. Furthermore, we explored the change in LVEF from baseline (before clinic visit) to 1 year and the proportions of patients who died or had worsening HF requiring hospitalization or an emergency department visit at 1 year from the initial clinic visit.

Data Collection

Only data necessary to complete the study, as outlined below, were extracted from the electronic medical records, iClinic (iClinic Systems Inc). The data were collected by one of the study authors (A.D.) and were validated by the same author, who selected 10 patients at random to confirm the collected data points. We used a standardized form listing the specific parameters for which data were to be collected.

We gathered the following routinely collected data from the iClinic system: age, sex, body mass index, comorbidities (hypertension, type 1 diabetes, type 2 diabetes, dyslipidemia, stroke or transient ischemic attack, chronic kidney disease [defined as estimated glomerular filtration rate or eGFR < 60 mL/min/1.73 m²], anemia, sleep apnea, hyperthyroidism, myocardial infarction, angina, percutaneous coronary intervention, coronary artery bypass graft, smoking status), laboratory data (serum creatinine, potassium, brain natriuretic peptide), transthoracic echocardiography measurements (LVEF, left atrial volume index, left atrial dimension), HFrEF medications and antiarrhythmic drugs, procedure data (direct current cardioversion, catheter ablation for AF [pulmonary vein isolation] or atrial flutter [cavotricuspid isthmus ablation]), HF-related hospitalization or emergency department visits, and death.

Statistical Analysis

All analyses were performed using Microsoft Excel 2020 and R 4.0 software. Age is reported as mean with standard deviation and LVEF as median and interquartile range (IQR). Categorical variables are expressed as frequencies and percentages.

RESULTS

Of 172 patients with newly diagnosed HFrEF and concomitant AF or atrial flutter, TMC was documented in 59 (34%) (Figure 1). The mean age was 73 (SD 10) years, 66% were male, and the median LVEF was 33% (IQR 26.5%–35%) at the initial clinic visit. Hypertension was the most common comorbidity, occurring in 42 (71%) of the patients, and 27 (46%) had eGFR of less than 60 mL/min/1.73 m² (Table 1).

Primary Outcomes

At 1 year, 42 (71%) of the patients were receiving triple therapy (Table 2). The combination of an ARNI, a β-blocker, and MRA was used in 13 (22%), whereas an ACEI/ARB, a β-blocker, and MRA were used in 29 (49%). Rhythm control was planned or undertaken within the first year of the initial visit in 20 (34%) patients, with most patients receiving a combination of rhythm-control strategies (Table 2).

Secondary Outcomes

Figure 2 outlines the proportions of patients receiving individual agents and target doses of HF medications. Among the 17 patients (29%) not receiving triple therapy at any dose, MRA was the agent most commonly omitted. Ten (17%) of the patients were receiving triple therapy at target doses. Other HF medications in use at 1 year included furosemide (n = 41, 69%), digoxin (n = 7, 12%), and SGLT2 inhibitors (n = 2, 3%).

FIGURE 1. Flow diagram for patient inclusion. HFrEF = heart failure with reduced ejection fraction, LVEF = left ventricular ejection fraction.
Fifty-five patients had LVEF measured at baseline and at 1 year; the median LVEF was 33% (IQR 26.5%–35%) at baseline and 52% (IQR 45%–55%) at the end of follow-up. Among the 19 patients in this group who were receiving a rhythm-control strategy, 17 (90%) had an improvement in LVEF to above 40%, compared with 30 (84%) of the 36 patients who were receiving a rate-control strategy. Overall, 47 (85%) of these 55 patients had an improvement in LVEF to above 40% at 1 year from the initial clinic visit.

**TABLE 1. Baseline Characteristics of Participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) of Participants&lt;sup&gt;a&lt;/sup&gt; (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean ± SD)</td>
<td>73 ± 10</td>
</tr>
<tr>
<td>Sex, male</td>
<td>39 (66)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>42 (71)</td>
</tr>
<tr>
<td>Chronic kidney disease&lt;sup&gt;b&lt;/sup&gt;</td>
<td>27 (46)</td>
</tr>
<tr>
<td>Current or former smoker</td>
<td>20 (34)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>20 (34)</td>
</tr>
<tr>
<td>Diabetes (type 1 or 2)</td>
<td>16 (27)</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Angina</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Except where indicated otherwise.

<sup>b</sup>Chronic kidney disease was defined as estimated glomerular filtration rate < 60 mL/min/1.73 m².

**TABLE 2. Co-primary Outcomes and Selected Secondary Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. (%) of Participants (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-primary outcome: Triple therapy at any dose</td>
<td>42 (71)</td>
</tr>
<tr>
<td>ACEI/ARB, β-blocker, plus MRA</td>
<td>29 (49)</td>
</tr>
<tr>
<td>ARNI, β-blocker, plus MRA</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Co-primary outcome: Received or planned rhythm control&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20 (34)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>11</td>
</tr>
<tr>
<td>Direct current cardioversion</td>
<td>9</td>
</tr>
<tr>
<td>Atrial fibrillation ablation</td>
<td>6</td>
</tr>
<tr>
<td>Atrial flutter ablation</td>
<td>5</td>
</tr>
<tr>
<td>Selected secondary outcomes</td>
<td></td>
</tr>
<tr>
<td>Triple therapy at target doses</td>
<td>10 (17)</td>
</tr>
<tr>
<td>ACEI/ARB, β-blocker, plus MRA</td>
<td>4 (7)</td>
</tr>
<tr>
<td>ARNI, β-blocker, plus MRA</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Improvement in LVEF to &gt;40%</td>
<td>47 (85)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Heart failure hospitalization</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, ARNI = angiotensin receptor–neprilysin inhibitor, LVEF = left ventricular ejection fraction, MRA = mineralocorticoid receptor antagonist.

<sup>a</sup>Categories not mutually exclusive.

<sup>b</sup>Percentage calculated from a denominator of 55, because 4 patients did not have follow-up LVEF value.

**FIGURE 2. Use and relative dosing of heart failure medications in patients with tachycardia-mediated cardiomyopathy.** Medication data were collected from the medication list in the patients’ electronic medical records during the last clinic visit of the 1-year follow-up period. Target doses were defined according to the Canadian Cardiovascular Society’s 2017 guideline for heart failure.<sup>8</sup> Data for “ACEI/ARB/ARNI” represent combined data for ACEI/ARB and ARNI. ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, ARNI = angiotensin receptor–neprilysin inhibitor, BB = β-blocker, MRA = mineralocorticoid receptor antagonist.
During the 1-year follow-up period, 1 patient (2%) died, whereas 12 (20%) had at least 1 episode of worsening HF for which hospitalization or an emergency department visit was required.

DISCUSSION

In this study of the management of TMC in a multidisciplinary HF clinic, 71% of patients received triple therapy at some dose and 34% received or had a plan to undergo rhythm control. In patients not receiving HFrEF triple therapy, MRA was the agent most commonly omitted. Among patients who underwent a rhythm-control strategy, most received a combination of modalities, including direct current cardioversion, amiodarone, or catheter ablation.

To the best of our knowledge, this is the first study providing real-world data on the use of HFrEF pharmacotherapy in patients with TMC. Despite Canadian Cardiovascular Society guideline recommendations to initiate guideline-directed medical therapy and to consider early rhythm control in patients with concomitant HFrEF and AF—which have been in place since 2014—utilization of MRA and rhythm-control strategies at a specialty HF clinic was relatively low, although comparable to or better than that in the broader HFrEF population. For example, in CHAMP-HF, a registry-based study performed in the United States between 2015 and 2017, only 22% of eligible patients were simultaneously receiving the combination of ACEI/ARB/ARNI, β-blocker, and MRA. Conversely, a study from the Montreal Heart Institute reported use of triple therapy in 76.5% of patients with HFrEF. Although relative to historical data, use of triple therapy was higher in the specialty HF clinic involved in the current study, several gaps in guideline-directed medical therapy remained evident. First, few patients (17%) received target doses of triple therapy. This problem was also reported in the aforementioned CHAMP-HF study, in which less than 1% of eligible HFrEF patients were simultaneously treated with target doses of ACEI/ARB/ARNI, β-blocker, and MRA at 1 year. Second, MRAs were a commonly omitted component of triple therapy. This is consistent with results from other studies of the broader HFrEF population, in which MRA use among eligible patients has ranged from 33% to 40%. Under-use of MRAs in the current study is not easily explained by the pharmacological action of this drug class. For example, the use of MRA was considerably lower than that of ACEI/ARB/ARNI, which have similar adverse effects related to the risk of hyperkalemia and hypotension. The CHAMP-HF study identified clinical inertia as an important factor contributing to suboptimal MRA use in the general HFrEF population. In TMC patients, clinicians may be reluctant to initiate MRA because of partial or complete recovery of LVEF to greater than 40% after initiation of a β-blocker and ACEI/ARB/ARNI.

Overall, 85% (47/55) of patients in this study had improvement of their LVEF to greater than 40% at 1 year from their initial clinic visit. Among the remaining 15%, all but one received triple therapy at any dose with β-blockers, ARNI, and MRA. There were no other emerging patterns to explain this lack of improvement in LVEF. There could certainly be elements of nonadherence and uncontrolled heart rate that led to the lack of improvement for 15% of the patients, but investigation of potential factors was beyond the scope of this study. Moreover, these data points were not consistently available in the electronic medical record and thus could not be collected.

A rate-control strategy was undertaken for two-thirds of the patients in this study. This practice is based on the AFFIRM trial, which compared pharmacological rhythm control (primarily with amiodarone or sotalol) with pharmacological rate control (with a β-blocker, non-dihydropyridine calcium-channel blocker, or digoxin, often in combination) in patients with AF, only about a quarter of whom had a history of HF or ejection fraction below 50%. The AFFIRM study failed to show the superiority of a pharmacological rhythm-control strategy, with numerically higher mortality (26.7% versus 25.9%, \( p = 0.08 \)) and significantly higher risk of hospitalization (80.1% versus 73.0%, \( p < 0.001 \)). Limited to patients with AF and HFrEF, the AF-CHF trial similarly did not identify a survival advantage with pharmacological rhythm control (mainly with amiodarone) relative to a rate-control strategy, with numerically higher all-cause hospitalizations (64% versus 59%, \( p = 0.06 \)), driven by more hospitalizations for AF (14% versus 9%, \( p = 0.001 \)). However, randomized trials focusing on the use of AF ablation rather than medications to restore sinus rhythm showed improved outcomes relative to pharmacological rate or rhythm control in patients with concomitant HFrEF and AF. The low utilization of catheter ablation as a rhythm-control strategy at our specialty HF clinic was particularly interesting, given that the clinic is located at a site where AF catheter ablation is a readily available option for rhythm control. Most recently, the EAST-AFNET 4 trial, published after the study timeframe, compared rhythm-control strategies (AF ablation or antiarrhythmic drugs) with rate control in patients with recent (i.e., within the previous year) diagnosis of AF. Early rhythm control reduced cardiovascular events relative to rate control (reduction to 3.9 versus 5.0 per 100 PY, respectively), and this held true for the 28% subgroup of patients with HF and ejection fraction less than 50% at baseline. The results of this trial did not lead to any change in the Canadian Cardiovascular Society guidelines specifically recommending catheter ablation for AF, but they may have driven practice change at the study site.

There is a significant scarcity of evidence for the appropriateness of guideline-directed medical therapy and rhythm versus rate control in the TMC population.
There have been no randomized controlled trials specific to this population, and current management is based on extrapolation of data from patients with concomitant HFrEF and AF, which includes both AF-induced HFrEF and HFrEF preceding AF. As such, the relative importance of HFrEF pharmacotherapy in TMC remains uncertain, particularly for agents beyond β-blockers, and it is unclear whether early rhythm control should be prioritized in these patients.

**Limitations**

The results of this descriptive study must be interpreted in the context of the study limitations. The study was a retrospective, single-centre study with small sample size. In addition, the reason for not receiving individual HFrEF medications or target doses of such medications were not consistently documented within the medical record, which prevented us from exploring the barriers to optimization. Although we were able to identify the number of patients undergoing rhythm control, we could not evaluate the characteristics of those who did not receive rhythm control to determine their eligibility for such an intervention.

**CONCLUSION**

In a specialty HF clinic, most patients with TMC received triple therapy, with MRAs being the agent that was most commonly missing among those not receiving triple therapy. One-third of TMC patients received a rhythm-control strategy. These gaps in HFrEF therapy and rhythm control represent key areas for quality improvement initiatives in the management of patients with TMC.

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Competing interests: None declared.

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Funding: None received.

Received: July 30, 2022
Accepted: April 22, 2023
Published: September 13, 2023