A sudden increase in Factor VIII inhibitor development in multitransfused hemophilia A patients in the Netherlands

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The development of antibodies to factor VIII (inhibitors) in response to clotting-factor concentrates administration in hemophilia is common during the first few years of treatment but rare in multitransfused patients. We have investigated the possible association of a recently introduced factor VIII concentrate (Factor VIII CPS-P) in The Netherlands with the occurrence of inhibitors. To this effect, we conducted two studies. First, we performed a national multicenter study in which clinical information and inhibitor test results were obtained for 447 hemophilia A patients over the period 1988 through 1991. Secondly, for a baseline comparison we estimated the frequency of inhibitor development in a closely followed cohort of 144 patients, from 1984 through 1989. Before the introduction of Factor VIII CPS-P, the incidence of new inhibitors was 4.4/1,000 patient-years in the national study from March 1988 through May 1990, and 3.9/1,000 patient-years in the cohort followed from 1984 through 1989. These figures are similar to the incidence of new inhibitors that was found in a large cohort of patients in the United States followed in the 1970s. In the period that the new concentrate Factor VIII CPS-P was on the market, from June 1990 through November 1991, 11 clinically relevant inhibitors were detected, which yielded an incidence over this interval of 20.1/1,000 patient-years, a 4.5-fold increase compared with the previous interval (CI95: 1.4 to 14.3). Nine of these 11 patients had in their lifetime received over 250 infusions with factor VIII preparations, whereas all of the inhibitors detected in the previous time interval, and all of the 24 inhibitor patients described in the US study, had received less than 250 infusions in their lifetime. All patients who developed inhibitors after June 1990 had been exposed to Factor VIII CPS-P, whereas only 75% of the patients who did not develop an inhibitor had been exposed to this product. In a prospective extension of the study, with a second inhibitor measurement after 3 months, we found that one additional inhibitor had developed during 52.5 patient-years of Factor VIII CPS-P use. In conclusion, there has been a sudden increase in the frequency of inhibitor patients, for a large part among multitransfused patients. It seems more than likely that this increase is associated with the introduction of a new factor VIII concentrate in The Netherlands. To avoid future and possibly larger epidemics of inhibitor development, physicians who treat hemophilia patients should perform inhibitor tests at regular intervals, especially when their patients change from one clotting factor preparation to another.

HEMOPHILIA A is a sex-linked hereditary bleeding disorder caused by a complete or partial deficiency of clotting factor VIII. In severe hemophilia (complete deficiency) bleeding occurs spontaneously, notably in joints and soft tissue In milder forms (partial deficiency) bleeding usually only results from trauma or surgery The disease predominantly affects men (approximately 20/100,000 live male births[1]), although in rare cases female carriers may prove symptomatic. Repeated bleeding in joints causes arthropathy that may lead to disability, whereas intracranial bleeding, intestinal tract bleeding, and traumatic bleeding may be fatal.[2]

In 1964 Pool et al[3] reported a simple method to purify factor VIII by cryoprecipitation from human plasma. This marked the beginning of the era of modern hemophilia treatment, in which the missing clotting factor is intravenously administered to either stop or prevent bleeding The availability of adequate replacement therapy has improved the life expectancy for severe hemophilia from less than 30 years before 1960 to a near-normal life span,[4,5] with accompanying improvements in physical condition and social circumstances.[6] These improvements have been set back by transmission of viruses through donated blood, especially hepatitis viruses and the human immunodeficiency virus (HIV) [7-9] Another major complication of hemophilia A treatment is the development of antibodies to factor VIII in some patients, the so-called inhibitors.[10,13] Inhibitors have been estimated to occur in 20% of all patients with severe hemophilia A,[14-17] although one recent study found an even larger risk of 52% in severe hemophilia A [18] Inhibitor formation greatly complicates therapy, because bleeding can no longer be effectively treated or prevented by factor VIII administration. This implies that inhibitor patients cannot fully enjoy the benefits of substitution therapy, and have a mortality that is higher than that of patients without inhibitors.[5]

Inhibitors usually develop in the early phase of treatment with clotting-factor preparations, in many cases after only a few infusions Once more than 100 to 250 infusions have been administered, inhibitor development appears to be rare.[13,19,20] Therefore, inhibitors are often detected at a young age, although occasionally transient inhibitors are detected in older multitransfused patients, usually without clinical sequelae [19] In a cohort of 1,306 hemophilia A patients of a US multicenter follow-up study on inhibitor development, inhibitors were detected in 31 patients, which yielded an incidence of 8/1,000 person-years.[19] Twenty-four of these in-

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hibitors were persistent (type A), whereas in seven patients transient inhibitors were found (type B) No inhibitors were found in patients who had received in their lifetime more than 250 infusions of factor VIII

The developments since the 1960s have led to the availability of more and more concentrated factor VIII products, factor VIII concentrates purified by monoclonal antibodies (MoAbs), and most recently, concentrates produced by recombinant DNA techniques [21 22] Concerns have been raised that these ultra-pure concentrates might entail an higher risk of inhibitor development compared with conventional concentrates [23 25] Because of the lack of comparable data, this issue remains unsettled at present, but it seems clear that the newest developments have at least not diminished the problem of inhibitor formation [21 25 28]

In 1990, a new plasma-derived pasteurized factor VIII concentrate (Factor VIII CPS-P) became licensed for hemophilia A treatment in The Netherlands, and was subsequently used to treat the majority of Dutch hemophilia A patients In 1991, we became aware of four patients who had developed inhibitors accompanied with severe clinical problems This was considered unusual, because these patients had received numerous infusions in their lifetime with several clotting factor preparations In addition, five recently discovered inhibitor patients were simultaneously reported by the hemophilia center in Leuven, Belgium, among 109 patients who were treated with Factor VIII CPS-P in a randomized trial [29] Several of these patients had received replacement therapy for many years before the occurrence of the inhibitor These reports of inhibitor patients were followed by additional reports from various hemophilia centers in The Netherlands

Because inhibitor development in multitransfused patients is rare, and an association with the introduction of a new factor VIII concentrate seemed relevant, we started a national study on the occurrence of inhibitors In addition, we have estimated retrospectively the incidence of inhibitors in a cohort of Dutch patients to obtain a baseline estimate for comparison and to avoid conclusions based solely on comparisons with experiences from other countries

MATERIALS AND METHODS

Hemophilia treatment in The Netherlands In The Netherlands, with a total population of almost 15 million inhabitants, there are approximately 1,100 patients with hemophilia A Sixty percent of these, ie, 600 to 700 patients, have severe (<1% factor VIII C) or moderately-severe (1% to 5% factor VIII C) hemophilia A and receive infusions with clotting factor preparations at more or less frequent intervals [1 6] The total national consumption of factor VIII for the treatment of hemophilia A is over 45 million IU per year [30] Until 1988, substitution treatment in hemophilia A consisted of small-pool dry-heat–treated cryoprecipitate and dry-heat–treated intermediate-purity concentrate, produced by regional blood banks and the Central Laboratory of The Netherlands Red Cross Blood Transfusion Service (CLB) These factor VIII products, produced from plasma of Dutch donors, covered most of the factor VIII need, whereas imported concentrates held a market share of 10% or less In March 1988, the CLB introduced a factor VIII concentrate to replace the previous concentrate Factor VIII CPS This concentrate was produced by a controlled-pore silica (CPS) adsorption technique developed in New Zealand [31] In May 1990, pasteurization in the fluid phase in the presence of a mixture of stabilizers replaced the dry-heat treatment as the method for virus inactivation,[32] and the product became known as Factor VIII CPS-P This concentrate contained about 1 U of factor VIII/mg protein Residual protein contamination consisted of fibrinogen, fibronectin, albumin, IgG gammaglobulins, and α_2-macroglobulin Factor VIII CPS-P became the almost solely used product for hemophilia A treatment in The Netherlands, because cryoprecipitate could not be pasteurized and was therefore not considered hepatitis C safe Consequently, in June 1991 cryoprecipitate lost its licence for the treatment of hemophilia A in The Netherlands Pasteurized Factor VIII CPS has, to our knowledge, only been used in The Netherlands and in Belgium

National study on recently developed inhibitors We asked the Dutch hemophilia treatment centers to supply us with clinical information and inhibitor test results of all their patients with hemophilia A who had been treated with human coagulation preparations since January 1, 1991 Clinical data included general information (date of birth, severity of hemophilia), the presence of overt clinical signs of an inhibitor, such as changes in type of bleeding or the response to treatment of bleeding (in which case an inhibitor was classified as clinically relevant), product (brand name and transfusion frequency), and inhibitor status (results of previous inhibitor tests, date of first detection) For product use, we asked information on two time periods March 1988 through May 1990 (period 1), and June 1990 through November 1991 (period 2), in which respective periods Factor VIII CPS and Factor VIII CPS-P had been on the market In all patients a Bethesda inhibitor test was performed for this national study by the classical method as described by Kasper et al [33]

In case of recently developed inhibitors, ie, after March 1988, we obtained additional information on the inhibitor titres, (cumulative) exposure days to factor VIII products before the inhibitor development, whether the inhibitor was detected because of clinical suspicion or routine investigations (or this study), whether the inhibitor had led to clinical symptoms, and whether the inhibitor had been persistent or transient The inhibitor tests of these patients were repeated and confirmed in one reference laboratory

We extended the study prospectively, by performing a second inhibitor test after 3 months in the non-inhibitor patients who had been exposed to factor VIII products during the interval

It has been shown that when a group of patients are tested on inhibitors, some patients will show low-titered inhibitors without any symptoms These inhibitors, that have been called type B,[19] may reflect an innocuous transient phenomenon, or a false-positive laboratory result In contrast, clinically relevant inhibitors (type A) are repeatedly detectable and usually have a higher titer [19] In case of a possible type B inhibitor, ie, a low-titer inhibitor without clinical symptoms, we repeated the inhibitor test after several weeks In our prevalence and incidence calculations we have restricted ourselves to clinically relevant inhibitors, ie, inhibitors that led to a decreased clinical response to treatment of bleedings

We analyzed the data separately for the two time periods that marked the introduction of Factor VIII CPS and the subsequent replacement by Factor VIII CPS-P Incidence rates were calculated by the patient-year method, by considering the patients reported on in the present as a cohort followed from March 1988 to the present Although this might lead to distortion because patients who died or were lost to follow-up between March 1988 and the present would be missing, we felt that the time frame was so short as to minimize this distortion Incidence rates were calculated as the ratio of the number of events over the patient-years of observation Confidence intervals (CI95) for the incidence rates were calculated under the assumption of a Poisson distribution, and for prevalence figures by the normal approximation of the binomial distribution Counts were compared by Fisher's exact tests and by chi-squared tests

Table 1 Patient Characteristics in the National Study and the Cohort 1984 Through 1989

	National Study (n = 447) n (%)	Cohort 1984 1989 (n = 144) n (%)
Severity of hemophilia		
Severe (<1% FVIII C)	292 (65)	99 (69)
Moderately-severe (1%-5% FVIII C)	74 (17)	26 (18)
Mild (5%-40% FVIII C)	81 (18)	19 (13)
Age distribution (yrs)		
0-5	33 (7)	18 (13)
6-10	36 (8)	15 (10)
11-15	37 (8)	15 (10)
16+	341 (76)	96 (67)
	Years	Years
Mean age (SD)	30 (17)	21 (13)
Age range	1-83	0-60

Retrospective cohort study on inhibitor development (cohort 1984 through 1989) We collected data on inhibitor measurements of all 240 patients with hemophilia A registered at the national hemophilia center Van Creveld Clinic and the University Hospital Utrecht, who were identified through the computer files on inhibitor tests Excluded were patients who were known to have (or have had) an inhibitor at the time of entry to the study (n = 23) or who had not been exposed to factor VIII during the study period (n = 73) The observation time for the remaining 144 patients was defined as the time from the first (negative) inhibitor test after January 1, 1984 until either the last negative test before January 1, 1990 or the first positive test (before January 1, 1990) A level exceeding 1 0 BU/mL was considered as a positive inhibitor test

RESULTS

National study on recently developed inhibitors Thirty-four centers reported 475 hemophilia A patients for our study and had performed inhibitor tests in 447 patients. This implied that we obtained data on two thirds of all patients with severe and moderately severe hemophilia A in The Netherlands. General characteristics of these patients are shown in Table 1

A total of 50 patients were reported in whom an inhibitor was present or had ever been present in the past; these were considered "ever" inhibitors In 33 patients the inhibitor was first detected before the beginning of our study interval in 1988; in 17 patients a new inhibitor was detected recently, ie, within the time frame of the study from March 1988 through November 1991 In 29 of these 50 "ever" inhibitor patients the inhibitor was still present at the measurement in 1991, and these 29 patients were considered "current" inhibitors.

Of the 17 inhibitors detected in or after 1988, 15 had clinical symptoms and were classified as type A inhibitors Four of these were first discovered in period I (March 1988 through May 1990), and 11 in period II (June 1990 through November 1991) (see Table 2). The maximum titres varied from 2 to 457 BU/mL All but 1 of these 15 type A inhibitors were detected because of a clinical suspicion. Two patients (of these 17), who were both detected in November 1991, had no symptoms and had low inhibitor titers (1.4 and 1.5 BU/mL); these were both classified as type B inhibitors. In 1 of these, the inhibitor was no longer detectable after several weeks, and in 1 it remained of a low titer (1 2 BU/mL) without any clinical symptoms.

Table 2. Type A Inhibitor Patients in the National Study and the Cohort 1984 through 1989

	Age (yrs)	% Severity (FVIII C)	Exposure to FVIII (d)	Date of Detection (mon yr)	Max Titer (BU/mL)
National study					
Period I (March 1988-May 1990)	32	>5	<50	03-88	2
	2	<1	<50	01-89	7
	1	<1	<50	09-89	22
	5	<1	<50	05-90	54
Period II (June 1990-November 1991)	57	1-5	<50	12-90	pos*
	2	<1	<50	02-91	14
	13	<1	>1,000	04-91	222
	4	<1	>250	06-91	35
	50	<1	>1,000	08-91	18
	14	<1	>1,000	10-91	3
	19	<1	>1,000	10-91	457
	37	<1	>1,000	10-91	6
	35	<1	>1,000	10-91	11
	8	<1	>250	10-91	10
	5	<1	>500	11-91	38
Prospective extension (December 1991-March 1992)	15	<1	>250	02-92	15
Cohort 1984-1989	2	<1	<50	04-84	68
	2	<1	<100	07-85	11

All patients listed in the table had clinical symptoms of an inhibitor, ie, decreased response to substitution treatment, all but two (one in the national study and one in the cohort 1984-1989) were detected because of clinical suspicion of an inhibitor The two patients with type B inhibitors in period II of the national study, and the 11 patients with type B inhibitors in the cohort 1984-1989 are not listed in this table

* No inhibitor measurement during treatment with over 20,000 IU FVIII/d

Table 3. Comparison of Type A Inhibitor Incidence in Dutch and US Cohorts

	Incidence ($\times 10^{-3}$ patient-years)	CI95*
US cohort†		
(n = 1,306)§	6 2‡	4 0-9 2
Cohort 1984-1989		
(n = 144)§	3 9	0 5-14 2
National study		
Period I		
(March 1988-May 1990)		
(n = 411)§	4 4	1 2-11 3
Period II		
(June 1990-November 1991)		
(n = 410)§	20 1	10 0-35 9
Prospective extension		
(December 1991-March 1992)		
(n = 210)§	16 6	0 4-92 4

* 95% confidence interval

† Data from McMillan et al [19]

‡ Recalculated from report by McMillan et al [19]

§ Patients entering the study period without an apparent inhibitor

Table 4. Exposure to Factor VIII CPS and Factor VIII CPS-P in the National Study

	Exposed (no of patients)	Not Exposed (no of patients)
Period I (March 1988-May 1990)*	Factor VIII CPS	No Factor VIII CPS
New inhibitor in this period	2	2
No inhibitor in this period	183	227
Period II (June 1990-November 1991)*	Factor VIII CPS-P	No Factor VIII CPS-P
New inhibitor in this period†	13	0
No inhibitor in this period	298	99

* Only patients without an inhibitor before each period

† Two type B inhibitors included

Forty-five of the 48 "ever" type A inhibitors had severe hemophilia, 1 moderately severe, and 2 mild hemophilia. Of the 27 "current" type A inhibitors, 25 had severe hemophilia and 2 had mild hemophilia.

The prevalence of "current" type A inhibitor (leaving out the two type B inhibitors) was 6.0% (27/447, CI95 3.8 to 8.3%), and for "ever" inhibitor it was 10.7% (48/447, CI95 7.9 to 13.6%). For severe hemophilia only, these figures for "current" inhibitor were 8.6% (25/292), and for "ever" inhibitor were 15.4% (45/292).

The incidence of type A inhibitor development (calculated for those who never had had an inhibitor previously) over the total period from March 1988 through November 1991 was 10.1/1,000 patient-years (15/1,490 years, CI95 5.6 to 18.3/1,000 patient-years). For period I (March 1988 through May 1990) the incidence of type A inhibitors was 4.4/1,000 patient-years (4/906 years, CI95 1.2 to 11.3/1,000 patient-years) and for period II (June 1990 through November 1991) it was 20.1/1,000 patient-years (11/548 years, CI95 10.0 to 35.9/1,000 patient-years) (Table 3). The risk (rate ratio) of inhibitor development was 4.5 times higher in the second period than in the first period (CI95 1.4 to 14.3).

When a particular factor is a risk factor for disease, one generally expects this factor to be more often present among patients than among nonpatients. Therefore, if a factor VIII concentrate gave rise to an increased risk of inhibitors, one would expect that this product was used by a higher proportion of the patients who developed inhibitors as compared with those who did not develop an inhibitor. In the first period (March 1988 through May 1990), 2 of the only 4 patients who developed an inhibitor had been exposed to Factor VIII CPS, which appeared not to differ from the proportion exposed among those who did not develop an inhibitor in this period (Table 4). However, in the second period (June 1990 through November 1991), there was a difference in exposure to pasteurized Factor VIII CPS-P between inhibitor and noninhibitor patients. All 13 patients who developed inhibitors in this second period had been exposed to Factor VIII CPS-P, whereas only 75 percent (298 patients) of the 397 patients who remained without an inhibitor until the end of the study period had been treated with Factor VIII CPS-P (χ^2 4.27, P = .039) (Table 4).

Four of the 11 type A inhibitor patients detected in period II (June 1990 through November 1991) were over 25 years old when their inhibitor was discovered, as compared with only 1 of the 4 inhibitor patients found in period I (March 1988 through May 1990). The 11 patients who developed a type A inhibitor in period II (June 1990 through November 1991) had been heavily exposed to factor VIII products before inhibitor development in all but 2 cases (over 250 transfusions in 9, and over 1,000 transfusions in 6). In contrast, the four patients who developed inhibitors in period I (March 1988 through May 1990) all had received less than 50 infusions before the inhibitor detection (P = .01) (Table 5).

The second inhibitor test after 3 months of additional follow-up was performed in 210 of 219 patients who had no inhibitor detected at the first measurement and who had received factor VIII products in these 3 months. Among 184 patients who had used Factor VIII CPS-P in the interval, with a total observation time of 52.5 years, one clinically

Table 5. Exposure Days to Factor VIII Preparations of Type A Inhibitor Patients in Dutch and US Cohorts

	Cumulative Exposure to FVIII Preparations	
	<250 d (no of patients)	>250 d (no of patients)
US cohort*		
(n = 24)	24	0
Cohort 1984-1989		
(n = 2)	2	0
National study		
Period I (March 1988-May 1990)		
(n = 4)	4	0
Period II (June 1990-November 1991)		
(n = 11)	2	9

* Data from McMillan et al [19]

relevant inhibitor (16 BU/mL) was detected (incidence 19 0/1,000 patient-years for patients who were treated with Factor VIII CPS-P, and 16 6/1,000 patient-years for all 210 patients in whom a follow-up measurement was performed) This 15-year-old patient had received well over 250 transfusions in his lifetime In addition, one transient inhibitor without symptoms (maximum titer 1 5 BU/mL) was detected in a 2-year-old patient

Retrospective cohort study on inhibitor development The cohort consisted of 144 patients who had at least two inhibitor measurements between 1984 and 1990 One patient, not known to have an inhibitor, died during the study period of intracerebral bleeding, four patients were lost to follow-up because they moved house These patients are included in the analysis until the last day of follow-up information The general characteristics of these patients are shown in Table 1

Most patients (102, 71%) had received over 100 infusions while under observation, and only nine (6%), less than 10 infusions Most patients had received treatment with either cryoprecipitate or Dutch concentrate (intermediate purity factor VIII concentrate and its successor factor VIII CPS), or both

A total number of 527 inhibitor determinations were performed during an observation period of 509 patient-years Inhibitor titers over 1 BU/mL were found in 13 patients In two patients, both aged 2 at first inhibitor detection, inhibitor activity was shown on multiple occasions, with maximum levels of 11 and 68 BU/mL Both patients developed bleeding problems, in one patient these were the reason to perform an inhibitor test These two patients were classified as type A inhibitors (Table 2) In 11 patients we found type B inhibitors These were all detected at routine screening and were not associated with clinical problems In nine patients the inhibitor activity had been shown only once, in one patient twice in 1 week, and in one patient once in 1987 (1 1 BU/mL) and once in 1989 (1 2 BU/mL), with subsequent negative tests in all 11 patients Inhibitor titers for these type B inhibitors ranged from 1 1 to 2 4 BU/mL, the ages of these patients ranged from 10 to 48 years Therefore, from this cohort we estimate an incidence of type A inhibitors of 3 9/1,000 patient-years (2/509 years, CI95 0 5 to 14 2/1,000 patient-years) (Table 3) and an incidence of type B inhibitors of 21 6/1,000 patient-years (11/509 years, CI95 10 8 to 38 7/1,000 patient-years)

DISCUSSION

Since June 1990, we have observed an increased incidence of inhibitor development among hemophilia A patients in The Netherlands, particularly among patients who had received numerous infusions with factor VIII preparations This increased incidence is likely to be associated with the usage of a recently introduced pasteurized factor VIII concentrate

Although inhibitor development is not uncommon in previously untreated patients (pups), it is rare in multitransfused patients McMillan et al[19] found an incidence of 8/1,000 patient-years in a cohort of previously treated patients (6 2/1,000 patient-years for type A inhibitors), which is much lower than the incidence of 20 1/1,000 patient-years we found since June 1990 It is important to note that even though inhibitors were detected among older patients in McMillan et al's study, all of these inhibitor patients had received less than 250 infusions in their lifetime (Table 3)

During period I (March 1988 through May 1990), before the introduction of Factor VIII CPS-P, as well as in the retrospective cohort observed from 1984 through 1990, we found incidence rates of new inhibitor development that were similar to the US figures 4 4/1,000 patient-years in period I (March 1988 through May 1990) and 3 9/1,000 patient-years in the cohort followed from 1984 through 1989 (Table 3) All combined, the increased incidence after the introduction of a new factor VIII concentrate, the occurrence of inhibitors in multitransfused patients, the exposure to this product in all inhibitor patients, as well as the independent reports from Belgium, render an association with the product more than likely

In a study like this, in which inhibitors were actively sought after, there may be overestimation because of detection bias, ie, positive test results in patients who would otherwise not have been tested, or have been tested later We have tried to minimize this possibility of bias by focusing on type A inhibitors, whose clinical symptoms were sufficiently severe to ensure detection also in the absence of a study like this Nevertheless, as the dates of first detection show (Table 2), some detection bias may have been present, and therefore our incidence estimates may have been slightly inflated

Among the 144 patients of the cohort 1984 through 1989, we found a high incidence of type B inhibitors (22/1,000 patient-years, as compared with approximately 2/1,000 patient-years in the US cohort[19]) The relevance of this observation is uncertain, and we feel that assay variability cannot be ruled out as an explanation [34] In this respect, it has to be borne in mind that these tests were performed in a routine clinical fashion, and no attempts were undertaken to confirm low-titered inhibitors that appeared without clinical importance

To our knowledge, this is the first instance in which inhibitor development has been associated with the use of a particular factor VIII product in multitransfused patients who switched from one product to another This may be related to an altered epitopic structure of the factor VIII molecule in pasteurized Factor VIII CPS Because this factor VIII concentrate has not been used outside The Netherlands and Belgium, the absolute number of patients who developed inhibitors remained limited, which would not have been the case if the product had been used in larger populations We believe that to avoid future and possibly larger epidemics of inhibitors, physicians who treat hemophilia patients should perform inhibitor tests at regular intervals, especially when their patients change from one clotting factor preparation to another

APPENDIX

Participating centers (9) were Van Creveldkliniek, Bilthoven (Dr H M van den Berg, Dr G Roosendaal, and Dr E P Mauser-Bunschoten), Academic Medical Center, Amsterdam (Dr H Heijboer and Dr M Peters), University Hospital Leiden (Dr E Briet, Dr F R Rosendaal, Dr E T van't Veer Korthof, and Dr M H van Weel-Sipman), University Hospital Groningen (Dr J van der Meer and

Dr J K M van Loon), University Hospital Rotterdam (Dr J Stibbe and Dr J J Michiels), Radboudziekenhuis Nijmegen (Dr I R O Novakova and Dr C van Oostrom), Leyenburgziekenhuis, 's-Gravenhage (Dr W B J Gerrits), University Hospital Utrecht (Dr H K Nieuwenhuis), Sophia Kinderziekenhuis Rotterdam (Dr A de Goede-Bolder), St Elisabethziekenhuis, Haarlem (Dr A Hensen), Diaconessenhuis, Eindhoven (Dr L J Bosch and Dr B Agoston), University Hospital Maastricht (Dr K Hamulyak), Grootziekengasthuis, 's-Hertogenbosch (Dr R M A Kurstjens), Twenteborgziekenhuis Almelo (Dr R P Beekman, Dr N Hofstee, and Dr F J A M Holtus), Ziekenhuis De Weezenlanden (Dr C J Russchen and Dr F van de Logt), Juliana-Lukasziekenhuis Apeldoorn (Dr G Fedder and Dr D W van Toorn), Oosterschelde Ziekenhuis, Goes (Dr P W de Haas), Refaja Ziekenhuis, Dordrecht (Dr E van Kammen) St Ignatius Ziekenhuis, Breda (Dr A C J M Holdrinet and Dr M H Th Arnoldussen), Carolus Ziekenhuis, 's-Hertogenbosch (Dr R Heydendael), Elkerliek Ziekenhuis, Helmond (Dr J P de Jager and Dr J C van Kesteren), St Clara Ziekenhuis, Rotterdam (Dr R Rodrigues Pereira), St Elisabethziekenhuis, Tilburg (Dr A Dolman and Dr A Veuger), Streekziekenhuis Midden Twente Hengelo (Dr H Dankbaar), Vereniging Het Ziekenhuis, Velp (Dr R C Schokker) Canisius-Wilhelmina Ziekenhuis, Nijmegen (Dr C L M van der Zee), Catharinaziekenhuis, Eindhoven (Dr H F P van Hillen), Medisch Spectrum Twente, Enschede (Dr R F H M Tummers), Spaarneziekenhuis, Haarlem (Dr A G Ketel), St Annaziekenhuis, Oss (Dr H Smeets) St Antoniusziekenhuis, Sneek (Dr R van Eijk), St Jans Gasthuis, Weert (Dr F M Lalisang), St Jozephziekenhuis, Kerkrade (Dr J Wolters), Ziekenhuis Gelderse Vallei, Ede (Dr B S Voorbrood)

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