Incremental Value of an Insertable Cardiac Monitor in Patients with Hypertrophic Cardiomyopathy with Low or Intermediate Risk for Sudden Cardiac Death

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Abstract
Aims: The aim of the present study was to compare the rate of actionable arrhythmic events between patients with hypertrophic cardiomyopathy (HCM) who are monitored with an insertable cardiac monitor (ICM) or Holter monitoring.

Methods: We studied 50 patients (mean age 52 years, 72% men) with HCM at low or intermediate risk for sudden cardiac death (SCD), of whom 25 patients received an ICM between November 2014 and February 2019. We retrospectively identified a control group of 25 patients who were matched on age, sex, and HCM Risk-SCD score category. The mean HCM Risk-SCD score was 3.41 ± 1.31 and 3.31 ± 1.43 for the ICM and Holter groups, respectively. The primary endpoint was an actionable event which was defined as an arrhythmic event resulting in a change in patient management. The secondary endpoint was the occurrence of ventricular tachycardia (VT). Results: The cumulative actionable event rate at 30 months was higher in the ICM group (51 vs. 27%, log-rank p value <0.01). De novo atrial fibrillation requiring oral anticoagulation occurred only in the ICM group (n = 3). Overall, 4 implantable cardioverter-defibrillators were implanted for primary prevention (n = 2 in each group). The cumulative rate of VT episodes at 30 months was similar between groups (23% [ICM group] vs. 42% [Holter group], log-rank p value = 0.71). Furthermore, the characteristics of VT were similar between groups with regard to the number of beats and rate. Conclusions: In adults with HCM, an ICM will detect more arrhythmic events requiring an intervention than a conventional Holter strategy. In contrast, the diagnostic yield of detecting VT seems similar for both groups.

Introduction

Insertable cardiac monitors (ICMs) provide continuous rhythm monitoring and are useful for the detection of infrequent arrhythmias, especially in patients with recurrent unexplained syncope [1]. The exact role of ICMs...
in patients with hypertrophic cardiomyopathy (HCM) is less clear. The current ESC guidelines recommend that HCM patients with recurrent episodes of unexplained syncope, who are at low risk of sudden cardiac death (SCD), should be considered for an ICM [1, 2]. Furthermore, an ICM may be considered for HCM patients with frequent unexplained palpitations [2]. However, these recommendations are based on scarce data and there are no comparative data with ambulatory Holter monitoring [3–5]. The 2014 ESC HCM guidelines recommend the use of ambulatory Holter monitoring to detect atrial and ventricular arrhythmias every 12–24 months or more often in the case of symptoms or left atrial dilatation [2]. Theoretically, the diagnostic yield for the detection of arrhythmias is higher for an ICM in comparison to intermittent Holter monitoring. This higher diagnostic yield may be clinically relevant in this patient population. For example, the detection of ventricular tachycardia (VT) may have an impact on risk stratification for SCD and the decision to implant an implantable cardioverter-defibrillator (ICD) [2, 6, 7]. Furthermore, HCM patients with documented atrial fibrillation (AF) should receive oral anticoagulation to prevent stroke [2]. In the past 5 years, we adopted a strategy to use an ICM in HCM patients at low to intermediate risk of SCD for the detection of subclinical arrhythmias, with a particular emphasis on the detection of VT. The aim of the present study was to evaluate the incremental value of ICMs compared to a conventional strategy (i.e., Holter monitoring) in adults with HCM and a low or intermediate HCM Risk-SCD score.

**Methods**

**Study Population**

This was a prospective observational study which included all consecutive adults with HCM who received a Reveal LINQ (Medtronic Inc., Minneapolis, MN, USA) between November 2014 and February 2019. All patients had an HCM Risk-SCD score <6%. The reason for an ICM was a combination of symptoms (e.g., recurrent [near] syncope, palpitations), presence of myocardial fibrosis (determined by the presence of late gadolinium enhancement [LGE] on cardiac MRI [CMR]) and/or an intermediate risk for SCD (5-year risk of SCD ≥ 4 to <6%). The decision to implant an ICM was made during a Heart Team consisting of a cardiac electrophysiologist and a cardiologist specialized in HCM. The control group was retrospectively identified from our prospective HCM registry and consisted of a matched cohort who received conventional follow-up (intermittent Holter monitoring every 6–24 months based on treating physician’s discretion). Matching was based on age (within a margin of 5 years), sex, and HCM Risk-SCD score category (<4% or ≥4 to <6%). Patients in the control group required a minimum of 1 Holter study during follow-up and at least a clinical follow-up of 1 year. This study was approved by the Ethics Committee of the Erasmus MC.

**ICM Settings**

All ICMs were implanted subcutaneously as recommended by the manufacturer using the incision and insertion tool. Furthermore, all patients received a handheld activator to indicate their symptoms when necessary. The ICM was routinely programmed with the following settings: tachycardia detection was set to 176 bpm for 16 beats; bradycardia setting to 30 bpm for 8 beats; pause setting to 4.5 s; and AF setting to “AF only.” Based on the implanting physician’s preferences, other settings could be programmed. All devices were connected to the Medtronic CareLink network for remote monitoring.

**Clinical Follow-Up of ICM Group**

ICM patients were discharged on the day of implantation. Ten days after implantation, the patients were seen at the outpatient clinic to check the implantation site and to interrogate the ICM. Afterwards, the patients were seen regularly at the outpatient clinic according to routine patient care. ICM checkups were performed at the outpatient clinic every 6 months or earlier when necessary based on symptoms or transmitted episodes. Remote monitoring was performed on a daily basis during weekdays. All patient-activated episodes and automatically detected episodes were classified. In case of an inappropriate automatically detected episode, the cause of inappropriate detection was specified, if possible. Multiple actionable events could occur in 1 patient.

**Study Endpoints**

The primary endpoint of the study was the occurrence of an actionable event which was defined as an arrhythmic event resulting in any change in patient management (e.g., start or increase of medication, implantation of pacemaker or ICD, catheter ablation). The secondary endpoint was the occurrence of any VT (at least 3 beats), irrespective if this resulted in an actionable event or not. A regular wide complex tachycardia was considered a VT if there was a sudden onset and a change in the QRS morphology in comparison to the baseline rhythm. An irregular wide complex tachycardia was considered a VT if there was a sudden onset and a polymorphic QRS morphology. A regular wide or narrow complex tachycardia was considered a supraventricular tachycardia (SVT) if there was a sudden onset and no change in QRS morphology. In case of doubt, a second electrophysiologist was consulted for the final diagnosis. For both endpoints, the cumulative event rate was determined at 30 months considering the estimated battery lifetime of the ICM.

**Statistical Analysis**

Continuous data are presented as mean ± SD or as median with interquartile range (IQR) (25th and 75th percentiles), as appropriate. Categorical variables are presented by frequencies and percentages. Differences of continuous variables between groups were analyzed with unpaired Student’s t test or the Kruskal-Wallis test, as appropriate. Differences between categorical variables were evaluated using the χ² test. Cumulative event rates were estimated with the Kaplan-Meier method, and differences were compared by log-rank test. Statistical analyses were performed using SPSS version 25 (IBM Corp., Somers, NY, USA).
Results

A total of 25 HCM patients received an ICM between 2014 and 2019. We identified 25 matched controls with HCM who were seen at the outpatient clinic in the same study period. Baseline characteristics of the study population are presented in Table 1. The ICM group more often had a history of syncope (32% vs. 4%, *p* = 0.01). Other baseline characteristics, including a history of nonsustained VT (NSVT), were similar between groups.

**ICM-Detected Arrhythmias and Holter Follow-Up**

During a mean follow-up of 17 ± 10 months with the ICM, a total of 1,015 episodes were transmitted to the CareLink network system. There were 270 (27%) patient-activated episodes and 745 (73%) automatically detected episodes. The majority of patient-activated episodes (93%) comprised sinus rhythm with or without ectopy. In the control group, 48 Holter recordings were performed during follow-up. The median number of Holter recordings per patient was 2 (IQR, 1–3). The median interval between Holter recordings was 12 (IQR, 5–23) months.

**Primary Endpoint**

The cumulative event rate for an actionable event was higher in the ICM group (51 vs. 27% at 30 months, log-rank *p* value < 0.01) (Fig. 1). In the ICM group, the following actionable events occurred: antiarrhythmic drug therapy (or change in dose) for documented arrhythmias (*n* = 6, 24%), start of non-vitamin K antagonist oral anticoagulation for documented AF (*n* = 3, 12%), electrophysiology study for symptomatic SVT (*n* = 2, 8%), implantation of ICD for primary prevention (*n* = 2, 8%), pacemaker implantation for sinus node dysfunction (*n* = 1, 4%), and external electrical cardioversion for AF (*n* = 1, 4%). In the control group, the following actionable events occurred: antiarrhythmic drug therapy (or change in dose) for documented arrhythmias (*n* = 1, 4%), start of non-vitamin K antagonist oral anticoagulation for documented AF (*n* = 1, 4%), implantation of ICD for primary prevention (*n* = 1, 4%), pacemaker implantation for sinus node dysfunction (*n* = 1, 4%), and external electrical cardioversion for AF (*n* = 1, 4%).

**Table 1. Clinical baseline characteristics**

| Characteristic | ICM group | Control group | *p* value |
|----------------|-----------|---------------|-----------|
| Age, years     | 51±16     | 52±16         | 0.94      |
| Sex, male      | 18 (72%)  | 18 (72%)      | 1.00      |
| NYHA functional class ≥II | 7 (28%) | 7 (28%) | 1.00 |
| History of myectomy | 2 (8%)  | 3 (12%) | 0.64 |
| Left ventricular systolic function Normal (EF ≥50%) | 25 (100%) | 24 (96%) | 1.00 |
| Mildly impaired (EF 45–49%) | 0 | 1 (4%) | 0.67 |
| Genetic testing | 21 (84%) | 23 (92%) | 0.67 |
| Pathogenic mutation | 12 (48%) | 14 (56%) | 0.57 |
| MYBPC3         | 8 (32%)   | 11 (44%)      | 0.38      |
| MYH7           | 3 (12%)   | 1 (4%)        | 0.30      |
| TPM1           | 1 (4%)    | 0             | 1.00      |
| TNN3           | 0         | 2 (8%)        | 0.49      |
| History of NSVT | 13 (52%) | 8 (32%) | 0.15 |
| History of unexplained syncope | 8 (32%) | 1 (4%) | 0.01 |
| Peak LVOT gradient | 6 (5–17) | 12 (6–82) | 0.19 |
| Family history of SCD | 3 (12%) | 3 (12%) | 1.00 |
| Left atrial size | 43±9 | 45±7 | 0.23 |
| Maximum left ventricular wall thickness | 18±5 | 18±5 | 0.49 |
| HCM Risk-SCD score | 3.41±1.31 | 3.31±1.43 | 0.79 |
| <4%            | 13 (52%)  | 13 (52%)      | 1.00      |
| ≥4 to ≤6%      | 12 (48%)  | 12 (48%)      | 1.00      |
| Electrocardiography | 25 (100%) | 25 (100%) | 1.00 |
| Sinus rhythm   | 24 (96%)  | 25 (100%)     | 1.00      |
| AF             | 1 (4%)    | 0             | 1.00      |
| PR interval, if sinus rhythm | 164±25 | 182±25 | 0.85 |
| QRS duration, ms | 105±18 | 102±28 | 0.56 |
| QTc duration, ms | 426±25 | 416±28 | 0.61 |
| Holter monitoring | 25 (100%) | 25 (100%) | 1.00 |
| <1% PVCs       | 23 (92%)  | 25 (100%)     | 0.49      |
| 1–10% PVCs     | 2 (8%)    | 0             | 0.49      |
| NSVT           | 11 (44%)  | 6 (24%)       | 0.14      |
| SVT            | 7 (28%)   | 12 (48%)      | 0.15      |
| AF             | 2 (8%)    | 0             | 0.49      |
| Cardiac medication | 16 (64%) | 19 (76%) | 0.35 |
| Beta blocker   | 12 (48%)  | 14 (56%)      | 0.57      |
| Loop diuretics | 5 (20%)   | 0             | 0.05      |
| ACE-inhibitor/ARB | 6 (24%) | 3 (12%) | 0.27 |
| Oral anticoagulants | 5 (20%) | 5 (20%) | 1.00 |
| Calcium channel blocker | 3 (16%) | 4 (16%) | 0.68 |
| Amiodarone/sotalol | 2 (8%) | 2 (8%) | 1.00 |

Data are presented as n (%), mean ± SD, or median with IQR. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PVC, premature ventricular complex; SCD, sudden cardiac death; IQR, interquartile range; SVT, supraventricular tachycardia; AF, atrial fibrillation.

Fig. 1. Cumulative event rate for actionable events. ICM, insertable cardiac monitor.
in dose) for documented arrhythmias (n = 6, 24%), implantation of ICD for primary prevention (n = 2, 8%), and electrophysiology study for symptomatic SVT (n = 1, 4%). De novo AF only occurred in the ICM group. Of the 3 patients with de novo AF, only 1 patient who experienced symptoms required an electrical cardioversion for persistent AF.

Overall, 4 patients received an ICD for primary prevention (2 in each group). A patient in the ICM group had an ICM-detected NSVT (7 beats, 171 bpm, patient-activated) which increased his HCM Risk-SCD score from 3.6% to 8.0%. He received a prophylactic ICD 15 months after his ICM implantation. The other patient in the ICM group had a history of NSVT, HCM Risk-SCD score of 4.44%, and patchy LGE anterior wall and interventricular septum on his CMR. He experienced an episode of fast monomorphic NSVT (32 beats, 200 bpm, automatically detected) 12 months post-ICM implantation. This did not increase his HCM Risk-SCD score, but based on his clinical profile and the malignant character of the VT, the patient received an ICD. In the control group, a patient received a prophylactic ICD after a Holter-detected monomorphic VT episode (3 beats, 135 bpm) increased his HCM Risk-SCD score from 4.4% to 9.6% at 27 months after initial risk evaluation. The second patient in the control group who received a prophylactic ICD had an HCM Risk-SCD score of 4.2% and had a history of NSVT. The combination of Holter-detected recurrent VT and recurrent near syncope was the indication for an ICD 26 months after initial risk evaluation.

Discussion

The present study is the first study comparing the value of an ICM to conventional Holter monitoring in HCM patients with a low or intermediate HCM Risk-SCD score. The main finding is that actionable arrhythmic events occurred more frequently in the ICM group in comparison to the Holter group. In contrast, the cumulative rate of detected VT was similar between both groups.

It is well-known that prolonged arrhythmia monitoring increases the yield of arrhythmia detection. The indications for an ICM has expanded over the years, and its use is currently not only limited to patients with recurrent unexplained syncope [1, 8]. Other important indications include the detection of subclinical AF, risk stratification in patients with inheritable heart disease by the detection of VT, and establishing a symptom-rhythm correlation in symptomatic patients [9]. In patients with HCM who are at low risk for SCD according to the HCM Risk-SCD score, the current ESC guidelines recommends that an ICM should be considered in patients with recurrent unexplained syncope and may be considered in those with unexplained palpitations [1, 2]. However, limited data exist on the clinical impact of ICMs in HCM patients, and most studies comprised <10 patients [3–5].

The present study is the first to provide insight into the incremental value of an ICM in patients with HCM. The rate of actionable arrhythmic events was higher in the ICM group in comparison to a matched group who had intermittent Holter monitoring. Interestingly, de novo AF requiring oral anticoagulation only occurred in the ICM group. It is known that AF occurs in approximately 20% of the patients with HCM and is associated with im-

![Fig. 2. Cumulative event rate for ventricular arrhythmias. ICM, insertable cardiac monitor.](https://example.com/fig2.png)
Incremental Value of an ICM in Patients with HCM

Incremental Value of an ICM in Patients with HCM

In patients with HCM, the use of an ICM resulted in more actionable arrhythmic events if compared to intermittent Holter monitoring. Interestingly, de novo AF was only detected in the ICM group. The diagnostic yield of detecting VT appeared similar between both rhythm detection strategies, which may be explained by the ICM not detecting short runs of VT.

Statement of Ethics

The Institutional Review Board of the Erasmus MC reviewed the study (MEC2017052), and this study was not subjected to the Dutch Medical Research Involving Human Subjects Act. This study was carried out according to the ethical principles for medical research involving human subjects established by Declaration of Helsinki, protecting the privacy of all the participants and the confidentiality of their personal information.
