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A COMPARISON OF SIX WEEKS WITH SIX MONTHS OF ORAL ANTICOAGULANT THERAPY AFTER A FIRST EPISODE OF VENOUS THROMBOEMBOLISM

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Abstract Background. The optimal duration of oral anticoagulant therapy after a first episode of venous thromboembolism is still a matter of debate.

Methods. We performed a multicenter trial comparing six weeks of oral anticoagulant treatment with six months of such therapy in patients who had a first episode of venous thromboembolism. Anticoagulant therapy consisted of warfarin or dicumarol. Of the 902 patients enrolled, 5 were later excluded because they had congenital protein C deficiency; 443 were randomly assigned to receive six weeks of oral anticoagulant therapy with a targeted international normalized ratio (INR) of 2.0 to 2.85, and 454 were randomly assigned to receive six months of such therapy. The initial diagnoses were confirmed by means of venography in cases of deep-vein thromboses (n = 790) and with perfusion-ventilation scanning or angiography in cases of pulmonary embolism (n = 107); recurrences were confirmed in the same way.

Results. After two years of follow-up, there had been 123 recurrences of venous thromboembolism that met the diagnostic criteria, 80 in the six-week group (18.1 percent; 95 percent confidence interval, 14.5 to 21.6) and 43 in the six-month group (9.5 percent; 95 percent confidence interval, 6.8 to 12.2). The odds ratio for recurrence in the six-week group was 2.1 (95 percent confidence interval, 1.4 to 3.1). There was no difference in mortality or the rate of major hemorrhage between the six-week and six-month groups.

Conclusions. Six months of prophylactic oral anticoagulation after a first episode of venous thromboembolism led to a lower recurrence rate than did treatment lasting for six weeks. The difference between the two groups occurred between 6 weeks and 6 months after the start of treatment, and the rates of recurrence remained nearly parallel for 1½ years thereafter. (N Engl J Med 1995;332:1661-5.)

DEEP-VEIN thrombosis has a reported annual incidence of about 1.6 per 1000 in urban populations.¹ The incidence of first episodes of pulmonary embolism in acute care hospitals in the United States has been estimated to be 0.23 per 1000.² For both these problems, secondary prophylaxis with oral anticoagulants is routinely given. This practice is based on a retrospective study by Coon et al.³ and on subsequent randomized trials in which the incidence of recurrence was

26 to 29 percent over 12 weeks if the initial treatment with heparin was followed only by ineffective prophylaxis with heparin (as indicated by a subsequent study using adjusted-dose heparin)^{4,5} or, for calf-vein thrombosis, by no prophylaxis at all⁶; there were no recurrences in the groups that received effective anticoagulation.^{4,6}

The optimal length of secondary prophylaxis has been a matter of debate. Several randomized studies conducted between 1972 and 1988 addressed this issue.⁷⁻¹⁰ Although the results seemed to indicate that it was possible to shorten the duration of anticoagulation from three or six months to three to six weeks without increasing the risk of recurrence, the studies were too small for this conclusion to be reached with certainty. A retrospective study of 2400 cases also recommended a reduction in the duration of anticoagulation,¹¹ but because of the wide variation in the duration of treatment and the lack of data on diagnostic procedures, the evidence for such a conclusion was weak. More recently, a multicenter study found fewer recurrences after three months of anticoagulation than after four weeks.¹² This study has been criticized, however, because objective

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*The investigators and institutions participating in the Duration of Anticoagulation (DURAC) Trial Study Group are listed in the Appendix.

confirmation of the initial diagnosis was not obtained for all patients and because less than half of the presumed recurrences were confirmed.¹³ On the basis of a decision analysis, it was recently suggested that 2.5 to 4 months of anticoagulation, depending on the risk of bleeding, would be optimal.¹⁴

This trial was designed to compare six weeks of oral anticoagulant therapy after a first episode of deep-vein thrombosis or pulmonary embolism with six months of such therapy. The outcomes measured were the rates of recurrence, hemorrhagic complications, and death. In this article, we present data on these end points over two years of follow-up.

METHODS

Study Design

The Duration of Anticoagulation (DURAC) Trial was a randomized, open trial of anticoagulation in patients with a first episode of venous thromboembolism, in which 16 centers in central Sweden participated. Consecutive patients at least 15 years of age who had acute pulmonary embolism or deep-vein thrombosis in the leg, the iliac veins, or both were enrolled.

The diagnosis of deep-vein thrombosis was based on the results of venography, according to the method of Rabinov and Paulin.¹⁵ One of the following criteria had to be present for the diagnosis to be confirmed: a constant, well-defined filling defect; abrupt discontinuation of the contrast-filled column at a constant level in the vein; or an absence of filling in the entire deep venous system or parts of it, without evidence of an external, compressing process, with or without diversion of the venous flow through collateral vessels.

The diagnosis of pulmonary embolism was based on the results of angiography or of the combination of chest radiography and perfusion-ventilation lung scanning. The scans had to demonstrate a ventilation-perfusion mismatch along with one of the following: lobar, wedged (i.e., triangular and pointing inward) perfusion defects; segmental, wedged perfusion defects; or at least two subsegmental, wedged defects, each occupying more than 50 percent of a segment. If pulmonary embolism was strongly suspected on clinical grounds but the perfusion defects were matched by radiographic infiltrates smaller than the perfusion defects, or if the retention of xenon was diffuse, pulmonary angiography was required for confirmation. Any case of combined deep-vein thrombosis and pulmonary embolism was classified as deep-vein thrombosis.

The grounds for exclusion from the study were as follows: a diagnosis of deep-vein thrombosis or pulmonary embolism that did not fulfill the criteria described above; unavailability of the patient for follow-up; pregnancy; allergy to warfarin or dicumarol; an indication for continuous oral anticoagulation (e.g., an artificial heart valve or chronic atrial fibrillation); permanent, total paresis of the affected leg; arterial insufficiency of the same leg that was graded at functional class III (pain at rest) or worse, constituting a contraindication to the use of compression stockings; a current or previous venous ulcer; cancer; and unwillingness to give oral informed consent. Patients who had had more than one thromboembolic event were also excluded. Furthermore, enrolled patients were later excluded from the analysis if the results of the initial biochemical screening revealed congenital deficiency of antithrombin, protein C, or protein S.

Randomization took place at the end of the hospitalization and was performed centrally. Patients were assigned according to a computer-generated allocation schedule in blocks of 10 to receive oral anticoagulation for either six weeks or six months; the length of therapy was counted from the date when stable prothrombin times within the target range had been achieved.

Anticoagulant Therapy

The initial treatment of the venous thromboembolism consisted of unfractionated or low-molecular-weight heparin administered intravenously or subcutaneously for at least five days, until a prothrombin time within the target range had been achieved. If it was thought to

be indicated by the treating physician, thrombolytic therapy could be given initially. Patients with deep-vein thrombosis were provided with a graded compression stocking (grade III) and instructed to wear it on the affected leg during the day for at least one year.

Oral anticoagulation with warfarin sodium (Waran, Nycomed, Oslo, Norway) or dicumarol (Apekumarol, Ferrosan, Malmö, Sweden) was usually started at the same time as heparin. Oral anticoagulation was targeted to an international normalized ratio (INR) of 2.0 to 2.85, partly on the basis of a pilot study that found an excess of hemorrhagic complications in patients with INRs above that range.¹⁶ The prothrombin times were analyzed with the Stago Prothrombin-Complex Assay (Diagnostic Stago, Paris) or Nycotest PT (Nycomed); the reagents used in these assays have international sensitivity indexes of 0.86 to 0.98 and 0.95 to 1.00, respectively, according to the manufacturers. We introduced a quality-control program, described elsewhere,¹⁷ to ensure that patients treated at different centers received therapy of a comparable intensity. When a stable prothrombin time within the target range had been achieved, the test was repeated weekly for the first three weeks and then at least once every four weeks. Effective anticoagulation in each individual case was defined as an INR of more than 2.0 in at least 75 percent of the tests for that patient. Oral anticoagulation was terminated without tapering after the randomly assigned treatment period, usually at the time of a follow-up visit.

Before anticoagulation was begun, we obtained plasma samples from patients less than 50 years of age and those with a family history of venous thromboembolism for measurement of antithrombin, protein C, and protein S. The antithrombin assay was performed with a method using a chromogenic substrate to measure the activity of antithrombin. Protein C was also measured with an activity method, and protein S (total and free fraction) with an immunochemical assay. Commercial kits were used for all these measurements.

The patients were instructed not to take analgesics containing aspirin and, if antiinflammatory treatment was required, to use only ibuprofen. All the patients were informed about the symptoms of deep-vein thrombosis and pulmonary embolism. They were told to report immediately to the emergency room of their medical center if any such symptoms occurred and were asked to report all hemorrhagic complications. Follow-up visits to one of the investigators or a specially trained nurse or physiotherapist were scheduled at 1.5, 3, 6, 9, 12, and 24 months after the target prothrombin time was reached. At each visit the patients were asked about new symptoms of venous thromboembolism and, if they were still receiving oral anticoagulation, about possible hemorrhage. They were also reminded of the symptoms of deep-vein thrombosis and pulmonary embolism and asked again to come to the emergency room if such symptoms developed and to report bleeding episodes.

End Points

The principal end points of the trial were major hemorrhage during oral anticoagulation and death or recurrent venous thromboembolism during the two-year study period. Major hemorrhage was defined by conditions requiring hospitalization, treatment with blood products or vitamin K, or both hospitalization and treatment. Recurrent thromboembolic events were objectively verified by the same methods as the index events. In addition, for a recurrent deep-vein thrombosis to be included in our analysis, the patient had to have one of the following: thrombus in the other leg or another deep vein of the same leg as the original thrombus or thrombus in the same venous system as the original event and either a proximal extension of at least 5 cm if the upper limit of the original thrombus had been visualized or, if the upper limit of the original thrombus had not been determined, the presence of a constant filling defect surrounded by contrast medium. Recurrent pulmonary embolism was considered to be indicated by defects in previously perfused areas, unless another scan since the initial episode had demonstrated resolution of the original defects. Cases of fatal pulmonary embolism were verified by autopsy. Initial and repeat venograms and lung scans in patients with confirmed or unconfirmed recurrent deep-vein thrombosis or pulmonary embolism, respectively, were interpreted by an independent radiologist who was blinded to the patients' treatment assignments and the dates of the examinations.

The names of patients lost to follow-up were repeatedly cross-

checked with the Swedish Death Registry; no deaths were missed. Names were also checked against the registry of hospitalizations; ascertainment of recurrences or major hemorrhage is almost certainly complete.

An independent safety committee reviewed the number of patients included and the numbers of major end points twice during the study.

Statistical Analysis

All statistical analyses were performed on an intention-to-treat basis, although some patients in both groups received oral anticoagulation for shorter or longer periods than called for in the protocol, and some turned out after randomization to have cancer. The statistical methods used were Wilcoxon's rank-sum test and the log-rank test (the Lifetest procedure in SAS software) and the chi-square test for two groups. Ninety-five percent confidence intervals are shown for all results. The study was approved by the regional and local ethics committees.

RESULTS

The first patient was enrolled on April 12, 1988, and the last on April 18, 1991. By then, 902 patients had been randomly assigned to treatment, but 5, who proved to have congenital protein C deficiency, were removed from the study and received long-term anticoagulant therapy. No congenital protein S or antithrombin deficiency was detected.

The log books of patients evaluated but excluded from the trial were available at 12 of the 16 centers (where 708 of the 902 patients [78 percent] were enrolled). At these 12 hospitals, 1185 patients were evaluated and 60 percent of these were enrolled. At the beginning of the trial, seven patients with extensive deep-vein thrombosis were excluded in violation of the protocol, because the physician did not wish them to be assigned to six weeks of therapy. The investigators were informed about these violations; no similar violations occurred later in the trial. Fourteen eligible patients were not enrolled, in most cases because of lack of time.

Of the 897 patients remaining in the study after the exclusion of those with congenital protein C deficiency, 443 were randomly assigned to six weeks of treatment and 454 to six months. The treatment groups were similar at entry (Table 1), except that fewer patients in the six-week group had previously received thrombolytic therapy. Since the total number of patients who received such therapy was very small, this difference had a negligible influence on the results.

In the 6-week group, one patient received treatment for a shorter period than intended (0.5 month shorter) and seven received treatment for a longer period (0.5 to 6.5 months longer); in the 6-month group, nine patients received a shorter period of treatment (1 to 5 months shorter) and seven patients a longer period (1 to 18 months longer). In each group, the mean duration of treatment was increased by less than 0.1 month per patient by these deviations from the protocol.

During the two years of follow-up, 39 patients died and 44 dropped out. Since the follow-up period ended, however, we have been able to collect information about deaths and hospitalizations among these patients from computer registries as well. The principal end

Table 1. Characteristics of the Patients at Enrollment, According to the Length of Treatment.

| CHARACTERISTIC | 6 WEEKS (N = 443) | 6 MONTHS (N = 454) |
|--|----------------------|-----------------------|
| Mean (\pm SD) age (yr) | 61.1 \pm 14.4 | 60.6 \pm 15.4 |
| | <i>no. (%)</i> | |
| Male sex | 247 (56) | 257 (57) |
| Initial pulmonary embolism | 56 (13) | 51 (11) |
| Initial deep-vein thrombosis | 387 (87) | 403 (89) |
| Proximal thrombosis | 211 (55) | 232 (58) |
| Permanent or unknown risk factor* | 266 (60) | 287 (63) |
| Subsequent cancer | 31 (7) | 23 (5) |
| Family history of venous thromboembolism | 72 (16) | 64 (14) |
| Received thrombolytic therapy | 5 (1)† | 17 (4)† |
| Received low-molecular-weight heparin | 20 (5) | 16 (4) |
| Oral anticoagulant therapy effective‡ | 287 (65) | 259 (59) |
| Lost to follow-up | 23 (5) | 21 (5) |

*Permanent risk factors were defined as venous insufficiency, systemic lupus erythematosus, and idiopathic venous thromboembolism, and temporary risk factors as surgery, trauma, temporary immobilization, travel, the receipt of estrogen medication, infection, Baker's cyst, and pregnancy.

† $P = 0.02$ for the comparison between groups.

‡Effective anticoagulant therapy was defined as an INR of ≥ 2.0 in 75 percent or more of the prothrombin-time tests. The numbers tested were 439 in the six-week group and 442 in the six-month group.

points are shown in Table 2. There was no significant difference in mortality or in the incidence of major hemorrhage between the two treatment groups. The major hemorrhages consisted of three episodes of intracranial bleeding (one of which occurred in the six-week group and two in the six-month group), an episode of severe epistaxis requiring hospitalization in the six-month group, a gastrointestinal hemorrhage probably related to diverticulosis in a patient in the six-month group that required outpatient treatment with vitamin K, and an episode of bleeding in joints and muscles that was treated with vitamin K in the hospital, also in the six-month group. Three of the patients with hemorrhagic complications were receiving excessive anticoagulation at the time of admission (INR, 4.0 to 5.6). None of the hemorrhages were fatal.

Five of the recurrent thromboembolic events were fa-

Table 2. Principal End Points after Two Years, According to the Length of Treatment.

| END POINT | 6 WEEKS (N = 443) | 6 MONTHS (N = 454) | ODDS RATIO (95% CI)* | P VALUE |
|------------------------------|----------------------|-----------------------|-------------------------|---------|
| | <i>no. (%)</i> | | | |
| Major hemorrhage | 1 (0.2)† | 5 (1.1) | 0.2 (0.0–1.7) | 0.23 |
| Recurrence | | | | |
| All cases | 90 (20.3) | 49 (10.8) | 2.1 (1.4–3.1) | <0.001 |
| Fulfilling criteria | 80 (18.1) | 43 (9.5) | 2.1 (1.4–3.1) | <0.001 |
| Month >0–1.5 | 3 (0.7) | 4 (0.9) | | |
| Month >1.5–6 | 42 (9.5) | 2 (0.4) | | |
| Month 6–24 | 35 (7.9) | 37 (8.1) | | |
| In hospitals with log books‡ | 62 (17.8) | 32 (9.0) | 2.2 (1.4–3.4) | <0.001 |
| Death | 22 (5.0) | 17 (3.7) | 1.3 (0.7–2.6) | 0.46 |

*Odds ratios are expressed as the ratio of the number of patients with the specified end point to the number of patients without that end point in the six-week group, divided by the corresponding ratio in the six-month group. CI denotes confidence interval.

†There were no additional hemorrhages between six weeks and six months.

‡A total of 349 patients were treated in hospitals with log books in the six-week group, as were 356 patients in the six-month group.

tal, two in the six-week group and three in the six-month group. The diagnoses were established by lung scanning in one case, and by autopsy in four cases. In an additional patient who died suddenly 10 days after total hip replacement, the diagnosis was not objectively confirmed and thus did not fulfill our criteria. Four of these six patients also had cancer.

Of the 123 recurrent events during the two years of follow-up, 101 occurred in patients with initial deep-vein thrombosis — ipsilateral thrombosis (n=33), contralateral thrombosis (n=44), or pulmonary embolism (n=24). The remaining 22 thromboembolic events, which occurred in patients who initially had pulmonary embolism, consisted of emboli (n=14) or thrombosis (n=8). There were 16 additional recurrences, all but 1 of which were evaluated with objective diagnostic procedures and which did not fulfill our criteria for recurrence; 10 were in the six-week group and 6 in the six-month group. Although the evidence for progression on venography or lung scanning was doubtful or lacking in those cases, the clinical picture was so suggestive of a recurrence that the physician in charge felt obligated to treat the patient. The addition of these cases to the analysis did not change the P values or the odds ratios in this study.

Only two of the recurrences (one in each group) were detected at a follow-up visit; five occurred during subsequent hospitalizations, and the remainder when the patients came to the emergency room because of new symptoms a median of 44 days (range, 3 to 334) after a follow-up visit. In 18 patients in the six-week group and 14 in the six-month group who came to the emergency room with new symptoms, venograms or lung scans showed no evidence of a recurrence.

There was a significant difference in the incidence of recurrent venous thromboembolism between the six-week group (18.1 percent; 95 percent confidence interval, 14.5 to 21.6 percent) and the six-month group (9.5 percent; 95 percent confidence interval, 6.8 to 12.2 percent; $P<0.001$). The cumulative probability of a recurrent event is shown in Figure 1. In the six-week group there was a sharp increase in the rate of recurrence immediately after the cessation of oral anticoagulant therapy. This increase seemed to stabilize as a

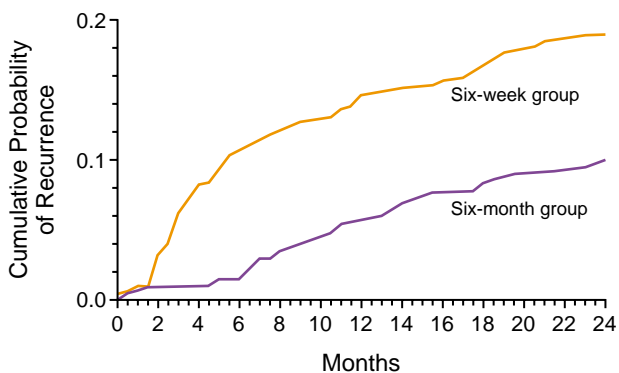


Figure 1. Cumulative Probability of Recurrent Venous Thromboembolism after a First Episode, According to the Duration of Anticoagulation.

Table 3. Two-Year Incidence of Recurrent Thromboembolism in Subgroups of the Study Population, According to the Length of Treatment.

| CHARACTERISTIC OF SUBGROUP | 6 WEEKS | 6 MONTHS | ODDS RATIO (95% CI)* | P VALUE |
|----------------------------------|--|-----------|----------------------|---------|
| | <i>no. with recurrence (% of subgroup)</i> | | | |
| Temporary risk factor† | 15 (8.6) | 8 (4.8) | 1.9 (0.8–4.5) | 0.24 |
| Permanent risk factor† | 65 (24.2) | 35 (12.1) | 2.3 (1.5–3.6) | <0.001 |
| Initial pulmonary embolism | 15 (26.8) | 7 (13.7) | 2.3 (0.9–6.2) | 0.15 |
| Initial deep-vein thrombosis | 65 (16.8) | 36 (8.9) | 2.1 (1.3–3.2) | 0.002 |
| Distal thrombosis | 20 (11.4) | 10 (5.8) | 2.1 (0.9–4.5) | 0.10 |
| Proximal thrombosis | 45 (21.3) | 26 (11.2) | 2.1 (1.3–3.6) | 0.006 |
| Family history | 11 (15.3) | 10 (15.4) | 1.0 (0.4–6.8) | 0.83 |
| No family history | 69 (18.6) | 33 (8.5) | 2.5 (1.6–3.8) | <0.001 |
| Effective oral anticoagulation | 49 (17.1) | 29 (11.2) | 1.6 (1.0–2.7) | 0.065 |
| Ineffective oral anticoagulation | 29 (19.1) | 12 (6.6) | 3.4 (1.6–6.8) | <0.001 |

*Odds ratios are expressed as the ratio of the number of patients with recurrent events to the number of patients without such events in the six-week group, divided by the corresponding ratio in the six-month group. CI denotes confidence interval.

†Risk factors were defined as in the first footnote to Table 1.

linear increase six months after discharge from the hospital. In the six-month group, the rate of recurrence was steady after the cessation of anticoagulation — a pattern similar to that in the six-week group at the same time.

Secondary prophylaxis with six months instead of six weeks of oral anticoagulants reduced the risk of recurrence by approximately 50 percent in almost every subgroup of patients (Table 3). The 42 patients in the six-week group who had a recurrence during the first six months had the same characteristics as the other patients with recurrent events. The combination of temporary risk factors and distal thrombosis occurred in 79 patients in the six-week group and 81 in the six-month group; these groups had 1 and 4 recurrences, respectively, during the two years. The small number of patients does not allow any conclusion regarding equivalence, however.

DISCUSSION

We found a significant reduction in the risk of recurrent thromboembolism when the duration of oral anticoagulant therapy was extended from six weeks to six months after a first episode of venous thromboembolism. There was clearly a lower incidence of recurrent events from the second to the sixth month in the six-month group. Only thereafter was the monthly incidence fairly constant and similar to the pattern in the six-week group after the cessation of anticoagulation. This finding suggests a high level of thrombogenic activity that continues for at least six months after the first event; the results thus support the use of six months of anticoagulation. Further clarification of the optimal duration of anticoagulant therapy should come from the ongoing *Durée Optimale du Traitement Anti-Vitamine K (DOTAVK)* trial, in which patients with proximal deep-vein thrombosis are randomly assigned to three or six months of prophylaxis.

Our study was sufficiently large to demonstrate a benefit of prolonged anticoagulation in several sub-

groups as well as in the six-month group as a whole. The risk of major hemorrhage was low and did not differ significantly between the two groups. There were no fatal hemorrhages during a total of 282 patient-years of oral anticoagulation. A 1992 review of hemorrhagic complications during oral anticoagulation reported major hemorrhages in 2.0 to 16.7 percent of the patients.¹⁸ The reason for the low incidence in our study could be the relatively low target range of 2.0 to 2.85 for the INR.

Four randomized studies on the duration of anticoagulation published between 1972 and 1988 suggested that short- and long-term treatment had equal efficacy.⁷⁻¹⁰ The multicenter trial of the Research Committee of the British Thoracic Society came to a different conclusion and found that three months of secondary prophylaxis gave better results than four weeks of prophylactic therapy.¹² The difference, however, was not statistically significant if only recurrences that were objectively confirmed were included. It was also concluded, on the basis of one recurrence in each group, that postoperative thromboembolism necessitated only four weeks of anticoagulation, but the statistical power of the study was too low for a definitive conclusion to be reached.

In our study the long-term outcome for patients with venous thromboembolism was discouraging, since there was no difference in the incidence of recurrent events in the two groups from 6 to 24 months after the initial episode. There was a linear increase in the cumulative risk, corresponding to 5 to 6 percent annually. It is thus important that venous thromboembolism be considered not a one-time event but, rather, part of an ongoing condition in which there is a definite risk of recurrence.

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APPENDIX

The DURAC Trial Study Group consisted of the following investigators (the number of patients enrolled at each institution is shown in parentheses): *Danderyd Hospital, Danderyd* (83): A. Carlsson, C. Gustafsson, and A. Gröndahl; *Huddinge Hospital, Huddinge* (129): A.-S. Rhedin, E. Törnebohm, M. Johansson, and D. Lockner; *Karolinska Hospital, Stockholm* (115): S. Schulman, P. Lindmarker, and H. Johnsson; *Köping Hospital, Köping* (62): P. Nicol, J. Kobosko, B. Malmros, N. Arcini, and J. Saaw; *Nacka Hospital, Stockholm* (59): E. Loogna and R. Stig; *Norrköping Hospital, Norrtälje* (41): S. Viering; *Nyköping Hospital, Nyköping* (48): B. Ljungberg, S. Wilhelmsson, and Å. Ohlsson; *Sabbatsberg Hospital, Stockholm* (47): H. Walter, K. Malmqvist, and F. Al-Khalili; *St. Göran Hospital, Stockholm* (36): B. Leijd

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