Declining Mortality in Cerebral Venous Thrombosis
A Systematic Review

Jonathan M. Coutinho, MD, PhD; Susanna M. Zuurbier, MD; Jan Stam, MD, PhD

Background and Purpose—Cerebral venous thrombosis (CVT) is nowadays considered a disease with a good outcome in most cases, but in the past, these patients were thought to have a grave prognosis. We systematically studied the apparent decline in mortality of patients with CVT over time.

Methods—A systematic review of the literature (MEDLINE and EMBASE) was performed. Studies with ≥40 patients with CVT that reported mortality at discharge or follow-up were eligible. Duplicate publications based on the same patient cohort were excluded. Studies were ranked according to the year halfway the period of patient inclusion. Two of the authors independently screened all eligible studies.

Results—We screened 4585 potentially eligible studies, of which 74 fulfilled the selection criteria. The number of patients per study varied from 40 to 706 (median, 76). Data from 8829 patients with CVT, included from 1942 to 2012, were analyzed. The average age was 32.9 years, and 64.7% were women. There was a significant inverse correlation between mortality and year of patient recruitment (Pearson correlation coefficient, −0.72; P<0.001). In a sensitivity analysis, the correlation remained significant after exclusion of studies published before 1990, retrospective studies, or single-center studies. Both the frequency of focal neurological deficits and coma also decreased significantly over time (correlation coefficient, −0.50 and −0.52).

Conclusions—There is a clear trend in declining mortality among patients with CVT over time. Possible explanations are improvements in treatment, a shift in risk factors, and, most importantly, the identification of less severe cases by improved diagnostic methods. (Stroke. 2014;45:1338-1341.)

Key Words: review • sinus thrombosis, intracranial

Cerebral venous thrombosis (CVT) is a rare type of stroke that mainly affects young adults and children.1–3 In the past, CVT was thought to carry a poor prognosis and the majority of patients did not survive.4 In recent studies, however, the prognosis seems to be much more favorable. In the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), mortality at discharge was only 4.3%.5 A multicenter study from Pakistan found a similar mortality of 5%.6 We performed a systematic review of the literature to examine the apparent decline in mortality of CVT over time and to identify possible causes.

Methods

Search Strategy
We searched MEDLINE and EMBASE databases for publications on CVT up until April 1, 2013, using the following search term: (sinus*[TI] and thrombosis[TI]) or (thrombosis[TI] and cerebral[TI]) and (venous*[TI] or vein*[TI] or sinus*[TI]) or (“Sinus Thrombosis, Intracranial”[MESH]) or (intracranial[TI] And thrombosis[TI]). To identify older case series, we also screened books and monographs on CVT. Furthermore, we cross-checked the reference lists of eligible studies to find additional studies. The entire screening process was performed independently by 2 of the authors (J.M.C. and S.M.Z.). If there was no consensus, the third author (J.S.) made the final decision to include or exclude a study.

Study Selection
Studies were eligible if they reported ≥40 patients with CVT and provided mortality data at discharge or follow-up for ≥80% of patients. Only studies with original data were included. Both adult and pediatric (including neonatal) series were eligible. We took care to exclude duplicate publications based on the same patient cohort (>50% overlap). Patient cohorts with a selection bias toward mortality (autopsy series) or survival (eg, studies on long-term complications) were excluded. We also excluded studies based on national hospital population databases because of lack of verification of the source data. Publications written in the following languages were eligible: English, French, German, Spanish, Portuguese, and Dutch. Publications in other languages were eligible if they had an English abstract that contained sufficient data. We initially screened the title and abstract of all articles identified by the primary search. Publications that were potentially eligible were analyzed in full detail.

Statistical Analysis
We extracted data on study design, demographics, baseline clinical manifestations, risk factors, ancillary investigations, treatment, and

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outcome from all eligible publications. Studies in which less than one third of patients were treated with heparin were scored as no heparin. Studies were ranked according to the year halfway the period of patient inclusion. If no time span was reported, we assumed a period of inclusion of 10 years before the year of publication. Based on the country of origin of the corresponding author, we classified studies as coming from high- (high or upper middle) or low- (lower middle or low) income countries, using the definition of the World Bank (http://data.worldbank.org). We used Pearson correlation to analyze trends in mortality over time. We used the mortality at discharge, or, if this was not reported, the mortality at follow-up. Sensitivity analyses on change in mortality over time were performed including only prospective studies, multicenter studies, studies published after 1990, studies from high-income countries, and studies with only adult patients. To identify potential explanatory factors for the decline in mortality, we analyzed the change in frequency over time of the following variables: age, coma, focal neurological deficits, seizures, intracerebral hemorrhage, infection-related CVT, malignancy-related CVT, traumatic CVT, and oral contraceptive use. All data were analyzed with SPSS version 20.

Results

Study Characteristics

Our search identified 4585 articles, of which 178 were potentially eligible (Figure 1). Of these, 104 studies were excluded, mostly because of redundant data (n=31) or because data on mortality were lacking (n=45). Thus, 74 studies were included in the analysis, with data of 8829 patients with CVT recruited between 1942 and 2012 (Table I in the online-only Data Supplement). The number of patients per study varied between 40 and 706 (median, 76; interquartile range, 56–138), and the duration of inclusion varied between 1 and 48 years (median, 10; interquartile range, 5–13). For 7 studies, we assumed a period of inclusion of 10 years because the time span was not reported. Sixteen (22%) studies were prospective, and 29 (39%) were multicenter. Studies originated mostly from India (15), United States (8), or Germany (6). Seventeen studies were performed in low or lower middle-income countries. Nineteen studies reported on a selected category of patients, namely pregnant women (9 studies), children (7 studies, of which 3 included neonates only), patients treated with thrombolysis (2 studies), and patients with Behcet disease (2 studies).

Baseline Characteristics and Treatment

The average age of patients was 32.9 years, and 64.7% were women (Table 1). There were 645 pediatric cases (12.1%). The most common symptoms at baseline were headache (77.2%), seizures (42.7%), and focal neurological deficits (39.9%). At admission, 15.6% of patients were comatose, and an intracranial hemorrhage was present in 34.6%. Oral contraceptive use (34.2% of women) and pregnancy/puerperium (32.8% of women) were the most common risk factors. Heparin was used in 54 of 74 studies (73%). In 9 studies (12%), no heparin was used, and 11...
studies (15%) did not report whether heparin was used. In total, 71.8% of patients were treated with anticoagulation. Of the 54 studies in which patients were treated with heparin, 13 used unfractionated heparin, 3 used low-molecular-weight heparin, and 27 used both types. The type of heparin was not disclosed in 11 studies. Endovascular thrombolysis was performed in 9.2% and decompressive craniotomy in 3.6% of patients.

Mortality
Seventy-one studies provided data on mortality at discharge, 23 at follow-up, and 20 studies reported both. The median duration of follow-up (reported in 18 studies) was 14 months (interquartile range, 3–31). There was a significant inverse correlation between mortality and year of patient recruitment (Pearson correlation coefficient, −0.72; P<0.001; Figure 2 and Table 2). In the sensitivity analyses, exclusion of single-center studies, retrospective studies, studies from low-income countries, and pediatric studies essentially yielded similar results. After exclusion of studies published before 1990, there was still a significant correlation between mortality and year of patient recruitment (Pearson correlation coefficient, −0.51; P<0.001), but if all studies published before 2000 were excluded, the correlation disappeared (Pearson correlation coefficient, −0.06; P=0.67). Reported mortality rates in studies published after 2000 ranged from 0% to 28%. We compared studies published after 2000 with a high mortality (>5%) with those with a low mortality (≤5%). Patients from studies with a high mortality were in a more severe clinical condition (coma, focal neurological deficits, and seizures all significantly more common). There were no significant differences between in study characteristics, risk factors, or treatment.

Potential Explanatory Factors
To examine which factors could explain the decline in mortality, we assessed the change in frequency of several parameters over time (Table 3). Both the frequency of focal neurological deficits and coma decreased significantly over time (correlation coefficient, −0.50 and −0.52, respectively). Trauma and infection-related CVT also decreased over time, although the latter was not significant.

Discussion
Our systematic review of the literature shows that the mortality of patients with CVT has substantially declined over time. There are several possible explanations for this finding. Part of the decline is probably the result of general improvement of studies (15%) did not report whether heparin was used. In total, 71.8% of patients were treated with anticoagulation. Of the 54 studies in which patients were treated with heparin, 13 used unfractionated heparin, 3 used low-molecular-weight heparin, and 27 used both types. The type of heparin was not disclosed in 11 studies. Endovascular thrombolysis was performed in 9.2% and decompressive craniotomy in 3.6% of patients.

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hospital care. Similar trends in declining mortality have been found in other diseases, such as ischemic stroke and pulmonary embolism. However, the decline in mortality in CVT is too large to be solely explained by this factor. The factor that has probably contributed most to the decline in mortality is the improvement in radiological investigations. Before the invention of cerebral angiography, CVT could only be diagnosed with certainty at autopsy or surgery, which resulted in a selection bias of patients in a severe condition. Even after introduction of angiography, many cases probably still went unnoticed because of the laborious and invasive nature of the procedure. Now that MRI (including magnetic resonance venography) and computed tomography venography have almost completely replaced cerebral angiography for the diagnosis of CVT, milder cases (e.g., patients with isolated headache) are more frequently identified. This hypothesis is supported by our finding that the severity of the clinical condition of patients with CVT has also decreased over time (less coma and focal neurological deficits) and the increased incidence of CVT over time. In addition, if the analysis was restricted to studies published after 2000—at which time of the study—use of computed tomography venography and MRI had become widespread—there was no longer a correlation between mortality and time of the study.

A third factor that probably contributed to the decline in mortality is a shift in risk factors. We found that both traumatic and septic CVT have decreased over time, whereas the number of patients using oral contraceptives increased. The latter group is known to have a better prognosis, whereas the number of patients using oral contraceptives increased. The correlation between mortality and time of the study.

Unfortunately, the majority of studies did not provide mortality at follow-up, and therefore there were insufficient data to analyze long-term mortality.

In conclusion, we have found a clear trend in declining mortality among patients with CVT over time, which is most likely explained by improvements in therapy, a shift in risk factors, and, most importantly, the identification of less severe cases.

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Disclosures
None.

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