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Complete List of Authors:	Magnusson, Peter; Center for Research and Development, Uppsala University/Region Gävleborg; Karolinska Institutet Mörner, Stellan; Umeå University, Department of Public Health and Clinical Medicine
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EvaLuation Using Cardiac Insertable Devices And TelephonE in Hypertrophic Cardiomyopathy (ELUCIDATE HCM) – rationale and design: a prospective interventional observational trial

Peter Magnusson[1,2] Stellan Mörner[3]

1. Cardiology Research Unit, Department of Medicine, Karolinska Institutet, Stockholm, SE-171 76, SWEDEN
2. Centre for Research and Development, Uppsala University/Region Gävleborg, Gävle, SE-801 87, SWEDEN
3. Department of Public Health and Clinical Medicine, Umeå University, Umeå, SE-90187, SWEDEN

Correspondence to:

Peter Magnusson

Cardiology Research Unit, Department of Medicine

Karolinska Institutet

Karolinska University Hospital/Solna

SE-171 76 Stockholm, SWEDEN

Phone: +46(0)705 089407

Fax: +46(0)26 154255

E-mail: peter.magnusson@regiongavleborg.se

ABSTRACT

Introduction: Hypertrophic cardiomyopathy (HCM) is heteregenous disease associated with sudden cardiac death (SCD) mainly due to ventricular tachycardia (VT) or fibrillation even though life threatening bradycardia occurs. Risk stratification takes several variables into consideration including non-sustained VT. An implantable cardioverter defibrillator effectively prevents SCD.

Atrial fibrillation (AF) is common among HCM patients and warrants anticoagulation even without conventional risk factors according to European guidelines. Routinely, the evaluation of arrhythmias using a 48 hour ambulatory external monitor takes place every 6 to 24 months if patients don't report palpitations. The remaining time the potential burden arrhythmia is unknown. Therefore, the aim of the present study is to assess NSVT and AF incidence during 18 months by an insertable cardiac monitor (ICM).

Methods: Adult patients, aged 18-65 years, with a validated diagnosis of HCM are eligible for the study. The study sample is planned to include 30 patients. A Confirm Rx^{TM} is implanted at the level of the fourth rib on the left side subcutaneously after local anesthesia. The application for monitoring is installed in the patients smart-phone and symptoms registrated by the patient activation and VT detection programmed as 160bpm during ≥8 intervals. An AF episode is recorded based on ≥2 minutes duration. Bradycardia is recorded at ≤40bpm or pause ≥3.0 seconds. The patients are followed during 18 months before explant.

Ethics: The study was approved by The Regional Ethical Committee in Umeå (protocol number 2017/13-31) The study protocol, including variables and pre-specfied research questions the study was registered at Clinical Trial Registration

NCT03259113. Each patient is informed about the study in both oral and written form by a physician and included after written consent.

Strengths and limitations of this study

- An insertable cardiac monitor (ICM) allows for monitoring of atrial fibrillation, significant bradycardia, and non-sustained ventricular tachycardia during 18 months.
- The study will evaluate true incidence of arryhtmia including symptom registration using a smart-phone.
- The detection of atrial fibrillation warrants anticoagulation but very short episodes lack evidence with regard to clinical management.
- Non-sustained ventricular tachycardia is a marker of sudden cardiac death but the decision to implant a defibrillator should be carefully evaluated using guidelines as an ICM is currently not an indication as a diagnostic tool in this regard.
- The costly and invasive ICM may need to be studied in larger hypertrophic cardiomyopathy cohorts to allow for subgroup analyses and to generalize findings.

Keywords: atrial fibrillation, hypertrophic cardiomyopathy, implantable loop recorder, insertable cardiac monitor, non-sustained ventricular tachycardia

INTRODUCTION

The hypertrophic cardiomyopathy (HCM) phenotype in adults requires at least 15mm thickness of the myocardial wall deemed unexplained by other myocardial diseases and abnormal loading conditions due to hypertension or aortic stenosis.[1] The point prevalence is approximately 1:500 in the general population but more than double if genotypes are also included.[2-4] Patients presents with unspecific symptoms such as dyspnea, chest discomfort, and dizziness. Echocardiogram is the cornerstone in diagnosing HCM but integrated medical information and awareness of differential diagnoses are important to avoid misclassification.[5-7] The severity and pattern of hypertrophy and disease progression varies considerably.[5] Life expectancy in general HCM cohorts seems to be acceptable but end-stage heart failure, cardiac embolization stroke, and devastating arrhythmias remain a challenge in order to improve prognosis.[8-12]

Sudden cardiac death (SCD) can be prevented by an implantable defibrillator cardioverter (ICD). In a recent review of HCM patients with ICDs, 4.8% experienced appropriate therapy annually due to ventricular tachycardia (VT) or fibrillation and antitachycardia pacing or cardioversion rarely fails.[13] The decision to implant an ICD as primary prevention of SCD is based evaluation of riskmarkers according to guidelines.[14,15] In both 2011 and 2014 guidelines, non-sustained VT (NSVT) is part of risk stratification based on evidence from several studies.[16-19] It is more common at higher age and correlates with increased left ventricular wall thickness.[16,20] NSVT may be revealed during an ambulatory ECG or at telemetry in the ward or at exercise test. HCM guidelines advocate follow-up including 48 hour ambulatory ECG whenever onset of palpitations or otherwise every 12-24 months but 6-12 months if the patient is in sinus rhythm and has enlarged left atrial diameter which predisposes

for AF and SCD.[15] This implies that during the remaining time the presence of NSVT/AF is unknown.

In HCM, AF is known to worsen symptoms due to vulnerablity to increased heart rate and lack of atrial filling. Furthermore, atrial fibrillation (AF) associated with ischemic stroke or systemic embolization is a major cause of death in HCM, which warrants attention to detection methods with increased sensitivity.[11] In fact, according to current HCM-guidelines, a history of AF, even without any CHA2DS2-VASc risk factor is an indication of anticoagulation.[15]

The insertable cardiac monitor (ICM) Confirm Rx™ (Abbott/St. Jude Medical, St. Paul, MN, USA) provides long-term monitoring of atrial and ventricular arrhythmias in addition to bradycardia.[21] This device could potentially reveal the true incidence of arrhythmia in HCM patients which is the rationale of the present study: EvaLuation Using Cardiac Insertable Devices And TelephonE in Hypertrophic Cardiomyopathy (ELUCIDATE HCM).

OBJECTIVES

Primary objective is to assess the incidence of NSVT during 18 months follow-up using an ICM.

Secondary objective is to assesses the incidence of AF during 18 months follow-up using an ICM.

METHODS

Setting and selection

Adult patients with a confirmed of HCM, will be recruited from the catchment area of Region Gävleborg and Umeå University hospital (tertiary center) in northern Sweden.

Eligible patients are identified from hospital data-bases (diagnostic codes I42.1 or I42.2) and validated using medical records. The recruitment started in August 2017.

Inclusion and exclusion

Patients, aged 18-65 years, with a confirmed diagnosis of HCM are eligible for the study. Exclusion criteria as follows: aortic stenosis (moderate, severe), hypertrophy assoacied with metabolic disease (e.g. Fabry-Andersen) and syndromes (e.g. Noonan syndrome), systolic heart failure with ejection fraction ≤55%, pacemaker, implantable defibrillator, myocardial infarction, percutenous coronary intervention, coronary by-pass grafting, pulmonaru vein isolation, Maze surgery, VT ablation, ectopica atrial tachycardia ablation, renal clearance ≤40, malignancy or other comorbidity with ≤5 years life expectancy, pregnancy (or planned ≤18 months), drug addition, severe psychiatric disease, not able to participate in 18 months follow-up, 5-year risk of sudden cardiac death ≥6% according to the risk calculator.[19]

Implantation and monitor set-up

The implantation procedure is performed in local infiltrative anesthesia (carbocaine with epinephrine) using the standard operation kit for Confirm Rx™ via a 5mm incision at the level of the fourth rib on the left side subcutaneusly. The application for monitoring is installed in the patients own smart-phone or a one that will be lent during the study period. The connection to the home-monitoring site Merlin™ is administrated and the patient is instructed how to use application and report potential symptoms according to guidelines.[22] Post-procedure, paracetamol (acetaminophen) is recommended to control pain.

Programming

VT detection is programmed as 160bpm during ≥8 intervals with high EGM priority and discrimanator sudden onset activated (onset delta 18%) a bigemini qualifier off. An AF episode is recorded based on ≥2 minutes duration, AF-burden ≥6 hours a day, or ventricular rate during AF 100bpm for 6 hours daily. Bradycardia is recorded at ≤40bpm or pause ≥3.0 seconds. Patient-activated symptom episodes have high EGM priority with 6 minutes symptom pre-trigger duration and 1 minute symptom post-trigger duration and the first 8 EGMs are stored. Maxmimal ventricular sensitivity is typically 0.15mV but adjusted if R-waves are low. Threshold start is 75% and sense refractory period 250ms and decay delay 60ms.

Power analysis

A power analysis is based on previous research findings and estimation of outcome with certain relevance of hypothesis testing. This is the first study on incidence of NSVT and AF in HCM using continuous monitoring for a period of 18 months. Thus the diagnostic yield is unknown. A power formal analysis is have not been conducted and estimation of sample size is based on clinical judgement and available resources.

Statistics

Numeric data will be presented as frequencies, percentages, means, and percentiles. Continuous variables are summarized as means, standard deviations, and percentiles, and compared using t-tests. The chi-squared test is used for categorical variables. Kaplan-Meier estimates is used to describe time to event analysis (time from implant to AF and NSVT respectively and cumulative incidence at 6,12, and 18 months will be reported.

A two-sided *p*-value of <0.05 is considered statistically significant. The database will be stored in Excel 2010 (Microsoft Corporation, Redmond, WA) and imported into SPSS version 22 (IBM, Armonk, NY) for statistical analyses.

Variables

Patient characteristics at enrollment as follows: age, family history of SCD, unexplained syncope, known HCM associated mutation, weight, length, NSVT at 48 ambulatory ECG. Echocardiography parameters such as maximal wall thickness, left ventricular outflow tract gradient, left atrial size will be recorded.

Ethics and Registration

The Regional Ethical Committee in Umeå approved the study the 7th of February 2017 (protocol number 2017/13-31), which is conducted in accordance with the Declaration of Helsinki.[23] The study protocol, including variables and pre-specfied research questions the study was registered at Clinical Trial Registration NCT03259113 and approved 24th of August 2017. Documentaton of research data and management of study follow Guideline for Good Clinical Practice.[24] Each patient is informed about the study in both oral and written form by a physician and included after written consent.

DISCUSSION

This is the first study on arrhythmia detection in HCM using an ICM. These devices offer the superior advantage of prolonged monitoring in comparison to external loop-recorders. ICM is currently used in certain cases of HCM such as syncope evaluation but not in routine evaluation. The application of ICM in the specific group of HCM has been proposed already in statements of research priorities.[25]

The newly launched Confirm Rx™ uses a smart-phone application that is used instead of a standard home-monitor and provide the possibility of remote monitoring and symptom registration.

Until now, 48 hour ambulatory monitoring is used, but often telemetry in hospital wards detect arrhythmias in HCM. That means that these modes of monitoring may coincidentially detect AF and VT but with increased likelihood in patients with higher incidence of arrhythmias. It is unclear if a higher incidence of arrhythmia reflects a higher risk of and our study has a small sample size and no long-term follow-up of outcomes of SCD. Even though this study will elucidate the true arrhythmia incidence, the clinical interpretation will remain partly unsolved. In addition, ICMs are costly devices and health economy analyses will be needed before potential use in broader HCM groups.

AF detection is important in HCM because of the increased of embolic stroke.[11] AF detection by ICM is superior compared to standard evaluation of monitoring in cryptogenic stroke.[26] However, it should be remembered that clinical management of patients whose AF was detected at pacemaker interrogation is controversial, but there is compelling evidence when duration is at least six minutes.[27] Patients with silent AF, i.e. asymptomatic still carry a considerable risk and should be managed the conventional way with regard to anticoagulation.[27] Even though the definition of AF is an atrial electrical activity of ≥300 per minutes during ≥30s, devices such as pacemaker register atrial high rate and the benefit of apixaban is currently studied. The correlation to symptoms is possible in our study and future smartphone-based ICM usage is promising.[28]

Safety aspects during the study imply referral to the patients physician for anticoagulation if AF is detected, sustained VT/ ventricular fibrillation for decision-making with regard to an ICD and if a significant bradycardia occur that implies a pacemaker indication.

Future research of larger series of HCM patients using ICM:s with a sample size and subgroups like patients who have undergone myectomy or alcohol septal ablation are welcomed. Interestingly, the ICM size has become reduced over time, and implantation techniques have become simpler, which allows for more favourable cost-benefit as implantation outside the electrophysiological laboratory is possible.

Still, this is the first study on arrhythmia burden and symptoms in consecutive unselected HCM patients using an ICM connected to a smart-phone for monitoring and symptom elucidation.

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Author contributions

PM: idea, design, project management, and writing the manuscript. SM: critical revision of the manuscript and project management.

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Competing interests

The authors received a research grant from Abbott /St Jude Medical (see funding section)

Ethics approval

The study was approved by the Regional Ethical committee in Umeå (Dnr 2017/13-31).

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Correspondence to:

Peter Magnusson

Cardiology Research Unit, Department of Medicine

Karolinska Institutet

Karolinska University Hospital/Solna

SE-171 76 Stockholm, SWEDEN

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Methods: Adult patients, aged 18-65 years, with a validated diagnosis of HCM are eligible for the study. The study sample is planned to include 30 patients. A Confirm Rx^{TM} is implanted at the level of the fourth rib on the left side subcutaneously after local anesthesia. The application for monitoring is installed in the patients smart-phone and symptoms registered by the patient activation and VT detection programmed as 160bpm during ≥8 intervals. An AF episode is recorded based on ≥2 minutes duration. Bradycardia is recorded at ≤40bpm or pause ≥3.0 seconds. The patients are followed during 18 months before explant.

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- An insertable cardiac monitor (ICM) allows for monitoring of atrial fibrillation, significant bradycardia, and non-sustained ventricular tachycardia during 18 months.
- The study will evaluate true incidence of arryhtmia including symptom registration using a smart-phone.
- The detection of atrial fibrillation warrants anticoagulation but very short episodes (<5 minutes) lack evidence with regard to clinical management.
- Non-sustained ventricular tachycardia is a marker of sudden cardiac death but the decision to implant a defibrillator should be carefully evaluated using guidelines as an ICM is currently not an indication as a diagnostic tool in this regard.
- The costly and invasive ICM may need to be studied in larger hypertrophic cardiomyopathy cohorts to allow for subgroup analyses and to generalize findings.

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INTRODUCTION

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Follow-up

Patients are encouraged to report symtoms by using the smart phone application. In addition, every third month there is an automatic interrogation of the device and transfer to the home-monitoring site Merlin,™ which is reviewed every second day except for weekends. False detection of arrhythmia by the device is expected to be frequent based on experience. Therefore all episodes are scrutinized as part of work-process. At 18 months, the device is explanted. Patients are scheduled for follow-up every third months but detection of arrhythmia warrants contact with the patient as part of clinical management.

Power analysis

A power analysis is based on previous research findings and estimation of outcome with certain relevance of hypothesis testing. This is the first study on incidence of NSVT and AF in HCM using continuous monitoring for a period of 18 months. Thus the diagnostic yield is unknown. A formal power analysis is have not been conducted and estimation of sample size is based on clinical judgement and available resources.

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A two-sided *p*-value of <0.05 is considered statistically significant. The database will be stored in Excel 2010 (Microsoft Corporation, Redmond, WA) and imported into SPSS version 22 (IBM, Armonk, NY) for statistical analyses.

Variables

Patient characteristics at enrollment as follows: age, family history of SCD, unexplained syncope, known HCM associated mutation, weight, length, NSVT at 48 hours ECG. Echocardiography parameters such as maximal wall thickness, left ventricular outflow tract gradient, left atrial size will be recorded.

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DISCUSSION

This is the first study on arrhythmia detection in HCM using an ICM. These devices offer the superior advantage of prolonged monitoring in comparison to external loop-recorders. ICM is currently used in certain cases of HCM such as syncope evaluation or possibly in patients with frequent palpitations, but not in routine evaluation. The application of ICM in the specific group of HCM has been proposed already in statements of research priorities.[25]

The newly launched Confirm Rx™ uses a smart-phone application that is used instead of a standard home-monitor and provide the possibility of remote monitoring and symptom registration.

Until now, 48 hour ambulatory monitoring is used, but often telemetry in hospital wards detect arrhythmias in HCM. That means that these modes of monitoring may coincidentially detect AF and VT but with increased likelihood in patients with higher incidence of arrhythmias. It is unclear if a higher incidence of arrhythmia reflects a

higher risk of SCD/stroke and our study has a small sample size and no long-term follow-up of outcomes of SCD. Even though this study will elucidate the true arrhythmia incidence, the clinical interpretation will remain partly unsolved. In addition, ICMs are costly devices and health economy analyses will be needed before potential use in broader HCM groups.

Detection of AF is important in HCM because of the increased of embolic stroke.[11] AF detection by ICM is superior compared to standard evaluation of monitoring in cryptogenic stroke.[26] However, it should be remembered that clinical management of patients whose AF was detected at pacemaker interrogation is controversial, but there is compelling evidence when duration is at least six minutes.[27] Patients with silent AF, i.e. asymptomatic still carry a considerable risk and should be managed the conventional way with regard to anticoagulation.[27] Even though the definition of AF is an atrial electrical activity of ≥300 beats per minutes during ≥30s, devices such as pacemaker register atrial high rate and the benefit of apixaban is currently studied.[28] The correlation to symptoms is possible in our study and future smartphone-based ICM usage is promising.[29]

Safety aspects during the study imply referral to the patients physician for anticoagulation if AF is detected, sustained VT/ ventricular fibrillation for decision-making with regard to an ICD and if a significant bradycardia occur that implies a pacemaker indication. If an ICD or pacemaker is indicated, the ICM will remain until study end at 18 months.

Future research of larger series of HCM patients using ICMs with a larger sample size allowing for analysis of subgroups like patients who have undergone myectomy or alcohol septal ablation are welcomed. Interestingly, the ICM size has become

reduced over time, and implantation techniques have become simpler, which allows for more favourable cost-benefit as implantation outside the electrophysiological laboratory is possible.

Still, this is the first study on arrhythmia burden and symptoms in consecutive unselected HCM patients using an ICM connected to a smart-phone for monitoring and symptom elucidation.

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Author contributions

PM: idea, design, project management, and writing the manuscript. SM: critical revision of the manuscript and project management.

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Competing interests

The authors received a research grant from Abbott /St Jude Medical (see funding section)

Ethics approval

The study was approved by the Regional Ethical committee in Umeå (Dnr 2017/13-31).

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EvaLuation Using Cardiac Insertable Devices And TelephonE in Hypertrophic Cardiomyopathy (ELUCIDATE HCM) – rationale and design: a prospective observational study on incidence of arrhythmias in Sweden

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EvaLuation Using Cardiac Insertable Devices And TelephonE in Hypertrophic Cardiomyopathy (ELUCIDATE HCM) – rationale and design: a prospective observational study on incidence of arrhythmias in Sweden.

Peter Magnusson[1,2] Stellan Mörner[3]

1. Cardiology Research Unit, Department of Medicine, Karolinska Institutet, Stockholm, SE-171 76, SWEDEN
2. Centre for Research and Development, Uppsala University/Region Gävleborg, Gävle, SE-801 87, SWEDEN
3. Department of Public Health and Clinical Medicine and Heart Center, Umeå University, Umeå, SE-90187, SWEDEN

Correspondence to:

Peter Magnusson

Cardiology Research Unit, Department of Medicine

Karolinska Institutet

Karolinska University Hospital/Solna

SE-171 76 Stockholm, SWEDEN

Phone: +46(0)705 089407

Fax: +46(0)26 154255

E-mail: peter.magnusson@regiongavleborg.se

ABSTRACT

Introduction: Hypertrophic cardiomyopathy (HCM) is heteregenous disease associated with sudden cardiac death (SCD) mainly due to ventricular tachycardia (VT) or fibrillation even though life threatening bradycardia occurs. Risk stratification takes several variables into consideration including non-sustained VT. An implantable cardioverter defibrillator effectively prevents SCD.

Atrial fibrillation (AF) is common among HCM patients and warrants anticoagulation even without conventional risk factors according to European guidelines. Routinely, the evaluation of arrhythmias using a 48 hour ambulatory external monitor takes place every 6 to 24 months if patients don't report palpitations. The remaining time the potential burden arrhythmia is unknown. Therefore, the aim of the present study is to assess NSVT and AF incidence during 18 months by an insertable cardiac monitor (ICM).

Methods: Adult patients, aged 18-65 years, with a validated diagnosis of HCM are eligible for the study. The study sample is planned to include 30 patients. A Confirm Rx^{TM} is implanted at the level of the fourth rib on the left side subcutaneously after local anesthesia. The application for monitoring is installed in the patients smart-phone and symptoms registered by the patient activation and VT detection programmed as 160bpm during ≥8 intervals. An AF episode is recorded based on ≥2 minutes duration. Bradycardia is recorded at ≤40bpm or pause ≥3.0 seconds. The patients are followed during 18 months before explant.

Ethics and dissemination: The study was approved by The Regional Ethical Committee in Umeå (protocol number 2017/13-31) The study protocol, including

variables and pre-specfied research questions the study was registered at Clinical Trial Registration NCT03259113. Each patient is informed about the study in both oral and written form by a physician and included after written consent.

Strengths and limitations of this study

- An insertable cardiac monitor (ICM) allows for monitoring of atrial fibrillation, significant bradycardia, and non-sustained ventricular tachycardia during 18 months.
- The study will evaluate true incidence of arryhtmia including symptom registration using a smart-phone.
- Non-sustained ventricular tachycardia is a marker of sudden cardiac death but the decision to implant a defibrillator should be carefully evaluated using guidelines as an ICM is currently not an indication as a diagnostic tool in this regard.
- The costly and invasive ICM may need to be studied in larger hypertrophic cardiomyopathy cohorts to allow for subgroup analyses and to generalize findings.

Keywords: atrial fibrillation, hypertrophic cardiomyopathy, implantable loop recorder, insertable cardiac monitor, non-sustained ventricular tachycardia

INTRODUCTION

The hypertrophic cardiomyopathy (HCM) phenotype in adults requires at least 15mm thickness of the myocardial wall deemed unexplained by other myocardial diseases and abnormal loading conditions due to hypertension or aortic stenosis.[1] The point prevalence is approximately 1:500 in the general population but more than double if genotypes are also included.[2-4] Patients present with unspecific symptoms such as dyspnea, chest discomfort, palpitations, and dizziness. Echocardiogram is the cornerstone in diagnosing HCM but integrated medical information and awareness of differential diagnoses are important to avoid misclassification.[5-7] The severity and pattern of hypertrophy and disease progression varies considerably.[5] Life expectancy in general HCM cohorts seems to be acceptable but end-stage heart failure, cardiac embolization stroke, and devastating arrhythmias remain a challenge in order to improve prognosis.[8-12]

Sudden cardiac death (SCD) can be prevented by an implantable cardioverter-defibrillator (ICD). In a recent review of HCM patients with ICDs, 4.8% experienced appropriate therapy annually due to ventricular tachycardia (VT) or fibrillation and antitachycardia pacing or cardioversion rarely fails in terminating the arrhythmia.[13] The decision to implant an ICD as primary prevention of SCD is based on evaluation of riskmarkers according to guidelines.[14,15] In both 2011 and 2014 guidelines, non-sustained VT (NSVT) is part of risk stratification based on evidence from several studies.[16-19] It is more common at an older age and correlates with increased left ventricular wall thickness.[16,20] NSVT may be revealed during an ambulatory ECG, telemetry in the ward or during exercise test. HCM guidelines advocate follow-up including 48 hour ambulatory ECG whenever onset of palpitations or otherwise every 12-24 months but 6-12 months if the patient is in sinus rhythm and has enlarged left

atrial diameter which predisposes for atrial fibrillation (AF) and SCD.[15] This implies that during the remaining time the presence of NSVT/AF is unknown.

In HCM, AF is known to worsen symptoms due to vulnerablity to increased heart rate and lack of atrial filling. Furthermore, AF associated with ischemic stroke or systemic embolization is a major cause of death in HCM, which warrants attention to detection methods with increased sensitivity.[11] In fact, according to current HCM-guidelines, a history of AF, even without any CHA2DS2-VASc risk factor is an indication of anticoagulation.[15]

The insertable cardiac monitor (ICM) Confirm Rx™ (Abbott/St. Jude Medical, St. Paul, MN, USA) provides long-term monitoring of atrial and ventricular arrhythmias in addition to bradycardia.[21] This device could potentially reveal the true incidence of arrhythmia in HCM patients which is the rationale of the present study: EvaLuation Using Cardiac Insertable Devices And TelephonE in Hypertrophic Cardiomyopathy (ELUCIDATE HCM).

OBJECTIVES

Primary objective is to assess the incidence of NSVT during 18 months follow-up using an ICM.

Secondary objective is to assesses the incidence of AF during 18 months follow-up using an ICM.

METHODS

Setting and selection

Adult patients with a confirmed diagnosis of HCM, will be recruited from the catchment area of Region Gävleborg and Umeå University hospital (tertiary center) in

northern Sweden. Eligible patients are identified from hospital data-bases (diagnostic codes I42.1 or I42.2) and validated using medical records. The recruitment started in August 2017. The device will be implanted in addition to standard care.

Inclusion and exclusion

Patients, aged 18-65 years, with a confirmed diagnosis of HCM are eligible for the study. Exclusion criteria as follows: aortic stenosis (moderate, severe), hypertrophy associated with metabolic disease (e.g. Fabry-Andersen) and syndromes (e.g. Noonan syndrome), systolic heart failure with ejection fraction ≤55%, pacemaker, implantable defibrillator, myocardial infarction, percutaneous coronary intervention, coronary by-pass grafting, pulmonary vein isolation, Maze surgery, VT ablation, ectopic atrial tachycardia ablation, renal clearance ≤40 mL/min (Cockcroft-Gault Equation), malignancy or other comorbidity with ≤5 years life expectancy, pregnancy (or planned ≤18 months), drug addition, severe psychiatric disease, not able to participate in 18 months follow-up, 5-year risk of sudden cardiac death ≥6% according to the risk calculator.[19] Myectomy or alcohol septal ablation is not an exclusion criterion.

Implantation and monitor set-up

The implantation procedure is performed in local infiltrative anesthesia (carbocaine with epinephrine) using the standard operation kit for Confirm Rx™ via a 5mm incision at the level of the fourth rib on the left side subcutaneusly. The application for monitoring is installed on the patients own smart-phone or a one that will be lent during the study period. The connection to the home-monitoring site Merlin™ is administrated and the patient is instructed how to use application and report potential

symptoms according to guidelines.[22] Post-procedure, paracetamol (acetaminophen) is recommended to control pain.

Programming

VT detection is programmed as 160bpm during ≥8 intervals with high electrogram (EGM) priority and discrimanator sudden onset activated (onset delta 18%) a bigemini qualifier off. An AF episode is recorded based on ≥2 minutes duration (the shortest programmable duration), AF-burden ≥6 hours a day, or ventricular rate during AF 100bpm for 6 hours daily. Bradycardia is recorded at ≤40bpm or pause ≥3.0 seconds. Patient-activated symptom episodes have high EGM priority with 6 minutes symptom pre-trigger duration and 1 minute symptom post-trigger duration and the first 8 EGMs are stored. Maximal ventricular sensitivity is typically 0.15mV but adjusted if R-waves are low. Threshold start is 75% and sense refractory period 250ms and decay delay 60ms.

Follow-up

Patients are encouraged to report symtoms by using the smart phone application. In addition, every third month there is an automatic interrogation of the device and transfer to the home-monitoring site Merlin,™ which is reviewed every second day except for weekends. False detection of arrhythmia by the device is expected to be frequent based on experience. Therefore all episodes are scrutinized as part of work-process. At 18 months, the device is explanted. Patients are scheduled for follow-up every third months but detection of arrhythmia warrants contact with the patient as part of clinical management.

Power analysis

A power analysis is based on previous research findings and estimation of outcome with certain relevance of hypothesis testing. This is the first study on incidence of NSVT and AF in HCM using continuous monitoring for a period of 18 months. Thus the diagnostic yield is unknown. A formal power analysis is have not been conducted and estimation of sample size is based on clinical judgement and available resources.

Statistics

Numeric data will be presented as frequencies, percentages, means, and percentiles. Continuous variables are summarized as means, standard deviations, and percentiles, and compared using t-tests. The chi-squared test is used for categorical variables. Kaplan-Meier estimates is used to describe time to event analysis (time from implant to AF and NSVT respectively and cumulative incidence at 6,12, and 18 months will be reported.

A two-sided *p*-value of <0.05 is considered statistically significant. The database will be stored in Excel 2010 (Microsoft Corporation, Redmond, WA) and imported into SPSS version 22 (IBM, Armonk, NY) for statistical analyses.

Variables

Patient characteristics at enrollment as follows: age, family history of SCD, unexplained syncope, known HCM associated mutation, weight, length, NSVT at 48 hours ECG. Echocardiography parameters such as maximal wall thickness, left ventricular outflow tract gradient, left atrial size will be recorded.

Ethics and dissemination

The Regional Ethical Committee in Umeå approved the study the 7th of February 2017 (protocol number 2017/13-31), which is conducted in accordance with the Declaration of Helsinki.[23] The study protocol, including variables and pre-specfied research questions the study was registered at Clinical Trial Registration NCT03259113 and approved 24th of August 2017. Documentaton of research data and management of study follow Guideline for Good Clinical Practice.[24] Each patient is informed about the study in both oral and written form by a physician and included after written consent. After the follow-up period is completed, the database will be close and followed by statistical work, interpretation of results, and dissemination to a scientific journal.

DISCUSSION

This is the first study on arrhythmia detection in HCM using an ICM. These devices offer the superior advantage of prolonged monitoring in comparison to external loop-recorders. ICM is currently used in certain cases of HCM such as syncope evaluation or possibly in patients with frequent palpitations, but not in routine evaluation. The application of ICM in the specific group of HCM has been proposed already in statements of research priorities.[25]

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Author contributions

PM: idea, design, project management, and writing the manuscript. SM: critical revision of the manuscript and project management.

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