Subarachnoid Hemorrhage in Type 1 Diabetes

A prospective cohort study of 4,083 patients with diabetes

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OBJECTIVE—To estimate for the first time the incidence of subarachnoid hemorrhage (SAH) in type 1 diabetes.

RESEARCH DESIGN AND METHODS—Using the nationwide Finnish Diabetic Nephropathy (FinnDiane) Study cohort of 4,083 patients with type 1 diabetes (mean age of 37.4 ± 11.8 years at enrollment), we analyzed the incidence of first-ever SAH events.

RESULTS—During the follow-up time of 36,680 person-years (median 9.4 years), 15 patients with type 1 diabetes experienced an aneurysmal or nonaneurysmal SAH, and thus the crude incidence of SAH was 40.9 (95% CI 22.9–67.4) per 100,000 person-years. One patient had a verified aneurysmal SAH, and four patients died suddenly of an SAH, which was most likely caused by an aneurysm. SAHs in 10 out of 15 patients were classified as nonaneurysmal SAH, and thus the crude incidence of nonaneurysmal SAH was 27.3 (13.1–50.1) per 100,000 person-years. None of the nonaneurysmal SAHs were fatal. In univariate analysis, current smokers had a hazard ratio of 4.82 (95% CI 1.31–17.81) for nonaneurysmal SAH.

CONCLUSIONS—The incidence of nonaneurysmal SAH is high among patients with type 1 diabetes. Our findings suggest that nonaneurysmal SAH is a distinct new microvascular complication in type 1 diabetes.

Subarachnoid hemorrhage (SAH) is a life-threatening cerebrovascular event, which is usually caused by a rupture of a cerebrovascular aneurysm. These aneurysms are mostly found in relatively large-caliber (≥1 mm) vessels and can often be considered as macrovascular lesions. The overall incidence of SAH has been reported to be 10.3 per 100,000 person-years (1), even though the variation in incidence between countries is substantial (1). Notably, the population-based incidence of SAH is 35 per 100,000 person-years in the adult (≥25 years of age) Finnish population (2). The incidence of nonaneurysmal SAH is globally unknown, but it is commonly believed that 5–15% of all SAHs are of nonaneurysmal origin. Prospective, long-term, population-based SAH risk factor studies suggest that smoking (2–4), high blood pressure (2–4), age (2,3), and female sex (2,4) are the most important risk factors for SAH, whereas diabetes (both types 1 and 2) does not appear to be associated with an increased risk of SAH (2,3).

An increased risk of cardiovascular disease is well recognized in people with diabetes. There are, however, very few studies on the risk of cerebrovascular disease in type 1 diabetes since most studies have focused on type 2 diabetes alone or together with type 1 diabetes. Cerebrovascular mortality in the 20–39-year age-group of people with type 1 diabetes is increased five- to sevenfold in comparison with the general population but accounts only for 15% of all cardiovascular deaths (5). Of the cerebrovascular deaths in patients with type 1 diabetes, 23% are due to hemorrhagic strokes (5). However, the incidence of SAH in type 1 diabetes is unknown.

By knowing the incidence of SAH in type 1 diabetes, the overall risk of stroke in patients with type 1 diabetes could be estimated more accurately. Moreover, comprehensive prospective patient cohorts that are susceptible to cerebrovascular events may provide new knowledge of the risk factors for SAH. In this prospective cohort study of 4,083 patients with type 1 diabetes, we aimed to determine the incidence and characteristics of SAH.

RESEARCH DESIGN AND METHODS

Study cohort

The study cohort included 4,083 patients with type 1 diabetes who participated in the Finnish Diabetic Nephropathy (FinnDiane) Study. Of the patients, 52% were men, the mean age was 37.4 ± 11.8 years, and the duration of diabetes was 21.6 ± 12.1 years at enrollment. The FinnDiane Study is a nationwide multicenter cohort study of genetic, clinical, and environmental risk factors for microvascular and macrovascular complications in type 1 diabetes. Data have been collected

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Received 31 January 2013 and accepted 14 May 2013.
DOI: 10.2337/dc13-0260
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-0260/-/DC1.
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*A complete list of the FinnDiane Study Centers can be found in the Supplementary Appendix online.
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Diabetes Care Publish Ahead of Print, published online July 22, 2013

since 1998 by the patient's physician, and data include thorough information on the patient's medical history and medication. Serum samples were analyzed for lipids, lipoproteins, and HbA_{1c}. Urine samples were collected for the measurement of urinary albumin excretion rate. Type 1 diabetes was defined as diabetes diagnosed before 40 years of age and treated with insulin within 1 year of diagnosis. For this study, all type 1 diabetic patients in the FinnDiane database with follow-up data and without a history of stroke at baseline were included. Patients with a traumatic brain hemorrhage or incomplete information on history of stroke at baseline were excluded ($n = 16$). More detailed information on the FinnDiane Study protocol has been reported previously (6). The local ethics committee approved the study protocol, and the study was carried out in accordance with the Declaration of Helsinki. Each participating patient signed a written consent.

Medical history and medication

Diabetic nephropathy was diagnosed when the urinary albumin excretion rate was ≥20 μg/min in two out of three urine collections, when the patient was on dialysis, or when the patient had received a renal transplant. Severe diabetic retinopathy was defined as a history of retinal laser treatment. Coronary heart disease was defined as diagnosed myocardial infarction, coronary revascularization, or treatment with long-acting nitroglycerin. Aspirin treatment was defined as the use of a low-dose aspirin for primary or secondary prevention of vascular events. Other anticoagulant treatments were defined as all other pharmacological therapies used for preventing blood coagulation (mainly vitamin K antagonists).

Follow-up data on SAH

Follow-up time in person-years was calculated for each patient as the follow-up time in years from the baseline data collection until the diagnosis of SAH, death from any cause, emigration, or last date of register-based (the Finnish National Hospital Discharge Register) follow-up without SAH. The loss to follow-up was 0%. The follow-up time for the entire cohort was 36,680 person-years. The median follow-up time was 9.4 years (interquartile range [IQR] 7.8–11.1) per patient. Patients that suffered a stroke were identified from various sources: 1) death certificates retrieved from Statistics Finland by March 2010, 2) the Finnish National Hospital Discharge Register by December 2009 (ICD-10 codes I60–I64), and 3) the FinnDiane follow-up visit registry. Medical records, computed tomography (CT) images, and magnetic resonance images of the patients with an identified register-based ischemic or hemorrhagic stroke were ordered from the corresponding hospitals. Based on the retrieved patient-specific data, stroke subtypes were verified and further classified into cerebral infarcts, intracerebral hemorrhages, or SAHs. For this study, patients with a new SAH after the baseline data collection were analyzed in detail.

Classification of SAH

Brain CT scans were performed on all patients who arrived at the study hospital alive, and CT scans confirmed the diagnosis of SAH. SAHs were divided into aneurysmal and nonaneurysmal SAHs on the basis of the SAH pattern on CT scans. All patients alive >24 h after the admission went through a CT angiography (CTA), magnetic resonance angiography (MRA), and/or digital subtraction angiography (DSA). Nonaneurysmal SAHs were further divided into perimesencephalic and diffuse SAHs, as previously described (7). In brief, perimesencephalic SAHs limited mainly to the anterior midbrain, without extension of blood to the anterior interhemispheric fissure, lateral Sylvian fissure, or ventricles. Subarachnoid blood in diffuse SAHs extended throughout multiple cisterns, such as Sylvian, suprasellar, interhemispheric, and perimesencephalic cisterns.

Statistical analyses

The incidence of SAH is presented per 100,000 person-years with 95% CIs. Continuous variables were compared with the Mann-Whitney *U* test, and the results are presented as median with IQR. For categorical variables, statistically significant differences between groups were tested using the χ^2 test.

We used the Cox proportional hazards model to estimate hazard ratios of SAH with 95% CIs. The timescale for the model was follow-up time. Departure from the proportional hazards assumption was evaluated by Schoenfeld residuals and by inspection of the "log-log" plots. Univariate analyses were adjusted for age and sex. *P* values <0.05 were considered statistically significant. All analyses were performed with the IBM SPSS Statistics 20 software (IBM Corporation, Armonk, NY).

RESULTS

Incidence of SAH

Sixteen patients with type 1 diabetes and a possible SAH were identified from the registries. After a review of the medical files, one patient was found to have a brain stem hemorrhage with secondary SAH. Fifteen patients were confirmed to have an SAH, and thus the crude incidence of SAH was 40.9 (95% CI 22.9–67.4) per 100,000 person-years. Ten out of these 15 SAHs were nonaneurysmal SAHs, as CT scans of these 10 patients showed SAH and subsequent cerebral angiographic studies (CTA, MRA, and/or DSA) did not reveal intracranial aneurysms. Of the 10 nonaneurysmal SAHs, 6, 4, and 7 patients had CTA, MRA, and DSA, respectively, as a diagnostic imaging modality for intracranial aneurysms. CTA, MRA, and DSA were obtained in one patient, CTA and DSA in three patients, and MRA and DSA in one patient. DSA was the only cerebral angiographic study in two patients. Of the 10 nonaneurysmal SAH patients, 6 patients had a diffuse SAH and 4 patients had a perimesencephalic SAH. Four out of six patients with diffuse SAHs were studied with DSA. The crude incidence of nonaneurysmal SAH was 27.3 (13.1–50.1) per 100,000 person-years. None of the 10 nonaneurysmal SAHs were fatal.

Only one aneurysmal SAH was confirmed, and thus the crude incidence of aneurysmal SAH was 2.7 (95% CI 0.1–15.2) per 100,000 person-years. Four patients with type 1 diabetes had a fatal SAH, and all these patients died within 24 h after SAH. Two out of these four patients died in the hospital, and SAH was diagnosed on admission by CT scans, but due to poor clinical and kidney status, cerebral angiographic studies were not performed. Another two patients died suddenly outside the hospital, and no imaging studies were obtained. According to the medicolegal autopsy reports, these two sudden deaths were caused by SAH. Unfortunately, autopsy did not include the examination of cerebral arteries, and therefore these fatal SAHs cannot be confirmed as aneurysmal SAHs. However, if all four fatal SAHs were classified as aneurysmal SAHs, the crude incidence of aneurysmal SAH (five cases) would be 13.6 (4.4–31.8) per 100,000 person-years.

Characteristics of patients with type 1 diabetes and nonaneurysmal SAH

Since only one confirmed aneurysmal SAH was identified, no characteristics for patients with type 1 diabetes and aneurysmal SAH are presented. The baseline characteristics of the 10 patients with nonaneurysmal SAH are presented in Table 1. In comparison with the patients without nonaneurysmal SAH, nonaneurysmal SAH patients were slightly older and more frequently used antihypertensive medication at baseline (Table 1). Moreover, the prevalence of severe diabetic retinopathy and the number of smokers among nonaneurysmal SAH patients was higher than among the patients without nonaneurysmal SAH (Table 1). No significant differences were observed in the age at onset of type 1 diabetes, BMI, blood pressure values, serum cholesterol or triglyceride levels, glycemic control, use of other than antihypertensive medication, or the prevalence of coronary heart disease and diabetic nephropathy between those with and without nonaneurysmal SAH (Table 1).

Case descriptions of the 10 patients with nonaneurysmal SAH are presented in Table 2. Only 3 out of 10 patients did not have verified diabetic microvascular or macrovascular complications prior to the nonaneurysmal SAH event. During the median post-SAH follow-up time of 4.8 years (IQR 1.8–7.0), 1 out of these 10 patients died due to an acute myocardial infarction and 2 patients suffered from nonfatal cardiovascular events. Four out of 10 nonaneurysmal SAH patients started anticoagulant therapy after the baseline survey, but prior to SAH, and therefore used anticoagulant medication at the time of SAH.

Risk factors for nonaneurysmal SAH

Table 3 shows the age- and sex-adjusted univariate risk factor analyses for nonaneurysmal SAH, as well as for all SAHs. Current smoking at baseline increased the risk of nonaneurysmal SAH (Table 3).

CONCLUSIONS—The presented study results suggest that the incidence of nonaneurysmal SAH is high among patients with type 1 diabetes. There are no previous studies that report an increased incidence of nonaneurysmal SAH in any disease or study population. It is of note that smoking type 1 diabetic patients had a significantly increased risk of nonaneurysmal and all-cause SAHs. Smoking also increases the risk of microvascular complications in insulin-treated diabetic patients, and these patients more often have retinal and renal microangiopathy than never-smokers (8). Thus, smoking per se or diabetes-related and/or smoking-related microvascular changes may have an effect on the risk of nonaneurysmal SAH. Given the high incidence of nonaneurysmal SAH in patients with type 1 diabetes and microvascular changes (i.e., diabetic retinopathy and nephropathy), the results support the hypothesis that nonaneurysmal SAH is a microvascular rather than macrovascular subtype of stroke. However, as long as the diagnosis of nonaneurysmal SAH relies on typical clinical and imaging findings, and not on identified vascular lesions, the exact etiology remains speculative.

Only one patient with type 1 diabetes had a confirmed aneurysmal SAH. Four other patients died suddenly due to an SAH. If these four patients with type 1 diabetes and a fatal SAH had an aneurysmal SAH, which, taking into account the autopsy reports and imaging findings, is very likely, aneurysmal SAH may be an exceptionally deathly event in type 1 diabetes. Population-based evidence suggests that up to 45% of people die during the first 30 days after SAH, and 18% die at emergency rooms or outside hospitals (9). Due to the overall rarity of patients with type 1 diabetes and an aneurysmal SAH, and the possible high fatality of this type of hemorrhage, most studies cannot reliably assess the risk of type 1 diabetes for SAH, especially if autopsies for sudden deaths are not performed.

Contrary to aneurysmal SAH, nonaneurysmal SAH is virtually always a nonfatal event (10–14). This also supports the view that nonaneurysmal SAH is a disease of small intracranial vessels, i.e., a microvascular disease. Diabetic retinopathy, a chronic microvascular complication, has been associated with an increased risk of stroke in patients with diabetes (15,16). Embryonically, the retina is an outgrowth of the brain and is similar in its microvascular properties to the brain (17). Thus, it has been suggested that assessments of the retinal vasculature could be used to determine the risk of cerebrovascular diseases, such as stroke (18). Moreover, the vascular beds of the kidney and the brain share several hemodynamic similarities (19), and renal microangiopathy in type 1 diabetes associates with an increased risk of cardiovascular diseases, such as stroke (20). Overall, the study patients have retinal, renal, and most probably

Table 1—*Baseline characteristics of the diabetic patients with (10 patients) and without (4,068 patients) nonaneurysmal SAH*

	SAH	No SAH	*P* value
Males	50%	52%	0.913
Age at enrollment	47.0 (44.6–54.2)	36.8 (28.2–46.0)	<0.001
Age at time of SAH	52.9 (50.9–55.5)	N/A	N/A
Duration of diabetes at SAH	34.2 (28.7–41.4)	N/A	N/A
Age at onset of diabetes	17.5 (11.3–28.0)	14.0 (9.0–22.0)	0.257
Systolic blood pressure (mmHg)	140 (131–145)	131 (121–144)	0.269
Diastolic blood pressure (mmHg)	78 (72–83)	80 (72–86)	0.617
S-cholesterol (mmol/L)	4.94 (4.17–5.58)	4.85 (4.26–5.49)	0.822
S-LDL cholesterol (mmol/L)	2.67 (2.24–3.71)	2.94 (2.42–3.55)	0.495
S-HDL cholesterol (mmol/L)	1.43 (1.21–1.76)	1.29 (1.08–1.56)	0.134
S-triglycerides (mmol/L)	1.21 (0.73–1.96)	1.03 (0.77–1.47)	0.640
BMI (kg/m^2)	23.5 (21.8–25.2)	24.6 (22.5–26.9)	0.159
HbA_{1c} (%)	8.4 (7.5–9.0)	8.3 (7.4–9.3)	0.909
HbA_{1c} (mmol/mol)	68 (58–75)	67 (57–78)	0.909
Antihypertensive treatment	70%	38%	0.037
Current smoking	50%	24%	0.057
Aspirin treatment	10%	13%	0.796
Severe diabetic retinopathy	60%	34%	0.077
Diabetic nephropathy	50%	35%	0.324
Other anticoagulant therapy	0%	1%	0.828
Coronary heart disease	10%	5%	0.511

Continuous variables are compared with Mann-Whitney *U* test, and the results are presented as median with IQR in parentheses. Categorical variables are compared with a χ^2 test, and results are presented as percentages. Timescales are reported in years. S, serum.

Table 2—*Case descriptions of patients with type 1 diabetes and nonaneurysmal SAH*

	Sex	Age (years)	SAH	Diabetes duration (years)	Smoking	DN	DR	CHD	AHT	ACT	Other
1	F	45	DIF	20	Yes	No	No	No	Yes	No	
2	F	47	DIF	30	Never	Yes	Yes	No	Yes	No	
3	F	52	DIF	43	Never	Yes	Yes	No	Yes	Baseline no, warfarin prior to SAH	
4	M	52	DIF	39	Never	Yes	Yes	No	Yes	Baseline no, aspirin prior to SAH	
5	M	53	PMSAH	46	Yes	Yes	Yes	No	Yes	Baseline no, warfarin prior to SAH	History of amputations, fatal AMI 2 years post-SAH
6	M	53	PMSAH	41	Yes	Baseline no, DN prior to SAH	Yes	No	No	Baseline no, aspirin prior to SAH	
7	F	54	DIF	37	Never	No	No	No	No	No	
8	M	54	PMSAH	26	Yes	Yes	Yes	No	Yes	No	Cerebral infarction 2 years post-SAH
9	F	58	DIF	31	Never	No	No	No	No	No	
10	M	62	PMSAH	31	Yes	No	No	Yes	Yes	Yes (baseline aspirin, aspirin and clopidogrel prior to SAH)	AMI 2 days post-SAH, CABG 5 days post-SAH, cerebral infarction 4 years post-SAH

ACT, anticoagulant treatment; AHT, antihypertensive treatment; AMI, acute myocardial infarction; CABG, coronary bypass; CHD, coronary heart disease; DIF, diffuse SAH; DN, diabetic nephropathy; DR, severe diabetic retinopathy; F, female; M, male; PMSAH, perimesencephalic SAH.

intracranial microvascular changes, which may relate to an exceptionally high risk of nonaneurysmal SAH in smoking type 1 diabetic patients. Most interestingly, the incidence of nonaneurysmal SAH was at least two times higher than the incidence of aneurysmal SAH in type 1 diabetic patients. In comparison, the incidence of nonaneurysmal SAH is >10 times lower than the incidence of aneurysmal SAH in the general adult population (21).

A few caveats apply to our data. The FinnDiane Study cohort is not a population-based cohort by strict definition, but it is a large, nationwide, multicenter study. In addition, the total number of SAH events in the cohort remains low, which hinders a detailed evaluation of SAH-associated risks in type 1 diabetes. However, this is the first large-scale and longitudinal study on SAH in type 1 diabetes. Moreover, the predictive value of single baseline risk factor assessments for any future disease or event can be questioned, and there is no doubt that longitudinal risk factor assessments would be more reliable. This is, however, a common drawback for a number of prospective cardiovascular risk factor studies. In addition, the definition of the term "nonaneurysmal SAH" is somewhat arbitrary, since current imaging modalities cannot identify microaneurysms on small intracranial vessels. Whether the pathogenesis and risk factors for these microaneurysms, if they even exist, differ from saccular intracranial aneurysm is speculative. The incidence of suspected aneurysmal SAH was 13.6 per 100,000 person-years, which is less than previously reported in the Finnish population. This may relate to the relatively low mean age at enrollment. However, the population-based incidence of SAH among 25–34-year-old Finnish people has been reported to be 15 per 100,000 person-years (2), which is higher than among this study cohort of older diabetic people. Moreover, despite the fact that the follow-up time of the cohort was relatively long, it may still be too short to reliably estimate the incidence of aneurysmal SAH. Given that 4 out of 10 patients with nonaneurysmal SAH used anticoagulant therapy at the time of SAH (not at enrollment), we cannot exclude the possibility that this may have contributed to the manifestation of SAH. Finally, two out of six patients with diffuse SAHs were not studied with DSA, and thus the possibility of an aneurysmal SAH cannot be excluded in these patients.

To conclude, the current study provides new knowledge on the cerebrovascular complications in patients with type 1 diabetes and suggests that smoking type 1 diabetic patients have a high risk of nonaneurysmal SAH. Retinal and renal microvascular features may associate with the risk of nonaneurysmal SAH in type 1 diabetes. The high incidence of nonaneurysmal SAH in type 1 diabetes is the first clinical piece of evidence supporting the view that nonaneurysmal SAH is of microvascular origin. Whether retinal and renal vascular changes are also evident in

Table 3—*Age- and sex-adjusted univariate analysis of baseline risk factors for nonaneurysmal* (n = *10) and all* (n = *15) SAHs in type 1 diabetes*

Risk factor	Nonaneurysmal SAHs	*P* value	All SAHs	*P* value
Current smoking	4.82 (1.31–17.81)	0.018	5.12 (1.77–14.81)	0.003
Antihypertensive treatment	2.34 (0.57–9.58)	0.238	2.97 (0.90–9.80)	0.074
Diabetic nephropathy	1.96 (0.54–7.09)	0.305	2.32 (0.81–6.64)	0.118
Severe diabetic retinopathy	1.78 (0.48–6.58)	0.388	1.89 (0.65–5.53)	0.243
Coronary heart disease	0.79 (0.09–6.70)	0.826	0.54 (0.07–4.31)	0.559
Aspirin treatment	0.36 (0.04–2.96)	0.339	0.54 (0.12–2.52)	0.432

Hazard ratios with 95% CIs in parentheses.

nondiabetic patients with nonaneurysmal SAH remains to be studied.

Acknowledgments—This study was supported by personal grants awarded by the Sigrid Jusélius Foundation, Emil Aaltonen Foundation, Biomedicum Helsinki Foundation, Orion-Farmos Research Foundation, and Finnish Medical Foundation to M.K. J.P. was supported by the Diabetes Research Foundation. T.T. receives/has received research support from the Finnish Academy of Sciences, Finnish Medical Foundation, European Union, Biocenter Finland, Biocentrum Helsinki, Helsinki University Central Hospital, Sigrid Juselius Foundation, Liv och Hälsa, Maire Taponen Foundation, and National Institutes of Health. The FinnDiane Study was supported by grants awarded by the Folkhälsan Research Foundation, Wilhelm and Else Stockmann Foundation, Academy of Finland, European Comission, Finska Läkaresällskapet, Medicinska Understödsföreningen Liv och Hälsa, Signe and Arne Gyllenberg Foundation, and Waldemar von Frenckell Foundation and an EVO governmental grant.

M.K. has received honoraria from serving on the advisory board of Medtronic. T.T. has served on scientific advisory boards for Boehringer Ingelheim and Mitsubishi Pharma and has received speaker's honorarium from the Professio Finland, University of Helsinki, Finnish Medical Association, University of Donau (Austria), Genzyme Oy, and Finnish Neurological Association and research support from Boehringer Ingelheim (payment for development of education material). P.H.G. has received speaker honorariums from Boehringer Ingelheim, Cebix, Eli Lilly, Genzyme, MSD, Novartis, and Novo Nordisk and is an advisory board member for Boehringer Ingelheim, Cebix, and Novartis. No other potential conflicts of interest relevant to this article were reported.

The study sponsors did not have any role in study design; the collection, analysis, and interpretation of data; the writing of the report; and the decision to submit the paper for publication.

M.K. and L.M.T. were responsible for analyzing the patient data and writing the paper. S.H. contributed to study design, acquisition of data, data analysis, and critical revision of the paper. J.P. contributed to study design, acquisition of data, data analysis, and revision of the paper. R.L. contributed to critical revision of the paper. V.H. contributed to data analysis and critical revision of the paper. C.M.F. contributed to study design, acquisition of data, and critical revision of the paper. D.G. contributed to study design and critical revision of the paper. T.T. contributed to the conceptualization of the study, study design, critical revision of the paper, and logistic and administrative arrangements. P.-H.G. contributed to study design, acquisition of data, critical revision of the paper, and coordination of the study. P.-H.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

This study was presented at the 26th Annual General Meeting of the European Diabetic Nephropathy Study Group, Barcelona, Spain, 24–25 May 2013.

The authors acknowledge all the physicians and nurses (listed in Supplementary Appendix) at each center participating in the collection of patient data.

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