# Supplemental material

## Supplementary results

### Analysis including the patients who had an ICD implanted within 7 days of flecainide initiation

The first analysis included the patients who were excluded because they received an ICD within 7 days of flecainide initiation. In this analysis including 251 patients, the implantation of an ICD during any study period was still a cut-off point for determining follow-up duration as it was in our main analysis. Thus, if a patient received an ICD while being treated with beta-blocker monotherapy, the ICD implantation date was the start of the pre-flecainide period. If a patient received an ICD while being treated with a beta-blocker and flecainide, the ICD implantation date was the end of the on-flecainide period. In this analysis, 4 additional patients could be included (n=251). Three of the newly included patients had no arrhythmic events during both study periods. One patient had one arrhythmic event during the pre-flecainide period and none during the on-flecainide period. Using generalized linear mixed model (GLMM) with the assumption of a negative binomial distribution, there was a significant reduction in the rate of arrhythmic events after flecainide (IRR 0.56 [0.36-0.86], p=0.009).

### Analysis including the patients who had an ICD implanted within 7 days of flecainide initiation *and* where the date of ICD implantation was not a cutoff point in limiting follow-up duration.

The second supplementary analysis included the patients who were excluded because they received an ICD within 7 days of flecainide initiation *and* the implantation of an ICD during any study period was *not* a cutoff point for determining follow-up duration in this analysis. In this analysis, 251 patients were included. The median pre-flecainide follow-up duration was 2.9 years (IQR 0.6-7.6) and the median on-flecainide follow-up duration was 3.5 years (IQR 1.5-6.9). During the pre-flecainide period, 45 patients experienced 67 arrhythmic events. During the on-flecainide period, 29 patients experienced a total of 51 arrhythmic events. Using negative binomial GLMM, there was a significant reduction in the rate of arrhythmic events after flecainide (IRR 0.66 [0.45-0.96], p=0.028).

### Characteristics of cases excluded for unequal background therapy

A total of 142 patients were excluded based on not being on equal background therapy for at least 7 days pre and/or post-flecainide. Of these, 107 (75%) were probands. Their median age at diagnosis was 14 years (IQR 9-22). Twenty-six (18%) patients were asymptomatic before diagnosis. Thirty-nine (27%) had arrhythmic events after diagnosis. The indications for starting flecainide were CPVT-related symptoms (n=15), ventricular arrhythmia or ventricular tachycardia despite other medication

(n=66), initial therapy (n=38), patient preference (n=4), other (n=15), or unknown (n=4). In conclusion, these patients were slightly younger and more symptomatic before diagnosis and on initial therapy as compared with the study population.

# Supplementary tables

## Table S1. Commonly used β-blockers, their dosing and frequency regimen, and indications. Reproduced from T.M. Roston et al.[18]

| β-blocker | Route | Frequency | Starting dose, mg/kg/d | Typical adult starting dose | Maximum dose, mg/kg/d | Typical adult maximal dose | Equivalent daily dose | Specific cardiac indications | Common noncardiac indications | Additional considerations |
|---|---|---|---|---|---|---|---|---|---|---|
| Acebutolol | PO | OD or BID | 1 | 200-400 mg divided OD or BID | 20 | 600 mg BID | 200 mg/d | HTN,* stable CAD | Hyperthyroidism (although other agents preferred) | > 100 mg/d unlikely to offer further antihypertensive benefit; higher doses often needed for angina |
| Atenolol | PO | OD or BID | 0.5 | 25-50 mg OD | 2 | 200 mg OD | 50 mg/d | HTN,* MI, stable CAD | Hyperthyroidism (second-line) | Not recommended in pregnancy > 100 mg/d unlikely to offer further antihypertensive benefit |
| Bisoprolol | PO | OD | 0.04 | 1.25-2.5 mg OD | 0.14 | 20 mg OD | 5 mg/d | HFrEF, arrhythmia, HTN (second-line)* | | May use up to 20 mg OD for hypertension; Target dose for HFrEF: 10 mg OD |
| Carvedilol | PO | BID | 0.1 | 3.125 mg BID | 0.7 | 50 mg BID | 25 mg/d | HFrEF, HTN (second-line),* MI with EF < 40% | Esophageal varices (second-line) | Target dose in HFrEF: 50 mg BID |
| Labetalol | PO | BID (for large doses may divide TID or QID) | 3 | 100 mg BID | 10 | 800 mg TID | 200 mg/d | HTN in pregnancy, HTN crisis, | Subarachnoid hemorrhage | Safe in pregnancy |
| Metoprolol | PO/I.V. | Depends on formulation | 1 | 12.5-25 mg BID | 6 (up to 400 mg/d) | 200 mg BID | 100 mg/d 50 mg BID | HTN,* HFrEF, arrhythmia, MI, stable CAD | Migraine (second-line), hyperthyroidism (second-line) | Safe in pregnancy, only succinate formulation |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | indicated in HFrEF |
| Nadolol | PO | OD | 0.6 | 40 mg OD | 3.4 | 320 mg OD | 80 mg/d | HTN,* CAD, arrhythmia, long QT syndrome | Esophageal varices; migraine | |
| Nebivolol | PO | OD | 0.07 | 5 mg OD | 0.6 | 40 mg OD | 10 mg/d | HFrEF, HTN (second-line) | | Useful in severe bronchospasm |
| Propranolol | PO/I.V. | Depends on formulation | 1 | 40 mg BID | 5 | 40 mg QID (arrhythmia) or 80 mg QID (angina) | 80 mg/d | Arrhythmia, long QT syndrome, HTN,* obstructive hypertrophic cardiomyopathy, stable CAD, MI | Hyperthyroidism; antipsychotic-induced akathisia (second-line), essential tremor, migraine, performance anxiety, esophageal varices | Superior to metoprolol in arrhythmic storm, used for hyperthyroidism in pregnancy |
| Sotalol | PO | BID | 1 | 40-80 mg BID | 4 | 160 mg BID | 80 mg/d | Arrhythmia, HOCM, ARVC | | Useful in AF or VT with EF > 35%<br>Assess baseline QTc and creatinine before initiation; adjust dose for renal impairment |
| Esmolol | I.V. | Continuous infusion | 1 (bolus); 0.05 infusion | 500 μg/kg load, then 50 μg/kg/min infusion | 0.2 | 200 μg/kg/min | N/A | Intraoperative arrhythmia or arrhythmia in shock | Hyperthyroidism | Rapid onset and offset are ideal in the critical care setting |

Equivalent daily dose is on the basis of an approximate conversion between the commonly prescribed doses for each type of β-blocker. Data are derived from Lexicomp.com, PrescribersLetter.com, BC Children's & Women's Hospital Pharmacy Formulary, Vancouver General Hospital Pharmacy Formulary, and Kaiser Permanente Formulary.

AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; BID, twice daily; CAD, coronary artery disease; EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction; HOCM, hypertrophic obstructive cardiomyopathy; HTN, hypertension; I.V., intravenous; MI, myocardial infarction; N/A, not applicable; OD, once daily; PO, by mouth; QID, 4 times daily; TID, 3 times daily; VT, ventricular tachycardia.

* Although certain β-blockers are approved as first- or second-line antihypertensive agents, contemporary guidelines do not support the use of β-blockers as a first-line option for primary HTN.

**Table S2. Characteristics of patients not treated with flecainide**

| | Patients not treated with flecainide (n=944) | Study cohort (n=247) |
|---|---|---|
| **Year of enrolment in registry, median (IQR)** | 2017 (2015-2017) | 2016 (2014-2017) |
| **Female sex, n (%)** | 507 (54) | 123 (50) |
| **Proband, n (%)** | 326 (35) | 156 (63) |
| **Asymptomatic before diagnosis, n (%)** | 452 (48) | 83 (34) |
| **Sudden cardiac arrest before diagnosis, n (%)** | 72 (8) | 48 (19) |
| **Age at diagnosis, median (IQR)** | 19 (11-43) | 13 (9-22) |
| **Beta-blocker therapy, n (%)** | 760 (81) | 247 (100) |
| **Intentional non-therapy, n (%)** | 168 (18) | 0 (0) |
| **ICD, n (%)** | 203 (22) | 70 (28)* |
| **LCSD, n (%)** | 37 (4) | 21 (9)* |
| **Arrhythmic event after diagnosis, n (%)** | 110 (12) | 59 (24) |

*ICDs implanted and LCSDs performed at baseline. ICD, implantable cardioverter-defibrillator; LCSD, left cardiac sympathetic denervation.

**Table S3. Characteristics of patients with arrhythmic events during the on-flecainide period**

| | All patients (n=23) | Suboptimal* therapy (n=7) | Optimal therapy (n=16) |
|---|---|---|---|
| **Female, n (%)** | 10 (43) | 2 (29) | 8 (50) |
| **Mental retardation/neurologic disease, n (%)** | 9 (39) | 1 (14) | 8 (50) |
| **Genotype unknown/not evaluated, n (%)** | 2 (9) | 0 | 2 (13) |
| **Genotype negative, n (%)** | 1 (4) | 0 | 1 (6) |
| **Genotype positive** | | | |
| ***RYR2*, n (%)** | 19 (83) | 7 (100) | 12 (75) |
| ***CASQ2*, n (%)** | 1 (4) | 0 | 1 (6) |
| **Worst symptom prior to diagnosis** | | | |
| **Asymptomatic, n (%)** | 4 (17) | 2 (29) | 2 (13) |
| **Syncope, n (%)** | 11 (43) | 4 (57) | 7 (44) |
| **Sudden cardiac arrest, n (%)** | 8 (35) | 1 (14) | 7 (44) |
| **Age at symptom onset, years, median (IQR)** | 10 (6-14) | 12 (11-14) | 9 (6-13) |
| **Age at diagnosis, years, median (IQR)** | 11 (8-13) | 11 (8-13) | 11 (8-15) |
| **Age at flecainide initiation, years, median (IQR)** | 13 (11-18) | 14 (11-22) | 13 (11-17) |
| **Age at first breakthrough event, years, median (IQR)** | 16 (13-20) | 15 (14-22) | 16 (13-20) |

*Flecainide therapy was considered suboptimal when patient was non-adherent or was prescribed a low flecainide dose (<100 mg). Patients in whom information on adherence was missing were classified as adherent. Patients who experienced at least 1 arrhythmic event on an optimal dosage of flecainide and in whom non-adherence was not confirmed were classified as having optimal therapy.