Impact of a Multidisciplinary Management Program on Recurrent Hospitalization and Mortality in Older Individuals With Chronic Atrial Fibrillation: A Multi-Center Randomized Trial

Australian New Zealand Clinical Trials Registry (2610000221055)

Simon Stewart on behalf of the SAFETY (Standard versus Atrial Fibrillation specific management) Trial Investigators
Acknowledgements

SAFETY Trial Investigators:
- Professor John D Horowitz & Dr Gnanadevan Mahadevan (The Queen Elizabeth Hospital, South Australia)
- Dr Chiew Wong (Western Hospital, Victoria)
- Professor Walter P Abhayaratna (Canberra Hospital, ACT)
- Professor Thomas H Marwick (University of Tasmania)
- Professor David R Thompson & Dr Jocasta Ball (ACU)
- Professor Paul Scuffham (Griffith University, Queensland)
- Dr Melinda J Carrington & Dr Yih Kai Chan (ACU/Baker IDI)

Trial Statistician: Professor Adrian Esterman (University of South Australia)


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Background & study hypothesis

With few exceptions\(^1\) there is minimal evidence to support atrial fibrillation (AF)-specific care.

Pilot data suggests potential to improve health outcomes in hospitalized patients with chronic AF\(^2\)

**SAFETY Trial** tested the following hypothesis:

*Relative to standard post-discharge hospital and primary care, an AF-specific, nurse-led, multidisciplinary management program would significantly improve the primary endpoint of death or recurrent unplanned hospitalization (both all-cause) in typically older individuals hospitalized with chronic, non-valvular forms of AF (but not CHF) during minimum follow-up of 24 months (the duration of the study intervention)*

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Study cohort & endpoints

Key inclusion criteria
All cardiology inpatients aged ≥ 45 years admitted to 3 tertiary hospitals in Australia with a chronic form of non-valvular AF (recurrent paroxysmal, persistent or permanent AF as per expert guidelines), living independently in the community post-index hospitalization (within a 40km radius) and capacity to provide informed consent.¹

Key exclusion criteria
A pre-existing diagnosis of chronic heart failure (availability of gold-standard, post-discharge management) or terminal condition/malignancy.¹

Study endpoints
Primary Endpoint: Event-free from death or all-cause readmission – analyzed as a) time to event and b) days alive and out-of-hospital

Health Utilization: Rate of hospitalization and stay (per participant/month) – unplanned and cardiovascular related hospitalization during minimum 24 month follow-up

Study design

- Multi-center RCT
- CONSORT compliant
- 1:1 blinded randomization (rate vs. rhythm control)
- Standardized clinical management
- Independent data management/trial statistician
- Blinded endpoint acquisition & adjudication

Cardiac inpatients from 3 tertiary hospitals in Australia

Patients discharged to home with chronic AF

Randomization (blocked for location & rate vs. rhythm control)

Standard Management

SAFETY Intervention

- Home visit 7-14 days post-discharge
- Routine rate and rhythm checks
- Stratified multidisciplinary care
- Nurse-led management
- GARDIAN Risk delineation
- Continued profiling & clinical follow-up

Clinical assessment at 12 & 24 months post index admission

Event-free survival from unplanned hospitalization & death (both all-cause)
Pattern of recurrent hospitalization and related hospital stay

Standard clinical & demographic profiling
2,450 high-risk individuals with chronic AF discharged to home from a tertiary referral hospital

545 eligible individuals

335 randomized (stratified for location & rate/rhythm control)

167 assigned to Standard Management
- 124 attended 1 year clinic
- 112 attended 2 year clinic
- 48 truncated follow-up
  - 18 withdrew consent
  - 30 died

168 assigned to SAFETY Intervention
- 123 attended 1 year clinic
- 116 attended 2 year clinic
- 38 truncated follow-up
  - 19 withdrew consent
  - 19 died

167 subjects assessed for primary outcomes during 893 (IQR 763 to 1050) days follow-up

168 subjects assessed for primary outcomes during 915 (IQR 775 to 1044) days follow-up

1,905 ineligible
- 323 Valvular AF/disease
- 234 Chronic heart failure

210 excluded
- 197 Refused participation

545 eligible individuals

210 excluded
- 197 Refused participation

335 randomized (stratified for location & rate/rhythm control)

38 truncated follow-up

19 withdrew consent

19 died
### Cohort profile

- Mean age 72 years
- 48% women
- 90% persistent AF
- **Rate control 64%**
- High thrombotic risk
- Multiple comorbidities
- Depression & cognitive impairment +++
- Preserved systolic function (no CHF)
- High standards of care & treatment

### Table: Demographic Profile

<table>
<thead>
<tr>
<th></th>
<th>SAFETY-Intervention (n = 168)</th>
<th>Standard Management (n = 167)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>72 ± 11</td>
<td>71 ± 12</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>84 (50%)</td>
<td>90 (54%)</td>
</tr>
<tr>
<td><strong>Risk Profile</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>127 (76%)</td>
<td>113 (68%)</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>80 (63%)</td>
<td>89 (67%)</td>
</tr>
<tr>
<td>Obese</td>
<td>67 (45%)</td>
<td>61 (41%)</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>57 (34%)</td>
<td>59 (37%)</td>
</tr>
<tr>
<td><strong>Clinical Profile</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>58 (35%)</td>
<td>54 (32%)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>51 (30%)</td>
<td>45 (27%)</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>27 (16%)</td>
<td>25 (15%)</td>
</tr>
<tr>
<td>Left atrial enlargement</td>
<td>64 (83%)</td>
<td>101 (89%)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>54 ± 11</td>
<td>60 ± 12</td>
</tr>
<tr>
<td>SBP/DBP (mmHg)</td>
<td>127±18 / 71±12</td>
<td>125±17 / 70±12</td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td>3·7 ± 1·8</td>
<td>3·6 ± 1·9</td>
</tr>
<tr>
<td>Charlson Index Score</td>
<td>4·8 ± 2·5</td>
<td>5·0 ± 2·6</td>
</tr>
<tr>
<td><strong>AF-Specific Profile</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF on admission ECG</td>
<td>137 (82%)</td>
<td>137 (82%)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>74 ± 16</td>
<td>75 ± 16</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>149 (89%)</td>
<td>153 (92%)</td>
</tr>
<tr>
<td>Newly diagnosed AF</td>
<td>44 (26%)</td>
<td>34 (20%)</td>
</tr>
<tr>
<td>Rate control strategy</td>
<td>109 (66%)</td>
<td>104 (62%)</td>
</tr>
<tr>
<td><strong>Index Admission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary diagnosis of AF</td>
<td>109 (65%)</td>
<td>112 (67%)</td>
</tr>
<tr>
<td>Cardioversion</td>
<td>23 (14%)</td>
<td>28 (17%)</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>4·6 ± 6·3</td>
<td>4·8 ± 7·1</td>
</tr>
<tr>
<td>Anti-coagulant</td>
<td>90 (54%)</td>
<td>96 (58%)</td>
</tr>
<tr>
<td>Anti-platelet</td>
<td>128 (70%)</td>
<td>105 (63%)</td>
</tr>
<tr>
<td>Anti-arrhythmic agent</td>
<td>144 (86%)</td>
<td>146 (87%)</td>
</tr>
</tbody>
</table>
Recurrent hospital events

1,411 hospitalizations subject to blinded review & adjudication
Event-free survival

Median event-free survival - 183 (Inter-Quartile Range [IQR] 116 to 409) days in the SAFETY-Intervention versus 199 (IQR 116 to 249) days in the Standard Management group (log-rank p=0.851).
**Alive & out-of-hospital**

- **127/168 SAFETY-Intervention (76%)** vs. **137/167 Standard Management (82%)** participants died or had an unplanned readmission

- SAFETY-Intervention participants experienced **146,967/159,133 days alive and out-of-hospital (92%)**

- Standard Management participants experienced **141,113/158,446 days alive and out-of-hospital (89%)**

- Actual vs. maximal event-free 99.5% (95% CI 99.3% to 99.7%) vs. 99.2%, 95% CI 98.8 to 99.4%; $p=0.039$
## Hospitalization & hospital stay

<table>
<thead>
<tr>
<th>Study Follow-up</th>
<th>SAFETY Intervention (n=168)</th>
<th>Standard Management (n=167)</th>
<th>Group Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total days of follow-up</strong></td>
<td>149,244</td>
<td>144,367</td>
<td>-</td>
</tr>
<tr>
<td><strong>Median days of follow-up</strong></td>
<td>915 (IQR 775 to 1044)</td>
<td>893 (IQR 763 to 1050)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Unplanned Admissions/Stay</strong></td>
<td>485 (2276 days)</td>
<td>502 (3254 days)</td>
<td><strong>17 less admissions &amp; 978 less days</strong></td>
</tr>
<tr>
<td><strong>Admissions/participant</strong></td>
<td>2 (IQR 0 to 4)</td>
<td>2 (IQR 1 to 4)</td>
<td>0·06 vs. 0·07 events/month: p=0·788</td>
</tr>
<tr>
<td><strong>Days of stay/participant</strong></td>
<td>4 (IQR 0 to 15)</td>
<td>7 (IQR 2 to 19)</td>
<td>0·13 vs. 0·24 days/month: p=0·082</td>
</tr>
<tr>
<td><strong>Median days of stay per event</strong></td>
<td>2·8 (IQR 1·5 to 6·0)</td>
<td>3·6 (IQR 2·0 to 8·0)</td>
<td><strong>p=0·035</strong></td>
</tr>
<tr>
<td><strong>CVD-related Admissions/Stay</strong></td>
<td>262 (929 days)</td>
<td>312 (1495 days)</td>
<td><strong>50 less admissions &amp; 566 less days</strong></td>
</tr>
<tr>
<td><strong>Admissions/participant</strong></td>
<td>1 (IQR 0 to 2)</td>
<td>1 (IQR 0 to 2)</td>
<td>0·03 vs. 0·04 events/month: p=0·095</td>
</tr>
<tr>
<td><strong>Days of stay/participant</strong></td>
<td>1 (IQR 0 to 5)</td>
<td>2 (IQR 0 to 8)</td>
<td><strong>0·03 vs. 0·07 days/month: p=0·018</strong></td>
</tr>
<tr>
<td><strong>Median days of stay per event</strong></td>
<td>2·0 (IQR 1·0 to 4·0)</td>
<td>2·3 (IQR 1·4 to 5·1)</td>
<td><strong>p=0·059</strong></td>
</tr>
<tr>
<td><strong>All Admissions/Stay</strong></td>
<td>674 (2989 days)</td>
<td>737 (4214 days)</td>
<td><strong>63 less admissions &amp; 1,225 less days</strong></td>
</tr>
<tr>
<td><strong>Admissions/participant</strong></td>
<td>3 (IQR 1 to 5)</td>
<td>3 (IQR 1 to 6)</td>
<td>0·11 vs. 0·11 events/month: p=0·491</td>
</tr>
<tr>
<td><strong>Days of stay/participant</strong></td>
<td>7 (IQR 1 to 26)</td>
<td>9 (IQR 3 to 28)</td>
<td>0·23 vs. 0·30 days/month: p=0·162</td>
</tr>
<tr>
<td><strong>Median cost/participant (AU$)</strong></td>
<td>$11,642</td>
<td>$18,269</td>
<td>$434 vs. $606/month: p=0·143</td>
</tr>
<tr>
<td><strong>Median days of stay per event</strong></td>
<td>2·5 (IQR 1·4 to 5·2)</td>
<td>3·0 (IQR 1·6 to 7·3)</td>
<td><strong>p=0·110</strong></td>
</tr>
</tbody>
</table>

*AU$1.00 = US$0.88*
All-cause mortality

Overall, there were 49 deaths comprising 19 SAFETY-Intervention (11%) and 30 Standard Management (18%) participants: mean survival 1,266 (95% CI 1,211 to 1,320) versus 1,204 (95% CI 1,145 to 1,263 days), log-rank p=0.099
Limitations

- Pragmatic trial (non-blinding of participants)
- Mainly sustained, not paroxysmal AF
- Historical context: mostly warfarin-therapy
- Under-powered for other endpoints/events: all-cause mortality & bleeding events
- Universal/subsidised health care system

Mechanism(s) of effect need to be explored:
- Early versus late impact of pro-active intervention?
- Role of mild cognitive impairment?
- Sub-group analyses showed significant difference between rate (worse) versus rhythm control (better)
Summary

- First reported trial to examine the benefits of AF-specific care on re-hospitalization & survival
- SAFETY-Intervention did not prolong event-free survival
  But, significantly prolonged days alive & out-of-hospital
- Also associated with a significant reduction in recurrent cardiovascular stay
- Clinically favourable trends in survival and unplanned hospitalization require verification in larger trial
- Pending a full health economic analysis, large differentials in hospital costs are encouraging
- As in heart failure, SAFETY represents a feasible strategy to markedly improve health outcomes in chronic AF
Standard versus atrial fibrillation-specific management strategy (SAFETY) to reduce recurrent admission and prolong survival: pragmatic, multicentre, randomised controlled trial

Simon Stewart, Jacasta Ball, John D Horowitz, Thomas H Moranick, Ganadevan Mahadevan, Chiu Wong, Walter P Abhayaratna, Yih K Chan, Adrian Esterman, David R Thompson, Paul A Scuffham, Melinda J Carrington

Summary

Background Patients are increasingly being admitted with chronic atrial fibrillation, and disease-specific management might reduce recurrent admissions and prolong survival. However, evidence is scant to support the application of this therapeutic approach. We aimed to assess SAFETY—a management strategy that is specific to atrial fibrillation.

Methods We did a pragmatic, multicentre, randomised controlled trial in patients admitted with chronic, non-valvular atrial fibrillation (but not heart failure). Patients were recruited from three tertiary referral hospitals in Australia. 335 participants were randomly assigned by computer-generated schedule (stratified for rhythm or rate control) to either standard management (n=167) or the SAFETY intervention (n=168). Standard management consisted of routine primary care and hospital outpatient follow-up. The SAFETY intervention comprised a home visit and Holter monitoring 7–14 days after discharge by a cardiac nurse with prolonged follow-up and multidisciplinary support as needed. Clinical reviews were undertaken at 12 and 24 months (minimum follow-up). Coprimary outcomes were death or unplanned readmission (both all-cause), measured as event-free survival and the proportion of actual versus maximum days alive and out of hospital. Analyses were done on an intention-to-treat basis. The trial is registered with the Australian New Zealand Clinical Trials Registry (ANZCTR1261000221053).

Findings During median follow-up of 905 days (IQR 773–1050), 49 people died and 987 unplanned admissions were recorded (totalling 5530 days in hospital). 127 (76%) patients assigned to the SAFETY intervention died or had an unplanned readmission (median event-free survival 183 days [IQR 116–409]) and 137 (82%) people allocated standard management achieved a coprimary outcome (159 days [116–249]; hazard ratio 0.97, 95% CI 0.76–1.23; p=0.851). Patients assigned to the SAFETY intervention had 99.5% maximum event-free days (95% CI 99.3–99.7), equating to a median of 900 (IQR 767–1025) of 937 maximum days alive and out of hospital. By comparison, those allocated to standard management had 99.2% (95% CI 98.9–99.4) maximum event-free days, equating to a median of 860 (IQR 752–1047) of 937 maximum days alive and out of hospital (effect size 0.22, 95% CI 0.21–0.23; p=0.039).

Interpretation A post-discharge management programme specific to atrial fibrillation was associated with proportionately more days alive and out of hospital (but not prolonged event-free survival) relative to standard management. Disease-specific management is a possible strategy to improve poor health outcomes in patients admitted with chronic atrial fibrillation.

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