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Clinical research

Effect of fixed low-dose warfarin added to aspirin in the long term after acute myocardial infarction
the LoWASA Study

Johan Herlitz[a]*, Johan Holm[b], Magnus Peterson[c], Björn W. Karlson[a], Maria Haglid Evander[a], Leif Erhardt[b], for the LoWASA study group

[a] *Division of Cardiology, Sahlgrenska University Hospital, Göteborg, Sweden*
[b] *Department of Cardiology, Malmö University Hospital, Malmö, Sweden*
[c] *Medical Department, Lidköping Hospital, Lidköping, Sweden*

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Aim To evaluate whether long-term treatment with a fixed low dose of warfarin in combination with aspirin improves the prognosis compared with aspirin treatment alone after an acute myocardial infarction (AMI).
Methods Patients who were hospitalized for AMI were randomized to either 1.25 mg of warfarin plus 75 mg of aspirin (n=1659) daily or 75 mg of aspirin alone (n=1641). The study was performed according to the PROBE (Prospective Open Treatment and Blinded End Point Evaluation) design and was conducted at 31 hospitals in Sweden. The median follow-up time was 5.0 years. In the aspirin+warfarin group, 30.2% were permanently withdrawn as opposed to 14.0% in the aspirin group (P<0.0001). Analyses were performed on an intention-to-treat basis.
Results The combination of cardiovascular death, reinfarction or stroke was registered in 28.1% in the aspirin+warfarin group versus 28.8% in the aspirin group (NS). Cardiovascular deaths occurred in 14.2% in the aspirin+warfarin group vs 15.7% in the aspirin group (NS). Whereas no difference was found with regard to total mortality or reinfarction, those randomized to aspirin+warfarin had a reduced occurrence of stroke (4.7% vs 7.1%; P=0.004). The percentage of patients who suffered a serious bleed was 1.0% in the aspirin group vs 2.2% in the combination group (P=0.0006).
Conclusion A fixed low dose of warfarin added to aspirin in the long term after AMI did not reduce the combined risk of cardiovascular death, reinfarction or stroke. The results did, however, indicate that a fixed low dose of warfarin added to aspirin reduced the risk of stroke, but this was a secondary end point. The combination of aspirin and warfarin was associated with an increased risk of bleeding.

Introduction

During the past two decades, we have learnt that a modification of various parameters in the coagulation system might improve the prognosis for patients after an acute coronary syndrome.[1] Of these modes of treatment, the use of warfarin in various dosages has attracted attention.[1] Recent studies have shown that high- or medium-intensity, dose-adjusted oral anticoagulation after an acute myocardial infarction[2–4] and an acute coronary syndrome[5] is associated with an improved prognosis. High intensity was used when anticoagulation was given alone and medium intensity was used when anticoagulation was given in combination with aspirin. Moreover, combination therapy with medium intensity dose adjusted warfarin and aspirin has been shown to be effective in reducing recurrent ischaemic events.[6] Experience indicates that low-dose warfarin is less

* Corresponding author: Johan Herlitz, Assoc. Prof., Division of Cardiology, Sahlgrenska University Hospital, SE-413 45 Göteborg, Sweden. Tel.: +46-31-342-1000; Fax: 46-31-829650
E-mail address: johan.herlitz@hjl.gu.se (J. Herlitz).

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successful.[7] The rationale for using low-dose warfarin was that several studies have shown that coagulation factor VII (F VII) is an epidemiological risk factor for myocardial infarction.[8] F VII plays a crucial part in the initiation of thrombus formation, as it is activated by tissue factor in endothelial plaques. Vitamin K-dependent coagulation factor VII, as well as prothrombin and factors IX and X, are reduced by warfarin. In a pilot study, we observed that plasma FVII levels could be reduced by 1.25 mg of warfarin daily, although INR/PT was within the normal range.[9]

Previous experience indicate that a dose adjusted low-dose of warfarin added to aspirin proved beneficial effect in the setting of primary prevention.[10] Such a regime would not require regular check-ups. One previous secondary prevention trial studied the impact of a fixed low-dose of warfarin which did not prove beneficial.[7]

The LoWASA trial (low-dose warfarin and aspirin), planned in the early 1990s, aimed to evaluate whether long-term treatment with warfarin at a fixed dose of 1.25 mg added to 75 mg of aspirin was superior to 75 mg of aspirin alone when given after an acute myocardial infarction. Our hypothesis was that a combination of this kind might reduce the risk of cardiovascular events without the necessary regular checkups for international normalized ratio values. The LoWASA trial is only the second trial in the secondary prevention to address this issue. Moreover, the dose of aspirin in both arms is similar, in contrast to CARS.[7] Therefore LoWASA really tests the impact of the addition of fixed low dose warfarin.

Patients and methods

In all, 31 hospitals in Sweden participated in the study. The first patient was randomized as 940208 and the last patient as 990224. All the patients were followed until 1 November 2000.

Inclusion criteria

1 Hospitalization for AMI according to set criteria within 42 days prior to randomization

Exclusion criteria

1 Indication of full-dose anticoagulation
2 Unwillingness to participate
3 Inability to participate
4 Contraindications for anticoagulants and aspirin
5 Participation in other studies
6 Expected survival less than one month (for example, terminal heart failure)
7 Other disease associated with shorter survival, such as cancer, severe renal failure and so on
8 Daily treatment with non-steroidal anti-inflammatory drugs

Primary end-points

1 Cardiovascular event (cardiovascular death or reinfarction or stroke)
2 Cardiovascular death

For a definition of primary end-points, see below.

Secondary end-points

1 Total mortality
2 Reinfarction
3 Stroke
4 Transitory cerebral ischaemic attack or reversible ischaemic neurological deficit
5 Hospitalization
6 Need for CABG and PTCA
7 Tolerability

Predefined subgroups

1 Patients who received thrombolysis for the index infarction
2 Patients with a history of diabetes
3 Patients prescribed a beta blocker
4 Patients aged 75 years or less and patients aged more than 75
5 Patients treated for congestive heart failure while in hospital
6 Patients with signs of residual myocardial ischemia (angina pectoris, ischemia at exercise test, scintigraphic evaluation or Holter monitoring)
7 Patients with previously known or recently developed atrial fibrillation

Practical performance

Patients were included as soon as possible after the AMI diagnosis was confirmed but after 42 days at the latest. The study was performed according to the PROBE (PRospective Open and Treatment Blind End Point Evaluation) design. All the end-points were, therefore, evaluated by a blinded end-point committee. As soon as the patient had given verbal and written informed consent and there were no contraindications, he/she was randomized via telephone or fax contact with the randomization centre in Göteborg, Sweden. Treatment was then started with either 75 mg of aspirin daily or a combination of 75 mg of aspirin and 1.25 mg of warfarin daily. The coagulation activity was measured as the prothrombin complex (factors II, VII and X) prior to and two to four weeks after randomization. Among patients with a value of less than 40% of normal at the two- to four-week control, the dose of warfarin was halved. No further prothrombin complex controls were required according to the protocol.

The patients were to continue on randomized treatment until 935 validated end-points were reached.

Withdrawal of study medication

The withdrawal of study medication took place if intolerable side-effects occurred or if the patient was incapable of or unwilling to continue the treatment. Patients who developed unstable angina pectoris or a reinfarction or underwent coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angio-plasty (PTCA) continued with the treatment with only a temporary withdrawal at the time of PTCA and CABG. There was no contraindication for thrombolysis due to the study treatment.

Study size

Based on previous experience, it was calculated that 30% of the patients who received aspirin would have a primary end-point during a three-year period. The study was dimensioned so that significance would be achieved with a two-sided test at the 5% level with 90% power if only 25% of the patients who received the

combination therapy developed an end-point during the same time period; a normal-theory-based test for binominal distribution was therefore assumed. According to these assumptions, 3400 patients needed to be randomized. The number of calculated end points was: 0.30×1700+0.25×1700=935. The study would continue until 935 end-points were reached.

Descriptive statistics
The distribution of variables is given as the means±standard deviation and percentages.

Statistical analyses
For comparisons of dichotomous variables between groups, Fisher's exact test was used. For comparisons between groups relating to continuous variables, Fisher's non-parametric permutation test[11] was used. With regard to primary and secondary end-points and withdrawals, Kaplan–Meier estimates and the log-rank test were used. A *P*-value of <0.05 was regarded as significant for primary end-points. With regard to secondary end-points, withdrawal and all other comparisons, a *P*-value of <0.01 was regarded as significant. All analyses were performed on an intention-to-treat basis.

Definitions

Index myocardial infarction
Two of the three following criteria had to be fulfilled:

1 Pain suggesting AMI
2 Elevated enzyme activity more than twice the upper normal limit for a myocardial specific enzyme
3 Development of Q-waves in at least two leads on a 12-lead standard ECG

Reinfarction
The same criteria were used for reinfarction as for index myocardial infarction. In addition, patients with atypical symptoms (pulmonary oedema, cardiogenic shock or syncope) in combination with elevated enzymes or Q-waves were classified as having a reinfarction. No patient was randomized within 24 h after hospital admission and there was therefore no need for us to consider reinfarction within 24 h after hospital admission.

Haemorrhagic stroke
The development of a focal neurological deficit with a duration of more than 24 h associated with a bleed verified on a CT scan.

Non-haemorrhagic stroke
The development of a focal neurological deficit with a duration of more than 24 h in association with a CT scan without any sign of a bleed.

Undetermined stroke
The development of a focal neurological deficit with a duration of more than 24 h without performing a CT scan.

A focal neurological deficit was defined as any of the following
One- or two-sided motor disturbance
One- or two-sided sensitivity disturbance
Aphasia or dysphasia
Hemianopsia
Deviation conjugee
Diplopia
Apraxia
Ataxia
Perception disturbance

Table 1 Baseline characteristics (%)

	Aspirin *n*=1641	Aspirin+warfarin *n*=1659	*P*[a]
1. Age (years)			
Mean±SD	66±11	66±11	–
2. Gender			
Women	25	28	–
Men	75	72	–
3. Previous history			
Myocardial infarction	24	23	–
Angina pectoris	34	36	–
Hypertension	33	35	–
Diabetes mellitus	13	13	–
Heart failure	7	7	–
Stroke	5	4	–
Atrial fibrillation	6	5	–
PTCA	2	2	–
CABG	4	4	–
Smoking	45	44	–

[a] *P*-value denoted if <0.05.

Serious bleeding complication
A bleed requiring transfusion or a bleed requiring hospitalization.

A less serious bleeding complication
All other reported bleeds.

Performance

Patients were randomized via telephone or fax at the co-ordination centre in Göteborg. All the end-points were sent to the co-ordination centre in Göteborg, where information relating to study drug treatment was blinded.

All the relevant data relating to end-points were then sent to the end-point committee for evaluation. The result of this evaluation was then sent to the safety committee.

Assessment of death
Death during follow-up was ascertained according to the National Registry of Deaths. The mode of death was described according to death certificates and hospital records.

Cardiovascular deaths were defined if death was judged to be primarily caused by cardiovascular disease.

Cardiac death was defined if death was primarily caused by cardiac disease.

Results

In all, 3300 patients were randomized, 1641 to aspirin alone and 1659 to the combination of aspirin plus warfarin. The number of patients randomized at the 31 centres varied from 479 to two. No patient was lost to follow-up.

Table 1 shows the age, gender and previous history of the two groups, while Table 2 shows the type of

Table 2 Type of infarction, treatment in hospital prior to randomization, complications in hospital prior to randomization and medication at discharge

	Aspirin *n*=1641 %	Aspirin+warfarin *n*=1659 %	*P*[a]
Presence of Q-waves (12)[b]	49	48	–
Anterior ([12])	32	35	–
Inferior ([12])	44	42	–
Other ([12])	25	25	–
Treatment in hospital prior to randomization			
Thrombolysis ([1])	42	44	–
PTCA	4	4	–
CABG	0.8	1.2	–
Complications in hospital prior to randomization			
Heart failure	23	23	–
Atrial fibrillation	7	7	–
Recurrent ischemia ([11])	26	28	–
Medication at discharge ([9])			
Beta blockers	84	86	–
Calcium channel blockers	11	10	–
ACE inhibitors	32	32	–
Lipid-lowering drugs	17	17	–

[a] *P*-value denoted if <0.05.
[b] Number of patients with missing information.

infarction, treatment and complications in hospital prior to randomization and medication at discharge. No differences were found.

The mean follow-up time was identical for both treatment groups, median 5.0 years (range 1.7–6.7 years). The percentage of patients who were temporarily withdrawn was 5.5% for the aspirin group and 6.8% for the aspirin-warfarin group (NS). Table 3 shows the percentage of patients who were permanently withdrawn for various reasons. With regard to withdrawal due to the need for anticoagulants, the most common reason was arrhythmias (aspirin 2.1% and aspirin+warfarin 2.2%); (NS), followed by unstable angina pectoris (aspirin 2.0% and aspirin+warfarin 1.8%); (NS) and stroke (aspirin 2.3% and aspirin+warfarin 1.3%); (*P*=0.030).

The mean prothrombin complex prior to randomization was 99.4±20.1% in the aspirin group versus 100.3±21.3% in the aspirin–warfarin group (NS).

The corresponding values two to four weeks later were 99.4±25.1% and 95.5±25.2% respectively (*P*<0.0001).

End-points

Table 4 shows the percentage of patients who developed primary and secondary endpoints. No difference was found between the groups with regard to primary end-points. When it came to secondary end-points, there was no difference in total mortality or the rate of reinfarction. However, patients randomized to the combination of aspirin plus warfarin developed stroke less frequently than patients randomized to aspirin alone. A difference was found for non-haemorrhagic stroke and stroke of undetermined aetiology. Other secondary end-points including revascularization did not differ between the groups with the exception of rehospitalization for cardiovascular disease, which tended to be lower in the aspirin+warfarin group (*P*=0.048).

Bleeding

The percentage of patients who had a less serious bleed was 2.6% in the aspirin group vs 5.8% in the aspirin-warfarin group (*P*=0.0001). The percentage of patients who suffered a serious bleed was 1.0% in the aspirin group vs 2.2% in the combination group (*P*=0.006). Of the latter, five (0.3% of all patients) in the aspirin group and 10 (0.6% of all patients) in the combination group had a haemorrhagic stroke. So slightly fewer than one third of the serious bleeds were haemorrhagic strokes. None of them were fatal (died within 14 days after onset of stroke).

Cause of death

Of all deaths, 78% had a cardiovascular aetiology, 69% had a cardiac aetiology, 12% were caused by cancer and 5% were caused by a stroke.

Predefined subgroups

There was no difference with regard to primary end points in any of the seven predefined subgroups.

Discussion

We tested the hypothesis that the combination of a fixed low dose of warfarin without INR controls, in combination with a low dose of aspirin, was superior to aspirin alone, when given long term after AMI. The results will be discussed in terms of primary end-points, secondary end-points, safety, study design and clinical implications.

Primary end-point

A fixed low dose of warfarin without INR monitoring did not protect patients from the combination of cardiovascular death, reinfarction or stroke. These findings are in good agreement with recent experience.

Fixed low-dose warfarin trials

No studies post myocardial infarction[7] or after an acute coronary syndrome[12] or in patients with non-rheumatic valvular disease[13] have shown that a regimen of this kind has a beneficial effect.

In spite of a dose of warfarin known to affect factor VII,[9] no effects have been demonstrated.

Dose-adjusted trials with an INR of <2.0

Among post-myocardial infarction patients, warfarin therapy at a mean INR of 1.8 (25–75th percentiles 1.4–2.2) combined with a low dose of aspirin did not produce any clinical benefit greater than that produced by aspirin monotherapy.[14] Nor was such a regimen (mean INR of 1.4) shown to reduce the progression of atherosclerosis in

Table 3 Reasons for withdrawal

	Aspirin *n*=1641		Aspirin+warfarin *n*=1649		*P*
	n	%	*n*	%	
Uncomplicated bleeding	29	1.8	91	5.5	<0.0001
Complicated bleeding	9	0.6	20	1.2	–
Other intolerability	31	1.9	84	5.1	<0.0001
Requirement of full-dose warfarin	132	8.0	113	6.8	0.15
Unwillingness to continue	17	1.0	83	5.0	<0.0001
Other reason	42	2.6	144	8.7	<0.0001
In all	230	14.0	501	30.2[a]	<0.0001

[a]A few patients had more than one reason for withdrawal.

Table 4 Primary and secondary end-points

	Aspirin *n*=1641		Aspirin+warfarin *n*=1649		*P*
	n	%	*n*	%	
Primary end-points					
Cardiovascular death, reinfarction or stroke	473	28.8	466	28.1	0.67
Cardiovascular death	257	15.7	236	14.2	0.27
Secondary end-points					
Total mortality	323	19.7	311	18.8	0.52
Reinfarction	268	16.3	283	17.1	0.54
Stroke	116	7.1	78[a]	4.7	0.004
Haemorrhagic	5	0.3	10	0.6	0.20
Non-haemorrhagic	82	5.0	56	3.4	0.016
Undetermined	29	1.8	13	0.8	0.016
TIA, RIND	35	2.1	30	1.8	0.57
CABG	340	20.7	311	18.8	0.15
PTCA	141	8.6	154	9.3	0.39
Rehospitalization for cardiovascular etiology (1583, 1596)[b]	964	60.9	916	57.4	0.048

[a]One patient had one haemorrhagic and one non-haemorrhagic stroke.
[b]Refers to the number of patients in whom this variable was evaluated.

grafts after coronary artery bypass grafting.[15] In the same study, warfarin treatment was not associated with improved survival during the treatment period (mean 4.3 years). However, during an extended follow-up (mean 7.5 years), patients who were treated with warfarin during the first four years had significantly lower long-term mortality.[16] Finally, in a primary prevention trial, treatment with warfarin (mean INR 1.47; interquartile ranges 1.41–1.54) was associated with a lower risk of ischemic heart disease (IHD) events, particularly fatal IHD events.[10]

Dose-adjusted trials with an INR of >2.0

In a number of studies, it has been shown that, after either a myocardial infarction or an acute coronary syndrome, a regimen of this kind helps to improve the prognosis. For example, in the WARIS I study, treatment with warfarin alone (INR 2.8–4.8) resulted in a lower mortality rate and a lower rate of reinfarction than placebo.[2]

In the APRICOT 2 trial, treatment with warfarin (median INR 2.6; 25–75th percentiles 2.1–3.1) added to aspirin markedly reduced reocclusion and recurrent events during a period of three months after successful fibrinolysis, as compared with aspirin alone.[4]

In the ASPECT 2 study, treatment with high-intensity oral anticoagulants (INR 3.0–4.0; mean of 3.2) alone or aspirin+medium-intensity anticoagulants (INR 2.0–2.5; mean of 2.4) was more effective than aspirin alone in reducing subsequent cardiovascular events after acute coronary syndromes.[5]

However, the results in a smaller study of moderate-intensity oral anticoagulation (INR 2.0–2.5) alone or in combination with a low dose of aspirin were not superior to those for a low dose of aspirin in the prevention of recurrent ischemic events in patients with

non-ST-elevation acute coronary syndromes and previous CABG.[17]

In the WARIS II trial, treatment with high-intensity anticoagulants (INR 2.8–4.2, mean 2.8) alone or the combination of aspirin+medium-intensity anticoagulants (INR 2.0–2.5, mean 2.2) was more effective than aspirin alone in reducing cardiovascular events during four years of follow-up after acute myocardial infarction.

Finally, in the OASIS pilot study, long-term treatment with moderate-intensity warfarin (INR 2.0–2.5, mean 2.3)+aspirin appeared to reduce ischemic events during a period of three months after an acute coronary syndrome.[12]

So, after an acute coronary syndrome or myocardial infarction, only dose-adjusted treatment with warfarin with an INR of >2.0 has been shown to be beneficial.

The fact that the positive results of the addition of oral anticoagulation are predominantly seen in trials that clearly affected the INR suggests that the impact is related to interference in the coagulation cascade at a level lower than factor VII (such as factor IX, X and prothrombin). An alternative hypothesis is that with a low fixed dose of warfarin, the reduction of factor VII activity is not substantial enough for a protective effect on further thromboembolic events. Other possible contributing factors to the lack of effect of a fixed low dose warfarin on primary end-points might have been the late initiation of treatment since patients were allowed to be randomised up to 42 days after the onset of infarction. Previous experience indicate that many recurrent ischaemic events occur within the first months post STEMI.[18] A final contributing factor to the lack of effect might have been the fact that the study included a relatively low risk group of post myocardial infarction patients. As a result, only 13% had a history of diabetes and only slightly more than 30% had an anterior myocardial infarction.

Secondary end-points

We found no significant difference between groups with respect to total mortality, reinfarction, need for revascularization and need for rehospitalization for cardiovascular reasons. However, there was a significant reduction in strokes in the group randomized to aspirin plus warfarin (P=0.004). A difference was found for non-haemorrhagic stroke and stroke of undetermined aetiology, whereas haemorrhagic strokes occurred slightly more often in the aspirin-warfarin group. As similar results have not been demonstrated in previous studies and, as it was a secondary end-point, this finding has to be interpreted with care. It is only possible to speculate about whether the mechanisms behind reinfarction and non-haemorrhagic stroke are different. Among patients suffering from stroke, it may be the case that a plaque rupture, followed by the activation of the platelets, is not as common as it is among patients suffering from a reinfarction.

In the CARS study, 160 mg of aspirin was found to result in lower stroke rates than the combined regimen of 80 mg of aspirin and 1 mg of warfarin. In LoWASA, the dose of aspirin in both arms of the trial was low and similar in size. These observations suggest that, in patients on low-dose aspirin after myocardial infarction, more aggressive antithrombotic treatment (either more aspirin, or the addition of anticoagulants) may have an impact on the prevention of non-haemorrhagic stroke.

Safety

Serious bleeds were more than twice as common in the aspirin-warfarin group as they were in the aspirin group. This indicates that even treatment with a fixed low dose of warfarin modifies the coagulation system and increases the risk of bleeding. It must be emphasized that the prothrombin complex was reduced from 100% to 95% two to four weeks after the start of treatment, which might explain the increased risk of bleeding. The occurrence of serious bleeds was higher than that reported in previous studies.[7,9] The withdrawal rate was more than twice as high in the combination group compared with the aspirin group. In terms of withdrawal due to intolerability, there were two reasons which were significantly more frequent in the aspirin-warfarin group: less serious bleeding and loss of hair. In the interpretation of these findings, it must be remembered that only the end-point committee was blinded and not the investigators. This might have influenced the reporting of various complications possibly associated with the study drug.

Design

This study was performed according to the PROBE design, i.e the treatment was open but the end-point evaluation was blinded. The major weakness of a design like this is the risk of bias for both the patient and the treating physician. Various symptoms regarded as possibly being associated with the drug treatment might, therefore, be falsely over-reported in the aspirin-warfarin group. Another major weakness of the trial was its very long duration; some patients were in the trial for almost seven years. This increases the risk of the withdrawal of study medication. Furthermore, during such a long period, changes in treatment routines take place, making the interpretation of the study results more difficult.

Limitations

1 The trial was powered to detect a difference in cardiovascular events. It was, therefore, underpowered to detect a difference in cardiovascular deaths.
2 Originally, there were plans to analyse all hospitalizations during follow-up. However, due to a lack of capacity, we were only able to analyse rehospitalization for cardiovascular etiology in a subset of patients.
3 The study included a relatively low-risk group of post-myocardial patients. As a result, only 13% had a history of diabetes and only slightly more than 30% had had an anterior infarction.
4 Patients were allowed to be randomized up to 42 days after the onset of infarction. Previous experience

indicates that many recurrent ischaemic events occur within the first month post STEMI.[18]

Conclusions and implications

Low-dose warfarin added to aspirin in the long term after AMI: (1) did not reduce the risk of the combination of cardiovascular death, reinfarction or stroke; (2) reduced the risk of stroke, although this was only a secondary end-point and; (3) was associated with an increased risk of bleeding.

Although our data suggest that patients may be protected from the development of stroke, this result needs to be confirmed in further trials and the LoWASA trial does not support the use of low-dose warfarin added to aspirin after AMI.

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Appendix A

Organisation

Steering committee: Leif Erhardt, chairman, Malmö University Hospital, Malmö, Sweden, Johan Herlitz, co-ordinator, Sahlgrenska University Hospital, Göteborg, Sweden, Johan Holm, Malmö University Hospital, Malmö, Sweden.

End-point committee: Kurt Boman, Jan-Håkan Jansson, Skellefteå Hospital, Skellefteå, Sweden.

Safety committee: Marianne Hartford, Sahlgrenska University Hospital, Göteborg, Sweden, Hans Wedel, Nordic School of Public Health, Göteborg, Sweden.

Practical co-ordinator: Maria Haglid Evander, Sahlgrenska University Hospital, Göteborg, Sweden.

Investigators

Per Brunmark, Ulf Forsman, Arvika Hospital; Per-Åke Moström, Barbro Lundqvist, Borås Hospital; Johan Herlitz, Sahlgrenska Hospital, Göteborg; Anette Lehto, Gällivare Hospital; Cornel Pater, Gerth Stehn, Hässleholm Hospital; Folke Rönn, Kalix Hospital; Claes Lagerstedt, Steen Jensen, Per Westerlund, Karlshamn Hospital; Ragnar Watz, Nils-Göran Alin, Kristinehamn Hospital; Karin Davidsson, Niklas Stenersen, Kungälv Hospital; Peter Nicol, Ortwin Herterich, Köping Hospital; Jan Kjellberg, Magnus Peterson, Lidköping Hospital; Tommy Fraser, Lena Rondahl, Lindesberg Hospital; Karl-Axel Svensson, Per-Åke Johansson, Ljungby Hospital; Anita Bjurman, Lycksele Hospital; Leif Erhardt, Johan Holm, Malmö Hospital; Lars Klintberg, Per-Åke Moström, Mölndal Hospital; Lennart Sikén, Rebecca Undén-Göransson, Norrtälje Hospital; Anders Dahlberg, Nyköping Hospital; Lars Svennberg, Sandviken Hospital; Arne Rindner, Skene Hospital; Ingrid Fagerström, Sollefteå Hospital; Claes Ringqvist, Torbjörn Sundelin, Sundsvall Hospital; Dieter Mohaupt, Hans Präntare, Söderhamn Hospital; Fridtjof Wandel, Kurt G Olsson, Strömstad Hospital; Bodil Gunnarsson, Tord Juhlin, Trelleborg Hospital; Björn W Karlson, Uddevalla Hospital; Arina Richter, Sven Erik Bysell, Visby Hospital; Britt Rasmussen, Ängelholm Hospital; Olof Lövheim, Bengt Göran Lundholm, Örnsköldsvik Hospital; Torgny Karlsson, Övertorneå Health Centre; Olof Lövheim, Östersund Hospital.

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