Remote management of heart failure using implanted devices and formalized follow-up procedures (REM-HF)

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On behalf of the REM-HF Investigators
Disclosures

• Personal disclosure:
  – Research funding from Boston Scientific, St Jude Medical, Bayer, ResMed
  – Consultancy and speaker fees from Novartis, Servier, AstraZeneca, Bayer, Boston Scientific, Medtronic, St Jude Medical, Pfizer

• Funding for REM-HF:
  – British Heart Foundation
  – Boston Scientific
  – Medtronic
  – St Jude Medical
Rationale

• Despite advances in heart failure care, patients remain at high risk of mortality and hospitalisation

• Many heart failure patients have a Cardiac Implantable Electronic Device (ICD; CRT-D or CRT-P) for therapeutic reasons

• To date, randomised controlled trials of remote monitoring have had variable results – presumably depending on patient characteristics, the monitoring technology, and the responses taken to data collected

• We wished to perform a pragmatic study of a care pathway informed by weekly remote monitoring of typical CIEDs – to determine the effect on mortality and hospitalisation
Objective

• To assess the clinical and cost-effectiveness of remote monitoring of heart failure patients with cardiac implanted electronic devices
Design

• Multicentre, prospective, randomised, non-blinded, controlled trial comparing:
  – Usual care + weekly Remote Monitoring, with
  – Usual care alone
Physiological variables measured by CIED and used to guide interventions

<table>
<thead>
<tr>
<th>Medtronic</th>
<th>Boston Scientific</th>
<th>St Jude Medical</th>
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<tbody>
<tr>
<td>Bi-ventricular pacing %</td>
<td>Bi-ventricular pacing %</td>
<td>Bi-ventricular pacing %</td>
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<td>Nocturnal HR</td>
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<td>Thoracic Impedance</td>
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<td>Thoracic Impedance (if programmed on)</td>
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<td>Activity levels</td>
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<tr>
<td>AT/AF burden</td>
<td>AT/AF burden</td>
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<td>Ventricular arrhythmias</td>
<td>Ventricular arrhythmias</td>
<td>Ventricular arrhythmias</td>
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<td>Therapy from device</td>
<td>Therapy from device</td>
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<td>Heart rate variability</td>
<td>Heart rate variability (SDANN)</td>
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<td>Lead integrity</td>
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<td>Lead integrity</td>
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<td>Device programming</td>
<td>Device programming</td>
<td>Device programming</td>
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<td>V-V interval at time of D/L</td>
<td>V-V interval at time of D/L</td>
<td>V-V interval at time of D/L</td>
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Patients

Inclusion criteria

• Age ≥ 18
• Heart failure, with stable medical therapy for ≥ 6 weeks prior to recruitment
• Cardiac implantable electronic device that can be remotely monitored (ICD/CRT-D or CRT-P) implanted for at least 6 months
• Both heart failure therapy and device functionality optimised by treating physician(s) at time of recruitment
• Ability to complete the study health-related quality of life questionnaires
• Ability to give informed consent

Exclusion criteria

• Unable to use the remote monitoring download technology due to mental or physical limitations
• Pregnancy
• Listed for heart transplantation
• Life expectancy < 12 months due to non-cardiovascular disease
• Current device-related complications
• Device change or lead replacement within 30 days
• Acute myocardial infarction or PCI/CABG in past 3 months

Outcomes

- **Primary outcome** – first event of death from any cause or unplanned hospitalisation for cardiovascular (CV) reason

- **Secondary outcomes**
  - Individual components of primary outcome
  - Death from CV reasons
  - Unplanned all-cause hospitalisation
  - Composite of death from CV reasons or unplanned hospitalisation for CV reasons
Statistics and Sample Size

– Event driven study: **546 events** to have 90% power to show a maximum hazard ratio of 0.755 in the rate of the first primary end-point event with RM, with a two-sided type 1 error of 5% and an event rate of 40% at 2 years

– Estimated to require 1394 patients (697 per group) with a minimum follow-up of 2 years, increased to allow for drop-out to **1650 patients**.

– Intention to treat analysis, P<0.048 for primary outcome (1 formal interim analysis)

– Survival analysis for time to first (adjudicated) event in Cox model, adjusted for recruiting site and device type

– **By database ‘lock’, 700 adjudicated events were included**
Recruitment and Management
Sept 2011 - March 2014: 1650 patients recruited from 9 English hospitals

1. John M. Morgan*, Sue Kitt, Paul Roderick, Scott Harris, James Raftery (Southampton)
2. Jas Gill (Guys’ and St Thomas’, London)
3. Janet McComb (Newcastle)
4. Andre Ng (Leicester)
5. Alison Seed (Blackpool)
6. Simon Williams (Manchester)
7. Klaus Witte (Leeds)
8. Jay Wright (Liverpool)
9. Martin R. Cowie* (Imperial College London)

* co-Principal Investigators

+ Independent Endpoint Review Committee (Guy Haywood, George Sutton, Adrian Rosckowicz)
+ Data Safety and Monitoring Committee (Henry Dargie, Richard Charles, Ian Ford)
1650 Patients were randomized

824 Usual Care pathway
- 5 Violated inclusion or exclusion criteria
- 807 Completed Baseline Assessment
- 674 Completed 1 year Assessment
- 595 Completed 2 year Assessment
- 2 Had data censored because they withdrew full consent (including for GP follow-up)
- 3 Underwent a heart transplant

826 RM pathway
- 13 Violated inclusion or exclusion criteria
- 810 Completed Baseline Assessment
- 669 Completed 1 year Assessment
- 596 Completed 2 year Assessment
- 8 Had data censored because they withdrew full consent (including for GP follow-up)
- 5 Underwent a heart transplant

Median follow-up: 2.8 years [Range 0-4.3 years]
In RM arm (826 patients):
33 patients (4%) did not download
Of those who did, 77% did so on at least 75% of monitored weeks at 6 months (75% at 12 months; 69% at 24 months)

100% follow-up for vital status
Only 10 patients (<1%) withdrew full consent for data collection
# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th><strong>RM</strong> N=824</th>
<th><strong>Usual care</strong> N=826</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD) years</td>
<td>69.5±10.3</td>
<td>69.5±10.0</td>
</tr>
<tr>
<td>Male %</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>585 (71%)</td>
<td>561 (68%)</td>
</tr>
<tr>
<td>III</td>
<td>238 (29%)</td>
<td>263 (32%)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (0.1%)</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>LVEF (mean ± SD)(%)</td>
<td>29.9 ± 10.2</td>
<td>30.0 ± 9.8</td>
</tr>
<tr>
<td>Documented coronary artery disease</td>
<td>563 (69%)</td>
<td>548 (67%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>208 (25%)</td>
<td>225 (27%)</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>339 (41%)</td>
<td>338 (41%)</td>
</tr>
<tr>
<td>Type of CIED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD</td>
<td>275 (33%)</td>
<td>276 (33%)</td>
</tr>
<tr>
<td>CRT-D</td>
<td>442 (54%)</td>
<td>438 (53%)</td>
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<tr>
<td>CRT-P</td>
<td>107 (13%)</td>
<td>112 (14%)</td>
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### Baseline Characteristics

<table>
<thead>
<tr>
<th>Drug class</th>
<th>RM N=824</th>
<th>Usual care N=826</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulant</td>
<td>394 (48%)</td>
<td>389 (47%)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>750 (91%)</td>
<td>754 (91%)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>749 (91%)</td>
<td>746 (90%)</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>430 (52%)</td>
<td>435 (53%)</td>
</tr>
<tr>
<td>Diuretic (excluding aldo antagonist)</td>
<td>635 (77%)</td>
<td>631 (76%)</td>
</tr>
<tr>
<td>Cardiac glycoside</td>
<td>153 (19%)</td>
<td>180 (22%)</td>
</tr>
<tr>
<td>Antiplatelet drug</td>
<td>485 (59%)</td>
<td>448 (54%)</td>
</tr>
<tr>
<td>Anti-arrhythmic (excluding beta-blocker)</td>
<td>205 (25%)</td>
<td>203 (25%)</td>
</tr>
</tbody>
</table>
## Actions taken in response to RM

<table>
<thead>
<tr>
<th>Action Taken</th>
<th>Number of Incidences</th>
<th>Number of Subjects impacted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remote monitor took action</td>
<td>3534</td>
<td>599 (72.5%)</td>
</tr>
<tr>
<td><strong>Action(s) taken (not mutually exclusive categories):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phoned Patient</td>
<td>2378</td>
<td>520 (62.9%)</td>
</tr>
<tr>
<td>Discussed download with clinician</td>
<td>1390</td>
<td>408 (49.4%)</td>
</tr>
<tr>
<td>Medication change by remote monitor without medical contact</td>
<td>226</td>
<td>134 (16.2%)</td>
</tr>
<tr>
<td>ADVISED to contact GP</td>
<td>206</td>
<td>124 (15.0%)</td>
</tr>
<tr>
<td>Advised to visit HF clinic</td>
<td>8</td>
<td>113 (13.7%)</td>
</tr>
<tr>
<td>Advised to attend device clinic</td>
<td>328</td>
<td>202 (24.5%)</td>
</tr>
<tr>
<td>Advised to attend cardiovascular out-patient clinic</td>
<td>178</td>
<td>109 (21.5%)</td>
</tr>
<tr>
<td>Other advice to patient</td>
<td>632</td>
<td>274 (33.3%)</td>
</tr>
</tbody>
</table>
Primary endpoint – neutral

All-cause mortality or CV hospitalisation

HR 1.01
[0.87-1.18]

P=0.87

(adjusted for site and device type)
Components of Primary endpoint (1): **mortality**

HR 0.83
[0.66-1.05]

P=0.12

(adjusted for site and device type)
Components of Primary endpoint (2): Unplanned CV hospitalisation

HR 1.07
[0.91-1.25]
P=0.42

(adjusted for site and device type)
Secondary endpoint and subgroup analyses

• No significant differences between the 2 groups in any of the secondary endpoints

• None of the baseline characteristics (age, gender, NYHA Class, type of device, history of coronary artery disease, or history of atrial fibrillation) identified a group in which RM was more effective than usual care alone
Conclusions

• The addition of weekly remote monitoring of CIED to usual care did not reduce mortality or unplanned hospitalisations for CV reasons despite good patient compliance to download schedule
• No suggestion that any subgroup appears to benefit from weekly RM guided therapy
• Patients had mild symptoms & were on high levels of background therapy – suggesting high quality ‘usual’ care
• We did not test the benefit of continuous haemodynamic monitoring in our study
• Our study suggests that in developed healthcare systems with high quality heart failure services, using data from weekly remote monitoring of CIEDs is unlikely to improve the outcome for patients
• Future technological innovations in remote monitoring require robust evaluation prior to widespread clinical adoption
Acknowledgments

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• Medtronic Ltd (Minneapolis, MN, USA)
• St Jude Medical (Minneapolis, MN, USA)

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