Patients Enrolled in Large Randomized Clinical Trials of Antiplatelet Treatment for Prevention After Transient Ischemic Attack or Ischemic Stroke Are Not Representative of Patients in Clinical Practice

The Netherlands Stroke Survey

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Background and Purpose—Many randomized clinical trials have evaluated the benefit of long-term use of antiplatelet drugs in reducing the risk of new vascular events in patients with a recent transient ischemic attack or ischemic stroke. Evidence from these trials forms the basis for national and international guidelines for the management of nearly all such patients in clinical practice. However, abundant and strict enrollment criteria may limit the validity and the applicability of results of randomized clinical trials to clinical practice. We estimated the eligibility for participation in landmark trials of antiplatelet drugs of an unselected group of patients with stroke or transient ischemic attack from a national stroke survey.

Methods—Nine hundred seventy-two patients with transient ischemic attack or ischemic stroke were prospectively and consecutively enrolled in the Netherlands Stroke Survey. We applied 7 large antiplatelet trials’ enrollment criteria.

Results—In total, 886 patients were discharged alive and available for secondary prevention. Mean follow-up was 2.5 years. The annual rate of transient ischemic attack, stroke, or nonfatal myocardial infarction was 6.7%. The proportions of patients fulfilling the trial enrollment criteria ranged from 25% to 67%. Mortality was significantly higher in ineligible patients (27% to 41%) than in patients fulfilling enrollment criteria (16% to 20%). Rates of vascular events were not higher in trial-eligible patients than in ineligible patients.

Conclusions—Our data confirm that patients with ischemic attack and stroke enrolled in randomized clinical trials are only partially representative of patients in clinical practice. Use of less strict enrollment criteria could enhance “generalizability” and result in more efficient selection of patients for randomized clinical trials. (Stroke. 2009;40:2662-2668.)

Key Words: antiplatelet drugs ■ RCT ■ survey

STROKE and coronary heart disease are the leading causes of death and disability among adults. Among those who survive ischemic stroke, the long-term risk of major vascular events is at least 5% annually. In the last decades, several treatments for the prevention of recurrent stroke and other vascular events have been proven safe and effective. Randomized clinical trials (RCTs) indicated that aspirin alone reduces the relative risk of stroke and other major vascular events by 13%. The addition of extended-release dipyridamole (400 mg/d) to aspirin is expected to contribute a further 18% (9% to 26%) reduction in relative risk of serious vascular events.

Well-designed and well-conducted RCTs are the best method to estimate the effect of an intervention. Evidence from RCTs forms the basis for many general clinical guidelines. RCTs often have strict enrollment criteria, which mainly serve to limit the risk of complications. Moreover, stroke prevention trials often require additional risk factors or symptoms beyond the presenting clinical syndrome to select patients who are at a higher risk for an outcome event and to increase homogeneity and statistical power. One study found that additional enrollment criteria in data sets from trials conducted between 1976 and 1994 increased the risk of outcome events only slightly. The
authors also suggested that these additional enrollment criteria would make recruitment more difficult and might limit external validity.

The aim of our study was to estimate the eligibility for participation in landmark trials of antiplatelet drugs of an unselected group of patients with stroke or transient ischemic attack (TIA) from a national stroke survey. We assessed the effect of additional enrollment criteria by comparing baseline characteristics, cardiovascular event, and mortality rates between trial-eligible and trial-ineligible patients.

### Table 1. Major Inclusion and Exclusion Criteria of Selected RCTs

<table>
<thead>
<tr>
<th></th>
<th>ESPS-2</th>
<th>CAPRIE</th>
<th>TACOP</th>
<th>MATCH</th>
<th>ESPORE</th>
<th>ProFESS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug comparison</strong></td>
<td>ASA, DP, or both vs placebo</td>
<td>Clopidogrel vs ASA</td>
<td>Trifusal vs ASA</td>
<td>ASA vs placebo on top of clopidogrel</td>
<td>ASA vs ASA and DP</td>
<td>ASA and DP vs clopidogrel</td>
</tr>
<tr>
<td><strong>No. of participants</strong></td>
<td>6602</td>
<td>6431</td>
<td>2113</td>
<td>7599</td>
<td>2739</td>
<td>20333</td>
</tr>
</tbody>
</table>

**Major inclusion criteria**

- **Age, years**
  - >18
  - >21
  - >40
  - >40
  - No age limit
  - >55 or 50-54*

- **Diagnosis**
  - Stroke or TIA
  - Stroke or TIA
  - Stroke or TIA
  - Stroke or TIA
  - Stroke

- **Additional criteria**
  - None
  - None
  - None
  - 1 or more RF
  - mRS < 4
  - 2 or more RF*

- **Inclusion time window**
  - 3 months
  - >1 week
  - 6 months
  - 3 months
  - 6 months
  - 3/3-4 months*

**Exclusion criteria**

- **Related to diagnosis**
  - Cerebral or subarachnoid hemorrhage: Exclude
  - Cardiac source of embolism: Exclude
  - Stroke cause other than atherosclerosis: Exclude

- **Related to bleeding risk**
  - Gastrointestinal bleeding/peptic ulcer: Exclude
  - Bleeding disturbances: Exclude
  - History of thrombocytopenia, neutropenia: Exclude
  - Anemia: Exclude
  - History of intracranial hemorrhage: Exclude
  - Major surgery or trauma < 6 weeks: Exclude

- **Related to prognosis**
  - Uncontrolled hypertension: Exclude
  - Uncontrolled diabetes: Exclude
  - Severe renal dysfunction: Exclude
  - (Acute) hepatic dysfunction: Exclude
  - Hyperkalemia: Exclude
  - Unstable AP or MI < 3 months: Exclude
  - Endarterectomy < 1 month: Exclude

- **Related to current medical conditions**
  - Life-threatening disease: Exclude
  - Dementia: Exclude
  - Unconsciousness: Exclude
  - Dysphagia: Exclude
  - Pregnancy: Exclude
  - Severe disability: Exclude

- **Related to concomitant therapy**
  - Anticoagulants: Exclude
  - Nonsteroidal anti-inflammatory drugs: Exclude
  - Angiotension II receptor blocker: Exclude

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**Methods**

### Study Population

The Netherlands Stroke Survey was conducted in 10 centers in The Netherlands. The participating sites included 2 small centers (<400 beds), 5 of intermediate size (400 to 800 beds), and 4 large centers (>800 beds). Two centers were university hospitals. All centers had a neurology department, a neurologist with expertise in stroke, and a multidisciplinary stroke team. All but one hospital had a stroke unit, 8 were participating in a regional stroke service, and 9 were equipped for thrombolytic therapy. These institutions deliver care to approximately 10% of all patients with acute stroke in The Netherlands, and
Table 2. Characteristics of Patients Enrolled in Randomized Trials as Compared With Trial-Eligible and Trial-Ineligible Patients in the Netherlands Stroke Survey

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</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>886</td>
<td>6602</td>
<td>556 (63%)</td>
<td>330 (37%)</td>
<td>6431</td>
<td>286 (32%)</td>
<td>600 (68%)</td>
<td>2107</td>
<td>592 (67%)</td>
<td>174 (33%)</td>
<td>7599</td>
<td>224 (25%)</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>68.6</td>
<td>66.7</td>
<td>66.0</td>
<td>72.9</td>
<td>64.6</td>
<td>67.5</td>
<td>69.1</td>
<td>64.5</td>
<td>67.2</td>
<td>70.7</td>
<td>66.3</td>
<td>69.6</td>
</tr>
<tr>
<td>Male gender</td>
<td>56%</td>
<td>58%</td>
<td>59%</td>
<td>53%</td>
<td>64%</td>
<td>58%</td>
<td>56%</td>
<td>66%</td>
<td>80%</td>
<td>52%</td>
<td>63%</td>
<td>65%</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Cerebrovascular</td>
<td>19%</td>
<td>17%</td>
<td>24%</td>
<td>19%</td>
<td>18%</td>
<td>18%</td>
<td>20%</td>
<td>22%</td>
<td>18%</td>
<td>22%</td>
<td>27%</td>
<td>42%</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>58%</td>
<td>61%</td>
<td>58%</td>
<td>65%</td>
<td>19%</td>
<td>16%</td>
<td>19%</td>
<td>20%</td>
<td>22%</td>
<td>22%</td>
<td>27%</td>
<td>42%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>40%</td>
<td>23%</td>
<td>36%</td>
<td>42%</td>
<td>38%</td>
<td>41%</td>
<td>39%</td>
<td>39%</td>
<td>43%</td>
<td>34%</td>
<td>56%</td>
<td>45%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17%</td>
<td>15%</td>
<td>15%</td>
<td>21%</td>
<td>26%</td>
<td>18%</td>
<td>17%</td>
<td>24%</td>
<td>15%</td>
<td>22%</td>
<td>68%</td>
<td>38%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>33%</td>
<td>24%</td>
<td>35%</td>
<td>30%</td>
<td>22%</td>
<td>37%</td>
<td>32%</td>
<td>31%</td>
<td>34%</td>
<td>33%</td>
<td>48%</td>
<td>33%</td>
</tr>
<tr>
<td>Ischemic heart</td>
<td>10%</td>
<td>35%</td>
<td>9%</td>
<td>12%</td>
<td>12%</td>
<td>9%</td>
<td>10%</td>
<td>2%</td>
<td>10%</td>
<td>10%</td>
<td>5%</td>
<td>23%</td>
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<tr>
<td>disease</td>
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Qualifying event

| Stroke               | 62%           | 76%            | 50%               | 81%         | 100%           | 100%            | 44%         | 74%           | 48%             | 83%         | 79%            | 55%              | 64%          |
| TIA                  | 38%           | 23%            | 50%               | 19%         | 0%             | 0%              | 56%         | 26%           | 52%             | 17%         | 21%            | 46%              | 33%          |
| Stroke severity      |               |                |                   |             |                |                  |             |               |                 |             |                |                  |              |
| mRS 0–1–2            | 77%           | 69%            | 92%               | 51%         | 84%            | 73%             | 82%         | 91%           | 48%             | 74%         | 88%            | 73%              |              |
| mRS 3–5              | 23%           | 31%            | 8%                | 49%         | 16%            | 27%             | 18%         | 9%            | 52%             | 26%         | 12%            | 27%              |              |

Bold represents significant difference (P<0.05).

mRS indicates modified Rankin Scale.

Data Collection

Trained research assistants collected all data from the patients’ hospital charts within 5 days after discharge. Research assistants worked independently of the hospital team. All data were entered into the electronic case record form and transferred regularly to a central database through the Internet. The overall proportion of missing values was 0.2%. At 1 and 3 years, survival status was obtained through the Civil Registries. In all survivors, a telephone interview was conducted by trained research assistants based on a structured questionnaire, which was sent to the patient in advance. The data collectors corroborated the diagnosis by information obtained from general practitioners and hospital discharge letters. An experienced vascular neurologist checked all collected information and the subsequent diagnosis. Follow-up of the last patient was completed in December 2006. Follow-up information at 3 years, including vital status, was complete in 86% of the patients. More details on the study population and methods of data collection can be found in earlier publications.8,9

Trial Selection

To compare patients in the RCTs with those enrolled in the Netherlands Stroke Survey, we selected trials that focused only on antiplatelet therapy for secondary prevention after a recent ischemic stroke or TIA or trials that reported a subgroup analysis of patients with recent TIA or ischemic stroke. Registers (Cochrane database, Current Controlled Trials, PubMed [Medline], and EMBASE) were systematically searched. We included multicenter international RCTs that investigated or are still investigating antiplatelet therapy for secondary prevention. Enrollment had to be started after 1990. We included 6 trials: European Stroke Prevention Study 2 (ESPS-2), Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE), Triflusal versus Aspirin in Secondary Stroke Prevention (TACIP), Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH), European/Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT), and Prevention Regimen for Effectively Avoiding Second Strokes Trial (PROFESS).10–16

The first 3 trials assessed the effectiveness and safety of antiplatelet agents compared with aspirin or placebo and were published before the start of this survey.10,13,16 The results of MATCH (aspirin+clopidogrel versus clopidogrel alone).17 and ESPRIT (a 3-armed trial comparing anticoagulation with coumarin or aspirin with dipyridamole with aspirin alone) were published during the follow-up of our survey.4 Results of the PROFESS study (dipyridamole+aspirin versus clopidogrel alone) were published in 2008.18

Identifying Trial-Eligible Survey Patients

We excluded patients from the stroke survey who did not survive to hospital discharge, because those patients are ineligible for secondary prevention. Major enrollment criteria for the 6 RCTs were extracted from the published trial protocols10–16 and summarized in Table 1. We then distinguished 5 categories of exclusion criteria: related to diagnosis, prognosis, bleeding risk, current medical condition, and concomitant therapy. Exclusion criteria related to diagnosis and prognosis form the criteria aimed at selection of patients at high risk for (recurrent) vascular events. Exclusion criteria related to bleeding risk, current medical condition, and concomitant therapy represent safety criteria. We considered patients who were severely disabled and therefore not eligible for participating in a secondary prevention trial if they had a score on the modified Rankin Scale of >4 at discharge, when they were living in a nursing home before hospital admission, stay when residence after discharge was a nursing home for permanent residence, or when patients had a severely disabling recurrent ischemic stroke, intracerebral hemorrhage, or a hip fracture during their hospital stay.
End Points
The end point was the first occurrence of nonfatal myocardial infarction, stroke, or TIA, or death, during the follow-up period, which extended from hospital discharge until the 3-year follow-up visit. End points were patient-reported; confirmation was sought from general practitioners and hospital discharge letters. Cause of death was not registered in our survey.

Statistical Analyses
Dichotomous data are described as numbers and percentages, and continuous data are presented as means with SDs. Comparison between trial-eligible and trial-ineligible patients were analyzed by $\chi^2$ test. We estimated the number of patient-years at risk and combined this with the number of first nonfatal vascular events to compute an event rate. Data on patients who did not reach an end point were censored on the date of the patients’ last assessment. Nonfatal event rates and mortality rates were calculated and compared with $\chi^2$ tests. STATA10 statistical software was used for all analyses.

Results
The stroke survey population consisted of 972 patients who were evaluated because of ischemic stroke or TIA. Of all patients, 86 (8.8%) died before discharge, leaving 886 patients suitable for secondary prevention. In our survey, 238 (61%) of the 393 outpatients had a TIA and 60 (10%) of the 579 admitted patients had a TIA. In total, 38% of all patients had a TIA (Table 2). Mean follow-up was 2.4 years (SD, 1.2). In our study, 2% of the patients were lost to follow-up at 1 year and 13% at 3 years. There were no significant differences in age, risk profile, trial eligibility, mortality, or nonfatal event rate at 1 year between patients lost and patients with a complete follow-up at 3 years.

The demographic and clinical characteristics of the survey population are presented in Table 2. The patients were more often male (56%) than female and had a mean age of 68.6 (SD, 13) years (range, 21 to 95 years).

As the Figure indicates, varying proportions of patients enrolled in the stroke survey would have qualified for participating in the MATCH (25%), CAPRIE (32%), PROFESS (39%), ESPRIT (58%), ESPS-2 (63%), and TACIP (67%). Exclusion criteria aimed at selection of high-risk patients of an outcome event and being severely disabled were the most important reasons for disqualification of patients as trial-eligible. If severely disabled patients in our stroke survey would have been considered as trial-eligible, the proportion of trial-eligible patients would increase by 10% to 20%.

Trial-eligible patients differed from those who did not qualify for inclusion in a trial. Patients who did not qualify for participation in a trial were significantly older, except for the MATCH and PROFESS trials. Trial-eligible patients had significantly better scores on the modified Rankin Scale at the time of assessment for inclusion (Table 2). Consistent with the results of the selected trials, more trial-eligible patients were male. There were no consistent significant differences in the cardiovascular risk profile between patients who participated in trials and those who were trial-eligible.

Mortality rates of hospital survivors during the 3 years follow-up period differed between study-eligible and study-ineligible patients (Table 3). Trial-ineligible patients had a significantly higher mortality rate, 11.4 to 18.7%/year versus 5.4 to 9.6%/year in trial-eligible patients. The annual rate of TIA, stroke, or nonfatal myocardial infarction was 6.7% for all 886 patients. The rates of a first nonfatal vascular event (myocardial infarction, stroke, or TIA) were not increased in trial-eligible patients of all studies, except for the MATCH trial in which the trial-eligible patients had a tendency to have a vascular event more often.
Discussion

Our study showed that patients enrolled in international, multicenter RCTs of antplatelet treatment for secondary prevention after TIA and stroke are not fully representative of patients treated in daily practice. After applying the trials’ inclusion and exclusion criteria to the stroke survey population, 33% to 75% of all patients in our stroke survey were not eligible for participation. We show also that trial-eligible patients were younger and had a better clinical outcome than those who did not fulfill enrollment criteria. Because only a small proportion of patients in clinical practice are trial-eligible, the question should be raised whether it is justified to extrapolate the results of the RCTs to the clinic. For example, Mant et al.19 found important differences between the characteristics of patients with cerebrovascular disease in primary care with those of the participants in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial.20 This so-called lack of external validity or generalizability of RCT results may be one explanation for the widespread underuse in clinical practice of treatments that were beneficial in trials and that have been recommended in guidelines.21

Our results are consistent with findings of other studies in different clinical domains. In a review of 41 US National Institutes of Health RCTs, an average exclusion rate of 73%
was reported. Another study showed that of the candidates for thrombolysis in the Copenhagen stroke study, 96% were ineligible based on the various criteria of the relevant RCTs.

The strength of our survey was the inclusion of a large number of unselected and consecutively enrolled patients from multiple hospitals in The Netherlands with a confirmed diagnosis of TIA or stroke, leading to a cohort that is representative of clinical stroke care in The Netherlands.

A limitation of our study is that its scope is national. Most of the RCTs we studied enroll patients worldwide. Because of differences between countries in methods of diagnosis and management, our stroke survey is not completely representative of stroke care worldwide.

There was a lack of information on several minor exclusion criteria used in the RCTs we studied. When these data would have been available, the proportion of patients fulfilling the enrollment criteria would have been smaller.

In our study, we aimed to distinguish between trial-eligible and trial-ineligible patients in our clinical practice population. We considered patients trial-eligible if they fulfilled the inclusion criteria and had no major exclusion criteria. We excluded patients who were severely disabled at discharge, because they probably would not have participated in a RCT. If we had not done this, but strictly applied the enrollment criteria to all our stroke survey patients, 10% to 20% more patients would have been eligible, but in our opinion, this would not have been realistic.

Another limitation is that end points in the register were self-reported by patients; a telephone interview was conducted by trained research assistants based on a structured questionnaire. One could argue that, especially, the end point TIA is not a reliable outcome with the method of outcome ascertainment as used. However, we do not think that the use of this not-so-robust outcome measure does distract importantly from the findings of the study.

Our results may provide an optimistic view of the representativeness of clinical trials. Our survey involved voluntarily participating hospitals and therefore the results may be biased toward better than average practice with lower rates of recurrent vascular events.

The possibility of early inclusion of hospitalized patients with recent ischemic stroke, as was done in the PROFESS trial, may have biased the comparison with our cohort. However, patients were required to be “stable” and mortality within the first few days after stroke is mostly caused by the index event, not by recurrent vascular events. Therefore, we consider the risk of bias small.

In our study, we have focused on RCTs of antiplatelet treatment for secondary prevention in patients with TIA and stroke. This included trials that primarily included patients with TIA/stroke or reported a subgroup of patients with recent TIA or ischemic stroke. We chose this approach to directly compare our results of patients with stroke with those of patients with stroke in the trials. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) and Blockade of the glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO) trials, which also investigated antiplatelets in patients with stroke and TIA, did not report subgroup analyses of patients with stroke.

A last limitation is that we could only study nonfatal cardiovascular and cerebrovascular events, because cause of death was not available in our data set. Because it concerns a systematic difference, the comparison between trial-related inclusion and exclusion criteria will not be affected.

Enrollment criteria aimed at selecting patients at high risk of vascular events were ineffective in our survey population. For example, the MATCH trial, which required additional risk factors for eligibility, had the lowest proportion of study-eligible patients (25%) in our stroke survey. MATCH-eligible patients did not have a significantly increased risk of vascular events compared with MATCH-ineligible patients (Table 3), but there is a trend toward more vascular events in MATCH-eligible patients in contrast to the other trials.

Howard et al analyzed the consequences of requiring additional risk factors in trials, like in the MATCH trial. They found that additional eligibility criteria undermine generalizability. Our data indicate that ineligible patients are older, more often female, or had a more severe stroke. To our knowledge, no clinical trials have reported follow-up in excluded patients. Subgroup analyses in trials are not often reported, and individual patient meta-analyses of antiplatelet therapy in stroke are scarce. However, so far, subgroup analyses in trials and individual patient meta-analyses do not raise a concern for a differential treatment effect of antiplatelets among these subgroups. This provides further arguments for using wide inclusion criteria and for limiting exclusion criteria as much as possible in Phase III RCTs.

Our results confirm that RCTs investigating antiplatelets enroll patients who are only partially representative of the entire spectrum of patients with TIA or stroke in clinical practice. Furthermore, we demonstrated that currently used enrollment criteria were not successful in selecting patients at a high risk of a vascular event. However, the enrollment criteria were successful in selecting patients on safety criteria. Use of less strict enrollment criteria could result in easier, more efficient, and valid selection of patients for RCTs.

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Disclosures

None.

References

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