PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Magnusson, Peter; Mörner, Stellan

VERSION 1 – REVIEW

REVIEWER	Prashanthan Sanders University of Adelaide Adelaide, Australia I have been an investigator on the Reveal Linq studies. I have served on the advisory board of St Jude Medical, Medtronic and Boston Scientific. My institution receives on my behalf research funding from St Jude Medical, Medtronic and Boston Scientific.
REVIEW RETURNED	24-Sep-2017

GENERAL COMMENTS	This manuscript submitted by Magnusson et al titled EvaLuation Using Cardiac Insertable Devices And TelephonE in Hypertrophic Cardiomyopathy (ELUCIDATE HCM) – rationale and design: A prospective interventional observational trail, proposes to be the first study using ICM to assess VT and AF episodes in patients with HCM. MAJOR COMMENTS • In the strengths and limitations section 'very short' episodes are mentioned, this requires more clarification as to the definition of very short. • ICMs are expensive and the battery life lasts 3 years, why is the study being stopped at 18 months, to ensure the cost effectiveness do the authors think that by only following up for half of the device life is appropriate? • In the introduction, the authors mention symptoms that patients present with, however there is no mention of arrhythmia, surely given the nature of the study it is warranted to include this as a symptom. • The methods section is lacking in detail. While the exclusion criteria is very thorough, the inclusion criteria is lacking. It states that patients with confirmed diagnosis of HCM are eligible – how is this diagnosis made? Do patients under testing for inclusion, what testing? Do patients have ECGs, exercise stress testing, MRI's etc? Echo's are a major part of the diagnosis, when are these performed to assist with diagnosis.

	• There is no section on follow up, how are patients followed up? How many appointments? Do patients require to do regular downloads of the device? How often is the Merlin website reviewed? What follow up tests are done, are repeat, EST, MRI's, and Echo's performed at all during follow up? • In the variables patient characteristics at enrolment include known HCM associated mutation – how and where is this collected? There is no prior mention of this in the methods. • Variables also includes NSVT at 48 ambulatory ECG – this presumably is on 48 Holter monitoring, there is no mention of any monitoring at baseline. • Page 10, Line 44-50 highlights the definition of AF, and suggests pacemakers register higher atrial rates and the benefit of apixaban is currently studied – there is no reference for this. Additionally, why is apixaban mentioned here – what is the benefit of other anticoagulants such as dabigatran, rivaroxaban and warfarin?? • As mentioned in previous point there is reference to the definition of AF being ≥30s why have the authors decided ≥2mins? Should this not be based on the current definition? • Given ICM's do often record episodes that are labelled as AF and are in fact false positives and not AF but rather PACs, PVCs, or bigeminy, are the recorded episodes being adjudicated? This is not mentioned in any of the methods. • Reference 13 is not referenced correctly, while it did demonstrate 4.8% experiencing appropriate therapy annually, there was a 4.9% rate of inappropriate therapy, however, this meta-analysis doesn't mention ATP or DCR and not sure what is meant by 'rarely fails'? • What is in the introduction regarding the recent 2014 guidelines misses an important factor, the current guidelines state that 'An ILR can be considered (Class IIb) for patients with frequent palpitations'. Given the focus of this study it is important one would think to include this piece of information. • It has been suggested in the literature that AF in patients with HC can be in up to 4-6 fold more than the general population, it is also reported that he prevalence is between 18-28%. The authors have not presented this at all in the introduction or discussion. Both these sections should include a thorough review of the current literature to give a firm baking to the purpose of the study. • The power analysis is weak at best – stating that a sample size can't be calculated seems a little substandard. Have the authors sought professional statistical support. This is a pilot study given the small sample and it is questionable as to if 30 patients is enough to provide this study with the power to considered a strong study, especially given the previous prevalence suggested in current literature. MINOR COMMENTS The English grammar in this paper is lacking with some poorly written sentences. The authors should carefully review this and correct this for ease of the reader. Examples are: • Page 2, Line 11 need to put (NSVT) after 'non-sustained VT' as (NSVT) used in line 29 • Page 5, Line 14 – patients presents…this doesn't make sense. • Page 5 Line32-34 – implantable defibrillator cardioverter (ICD) should be implantable cardioverter defibrillator. • Page 5, Line 41 – 'prevention of SCD is based evaluation' should be 'base on evaluation' • Page 5, Line 48 – 'more common at higher age' consider 'more common at an older age'

	• Page 5, Line 50 – sentence starting with NSVt may be revealed….place ‘,’ after ECG and delete ‘or at’ used twice in this sentence. • Page 6, Line 10 – ‘furthermore, atrial fibrillation (AF) associated’ either use just atrial fibrillation or AF not both. • Page 6, Line 55 – ‘Adult patients with a confirmed of HCM’ – should be ‘confirmed diagnosis’ • Page 7, Line 16 – word associated, spelt incorrectly • Page 7, Line 33 – word pulmonary spelt incorrectly • Page 7, Line 24 – ectopica atrial tachycardia ablation – should this be ectopic • Page 7, Line 44 – ‘application for monitoring is installed in’ should be installed ‘on’ • Page 10, Line 19 – ‘higher risk of and our study’ – higher risk of what?? • Page 10, Line 31 – sentence beginning ‘AF detection is important in HCM’ bad English restructure • Page 10, Line 47 – atrial electrical activity of ≥300 per minutes….≥300 what??? • Pate 11, Line 13 – word ‘ICM:s’ should not use ‘:’ incorrect grammar

REVIEWER	Mateusz Spiewak Institute of Cardiology, Warsaw, Poland
REVIEW RETURNED	25-Sep-2017

GENERAL COMMENTS	The authors have planned an interesting study in patients with hypertrophic cardiomyopathy (HCM) in order to assess non-sustained ventricular tachycardia (nsVT) and atrial fibrillation (AF) incidence with the use of an insertable cardiac monitor (ICM). Overall strengths: The study is well designed and well written. The study is of clinical value. The majority of data on incidence of nsVT and AF in patients with HCM come from short term ECG monitoring with all inherent limitations of this approach. The incidence of these arrhythmias in HCM patients is probably underestimated. Since both the presence nsVT as well as AF change management in patients with HCM, it is crucial to know the true incidence of these arrhythmias. This problem has been adequately addressed by the authors. Minor issues: - Page 7, line 10: It is written: “renal clearance ≤40” - please provide unit and the method of calculation (Cockcroft-Gault Equation? MDRD? CKD-EPI?) - Page 7, Inclusion and exclusion. Please clarify whether previous septal reduction therapies (surgical myectomy, alcohol septal ablation) are an exclusion criterion? - Page 11, first paragraph: Please explain what will happen with ICM if ICD/pacemaker is implanted due to ventricular arrhythmia/increase in estimated SCD risk or bradycardia? Will the ICM be explanted? Or left till 18 months?

	- Please explain the abbreviation EGM in the manuscript text - There are some syntax/grammar/typo errors: Page 8 line 14: “A power formal analysis is have not been conducted…” Page 9, lines 6-7: “NSVT at 48 ambulatory ECG.” (should be: NSVT at 48 hours ambulatory ECG.”) Page 11 line 5: “Future research of larger series of HCM patients using ICM:s with 5 a sample size...”

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1.

3. In the strengths and limitations section ‘very short’ episodes are mentioned, this requires more clarification as to the definition of very short.

Authors: Agree. We clarified this “…(<5 minutes)…”

page 4, line 7.

4. ICMs are expensive and the battery life lasts 3 years, why is the study being stopped at 18 months, to ensure the cost effectiveness do the authors think that by only following up for half of the device life is appropriate?

Authors: We decided 18 months for several reasons. First, the ICM device is newly launched and battery longevity is unknown so we wanted a margin in this regard. Secondly, longer follow-up time would risk to intervene with clinical management of the patient and baseline characteristics would possibly change. Thirdly, we do not believe additional time would increase diagnostic yield. The time of 18 months is far longer than standard 24-48 hours annually.

5. In the introduction, the authors mention symptoms that patients present with, however there is no mention of arrhythmia, surely given the nature of the study it is warranted to include this as a symptom.

Authors: Agree.

We included “palpitations”. The other symptoms could also be attributed to arrhythmia i.e. prolonged episode of AF may cause chest discomfort and/or dyspnea.

6. The methods section is lacking in detail. While the exclusion criteria is very thorough, the inclusion criteria is lacking. It states that patients with confirmed diagnosis of HCM are eligible – how is this diagnosis made? Do patients under testing for inclusion, what testing? Do patients have ECGs, exercise stress testing, MRI’s etc? Echo’s are a major part of the diagnosis, when are these performed to assist with diagnosis.

Authors: The definition of HCM is described in the first sentence of the Introduction with reference to ESC guidelines. In the guidelines there is a whole section on diagnosis of HCM and potential differential diagnosis and role of cardiac imaging.

“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”

As described in the Method section the patient cohort has been validated using medical records.

7. There is no section on follow up, how are patients followed up? How many appointments? Do patients require to do regular downloads of the device? How often is the Merlin website reviewed? What follow up tests are done, are repeat, EST, MRI's, and Echo's performed at all during follow up?

Authors: Agree.

"Follow-up
Patients are encouraged to report symptoms 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,TM 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."

page 8, line 12-20.

No follow-up tests are scheduled according to the study protocol but patient management outside the study (standard care) may lead to such follow-up.

8. In the variables patient characteristics at enrolment include known HCM associated mutation – how and where is this collected? There is no prior mention of this in the methods.

Authors: A positive genotype is not mandatory for the diagnosis of HCM. Several patients may have undergone genetic testing serval years ago and panel may differ. The site where the genetic testing had been performed had varied over the years depending on availability and preferences of the physician who managed the patient.

9. Variables also include NSVT at 48 ambulatory ECG – this presumably is on 48 Holter monitoring, there is no mention of any monitoring at baseline.
Page 10, Line 44-50 highlights the definition of AF, and suggests pacemakers register higher atrial rates and the benefit of apixaban is currently studied – there is no reference for this. Additionally, why is apixaban mentioned here – what is the benefit of other anticoagulants such as dabigatran, rivaroxaban and warfarin??

Authors: The baseline 48-hour monitoring is the last clinical follow-up.
Agree.

We added the following reference:
"NCT01938248. Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA); https://clinicaltrials.gov/ct2/show/NCT01938248 (2 October 2017, date last accessed).

page 11, line 11.

10. As mentioned in previous point there is reference to the definition of AF being ≥30s why have the authors decided ≥2mins? Should this not be based on the current definition?

Authors: Agree, but the shortest duration that is programmable is 2 minutes.

"…(the shortest programmable duration),…"

page 8, line 3.

11. Given ICM's do often record episodes that are labelled as AF and are in fact false positives and not AF but rather PACs, PVCs, or bigeminy, are the recorded episodes being adjudicated? This is not mentioned in any of the methods.

Authors: Agree. 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.

page 8, line 16.

12. Reference 13 is not referenced correctly, while it did demonstrate 4.8% experiencing appropriate therapy annually, there was a 4.9% rate of inappropriate therapy, however, this meta-analysis doesn't mention ATP or DCR and not sure what is meant by 'rarely fails'?

Authors: Ok. We added "in terminating the arrhythmia"

"…antitachycardia pacing or cardioversion rarely fails in terminating the arrhythmia…"

page 5, line 17.

This reference is the most updated review on the topic and does include a meta-analysis on appropriate therapy (ATP or cardioversion i.e. "shock"). The number of inappropriate shocks is not relevant for this discussion.

13. What is in the introduction regarding the recent 2014 guidelines misses an important factor, the current guidelines state that 'An ILR can be considered (Class IIb) for patients with frequent palpitations'. Given the focus of this study it is important one would think to include this piece of information.

Authors: Agree. Thanks for noting this. Even though 2b is not a strong indication it deserves to be mentioned. We added this in the first section of the Discussion.

"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."

page 10, line 11.

14. It has been suggested in the literature that AF in patients with HC can be in up to 4-6 fold more than the general population, it is also reported that he prevalence is between 18-28%. The authors have not presented this at all in the introduction or discussion. Both these sections should include a thorough review of the current literature to give a firm baking to the purpose of the study.

Authors: We decided to omit the detailed discussion on the prevalence of AF in HCM. It depends on the selection of patients and how AF is detected. We did not include patients with pacemakers/ICDs and several studies on the subject concern patients diagnosed at device monitoring.

In the coming paper after the study has been completed this topic deserves thorough discussion but in a Study protocol this is beyond the scope.

15. The power analysis is weak at best – stating that a sample size can't be calculated seems a little substandard. Have the authors sought professional statistical support. This is a pilot study given the small sample and it is questionable as to if 30 patients is enough to provide this study with the power to considered a strong study, especially given the previous prevalence suggested in current literature.

Authors: This is a prospective observational study on incidence of arrhythmias. Power analysis is mainly used in studies using a hypothesis that is addressed by a statistical significance test.

16.
a) • Page 2, Line 11 need to put (NSVT) after 'non-sustained VT' as (NSVT) used in line 29
b) • Page 5, Line 14 – patients presents…this doesn't make sense.
c) • Page 5 Line32-34 – implantable defibrillator cardioverter (ICD) should be implantable cardioverter defibrillator.
d) • Page 5, Line 41 – 'prevention of SCD is based evaluation' should be 'base on evaluation'
e) • Page 5, Line 48 – 'more common at higher age' consider 'more common at an older age'
f) • Page 5, Line 50 – sentence starting with NSVt may be revealed….place ',' after ECG and delete 'or at' used twice in this sentence.
g) • Page 6, Line 10 – 'furthermore, atrial fibrillation (AF) associated' either use just atrial fibrillation or AF not both.
h) • Page 6, Line 55 – 'Adult patients with a confirmed of HCM' – should be 'confirmed diagnosis'
i) • Page 7, Line 16 – word associated, spelt incorrectly
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k) • Page 7, Line 24 – ectopica atrial tachycardia ablation – should this be ectopic
l) • Page 7, Line 44 – 'application for monitoring is installed in' should be installed 'on'
m) • Page 10, Line 19 – 'higher risk of and our study' – higher risk of what??
n) • Page 10, Line 31 – sentence beginning 'AF detection is important in HCM' bad English restructure
o) • Page 10, Line 47 – atrial electrical activity of ≥300 per minutes….≥300 what???
p) • Pate 11, Line 13 – word 'ICM:s' should not use ':' incorrect grammar

Authors:
a) We did introduce the abbreviation "VT" in the abstract but not NSVT. That is why we did not write NSVT.

b) Ok. "present" page 2, line 11.

c) Ok. "implantable cardioverter-defibrillator" page 5, line 14.

d) Ok. "based on…" page 5, line 20.

e) Ok. "..at an older age" page 5, line 21.

f) Ok. "…ECG, telemetry in the ward or during exercise test" page 5, line 23.

g) Ok. Corrected. Page 6, line 1.

h) Ok. "…diagnosis…" Page 6, line 22.

i) Ok. "…associated…" page 7, line 7.

j) Ok. "…pulmonary…" page 7, line 10.

k) Ok. “…ectopic…” page 7, line 11.

l) Ok. “…on…” page 8, line 20.

m) Ok. “…higher risk of SCD/stroke…” page 11, line 21.

n) Ok. “Detection of AF…” page 11, line 3.

o) Ok. …”beats” page 11, line 10.

p) Ok.”…ICMs…” page 11, line 19.

REVIEWER 2.

17. The study is well designed and well written. The study is of clinical value.

Authors: We are pleased to hear this positive impression. Thanks for recognizing the value of the study.

18. Page 7, line 10: It is written: “renal clearance ≤40” - please provide unit and the method of calculation (Cockcroft-Gault Equation? MDRD? CKD-EPI?)

Authors: Ok. We added “…renal clearance ≤40 mL/min (Cockcroft-Gault Equation),…” page 7, line 11.

19. Page 7, Inclusion and exclusion. Please clarify whether previous septal reduction therapies (surgical myectomy, alcohol septal ablation) are an exclusion criterion?

Authors: Ok. “Myectomy or alcohol septal ablation is not part of exclusion criterion.” page 7, line 15.

20. Page 11, first paragraph: Please explain what will happen with ICM if ICD/pacemaker is implanted due to ventricular arrhythmia/increase in estimated SCD risk or bradycardia? Will the ICM be explanted? Or left till 18 months?

Authors: Ok. “If an ICD or pacemaker is indicated, the ICM is will remain until study end at 18 months.” page 11, line 17-18.

21. Please explain the abbreviation EGM in the manuscript text

Authors: Ok. “electrogram (EGM)…) page 8, line 1.

22. There are some syntax/grammar/typo errors:
Page 8 line 14: “A power formal analysis is have not been conducted…”
Page 9, lines 6-7: “NSVT at 48 ambulatory ECG.” (should be: NSVT at 48 hours ambulatory ECG.”)
Page 11 line 5: “Future research of larger series of HCM patients using ICM:s with 5 a sample size...”

Authors:
Ok. “A formal power analysis…” page 9, line 1.

Ok. “…hours…” page 9, line 17.

Ok. “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.” page 11, line 19-20.

VERSION 2 – REVIEW

REVIEWER	Mateusz Spiewak Institute of Cardiology, Poland
REVIEW RETURNED	04-Oct-2017

GENERAL COMMENTS	All issues have been adequately addressed.