Targeted therapy of underlying conditions improves quality of life in patients with persistent atrial fibrillation

RACE 3 Investigators; De With, Ruben R.; Rienstra, Michiel; Smit, Marcelle D.; Weijs, Bob; Zwartkruis, Victor W.; Hobbelt, Anne H.; Atings, Marco; Tijssen, Jan G. P.; Brugemann, Johan

Published in:
Europace

DOI:
10.1093/europace/euy311

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Targeted therapy of underlying conditions improves quality of life in patients with persistent atrial fibrillation: results of the RACE 3 study

Ruben R. De With1, Michiel Rienstra1, Marcelle D. Smit1,2, Bob Weij3, Victor W. Zwartkruis1, Anne H. Hobbelt1, Marco Alings4, Jan G.P. Tijsen5, Johan Brügemann1, Bastiaan Geelhoed1, Hans L. Hillege1, Raymond Tukkie6, Martin E. Hemels7, Robert G. Tieleman2, Adelita V. Ranchor8, Dirk J. Van Veldhuisen1, Harry J.G.M. Crijns3, and Isabelle C. Van Gelder1*; for the RACE 3 Investigators

1Department of Cardiology, University Medical Centre Groningen, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, Netherlands; 2Department of Cardiology, Martini Hospital, Groningen, The Netherlands; 3Department of Cardiology, Maastricht University Medical Centre+, Cardiovascular Research Institute Maastricht, Maastricht, The Netherlands; 4Department of Cardiology, Amphia Hospital Breda, Julius Clinical, Zeist, The Netherlands; 5Department of Clinical Epidemiology and Biostatistics, Academic Medical Centre, Amsterdam, The Netherlands; 6Department of Cardiology, Spaarne Hospital, Haarlem, The Netherlands; 7Department of Cardiology, Rijnstate Hospital Arnhem, and Department of Cardiology, Radboud University Medical Centre Nijmegen, The Netherlands; and 8Department of Health Psychology, University of Groningen, Groningen, The Netherlands

Received 19 July 2018; editorial decision 3 November 2018; accepted 3 December 2018; online publish-ahead-of-print 9 January 2019

Aims
Atrial fibrillation (AF) reduces quality of life (QoL). We aim to evaluate effects of targeted therapy of underlying conditions on QoL in patients with AF and heart failure (HF).

Methods and results
The Routine versus Aggressive risk factor driven upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) study randomized patients with early persistent AF and HF to targeted or conventional therapy. Both groups received guideline-driven treatment. The targeted group received four additional therapies: mineralocorticoid receptor antagonists; statins; angiotensin converting enzyme inhibitors and/or receptor blockers; and cardiac rehabilitation including physical activity, dietary restrictions, and counselling. Quality of life was analysed in 230 patients at baseline and 1 year with available Medical Outcomes Study Short-Form Health Survey (SF-36), University of Toronto AF Severity Scale (AFSS) questionnaires, and European Heart Rhythm Association (EHRA) class. Improvements in SF-36 subscales were larger in the targeted group for physical functioning ($D_{12} = 12 \pm 19$ vs. $D_{6} = 6 \pm 22$, $P = 0.007$), physical role limitations ($D_{32} = 32 \pm 41$ vs. $D_{17} = 17 \pm 45$, $P = 0.018$), and general health ($D_{8} = 8 \pm 16$ vs. $D_{0} = 0 \pm 17$, $P < 0.001$). Dyspnoea at rest improved more ($\Delta = 0.8 \pm 1.3$ vs. $\Delta = 0.4 \pm 1.2$, $P = 0.018$) and EHRA class was lower at 1-year follow-up in the targeted group. Patients with AF at 1 year, improvement in physical functioning ($\Delta = 0.9 \pm 1.6$, $P = 0.001$), general health ($\Delta = 16 \pm 16$, $P = 0.004$), and social functioning ($\Delta = 23 \pm 16$, $P = 0.041$) were larger in the targeted group.

Conclusion
A strategy aiming to treat underlying conditions improved QoL more compared with conventional therapy in patients with early persistent AF and HF. Its benefit was even observed in patients in AF at 1 year.

Trial registration number
Clinicaltrials.gov NCT00877643.

Keywords
Atrial fibrillation • Quality of life • Risk factor • Targeted therapy • Randomized clinical trial
What’s new?

- Multilevel-targeted risk factor management improves quality of life (QoL) in patients with atrial fibrillation (AF) and heart failure.
- Quality of life in patients with AF is not only determined by heart rhythm. Even if patients are in AF at 1-year follow-up, QoL can still be improved by targeted risk factor management—compared with conventional therapy.
- This is a relatively short-term study with a 1-year follow-up. Long-term follow-up of the RACE 3 will be able to show whether these changes in QoL between both groups are sustained, increased, or only temporary.

Introduction

Apart from being a major cause of cardiovascular morbidity and mortality, atrial fibrillation (AF) is associated with reduced quality of life (QoL). Patients with AF have lower QoL compared with healthy controls, and similar to or worse than QoL seen in patients after myocardial infarction. Restoration and maintenance of sinus rhythm has been associated with improvement of QoL, but in contrast, rate vs. rhythm control studies showed a similar QoL in both groups. This can probably be explained by a low success rate of sinus rhythm maintenance.

Recently, the Routine versus Aggressive risk factor driven upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) study showed that targeted therapy of underlying conditions in patients with early persistent AF and mild to moderate heart failure (HF) was associated with a reduction of blood pressure, body mass index, lipid levels, and lowering of N-terminal pro-brain natriuretic peptide, indicating improvement of HF. On top of those beneficial effects on underlying conditions, this strategy improved maintenance of sinus rhythm at 1-year follow-up. Targeted therapy of underlying conditions aims to improve risk factors associated with AF and, in relation to that, to slow down the atrial remodelling processes, which underlies the progression of AF. In the RACE 3 trial, targeted therapy included four additional therapies on top of conventional care: mineralocorticoid receptor antagonists (MRAs), statins, angiotensin-converting enzyme inhibitors (ACE-Is) and/or angiotensin receptor blockers (ARBs), and cardiac rehabilitation including physical therapy, dietary restrictions, and counseling.

We hypothesized that targeted therapy could increase QoL through the improved maintenance of sinus rhythm, in combination with a better treatment of underlying conditions. Secondly, we hypothesized that because of the latter, it might also improve QoL by other mechanisms than sinus rhythm maintenance, since it focuses on optimal blood pressure regulation, treatment of HF, and physical activity to improve fitness. Meanwhile, side effects of the additional drugs could impact QoL in a negative way. Therefore, in this predefined secondary endpoint analysis of the RACE 3 study, we aimed to evaluate the effects of targeted therapy of AF on QoL.

Methods

Study design and population

This study was performed in patients with early persistent AF and mild to moderate HF included in the RACE 3 study. The institutional review board of each participating hospital approved the study, and all patients provided written informed consent. The RACE 3 study has been described previously. In brief, the RACE 3 study was a multicentre, prospective, randomized, open-label trial in patients with early persistent AF and mild to moderate HF (ClinicalTrials.gov identifier NCT00877643). All patients received causal treatment of AF and HF and were subsequently randomized to receive either targeted therapy of underlying conditions or conventional therapy. Patients in the targeted therapy group received four therapies on top of conventional therapy: MRAs, statins, ACE-Is and/or ARBs, and cardiac rehabilitation including counselling on drug adherence, sodium restriction, dietary restriction, alcohol use, caffeine use, fluid restriction, and physical activity. Psychological counselling was not part of the intervention. Full details on the counselling programme in RACE 3 are given in the Supplementary material online. Three weeks after inclusion, patients in both groups underwent electrical cardioversion. Both groups received rhythm control and treatment of HF according to the guidelines. Follow-up duration was 1 year. The primary endpoint was sinus rhythm during more than 6/7th of the time on 7-day Holter monitoring at 1 year. Quality of life-related questionnaires were administered at baseline immediately after inclusion and at 1 year. A total of 230 out of 245 patients had available questionnaire data and were included in the present analysis.

Quality of life-related questionnaires

Quality of life-related questionnaires used included the Medical Outcomes Study Short-Form Health Survey (SF-36) questionnaire, the University of Toronto AF Severity Scale (AFSS) Part C, the Multidimensional Fatigue Index (MFI-20), and the Minnesota Living with Heart Failure Questionnaire (MLHFO). Additionally, the European Heart Rhythm Association (EHRA) class and New York Heart Association (NYHA) function class was assessed.

The SF-36 is a well-validated questionnaire that is often used to assess health-related QoL in AF. It consists of 36 questions, which are used to calculate eight subscales, with three physical scales (physical functioning, physical role limitations, and bodily pain), three mental scales (social functioning, emotional role limitations, and mental health), two mixed scales (general health and vitality), and one question regarding health change. Each scale consists of varying numbers of questions, which in turn have response levels varying from two to six. Each scale was translated to a score from 0 to 100, with scores of 100 indicating the best possible QoL. Scores were calculated using the SF-36 scoring method as originally described by Ware and Sherbourne.

The AFSS Part C was used to assess AF-related symptoms. It contains seven questions on seven AF-related symptoms during the past week (palpitations, dyspnoea at rest, dyspnoea during exercise, reduced exercise capacity, fatigue at rest, and chest pain), from which a total score of 0–35 is calculated, with higher scores indicating more AF-related symptoms. The EHRA class was also used to classify the severity of AF-related symptoms, dividing patients into four classes: asymptomatic (Class I), mild symptoms (Class II), severe symptoms (Class III), and disabling symptoms (Class IV). The EHRA class was determined by physicians at study visits.

The MFI-20 was used in order to assess fatigue. It is composed of 20 questions, divided across five subscales (general fatigue, physical fatigue,
reduced activity, reduced motivation, and mental fatigue), with higher scores indicating higher levels of fatigue.10 The MLHFQ consists of 21 questions related to HF. Three scores are calculated: a physical score ranging from 0 to 40, a mental score ranging from 0 to 25, and a total score ranging from 0 to 105, with higher scores indicating more HF-related constraints.11 The NYHA class is an international standard for HF-related complaints, divided in Class I (no symptoms), Class II (mild symptoms), Class III (marked limitation in activity), and Class IV (severe limitations).

Statistical analysis
Baseline characteristics are presented as mean ± standard deviation (SD) for normally distributed data, as median and interquartile range for non-normally distributed continuous data, and as number and percentage for categorical data. The results of the QoL-related questionnaires and EHRA class are presented as mean ± SD.

Scores of questionnaire data at baseline and 1 year were compared between the targeted and conventional therapy group using a Mann-Whitney U test. A within-group comparison of scores at baseline and 1 year was performed using the Wilcoxon signed-rank test. For each patient, the changes in scores between baseline and 1 year were calculated (overall change). The overall changes between groups were compared using a Mann-Whitney U test.

Additionally, the number of patients with a relevant improvement or worsening was determined for each SF-36 subscale, as well as for the scores of the AFSS, MFI-20, and MLHFQ. Relevant changes per questionnaire were pre-specified.3 For the SF-36, a relevant change was defined as an improvement or worsening of a predetermined number of steps on a subscale score (i.e., before conversion to a 0–100 score). For physical functioning, general health, vitality, and mental health, an increase or decrease of three steps was considered a relevant change. For bodily pain and social functioning the required number was two, for physical and emotional role limitations one step was required. Corresponding with the relevant changes of SF-36 subscales, an effect size of 0.58 SD was used in determining relevant changes for the AFSS, MFI-20, and MLHFQ. The proportions of relevant improvement and worsening were compared between the two randomization groups using a Fisher’s exact test.

In order to identify differences in QoL based on heart rhythm at 1-year follow-up, the study population was subdivided according to heart rhythm at 1 year (as defined for the primary endpoint of the RACE 3 study). For both subgroups, scores at baseline and 1 year, as well as within-group and between-group changes were compared between the targeted and conventional therapy group, in the same manner as described above.

All analyses were performed on an intention-to-treat basis. For all analyses, a P-value <0.05 was considered statistically significant.

Results
Patients and baseline characteristics
Of the 230 patients included in this analysis, 114 were randomized to targeted therapy and 116 to conventional therapy. Baseline characteristics were comparable between the targeted and conventional therapy group (Table 1) and not different from the total RACE 3 population (data not shown). Mean age was 65 ± 9 years and 180 (78%) were men. The median duration of AF and HF was short, 3 (2–6) and 2 (1–4) months, respectively. Left ventricular ejection fraction was below 45% in 63 patients (27%).

Medical Outcomes Study Short-Form Health Survey
At baseline, there were no differences in SF-36 scores between the targeted and conventional group (Table 2). Between baseline and 1 year of follow-up, all eight SF-36 subscales improved in the targeted group, compared with six out of eight subscales in the conventional group. Figure 1 shows the overall change between baseline and 1 year for each SF-36 subscale in the targeted and conventional therapy group. The targeted therapy group improved more in physical functioning (Δ12 ± 19 vs. Δ6 ± 22, P = 0.007), physical role limitations (Δ32 ± 41 vs. Δ17 ± 45, P = 0.018), and general health (Δ8 ± 16 vs. Δ0 ± 17, P < 0.001). The targeted group showed a larger proportion of patients with a relevant improvement between baseline and 1 year in physical functioning (43% vs. 28%, P = 0.035) and general health (37% vs. 20%, P = 0.010) when compared with the conventional group (Figure 2). On top of that, relevant worsening was less often seen in the targeted group for physical role limitations (5% vs. 16%, P = 0.018) and general health (7% vs. 20%, P = 0.019).

At 1 year, 85 patients (75%) in the targeted group and 73 (63%) in the conventional group were in sinus rhythm during more than 6/7th of the time during a 7-day Holter recording. There was no difference in the number of atrial ablations or cardioversions performed, nor was there any difference in antiarrhythmic drugs instituted between groups during follow-up. Clinical characteristics for both sinus rhythm and AF groups were not different for both randomization strategies. In all patients who were in sinus rhythm at 1-year follow-up, overall change in general health was larger in the targeted group (Δ8 ± 16 vs. Δ4 ± 14, P = 0.043; Figure 3A). Improvement in SF-36 subscales were smaller in patients in AF at 1 year, compared with patients in sinus rhythm. However, differences between both randomization groups were more prominent in patients who were in AF. The targeted group improved more in physical functioning (Δ9 ± 9 vs. Δ–3 ± 16, P = 0.001), general health (Δ7 ± 16 vs. Δ–7 ± 19, P = 0.004), and social functioning (Δ6 ± 23 vs. Δ–4 ± 16, P = 0.041; Figure 3B).

University of Toronto AF Severity Scale and European Heart Rhythm Association class
Table 3 shows the AFSS scores at baseline and 1 year for both groups. All scores improved during follow-up, except for dizziness in the targeted group. Dyspnoea at rest improved more in the targeted group between baseline and 1 year (Δ–0.8 ± 1.3 vs. Δ–0.4 ± 1.2, P = 0.018). Patients who received targeted therapy were also more likely to have a relevant improvement of dyspnoea at rest (52% vs. 37%, P = 0.041) and exercise capacity (59% vs. 44%, P = 0.044). The proportions of relevant worsening did not differ between groups.

Patients of the conventional group who were in sinus rhythm at the 7-day Holter showed more reduction in dizziness compared to the targeted group (conventional group Δ–0.3 ± 1.3 vs. targeted group Δ0 ± 1.4, P = 0.015). Patients of the targeted group who were in AF at 1 year had more improvement in exercise capacity, as shown by a larger reduction in the reduced exercise capacity score (targeted Δ–0.9 ± 1.2 vs. conventional Δ–0.2 ± 1.2, P = 0.024). This was also true for the total AFSS score (targeted Δ–3.6 ± 4.6 vs. conventional Δ–0.8 ± 4.9, P = 0.045).
Baseline EHRA class was not different between both groups (2.0 ± 0.5 vs. 2.1 ± 0.5, P = 0.520). At 1 year both groups had a lower EHRA class compared with baseline. At that time the targeted group showed a lower EHRA class (1.3 ± 0.5 vs. 1.5 ± 0.6, P = 0.003).

**Multidimensional Fatigue Index**

Baseline scores on all MFI-20 subscales were comparable in both groups (Table 3). In the targeted group, all five MFI-20 subscales improved during the study. In the conventional group, all except the

---

**Table 1  Baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n = 230)</th>
<th>Targeted therapy (n = 114)</th>
<th>Conventional therapy (n = 116)</th>
<th>P-value (between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 ± 9</td>
<td>64 ± 9</td>
<td>65 ± 8</td>
<td>0.332</td>
</tr>
<tr>
<td>Male sex</td>
<td>180 (78)</td>
<td>89 (78)</td>
<td>91 (78)</td>
<td>1.000</td>
</tr>
<tr>
<td>Total duration AF (months)</td>
<td>3 (2–6)</td>
<td>4 (2–7)</td>
<td>3 (2–5)</td>
<td>0.084</td>
</tr>
<tr>
<td>Total persistent AF (months)</td>
<td>2 (1–4)</td>
<td>2 (1–4)</td>
<td>2 (1–4)</td>
<td>0.357</td>
</tr>
<tr>
<td>Duration HF (months)</td>
<td>2 (1–4)</td>
<td>2 (1–4)</td>
<td>2 (1–3)</td>
<td>0.677</td>
</tr>
<tr>
<td>Hospital admission for HF</td>
<td>29 (13)</td>
<td>14 (12)</td>
<td>15 (13)</td>
<td>1.000</td>
</tr>
<tr>
<td>LVEF &lt;45%</td>
<td>63 (27)</td>
<td>33 (29)</td>
<td>30 (26)</td>
<td>0.658</td>
</tr>
<tr>
<td>Hypertension</td>
<td>139 (60)</td>
<td>65 (57)</td>
<td>74 (64)</td>
<td>0.345</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22 (10)</td>
<td>9 (8)</td>
<td>12 (11)</td>
<td>0.502</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>30 (13)</td>
<td>18 (16)</td>
<td>12 (10)</td>
<td>0.245</td>
</tr>
<tr>
<td>Ischaemic thromboembolic complication</td>
<td>10 (4)</td>
<td>6 (5)</td>
<td>4 (3)</td>
<td>0.537</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>18 (8)</td>
<td>9 (8)</td>
<td>9 (8)</td>
<td>1.000</td>
</tr>
<tr>
<td>History of moderate or severe valvular heart disease</td>
<td>21 (9)</td>
<td>11 (10)</td>
<td>10 (9)</td>
<td>0.822</td>
</tr>
<tr>
<td>CHA2DS2-VASc scorea</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>0.525</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28 (26–31)</td>
<td>29 (26–31)</td>
<td>28 (25–31)</td>
<td>0.525</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>129 ± 15</td>
<td>131 ± 16</td>
<td>128 ± 15</td>
<td>0.299</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83 ± 10</td>
<td>84 ± 11</td>
<td>82 ± 10</td>
<td>0.311</td>
</tr>
<tr>
<td>Heart rate at rest in AF (b.p.m.)</td>
<td>88 (78–97)</td>
<td>87 (77–95)</td>
<td>88 (78–99)</td>
<td>0.435</td>
</tr>
<tr>
<td>NYHA classification</td>
<td></td>
<td></td>
<td></td>
<td>0.670</td>
</tr>
<tr>
<td>I</td>
<td>51 (22)</td>
<td>28 (25)</td>
<td>23 (20)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>155 (67)</td>
<td>75 (66)</td>
<td>80 (69)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>24 (10)</td>
<td>11 (10)</td>
<td>13 (11)</td>
<td></td>
</tr>
<tr>
<td>EHRA classification</td>
<td></td>
<td></td>
<td></td>
<td>0.813</td>
</tr>
<tr>
<td>I</td>
<td>26 (11)</td>
<td>14 (12)</td>
<td>12 (10)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>171 (74)</td>
<td>85 (75)</td>
<td>86 (74)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>33 (14)</td>
<td>15 (13)</td>
<td>18 (16)</td>
<td></td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>1045 (698–1628)</td>
<td>1055 (691–1635)</td>
<td>1008 (711–1567)</td>
<td>0.926</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>201 (88)</td>
<td>99 (87)</td>
<td>102 (88)</td>
<td>0.692</td>
</tr>
<tr>
<td>Verapamil/diltiazem</td>
<td>11 (5)</td>
<td>1 (1)</td>
<td>10 (9)</td>
<td>0.010</td>
</tr>
<tr>
<td>Digoxin</td>
<td>59 (26)</td>
<td>32 (28)</td>
<td>27 (23)</td>
<td>0.453</td>
</tr>
<tr>
<td>ACE-inhibitor</td>
<td>80 (35)</td>
<td>37 (32)</td>
<td>43 (37)</td>
<td>0.489</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>50 (22)</td>
<td>23 (20)</td>
<td>27 (23)</td>
<td>0.632</td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonist</td>
<td>3 (1)</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>1.000</td>
</tr>
<tr>
<td>Statin</td>
<td>77 (34)</td>
<td>38 (33)</td>
<td>39 (34)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diuretic</td>
<td>93 (41)</td>
<td>50 (44)</td>
<td>43 (37)</td>
<td>0.348</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>226 (98)</td>
<td>112 (98)</td>
<td>114 (98)</td>
<td>0.622</td>
</tr>
<tr>
<td>Echocardiographic variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial size, long axis (mm)</td>
<td>43 (40–47)</td>
<td>43 (40–47)</td>
<td>44 (39–47)</td>
<td>0.674</td>
</tr>
<tr>
<td>Left atrial volume (mL/m²)</td>
<td>38 (31–48)</td>
<td>38 (30–48)</td>
<td>38 (32–48)</td>
<td>0.685</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>52 (43–60)</td>
<td>50 (43–58)</td>
<td>53 (44–60)</td>
<td>0.449</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, number of patients (%), or median (IQR).

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; b.p.m., beats per minute; EHRA, European Heart Rhythm Association class for symptoms; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; NT-pro BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

aThe CHA2DS2-VASc score assesses thromboembolic risk. C, congestive heart failure/LV dysfunction; H, hypertension; A 2, age > 75 years; D, diabetes mellitus; S2, stroke/transient ischaemic attack/systemic embolism; V, vascular disease; A, age 65–74 years; Sc, sex category (female sex).
mental fatigue scale improved. Targeted therapy showed larger improvements of physical fatigue (Δ−4 ± 5 vs. Δ−2 ± 6, P = 0.001) and reduced activity scales (Δ−3 ± 4 vs. Δ−1 ± 6, P = 0.030) between baseline and 1 year. Patients in the targeted group were also more likely to have a relevant improvement on fatigue (61% vs. 44%, P = 0.021) and reduced activity (54% vs. 39%, P = 0.040) compared with conventional therapy. There were no differences in the proportions of relevant worsening.

### Table 2  SF-36 scores at baseline and 1 year

<table>
<thead>
<tr>
<th>SF-36 subscale</th>
<th>Treatment strategy</th>
<th>Baseline</th>
<th>1 year</th>
<th>P-value within-group change</th>
<th>P-value between-group change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>Targeted</td>
<td>67 ± 23</td>
<td>79 ± 21</td>
<td>&lt;0.001</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Conventional</td>
<td>69 ± 25</td>
<td>75 ± 23</td>
<td>0.024</td>
<td></td>
</tr>
<tr>
<td>Physical role limitations</td>
<td>Targeted</td>
<td>43 ± 43</td>
<td>75 ± 37</td>
<td>&lt;0.001</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>Conventional</td>
<td>51 ± 45</td>
<td>68 ± 41</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Bodily pain</td>
<td>Targeted</td>
<td>80 ± 22</td>
<td>85 ± 21</td>
<td>0.018</td>
<td>0.830</td>
</tr>
<tr>
<td></td>
<td>Conventional</td>
<td>77 ± 25</td>
<td>81 ± 22</td>
<td>0.047</td>
<td></td>
</tr>
<tr>
<td>General health</td>
<td>Targeted</td>
<td>59 ± 19</td>
<td>68 ± 19</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Conventional</td>
<td>59 ± 19</td>
<td>59 ± 21</td>
<td>0.866</td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>Targeted</td>
<td>58 ± 22</td>
<td>66 ± 20</td>
<td>&lt;0.001</td>
<td>0.361</td>
</tr>
<tr>
<td></td>
<td>Conventional</td>
<td>60 ± 21</td>
<td>66 ± 19</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>Targeted</td>
<td>77 ± 24</td>
<td>86 ± 19</td>
<td>0.001</td>
<td>0.277</td>
</tr>
<tr>
<td></td>
<td>Conventional</td>
<td>81 ± 20</td>
<td>86 ± 17</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>Emotional role limitations</td>
<td>Targeted</td>
<td>74 ± 41</td>
<td>86 ± 30</td>
<td>0.009</td>
<td>0.414</td>
</tr>
<tr>
<td></td>
<td>Conventional</td>
<td>77 ± 38</td>
<td>84 ± 34</td>
<td>0.136</td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>Targeted</td>
<td>79 ± 16</td>
<td>83 ± 14</td>
<td>0.001</td>
<td>0.405</td>
</tr>
<tr>
<td></td>
<td>Conventional</td>
<td>77 ± 15</td>
<td>80 ± 15</td>
<td>0.027</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. SD, standard deviation; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey.

### Figure 1  Changes in mean SF-36 subscale scores from baseline to 1-year follow-up. *P < 0.05 for difference between the targeted and conventional therapy group. **P < 0.001 for difference between the targeted and conventional therapy group. SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey.
Minnesota Living with Heart Failure Questionnaire and New York Heart Association class

Total scores of MLHFQ were low in both groups at baseline (Table 3) and were not different, indicating that HF-related symptoms were mild. In both groups, physical, emotional, and total scores improved between baseline and 1 year. At 1 year, there were no differences between the two groups, nor were there any differences in the overall changes of MLHFQ scores or the proportions of relevant improvement or worsening.

New York Heart Association class was not different between both groups at baseline (1.9 ± 0.6 vs. 1.9 ± 0.6, \( P = 0.387 \)), nor at 1 year (1.2 ± 0.5 for targeted therapy vs. 1.3 ± 0.6 for conventional therapy, \( P = 0.711 \)).

**Discussion**

The present study demonstrates that targeted therapy of underlying conditions improved QoL more compared with conventional therapy in patients with early persistent AF and HF. Interestingly, we found that beneficial effects of targeted therapy were also observed in patients who were in AF at 1-year follow-up.

Improvement of QoL was observed in both randomization groups, which can partly be explained by the fact that a high proportion of both groups was in sinus rhythm at 1-year follow-up. Improvement of QoL through sinus rhythm maintenance has been demonstrated before, albeit not in all studies. In a post hoc analysis from the RACE study, no differences in QoL between permanent AF and long-term sinus rhythm were found—nor did long-term sinus rhythm improve prognosis. This might have been caused by non-optimal risk factor management at that time, including, for example, a more lenient blood pressure target compared with current standards.

The finding that targeted therapy improves several aspects of QoL more than conventional therapy is relevant, especially considering that rhythm control is mainly instituted to relieve symptoms and thereby improve QoL. The four interventions were specifically chosen to optimize blood pressure, improve the treatment of HF, and improve the overall cardiovascular risk profile. It is thought that a combined intervention would have a synergistic effect. The RACE 3 study, as well as several Australian studies, showed beneficial effects of treating underlying risk factors of AF more aggressively, including lifestyle interventions. Abed et al. randomized patients with symptomatic AF and overweight to either weight management or general lifestyle advice. The weight management group showed a reduction in symptom burden and severity as well as reduced cardiac remodelling. The use of ACE-I and/or ARBs aimed to optimize blood pressure. Lee et al. included 899 patients with uncontrolled hypertension and divided these patients as having either controlled or non-controlled hypertension at 6-month follow-up. The main finding included that blood pressure control was correlated with health-related QoL. MRAs were added to improve HF treatment. In patients with HF with a preserved ejection fraction, the use of spironolactone has shown to improve QoL. Of interest, in that same population several modifiable cardiovascular risk factors were associated with QoL deterioration, e.g. obesity. The last intervention, the use of statins, was mainly instituted to prevent coronary and other vascular events. On top of that, the anti-inflammatory effect might contribute to limiting atrial remodelling. Clear positive effects on QoL have thus far not been described. Carlson et al. found no change in QoL in elderly patients taking pravastatin during 1 year.

The beneficial effects of targeted therapy on QoL could be caused by higher proportion of sinus rhythm, as well as optimal treatment of
comorbidities and improvement of lifestyle. These beneficial effects of targeted therapies of comorbidities on QoL based on other mechanisms than sinus rhythm maintenance are supported by the results from our subgroup analysis based on the actual rhythm at 1 year. Patients in whom sinus rhythm was not maintained seem to have also benefited from targeted therapy in terms of QoL.Several SF-36 subscales did not show any differences between groups, which can partly be explained by the already high scores, with limiting power to detect any differences.

Analyses of AFSS scores showed that in both groups all AF-related complaints improved, except for dizziness in the targeted therapy group, which remained stable. This may be explained by the more aggressive blood pressure control as a result of adding MRAs, ACE-Is, and ARBs as part of the intervention, possibly causing orthostatic hypotension. The SPRINT trial, which randomized patients to either intensive or standard blood pressure control, showed that intensive blood pressure control caused less fatal and non-fatal cardiovascular events and mortality compared with standard blood pressure control.20 Despite intensive blood pressure control, the number of serious adverse events due to hypotension (2.4%) and syncope (2.3%) was relatively low.

Apart from the scores for dizziness, the other questionnaire data showed better scores in the targeted group fairly consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL consistently, although not all differences between the groups were significant.
especially at 1-year follow-up. Similar to the SF-36 scores, AFSS scores between groups of patients in AF at 1 year also showed a difference in favour of the targeted group.

Scores of MLHFQ at baseline and 1-year follow-up were fairly low, indicating that HF-related symptoms were mild. This is supported by the relatively low NYHA class at 1-year follow-up. This might have to do with the fact that the questionnaire was originally designed for patients with more advanced stages of HF.11

Symptoms of AF and HF often overlap. We aim to contribute to a better collaboration between HF cardiologists and electrophysiologists in order to improve outcome in AF-HF patients, as they often intertwine.

**Limitations**

Limitations of the present study include the fact that it was not primarily designed to detect differences in QoL, and the fact that the institution of four targeted therapies at once makes it difficult to analyse individual contributions of each therapy on QoL. Furthermore, the open-label design of the study for both patient and physician with lack of placebo, might have accounted to additional positive effects on QoL in the targeted therapy group. This could have contributed to a potential bias that influenced the self-assessment in the targeted group. Study-related follow-up visits were very frequent for both randomization groups, which may have had an additional positive effect on QoL in both groups compared to

---

**Table 3** AFSS, MFI-20, and MLHFQ scores at baseline and 1 year

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Baseline</th>
<th>1 year</th>
<th>P-value within-group change</th>
<th>P-value between-group change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AFSS scores</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted</td>
<td>1.5 ± 1.5</td>
<td>0.5 ± 0.8</td>
<td>&lt;0.001</td>
<td>0.383</td>
</tr>
<tr>
<td>Conventional</td>
<td>1.5 ± 1.5</td>
<td>0.7 ± 1.1</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea at rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted</td>
<td>1.3 ± 1.3</td>
<td>0.5 ± 0.8</td>
<td>&lt;0.001</td>
<td>0.018</td>
</tr>
<tr>
<td>Conventional</td>
<td>1.2 ± 1.2</td>
<td>0.8 ± 1.2</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea during exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted</td>
<td>2.5 ± 1.4</td>
<td>1.4 ± 1.4</td>
<td>&lt;0.001</td>
<td>0.215</td>
</tr>
<tr>
<td>Conventional</td>
<td>2.4 ± 1.4</td>
<td>1.6 ± 1.4</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Reduced exercise capacity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted</td>
<td>2.1 ± 1.5</td>
<td>1.1 ± 1.2</td>
<td>&lt;0.001</td>
<td>0.052</td>
</tr>
<tr>
<td>Conventional</td>
<td>1.9 ± 1.5</td>
<td>1.3 ± 1.3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Fatigue at rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted</td>
<td>1.4 ± 1.5</td>
<td>0.7 ± 1.0</td>
<td>&lt;0.001</td>
<td>0.138</td>
</tr>
<tr>
<td>Conventional</td>
<td>1.2 ± 1.2</td>
<td>0.9 ± 1.1</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted</td>
<td>0.9 ± 1.2</td>
<td>0.8 ± 1.1</td>
<td>0.512</td>
<td>0.157</td>
</tr>
<tr>
<td>Conventional</td>
<td>1.2 ± 1.3</td>
<td>0.9 ± 1.2</td>
<td>0.023</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted</td>
<td>0.6 ± 1.0</td>
<td>0.3 ± 0.5</td>
<td>0.001</td>
<td>0.517</td>
</tr>
<tr>
<td>Conventional</td>
<td>0.8 ± 1.3</td>
<td>0.5 ± 0.8</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted</td>
<td>10.5 ± 6.8</td>
<td>5.5 ± 5.0</td>
<td>&lt;0.001</td>
<td>0.081</td>
</tr>
<tr>
<td>Conventional</td>
<td>10.2 ± 6.9</td>
<td>6.7 ± 5.8</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>MFI-20 subscales</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted</td>
<td>15 ± 6</td>
<td>12 ± 6</td>
<td>&lt;0.001</td>
<td>0.163</td>
</tr>
<tr>
<td>Conventional</td>
<td>15 ± 6</td>
<td>13 ± 6</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Physical fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted</td>
<td>15 ± 6</td>
<td>11 ± 5</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Conventional</td>
<td>14 ± 6</td>
<td>13 ± 6</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Reduced activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted</td>
<td>15 ± 6</td>
<td>12 ± 5</td>
<td>&lt;0.001</td>
<td>0.030</td>
</tr>
<tr>
<td>Conventional</td>
<td>13 ± 5</td>
<td>12 ± 5</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Reduced motivation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted</td>
<td>12 ± 6</td>
<td>10 ± 5</td>
<td>0.001</td>
<td>0.415</td>
</tr>
<tr>
<td>Conventional</td>
<td>11 ± 5</td>
<td>10 ± 5</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>Mental fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted</td>
<td>10 ± 5</td>
<td>9 ± 5</td>
<td>0.029</td>
<td>0.141</td>
</tr>
<tr>
<td>Conventional</td>
<td>9 ± 5</td>
<td>9 ± 5</td>
<td>0.945</td>
<td></td>
</tr>
<tr>
<td><strong>MLHFQ scores</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted</td>
<td>14 ± 11</td>
<td>7 ± 7</td>
<td>&lt;0.001</td>
<td>0.164</td>
</tr>
<tr>
<td>Conventional</td>
<td>13 ± 10</td>
<td>8 ± 8</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted</td>
<td>4 ± 5</td>
<td>3 ± 5</td>
<td>0.002</td>
<td>0.837</td>
</tr>
<tr>
<td>Conventional</td>
<td>4 ± 4</td>
<td>3 ± 4</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted</td>
<td>26 ± 21</td>
<td>15 ± 15</td>
<td>&lt;0.001</td>
<td>0.064</td>
</tr>
<tr>
<td>Conventional</td>
<td>23 ± 18</td>
<td>18 ± 16</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD.

AFSS, University of Toronto Atrial Fibrillation Severity Scale Part C; MFI-20, Multidimensional Fatigue Index; MLHFQ, Minnesota Living with Heart Failure Questionnaire; SD, standard deviation.
real-life healthcare. Finally, as with any subgroup analysis, the results of the post hoc subgroup analysis based on heart rhythm should be interpreted with caution because of the modest sample size, even though baseline characteristics were comparable within the subgroups.

Conclusion

In conclusion, the present study demonstrates that targeted therapy of underlying conditions results in larger improvements in QoL compared with conventional therapy in patients with early persistent AF and mild to moderate HF. These effects seem to be at least partially related to mechanisms other than sinus rhythm maintenance. The results further underline the importance of risk factor management in AF and may thus contribute to improving current treatment strategies and improvement of QoL in patients with AF.

Supplementary material

Supplementary material is available at Europace online.

Funding

This work was supported by the Netherlands Heart Foundation (grant 2008B0035). Unrestricted grants from AstraZeneca, Bayer, Biotronik, Boehringer-Ingelheim, Boston Scientific, Medtronic, Sanofi-Aventis, and St Jude Medical paid to the Netherlands Heart Institute.

Conflict of interest: M.A. reports personal fees from Bayer, Boehringer-Ingelheim, Daiichi-Sankyo, Bristol-Myers-Squibb, Pfizer, and Sanofi. R.G.T. reports grants and personal fees from Bayer, Bristol-Myers-Squibb, Pfizer, and Daiichi-Sankyo. All other authors have no competing interests.

References