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International Journal of Cardiology 77 (2001) 131–138

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Effects of the replacement of the angiotensin converting enzyme inhibitor enalapril by the angiotensin II receptor blocker telmisartan in patients with congestive heart failure
The replacement of angiotensin converting enzyme inhibition (REPLACE) investigators

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Received 22 March 2000; received in revised form 21 August 2000; accepted 4 September 2000

Abstract

Aim: To compare the effects on maximal exercise tolerance of 12 weeks of four dosages of telmisartan (10/20/40/80 mg once daily), an AT_1 specific angiotensin II receptor antagonist, or continuation on the angiotensin converting enzyme inhibitor enalapril, in patients with stable, mild-to-moderate congestive heart failure (NYHA Class II and III and left ventricular ejection fraction ≤40%). *Design*: Multicenter, double-blind, parallel-group trial in 378 patients, randomized to once-daily treatment with telmisartan 10, 20, 40 mg, 80 mg, or continuation of enalapril 10 mg twice daily for 12 weeks. *Methods*: Primary efficacy parameter: change from baseline to final visit in bicycle exercise duration. Secondary efficacy parameters included left ventricular ejection fraction, quality-of-life parameters, arterial blood pressures, neurohormonal changes and NYHA classification. *Patients*: The mean age of the patients was 64±9 years, 89% male, history of myocardial infarction in 68%, NYHA-II: 63%, NYHA-III: 37%, ejection fraction 26.4(7)%, and a reproducable impaired exercise capacity. All patients were on diuretics and enalapril 10 mg twice daily, and 39% were taking digitalis at study entry. *Results*: No clinically relevant or statistically significant ($P<0.05$) differences were observed in the primary efficacy parameter: mean changes (s) in exercise tolerance were +8.6, +8.2, +2.2, and +7.1 for the telmisartan 10-, 20-, 40-, and 80-mg groups, respectively, and +1.4 for enalapril. There was a small but significant increase in blood pressure in all but the 80 mg telmisartan groups, compared to enalapril. Telmisartan and enalapril had comparable adverse event profiles. Cough occurred in 5.6% of the enalapril patients and in 3% of the telmisartan patients (NS). *Conclusions*: (1) In patients with stable, mild-to-moderate congestive heart failure, enalapril could be replaced by telmisartan for a period of 12 weeks without deterioration in exercise capacity or clinical status. (2) No differences were observed in exercise capacity between the four dosages of telmisartan.

Keywords: Angiotensin-II receptor blockade; Angiotensin converting enzyme inhibition; Heart failure; Exercise capacity

1. Introduction

As one of the most important contributors to cardiovascular mortality, congestive heart failure (CHF) remains a serious health problem, and the impact of this disease will become more widespread as the numbers of elderly patients increase [1–3]. In patients with CHF, reduced cardiac output activates baroreceptors of the juxtaglomerular apparatus of the kidney resulting in renin release and subsequent angiotensin II (A-II) synthesis. A-II induces vasoconstriction and sodium and fluid retention, exacerbating the peripheral vasoconstriction and volume overload already present in these patients [4]. In addition, A-II

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0167-5273/01/$ – see front matter
PII: S0167-5273(00)00426-5

has been shown to contribute to the development of cardiac hypertrophy [5], a fundamental morphologic characteristic of CHF [6]. Thus, agents that interfere with the actions of A-II are logical choices for pharmacologic intervention in the treatment of CHF. Indeed, abundant clinical data [7–9] have clearly demonstrated the value of angiotensin converting enzyme (ACE) inhibitors in patients with CHF. These agents have been shown not only to induce significant acute hemodynamic and symptomatic improvements, they also reduce cardiovascular morbidity and mortality.

The pharmacologic actions of ACE inhibitors are nonspecific, however. ACE, or kininase II, has several biologically important substrates. ACE inhibition not only attenuates A-II formation but also prevents the catabolism of certain kinins, including bradykinin, and increases prostaglandin levels [10]. Although increased prostaglandin levels may mediate some of the beneficial vasodilatory actions of ACE inhibitor therapy [11], the enhanced levels and actions of bradykinin may induce troublesome clinical effects. Specifically, a buildup of bradykinin secondary to ACE inhibitor blockade is believed to underlie the development of a persistent, dry cough [10]. The occurrence of ACE inhibitor-related cough limits the beneficial effects of these agents in patients with CHF.

By contrast, selective A-II receptor antagonists specifically inhibit the binding of A-II to the AT_1 receptor, the receptor sub-type thought to mediate all of the known vasoconstrictive and hypertrophic effects of A-II [12]. Because these agents are highly selective in their pharmacologic action, they do not affect kinin metabolism, and, therefore, should display a favorable tolerability profile. Indeed, clinical studies suggest that the side effect profile associated with AT_1 receptor antagonists is similar to that of placebo [13]. Moreover, clinical studies reveal that AT_1 receptor antagonists can induce both hemodynamic and symptomatic benefits in patients with CHF [14,15].

The present double blind study was the first to evaluate telmisartan, a new and selective nonpeptide AT_1 receptor antagonist [16,17], in patients with CHF. The principal objective of this study was to examine the effects of telmisartan, at four different dosages, in comparison to enalapril 10 mg bid, on exercise capacity after a treatment period of 12 weeks.

2. Methods

2.1. Patients

Included were ambulatory patients at least 21 years of age, in sinus rhythm, with chronic moderate symptomatic heart failure (New York Heart Association class II–III) and a left-ventricular ejection fraction of 40% or lower. All patients had to be in a stable condition on a diuretic plus the ACE inhibitor enalapril 10 mg twice daily for 28 days before randomisation, with or without digoxin. Other medication as long-acting nitrates, hydralazine, prazosin, and beta-blockers were allowed. The same applied to anti-coagulants and/or platelet aggregation inhibiting drugs. At two exercise tests at least 1 week apart, maximal exercise duration was not to differ more than 1 min, and had to be below an age and sex specific upper limit [18]. Excluded were patients with any life-threatening disease (cancer, hemodynamically significant pulmonary embolism, AIDS, etc.), clinically significant stenotic valvular disease, aortic or mitral regurgitation, or hypertrophic or restrictive cardiomyopathy, a history of myocardial infarction, unstable angina, syncopal episodes, or surgery within 6 months of the study. Also excluded were patients with fever, primary renal, hepatic, or metabolic diseases, and those requiring treatment with phosphodiesterase inhibitors, dopamine or beta-agonists (e.g. ibopamine), class I antiarrhythmic agents, or chronic administration of high doses of non-steroidal anti-inflammatory drugs or acetaminophen. Women of child-bearing potential, and those treated with telmisartan or any other investigational drug within 4 weeks of this study were also excluded.

2.2. Study design

The REPLACE study was a randomized, double blind, parallel-group, multi-centre study. There were five treatment groups, each planned to consist of 66 patients started on study treatment. The study consisted of two phases; a screening phase during which the patients had to be stable on background treatment

consisting of at least enalapril 10 mg twice daily and a diuretic. At the end of the screening phase baseline evaluations were performed. If the patients met all of the inclusion and none of the exclusion criteria, they were randomized to a 12 week treatment phase. During this period patients continued with their background therapy and either telmisartan 10, 20, 40, or 80 mg once daily instead of enalapril, or continued enalapril 10 mg twice daily.

The primary efficacy parameter was the change from baseline in exercise capacity at the last available exercise test on study treatment. Secondary efficacy parameters included changes from baseline in ejection fraction, NYHA class, and quality-of-life parameters.

This study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the institutional review board of each center, and was monitored in accordance with the European Union Standards of Good Clinical Practice.

All patients were to give written informed consent before the start of the study.

2.3. Study procedures

2.3.1. Efficacy

Exercise capacity was assessed in the upright sitting position using a bicycle exercise testing protocol [18]. Exercise testing was conducted at the same time each day, 2 h after morning administration of study medication. Heart rate and blood pressure were measured before testing, during the last 30 s of each work step of 1 min, immediately after testing, and after recovery. The exercise test was performed at least twice during screening and at 4 and 12 weeks of double-blind treatment.

Left-ventricular ejection fraction (LVEF) was determined by two-dimensional echocardiography. Apical long axis, apical four chamber, and parasternal short axis views were recorded on video tape and analyzed at a central laboratory (SOCAR Research, Switzerland) on a Nova Microsonics Image Vue™ work station. LVEF in percent was defined as (end diastolic volume−end systolic volume)×100/end diastolic volume. LVEF was measured at baseline and after 4 and 12 weeks of double-blind therapy.

The patient's CHF symptomatology and subjective functional capacity were assessed by the New York Heart Association classification system as follows: Class I, no limitation; Class II, slight limitation; Class III, marked limitation; and Class IV, inability to carry on any physical activity without discomfort. This assessment was completed at screening and during double-blind treatment. Quality-of-life parameters were assessed using the Minnesota Living with Heart Failure questionnaire [19] during screening and after 4 and 12 weeks of double-blind treatment. In patients of selected centers, blood was collected to assess changes from baseline in levels of the neurohormones aldosterone and angiotensin II.

2.3.2. Safety

Safety was assessed by monitoring vital signs and standard laboratory tests at 4 and 12 weeks of double-blind treatment. A standard 12-lead ECG was performed before each exercise test. A 24-h Holter ECG was recorded at baseline and after 12 weeks of double-blind therapy. For patient safety, episodes of ventricular tachycardia in excess of three consecutive beats observed in these centrally analysed 24 h Holter ECG's were reported to the investigator.

Data on serious adverse events were regularly reviewed by an independent monitoring committee, which was in the possession of the treatment code from the start of the study. All adverse events occurring during the study were documented as to type, onset, duration, intensity, treatment required, outcome, and relationship to study drug. Serious adverse events included those that were fatal, life-threatening, disabling, or any requiring or prolonging hospitalization. All adverse events occurring during treatment or up to 2 weeks after treatment were reported.

2.3.3. Statistics

For the primary analysis, all patients who correctly fulfilled all entry criteria, completed the baseline exercise test according to protocol and who had taken at least one dose of study treatment were selected. The primary efficacy parameter was the change from baseline to the last available exercise test duration measured while the patient was on study treatment. In case no on-treatment follow-up exercise test was available for reasons unrelated to the patients medical condition, the change from baseline was to be taken as zero. If the exercise test could not be performed

for reasons which clinically precluded exercise testing (worsening heart failure, serious arrhythmias, death), the last exercise duration was taken as zero minutes. Descriptive statistics are described by means and standard deviations for continuous variables and percentages for categorical variables. Efficacy parameters are presented as change from baseline relative to enalapril, with a corresponding standard error as a measure of precision. *P*-values were computed by means of an ANOVA procedure or Wilcoxon test where appropriate. Categorical efficacy and safety parameters were assessed by means of the Chi-square or Fisher exact test. Statistical significance was defined as a two-sided $P<0.05$.

3. Results

3.1. Patient disposition

Three hundred and seventy eight (378) patients took at least the first dose of study treatment. Of these, 378 patients were included in the safety analysis, and 11 were declared ineligible due to protocol violations that were pre-existing at the time of randomisation. They were excluded from all efficacy analyses in a blinded manner by the Steering Committee. The excluded patients were not clustered in any one treatment group (4 patients on telmisartan 10 mg/day; 2 patients on telmisartan 40 mg/day; 3 patients on telmisartan 80 mg/day; and 2 patients on enalapril 20 mg/day). Reasons for their exclusion included: failure to follow the exercise test protocol, no background diuretic, and baseline potassium levels outside the normal range of the local laboratory. As these 11 patients were declared ineligible due to violations of the protocol which occurred prior to randomisation, the population evaluated for efficacy consisted of 367 patients.

Baseline characteristics were similar across groups (Table 1). The mean time since first diagnosis of heart failure was 53 months; 46% had been previously hospitalized for this condition. For most patients (78%), the etiology of heart failure was ischemia. Sixty-nine percent (69%) had a history of myocardial infarction, 14% of percutaneous transluminal coronary angioplasty, and 30% of coronary artery bypass grafting. A total of 147 (39%) patients were on concomitant digitalis at baseline, with an equal distribution across treatment groups.

3.2. Efficacy

3.2.1. Exercise duration

For all treatment groups, mean changes from baseline in exercise duration were neither clinically relevant nor statistically significant, ranging from a 1.4-s mean increase for enalapril 20 mg/day to a 8.6-s mean increase for telmisartan 10 mg/day. With adjustment for the baseline exercise duration (which differed between the groups, cf. Table 1), the change of exercise duration in patients in all four telmisartan groups relative to the enalapril group was also not statistically significant (Fig. 1).

3.2.2. Ejection fraction

No significant differences were seen among groups in changes from baseline for ejection fraction.

Table 1
Patient characteristics[a]

	Telmisartan 10 mg ($n=75$)	Telmisartan 20 mg ($n=72$)	Telmisartan 40 mg ($n=77$)	Telmisartan 80 mg ($n=77$)	Enalapril 20 mg($n=77$)	Total ($n=378$)
Age (yrs)[b]	64±8	65±10	65±10	64±9	63±10	64±10
Males[c]	67 (89%)	63 (88%)	71 (92%)	68 (88%)	68 (88%)	337 (89%)
NYHA-II[c]	53 (71%)	47 (65%)	47 (61%)	46 (60%)	48 (62%)	241 (64%)
NYHA-III[c]	22 (29%)	25 (35%)	30 (39%)	31 (40%)	29 (38%)	137 (36%)
SBP (mmHG)[c]	122.5±19	124.2±19	123.1±18	121.5±16	124.3±17	123.1±18
Exercise duration (s)[b]	409.9±107	403.0±102	385.9±107	397.6±107	408.7±109	400.9±106
Ejection fraction (%)[b]	25.9±6.9	26.5±7.3	26.6±7.8	25.9±6.3	27.1±7.6	26.4±7.2

[a] Patient characteristics at study entry. NYHA, New York Heart Association; SBP, Systolic Blood Pressure; no significant differences between the treatment groups.
[b] Mean±S.D.
[c] Number of patients (%).

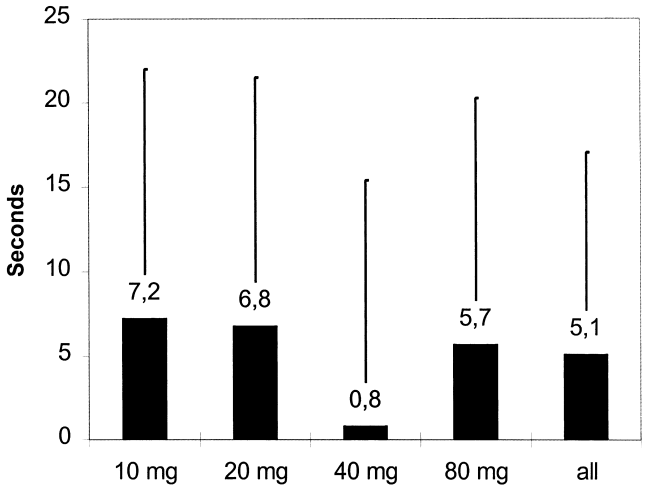

Fig. 1. Effects of four different dosages of telmisartan on mean exercise duration (S.D.), relative to enalapril.

3.2.3. NYHA classification

There were no significant changes detected for any group in NYHA classification. Most patients (about 60% in all groups) reported no change in their functional capacity.

3.2.4. Quality of life questionnaire

Of the 365 patients who completed the Minnesota Living with Heart Failure (MLHF) questionnaire at baseline, mean baseline total scores from the MLHF questionnaire were comparable among the treatment groups and ranged from 22 to 24 (out of a possible 110). Replacement of enalapril by any dose of telmisartan studied did not significantly affect the total MLHF score.

3.2.5. Neurohormones

The number of patients that had baseline and final values for one or more neurohormone measures ranged from 96 to 113. There was a dose-related trend among telmisartan-treated patients in median changes in aldosterone level. A slight decrease was seen at the telmisartan 80-mg dose, and increases with telmisartan 10, 20 and 40 mg that were inversely related to dose. Telmisartan raised angiotensin II levels in a dose-dependent manner (Table 2) as would be expected for an AT1 receptor antagonist, but no further raise in angiotensin II levels was observed between the 40 mg and 80 mg dose group. Due to limited sample sizes for these parameters and the large variability associated with these parameters, no comparisons to enalapril 20 mg/day were made.

3.2.6. Blood pressures

Mean systolic blood pressures did not differ between the groups (Table 1). Relative to the change of systolic blood pressure in patients on enalapril (−6.2 mmHg), the effect of telmisartan 10 mg/day on the change in systolic blood pressure was +9.2 mmHg (SE 3.3, $P=0.005$). The corresponding relative effects for the telmisartan 20 mg/day, 40 mg/day and 80 mg/day groups were +9.4 ($P=0.004$), +10.5 ($P=0.001$) and +2.7 (ns) mmHg respectively (SE 3.3, 3.2, 3.3).

3.2.7. Safety and tolerability

All treatment regimens were equally well tolerated. At least one adverse event was reported during treatment by 54% (206/378) of patients randomized, and the incidence of adverse events was similar across treatment groups. Telmisartan and enalapril had similar adverse event profiles. There were 9/301 telmisartan patients who complained about cough, as compared to 4/71 on enalapril. This difference is not significant ($P=0.3$, chi-square test with one degree of freedom). Treatment-related serious adverse events that led to withdrawal were uncommon, occurring in three telmisartan patients (two patients with worsening cardiac failure and one with ataxia, dizziness and dyspepsia). There were six deaths: two on telmisartan

Table 2
Median change from baseline in neurohormones by treatment group[a]

Neurohormone	Telmisartan 10 mg	Telmisartan 20 mg	Telmisartan 40 mg	Telmisartan 80 mg	Enalapril 20 mg
Aldosterone (pmol/l)	157.0 (17)	48.5 (20)	10.0 (23)	−21.0 (27)	−57.5 (26)
Angiotensin II (pg/ml)	17.0 (15)	28.0 (17)	58.5 (18)	59.0 (25)	12.0 (21)

[a] Median change from baseline (number of patients).

20 mg (ventricular fibrillation; sudden death); one on telmisartan 40 mg (sudden death); one on telmisartan 80 mg (sudden death), and two on enalapril 20 mg (sudden death; myocardial infarction, dyspnea, pulmonary edema). No significant differences between the treatment groups were detected for standard laboratory tests, including hematology, electrolytes, renal, metabolic, and liver function. Few clinically relevant laboratory test abnormalities were observed during study treatment.

4. Discussion

The effectiveness of pharmacologic therapy in the treatment of CHF is measured by how well a particular treatment reduces symptoms, increases functional capacity, and prolongs survival [20]. In addition to efficacy, however, tolerability is an important consideration in the successful management of CHF, since it can affect the patient's quality-of-life and, thus, compliance with the prescribed medication regimen [21]. Because its survival benefits have been clearly demonstrated, ACE inhibitor therapy is currently the preferred modality in the treatment of CHF [20]. In this patient population, however, AT_1 receptor antagonists, like telmisartan, may offer certain advantages resulting from the selective nature of their mechanism of action. Theoretically, AT_1 receptor antagonists should be at least as effective as ACE inhibitors in attenuating the deleterious influences of A-II in patients with CHF, and, because they do not affect kinin metabolism, they should display a more favorable side effect profile. It is important to note that, although the clinical experience with selective AT_1 receptor antagonists in the treatment of CHF seems encouraging in terms of reduced mortality [22], any long-term survival benefits conferred by these agents still remain to be clearly demonstrated.

The primary intent of this short-term (12 week) study was to assess whether functional capacity, as measured by exercise tolerance, in patients with chronic stable CHF treated with the ACE inhibitor enalapril 10 mg twice daily, would be maintained with the selective AT_1 receptor antagonist telmisartan at doses ranging from 10 to 80 mg once daily. The primary efficacy criterion was exercise duration as measured by standardised bicycle ergometry. This is a generally accepted measure of functional status in heart failure. The design followed a standard pattern for this type of study: a screening phase to assess stability, randomized double-blind study treatment and repeated exercise testing during a treatment phase of, in this case, 12 weeks. During this treatment period, exercise capacity, as measured by bicycle ergometry, was essentially stable for the patients who continued enalapril therapy. The central finding of this study, however, was that no acute deterioration in exercise performance was detected when patients were switched to telmisartan therapy, irrespective of dose. By the end of the double-blind period, enalapril and all doses of telmisartan produced only small enhancements in exercise tolerance duration, and none reached statistical significance compared with baseline values. A small improvement in exercise duration in all five groups is not unusual when all groups are treated with active treatment. The absence of a dose-effect response with telmisartan on exercise duration may be due to the design of the study, with a treatment period of only 12 weeks. The results of similar studies are consistent with the current findings. In a study [23] comparable in design, but somewhat shorter in duration (8 weeks) and with a different measure of exercise capacity (6-min walk test), exercise performance was maintained when patients were switched from enalapril 20 mg/day to the prototypical AT_1 antagonist losartan at doses of 25 mg or 50 mg. In another study [24] in 116 patients, with an almost identical design, where enalapril 20 mg/day was compared with losartan at 25 and 50 mg/day during 12 weeks, treadmill exercise time and 6-min walk test did not change significantly after replacement of ACE inhibitor therapy with losartan. Taken together, these results and those of the current study indicate that the exercise capacity achieved with ACE inhibitor therapy can be preserved, at least over the short term, when patients with CHF are switched from enalapril to selective AT_1 receptor antagonist therapy. Moreover, that no significant changes were detected in ejection fraction, NYHA classification or MLHF-questionnaire scores for any group during the current study indicates that telmisartan can successfully replace enalapril therapy without causing an acute deterioration in cardiac function, patient symp-

tomatology, or quality-of-life parameters. An interesting observation is the dose dependant effect on aldosterone levels and the lack of extra feedback on angiotensin II production in the 80 mg group, compared to the 40 mg group. Because of the limited sample size for these observations and the large variability associated with these neurohormonal parameters, one should be cautious with the interpretation of these results, though it could be speculated that the 40 mg dose in this patient group may be considered as optimal. There was a small increase in arterial blood pressure during telmisartan treatment, compared to enalapril. This may be related to the observed and expected increase in angiotensin II levels after change from enalapril to telmisartan. It may be hypothesized that the doses up to 40 mg telmisartan are not high enough to satisfactorily block the AT_1 receptors.

In this study, all treatments appeared equally well tolerated. The incidence of cough reported on study treatment was only four out of 71 patients on enalapril (5.6%). In all telmisartan groups combined, the incidence of cough was even lower (9/301 or 3%). The fact that the difference failed to reach statistical significance is probably due to the low incidence of cough in this study, where patients who were already on treatment with enalapril were selected, creating a selection bias for patients who tolerate enalapril.

In summary, the data from this study are consistent with similar published studies for other AT_1 receptor antagonists and provide at least preliminary data to suggest that, as replacement therapy for enalapril in patients with stable, chronic CHF, the use of telmisartan would not produce acute deterioration in exercise tolerance, symptomatology, or quality-of-life parameters. Studies of greater duration, however, will be needed to establish the survival benefits of telmisartan and other AT_1 receptor antagonists when used as long-term replacement therapy for ACE inhibitors in the treatment of CHF.

Acknowledgements

Grant support: Boehringer-Ingelheim Limited, Germany.

Appendix A

The Replacement of Angiotensin Converting Enzyme (REPLACE) Investigators consisted of:

Clinical investigators: *Belgium*: A Friart (CHU de Tivoli, La Louvière), G Heyndrickx (O-L Vrouwziekenhuis, Aalst), V. Legrand (CHU Sart-Tilman, Liège), B Marchandise (CU de Mont Godinne, Yvoir). *Germany*: W Doering (Städt. Krankenhaus München-Schwabing), HJ Just (Medizinischen Universitätsklinik, Freiburg), H Klepzig (Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt), W. Kübler (Ruprecht-Karls Universität, Universitätsklinikum, Heidelberg), U Nixdorff (Medizinische Klinik und Poliklinik der Johannes Gutenberg Universität, Mainz). *Israel*: A Battler (Soroko Medical Center, Beer-Sheva), D David (Sapir Medical Center, Kfar Saba), A Keren (Bikur Cholim Hospital, Jerusalem), BS Lewis (Lady Davis Carmel Hospital, Haifa), M Motro (Chaim Sheba Medical Center, Tel Hashomer). *Ireland*: D O'Callaghan (Beaumont Hospital, Dublin), M Murphy (Mercy Hospital, Cork), P Quigley (St. Vincent's Hospital, Dublin), DD Sugrue (Mater Misericordiae Hospital, Dublin). *The Netherlands*: PJLM Bernink (Martini Ziekenhuis, Groningen), A Bosma (Sint Joseph Ziekenhuis, Veldhoven), PN Breuls (Merwede Ziekenhuis, Dordrecht), PH van der Burg (Medisch Spectrum Twente, Enschede), HJM Dohmen (Groot Ziekengasthuis, Den Bosch), PHJM Dunselman (Ignatius Ziekenhuis, Breda), NJ Holwerda (St. Elisabeth Ziekenhuis, Tilburg), JCA Hoorntje (Ziekenhuis de Weezenlanden, Zwolle), LHJ van Kempen (Ziekenhuis Velp, Velp), JH Kingma, C Lodewijks-van der Bolt (St. Antonius Ziekenhuis, Nieuwegein), JA Kragten (Ziekenhuis de Wever, Heerlen), K van Leeuwen (Ziekenhuis Overvecht, Utrecht), DJA Lok (Deventer Ziekenhuizen, Deventer), HR Michels (Catharina Ziekenhuis, Eindhoven), AR Ramdat Misier (Sophia Ziekenhuis, Zwolle), AJAM Withagen (R de Graaf Gasthuis, Delft). *United Kingdom*: MIM Noble (Charing Cross Hospital, London).

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Critical Events committee: DJA Lok, chairman

(Deventer, the Netherlands); NJ Holwerda (Tilburg, The Netherlands), A. Merdler (Haifa, Israel).

Data Monitoring and Ethical Review committee: SJ Pocock (London School of Hygiene and Tropical Medicine, UK)

Co-ordinating centre, core laboratory for echocardiography and 24-h electrocardiography, on-site monitoring: Sociéte pour la Recherche Cardiologique (SOCAR) SA, Givrins, Switzerland (FJ van Dalen, J-M Dumont, P Jonkers, BA Kirwan, D La Framboise, L Le Roux, J Lubsen; M-J Roulin, M St John Sutton; D Sekarski, A Sublet, X-F Suckow).

Sponsor: Boehringer Ingelheim Deutschland GmbH (W. Feuerer; T. Meinicke)

Report prepared by: PHJM Dunselman, C Lodewijks-van der Bolt, AJS Coats, JK Lubsen.

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