Clarithromycin for 2 Weeks for Stable Coronary Heart Disease: 6-Year Follow-Up of the CLARICOR Randomized Trial and Updated Meta-Analysis of Antibiotics for Coronary Heart Disease

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Key Words
Coronary heart disease \textsuperscript{1} \cdot Clarithromycin \textsuperscript{1} \cdot Macrolides \textsuperscript{1} \cdot Antibiotics \textsuperscript{1} \cdot Cardiovascular mortality \textsuperscript{1} \cdot Chlamydia pneumoniae

Abstract
Objectives: We have reported increased 2.6-year mortality in clarithromycin- versus placebo-exposed stable coronary heart disease patients, but meta-analysis of randomized trials in coronary heart disease patients showed no significant effect of antibiotics on mortality. Here we report the 6-year mortality of clarithromycin- versus placebo-exposed pa-

Patients and updated meta-analyses. Methods: Centrally randomized, placebo controlled multicenter trial. All parties were blinded. Analyses were by intention to treat. Meta-

analyses followed the Cochrane Collaboration methodology. Results: We randomized 4,372 patients with stable coronary heart disease to clarithromycin 500 mg (n = 2,172) or placebo (n = 2,200) once daily for 2 weeks. Mortality was followed through public register. Nine hundred and twenty-three patients (21.1\%) died. Six-year mortality was signifi-

\textsuperscript{1} Members are listed in the Appendix.
dition of our data to that of other randomized trials on antibiotics for patients with coronary heart disease versus placebo/no intervention (17 trials, 25,271 patients, 1,877 deaths) showed a significantly increased relative risk of death from antibiotics of 1.10 (1.01–1.20) without heterogeneity. **Conclusions:** Our results stress the necessity to consider carefully the strength of the indication before administering antibiotics to patients with coronary heart disease.

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**Introduction**

The idea that bacterial colonization of arteries worsened atherosclerosis gained increasing support during the 1990s and several antibiotic trials were launched [1]. Most of these trials were meta-analyzed in 2005 by Andrews et al. [1]. They found no significant effect of antibiotics on all-cause mortality (odds ratio 1.02, 95% confidence interval 0.89–1.16), but the confidence interval could not exclude an 11% decrease or a 16% increase in mortality [1].

We recently reported significantly increased mortality in clarithromycin-exposed patients with stable coronary heart disease [2]. The 2.6-year mortality was 9.8% in the clarithromycin group compared with 7.8% in the placebo group (hazard ratio 1.27, 1.03–1.54). When we added these data [2] and data from the trial of Berg et al. [3] to the meta-analysis of Andrews et al. [1], we found no significant effect of antibiotics across dosages, regimens, and duration of follow-up on mortality of coronary heart disease patients (odds ratio 1.09, 0.97–1.22) [2]. The confidence interval could not exclude a 3% decrease or a 22% increase in mortality [2]. When we pooled the data of three trials following patients for more than 2 years, i.e., the CLARICOR, PROVE-IT, and ACES trials [2, 4, 5], antibiotics were associated with a significantly increased mortality (1.20, 1.04–1.39) [2].

To examine the association between short-term clarithromycin and long-term mortality, we did an extended follow-up of the CLARICOR patients. Further, we updated our meta-analyses to examine the effect of antibiotics on mortality in patients with coronary heart disease.

**Methods**

CLARICOR is a randomized, placebo-controlled, blinded, parallel-group multicenter trial in patients with stable coronary heart disease [2, 6]. The Copenhagen Trial Unit handled all administrative functions, including centralized randomization, communication with blinded outcome assessors, and contact with database managers. The patients were enrolled at five academic cardiology departments in Copenhagen.

The central hospital database of Copenhagen enabled us to identify all patients with a diagnosis of myocardial infarction and/or angina pectoris (ICD 209–219) during the years 1993–1999. Patients, aged 18–85 years, were invited for an interview at one of the five cardiology units. The exclusion criteria have previously been described [2, 6]. Ethical approval was given by the local ethics committee (KF 01-076/99), the Danish Medicines Agency (2612-975), and The Danish Data Protection Agency (1999-1200-174).

**Randomization and Interventions**

Eligible patients were stratified according to sex, prior myocardial infarction, age below 60 years, and center and were randomly assigned to oral clarithromycin (Klacid Uno®, Abbott, UK) 500 mg or matching placebo once daily for 2 weeks [2, 6]. Four thousand three hundred and seventy-two patients were randomized between October 5, 1999 and April 15, 2000: 2,172 to clarithromycin and 2,200 to placebo. The intervention groups were well matched with the exception of smoking habit [2].

**Treatment Diary, Outcomes, and Follow-Up**

More than 90% of the patients in each arm reported taking at least 13/14 tablets prescribed during the trial [2]. Clarithromycin was well tolerated during and just after its administration [2]. A blinded search of the Danish Central Civil Register records for the vital status of the participants was carried out on December 5, 2005. The Register has almost 100% validity. The search more than doubled our observation time and forms the basis of the extended follow-up. The participants that were still alive were informed about the results of the trial.

**Statistical Analyses and Meta-Analyses**

SAS statistical package version 6.12–8 was used for the statistical analyses. The hazard ratios and their confidence intervals are based on a Cox regression model, which according to the protocol included sex, prior myocardial infarction, age, and center as covariates. All covariates not well matched at randomization (i.e., smoking) [2] and information on medication and diabetes at entry holding prognostic information were introduced in exploratory analyses. Event curves were constructed according to the Kaplan-Meier method.

We updated our previous meta-analyses [2] with data from the extended follow-up of CLARICOR patients as well as data from new trials identified in January 2007 through searches in The Cochrane Library, PubMed, and EMBASE according to our protocol [7]. Meta-analyses followed the Cochrane Collaboration methodology [7], including Review Manager [8] for calculation of relative risks with 95% CI with random-effect models and inconsistency (I²) as a measure of heterogeneity [9].

**Results**

The mean follow-up from randomization was 5.9 years (range 5.7–6.2 years). In the clarithromycin group 13 patients (0.6%) and in the placebo group 15 patients (0.7%) were censored due to emigration or disappearance. Of
the remaining 99.4% of the patients, survival status was known.

All-Cause Mortality
As of December 5, 2005, 923/4,372 (21.1%) patients had died. The number of deaths among clarithromycin patients was 497/2,172 (22.9%) compared with 426/2,200 (19.4%) among placebo patients. This difference is significant during the first 2.6-year follow-up (univariate hazard ratio 1.26, 1.03–1.54, p = 0.024) (fig. 1) and during the 6-year follow-up (univariate hazard ratio 1.21, 1.06–1.38, p = 0.004) (fig. 2). The excess mortality was uniform over time (fig. 3). The increased mortality corresponds to one death during 6 years of follow-up out of 22 patients (13–70 patients) treated with clarithromycin.

Table 1 shows the number of patients dying in the clarithromycin group and the placebo group stratified according to sex, age, prior myocardial infarction, diabetes, and smoking habits at entry. In all subgroups, the proportion of patients dying in the clarithromycin group was larger than in the placebo group.

Multivariate Analyses
The increased mortality risk in the clarithromycin group persists in the multivariate analysis including sex, age, prior myocardial infarction, and center as covariates (1.20, 1.06–1.37, p = 0.0048). When smoking status at entry was added as an additional covariate, the increased mortality risk in the clarithromycin group also
persists (1.18, 1.04–1.35, p = 0.0108). We observed similar odds ratios for death comparing clarithromycin versus placebo in never-smokers, ex-smokers, and current smokers. Further analyses demonstrated that only few of the extra deaths in the clarithromycin group could be ascribed to smoking (data not shown). The hazard ratio remains stable when additional adjustments were made for the following eight binary entry covariates: use of digoxin; diuretics; ACE inhibitors; antiarrhythmics; long-acting nitrates and diabetes (all associated with poor prognosis), and use of acetylsalicylic acid and statins (both associated with favorable prognosis) (1.18, 1.03–1.35, p = 0.015).

**Meta-Analyses**

Figure 4 shows the updated meta-analysis including data from the 11 randomized trials from the meta-analysis of Andraws et al. [1] and the Berg et al. [3], ISAR-3 [10], Parachure et al. [11], Brown et al. [12], Radoi et al. [13], and CLARICOR trials. We were unable to obtain mortality data from one trial including 141 patients [14].

The 17 randomized trials randomized 12,643 patients to antibiotics and 12,628 patients to placebo or no intervention. The number of deaths was 1,877. The corresponding overall relative risk ratio is 1.10 (1.01–1.20, p = 0.02) without heterogeneity ($I^2 = 0\%$), favoring placebo or no intervention (fig. 4).

We found no significant difference between our CLARICOR mortality data (1.18, 1.05–1.33) compared to those of the other 16 trials (1.02, 0.90–1.16) in a test of interaction ($z = 1.65$, nonsignificant).

Two other trials on clarithromycin for coronary heart disease patients have been published [3, 15]. Meta-analyzing these data with our present data shows a statistically significant increased mortality in the clarithromycin group compared with the placebo group (1.19, 1.06–1.33, p = 0.004) without heterogeneity ($I^2 = 0\%$) (data not shown). The intervention effect of clarithromycin in these trials seemed more pronounced than in the remaining 14 trials on other antibiotics (1.01, 0.89–1.15), but the difference was not significant ($z = 1.78$).

Meta-analysis of the three trials that followed patients for more than 2 years, i.e., PROVE-IT [4], ACES [5], and CLARICOR, showed that antibiotics are associated with significantly increased mortality (1.17, 1.06–1.29, p = 0.002) without heterogeneity ($I^2 = 0\%$) (data not shown).

**Discussion**

According to our findings, short-term intervention with clarithromycin seems to be associated with a significantly increased long-term mortality in patients with stable coronary heart disease. Our findings persist after multivariate adjustment. Furthermore, our findings are supported by analyses of subgroups, which all had higher mortality in the clarithromycin group compared with the placebo group. The results of our updated meta-analyses may potentially incriminate all antibiotics given to patients with stable coronary heart disease and acute coronary syndromes. Clarithromycin (or potentially antibiotics at large) may cause the detrimental effect by interfering with the host-parasite balance. *Chlamydia pneumoniae* replicate in monocytes in atherosclerotic lesions and secure their local persistence by inhibiting host cell apoptosis [16]. A short clarithromycin course may not eradicate *C. pneumoniae* from the monocytes [17, 18]. On the contrary, clarithromycin may induce apoptosis of infected monocytes [19–21]. This could lead to enhanced release of viable *Chlamydia* into the bloodstream and dissemination of infection. This may increase inflammation and aggravate the cardiovascular disease, which eventually leads to death. The reason why this detrimental effect has not been noticed

### Table 1. Six-year all-cause mortality in subgroups of patients with stable coronary heart disease treated with clarithromycin or placebo

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Clarithromycin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>148/658 (22.4)</td>
<td>122/681 (17.9)</td>
</tr>
<tr>
<td>Male</td>
<td>349/1,514 (23.0)</td>
<td>304/1,519 (20.1)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below 60 years</td>
<td>70/640 (10.9)</td>
<td>45/663 (6.7)</td>
</tr>
<tr>
<td>At or above 60 years</td>
<td>427/1,532 (27.8)</td>
<td>381/1,537 (24.7)</td>
</tr>
<tr>
<td><strong>Prior myocardial infarction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>124/702 (17.6)</td>
<td>123/706 (17.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>373/1,470 (25.3)</td>
<td>303/1,494 (20.2)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>405/1,831 (22.1)</td>
<td>341/1,863 (18.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>92/341 (26.9)</td>
<td>85/337 (25.2)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>65/372 (17.5)</td>
<td>66/435 (15.2)</td>
</tr>
<tr>
<td>Previous</td>
<td>218/891 (22.2)</td>
<td>192/1,012 (18.9)</td>
</tr>
<tr>
<td>Current</td>
<td>214/819 (26.1)</td>
<td>168/753 (22.3)</td>
</tr>
</tbody>
</table>

1 One surviving placebo-treated patient lacked information on diabetes status and is included in the no diabetes mellitus group.
may be due to too short a follow-up time in previous randomized trials.

**Strengths and Limitations**

Our trial offers several strengths, including its size, the long follow-up time, and the high number of outcomes. These components should reduce random errors. One may get the impression that it takes 12–24 months before the intervention curves depart. In fact, we observed a constant increase in mortality in the clarithromycin-treated patients, with minimal fluctuation during the first 18 months. This can be ascribed to too few outcomes occurring during this period. The central randomization, the placebo-controlled intervention coupled with blinded outcome assessment, and intention-to-treat analyses [2] should have reduced systematic errors [22–24]. Furthermore, follow-up was via public registers, ensuring few losses. We looked exclusively at all-cause mortality, which should not carry the interpretative difficulties that are often encountered with cardiovascular composite outcomes [25].

Even if we adjust our univariate \( p = 0.004 \) for previous analyses of our primary, secondary, and tertiary outcomes as well as our previous mortality analysis, we find a significant detrimental effect of clarithromycin. However, we cannot of course exclude the possibility of random errors. For completeness, further information on physical and medical status at randomization and chang-

**Fig. 4.** Intervention effect of different antibiotics versus placebo or no intervention on mortality of patients with coronary heart disease. CI = Confidence interval; n = number of patients with outcome; N = number of participants at risk; d.f. = degrees of freedom; \( I^2 \) = percentage of total variation across studies that is due to heterogeneity rather than chance. Relative risks are plotted (black squares with area proportional to the amount of statistical information in each trial) comparing outcome among participants allocated to antibiotic with those allocated to placebo or no intervention, alongside their 95% CI (horizontal lines). For totals, the result and its 95% CI are represented by a diamond with the relative risk and 95% CI given alongside. Squares or diamonds to the right of the solid vertical line indicate harm from antibiotics. This is conventionally significant (\( p < 0.05 \)) only if the horizontal line or diamond does not overlap the solid vertical line.

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Ref. No.</th>
<th>Antibiotics n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parachure et al., 2002</td>
<td>11</td>
<td>0/20</td>
<td>0/20</td>
<td>not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown et al., 2004</td>
<td>12</td>
<td>1/26</td>
<td>0/24</td>
<td>0.07</td>
<td>2.78 (0.12, 65.08)</td>
<td></td>
</tr>
<tr>
<td>Leowattana, 2001</td>
<td>from 1</td>
<td>1/43</td>
<td>1/41</td>
<td>0.09</td>
<td>0.95 (0.06, 14.75)</td>
<td></td>
</tr>
<tr>
<td>Gupta et al., 1997</td>
<td>30</td>
<td>1/40</td>
<td>1/20</td>
<td>0.10</td>
<td>0.50 (0.03, 7.59)</td>
<td></td>
</tr>
<tr>
<td>CLARIFY, 2002</td>
<td>from 1</td>
<td>4/74</td>
<td>1/74</td>
<td>0.15</td>
<td>4.00 (0.46, 34.95)</td>
<td></td>
</tr>
<tr>
<td>ROXIS, 1999</td>
<td>from 1</td>
<td>2/102</td>
<td>5/100</td>
<td>0.27</td>
<td>0.39 (0.08, 1.97)</td>
<td></td>
</tr>
<tr>
<td>Academic, 1999</td>
<td>from 1</td>
<td>5/150</td>
<td>4/152</td>
<td>0.42</td>
<td>1.27 (0.35, 4.63)</td>
<td></td>
</tr>
<tr>
<td>Stamina, 2002</td>
<td>from 1</td>
<td>5/111</td>
<td>5/107</td>
<td>0.49</td>
<td>0.96 (0.29, 3.24)</td>
<td></td>
</tr>
<tr>
<td>Radoi et al., 2003</td>
<td>13</td>
<td>7/68</td>
<td>5/41</td>
<td>0.61</td>
<td>0.84 (0.29, 2.49)</td>
<td></td>
</tr>
<tr>
<td>Berg et al., 2005</td>
<td>3</td>
<td>10/238</td>
<td>9/235</td>
<td>0.91</td>
<td>1.10 (0.45, 2.65)</td>
<td></td>
</tr>
<tr>
<td>ISAR-3, 2001</td>
<td>from 1</td>
<td>16/506</td>
<td>13/504</td>
<td>1.37</td>
<td>1.23 (0.60, 2.52)</td>
<td></td>
</tr>
<tr>
<td>AZACS, 2003</td>
<td>from 1</td>
<td>23/716</td>
<td>29/723</td>
<td>2.46</td>
<td>0.80 (0.47, 1.37)</td>
<td></td>
</tr>
<tr>
<td>ANTIBIO, 2003</td>
<td>from 1</td>
<td>28/431</td>
<td>26/437</td>
<td>2.66</td>
<td>1.09 (0.65, 1.83)</td>
<td></td>
</tr>
<tr>
<td>PROVE-IT, 2005</td>
<td>from 1</td>
<td>64/2,076</td>
<td>50/2,086</td>
<td>5.34</td>
<td>1.29 (0.89, 1.85)</td>
<td></td>
</tr>
<tr>
<td>ACES, 2005</td>
<td>from 1</td>
<td>142/2,004</td>
<td>133/2,008</td>
<td>13.66</td>
<td>1.07 (0.85, 1.34)</td>
<td></td>
</tr>
<tr>
<td>WIZARD, 2003</td>
<td>from 1</td>
<td>175/3,866</td>
<td>188/3,856</td>
<td>17.61</td>
<td>0.93 (0.76, 1.14)</td>
<td></td>
</tr>
<tr>
<td>CLARICOR, 2007</td>
<td>present trial</td>
<td>497/2,172</td>
<td>426/2,200</td>
<td>53.77</td>
<td>1.18 (1.05, 1.33)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>12,643</td>
<td>12,628</td>
<td>100.00</td>
<td>1.10 (1.01, 1.20)</td>
<td></td>
</tr>
<tr>
<td>Total events:</td>
<td></td>
<td>981 (antibiotics), 896 (control)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Test for heterogeneity: \( \chi^2 = 10.34, \) d.f. = 15 (\( p = 0.80 \)), \( I^2 = 0\% \)

Test for overall effect: \( Z = 2.31 \) (\( p = 0.02 \))
es in medical treatment or life style during follow-up could have been sought. However, we find it unlikely that these factors should differ substantially in the two intervention groups. The only difference recorded at entry was a small difference in smoking status [2]. Taking this difference into consideration did not modify our results noticeably. In fact, the overrepresentation of current smokers in the clarithromycin group could only account for some few extra deaths and we observed very similar relative risk ratios of clarithromycin versus placebo in the subgroups of never-smokers, ex-smokers, and current smokers (table 1). When one factor is not fully balanced, other unaccounted factors could be out of balance. We cannot exclude this possibility, but at least four arguments speak against it. We found no inconsistency among the trials of our meta-analyses. \( I^2 \) was 0%. \( I^2 \) is the percentage of between-trial variability that is due to true differences between trials (heterogeneity) rather than sampling error (chance). The estimates of intervention effect in the CLARICOR trial or the three clarithromycin trials were not significantly different from that observed in meta-analyses of the remaining trials. Our results are in accordance with the results of other antibiotic trials with long-term follow-up.

**Comparison with Related Research**

Several randomized trials on clarithromycin, azithromycin, roxithromycin, spiramycin, gatifloxacin, or doxycycline for coronary heart disease patients have been published [1–3, 10–15]. Our meta-analysis shows that antibiotics irrespective of type, duration of treatment, dose, and duration of follow-up are associated with a significantly increased mortality. This effect was seen both in patients with stable coronary heart disease and in patients with acute coronary syndromes, although it only reached for-
tice error (chance). The estimates of intervention effect in the CLARICOR trial or the three clarithromycin trials were not significantly different from that observed in meta-analyses of the remaining trials. Our results are in accordance with the results of other antibiotic trials with long-term follow-up.

Duration of follow-up is critical. If we had stopped follow-up within 2 years, we could have had an insignificant result as most other trials did. If we pool the data of the three trials following patients for more than 2 years, antibiotics are associated with significantly increased mortality. The CLARICOR trial randomized less than 19% of the patients in the meta-analyses including all trials, but carries more than 53% of the weight due to the high occurrence of outcomes.

Our previously blinded adjudication of 384 deaths identified cardiovascular causes as responsible for the increased mortality [2]. This increases the likelihood that the observed association is causal compared to a finding of a diffuse increase in all causes of mortality. Macrolides possess potassium channel blocker properties, which may increase the risk of torsades de pointes tachycardia and sudden death [26]. We observed no differences in cardiovascular mortality during the treat-
ment itself or during the first months of follow-up [2]. As stressed above, the excess mortality was uniform over time and we found no significant association between time and the increase in mortality. As suggested, antibiot-
ics might interfere unfavorably with the host-parasite balance in atherosclerotic lesions and result in thrombotic events. The US FDA has reacted with concern to our trial result [27], and so has the EU EMEA. The Danish Medicines Agency, however, found no reason for concern [28]. They conducted a prescription study of pa-
tients on regular acetylsalicylic acid, comparing clari-

**Conclusions**

A short clarithromycin course for patients with stable coronary heart disease was associated with significantly (\( p = 0.004 \)) more deaths during long-term follow-up of patients living in Copenhagen. Updated meta-analyses of randomized trials suggest that this detrimental effect may involve antibiotics at large (\( p = 0.02 \)). These \( p \) values are too small to be ignored and more importantly so is the direction of the effect of antibiotics. At the same time, the \( p \) values are not small enough to completely exclude the risk of random errors. Accordingly, more data are needed. Until such data have been scrutinized we urge the public and health care workers to consider that we have observed the detrimental effect among patients who are not nor-

**Antibiotics for Coronary Heart Disease Patients**

Cardiology 2008;111:280–287
Antibiotics for patients with coronary heart disease may be yet another intervention area [29] where initial small positive trials [30, 31] led to false hopes, numerous large trials, and negative conclusions [32, 33]. The initial trials also generated a plethora of proposed disease mechanisms. Only future studies can tell if too little or too much antibiotic has been used [32, 34]. The links between antibiotics, inflammation, and atherothrombosis may be more complicated than previously perceived [34].

Acknowledgments

We thank The Danish Heart Foundation, The Copenhagen Hospital Corporation, The Danish Research Council, and the 1991 Pharmacy Foundation for unrestricted grants. The clarithromycin and placebo tablets were supplied by Abbott Laboratories, IDC, Queensborough, UK. We thank Jørn Weterslev for help during the inspection of the CLARICOR Trial. We thank Mariana Radi and Ioana Agashe for providing us with 4-year mortality data from their randomized trial.

Funding: The CLARICOR Trial is investigator initiated and controlled. This work was supported by grants from nonprofit funds (The Danish Heart Foundation, The Copenhagen Hospital Corporation, The Danish Research Council, and The 1991 Pharmacy Foundation). Abbott Laboratories, IDC, Queensborough, UK supplied the clarithromycin and placebo tablets. Those supporting the trial had no role in design, data collection, data analyses, data interpretation, or writing the report. The Steering Group had full access to all the data and had final responsibility for the decision to submit the report for publication.

References


Appendix

Contributors: HJK had the original idea for the trial. The Steering Committee consisted of CG (chair), JFH, PH, GBJ, JK, HJK, IL, HN, and CMJ. CG, JFH, PH, GBJ, JK, IL, HN, and CMJ were principle investigators. BA-N, MD, LP, SH, and OHH were clinical investigators. CG and CMJ were coordinating investigators. CG and CMJ drafted the protocol. CG and JH drafted this report. CG is guarantor. EK was chairman of the Event Committee. JH was member of the independent Data Monitoring and Safety Committee and conducted the statistical survival analyses assisted by Per Jensen and Christian Piper. CG conducted the meta-analyses. Of the contributors who are not listed as authors Jette Mieritz (Amager Hospital), Lene Thuesen (Bispebjerg Hospital), Hanne Larsen, Per Nielsen, Merethe Hildebrandt (Frederiksberg Hospital), Mette Bommerholdt (Hvidovre Hospital), and Lone Kristensen (Rigshospitalet) were study nurses. Jette V Petersen and Pia Hughes coordinated the trial data accrual and data entry. Bitten Hansen, Ninna Frydendahl, Bessie Hedholdt, Karen Juliusen, and Mette Hansen executed data accrual. Kjell Niillson and Nader Salas developed the randomization system and the data management systems. Nader Salas was responsible for data management. The independent Data Monitoring and Safety Committee was chaired by Kristian Thygesen (Århus, Denmark) with John Kjekshus (Oslo, Norway) and JH (Copenhagen, Denmark) as members. Stig Haunso (Rigshospitalet, Copenhagen, Denmark), Rolf Steffensen (KAS Gentofte, Hellerup, Denmark), and Thorkild I.A. Sørensen (Institute of Preventive Medicine, Copenhagen, Denmark) advised the Steering Group during the planning of the trial.
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