Differences in Medical and Surgical Therapy for Stroke Prevention Between Leading Experts in North America and Western Europe

Florian Masuhr, MD; Markus Busch; Karl M. Einhaupl, MD

Background and Purpose—Large multicenter trials have evaluated the benefit of different medical and surgical therapies to prevent stroke. However, the application of trial results to clinical practice remains uncertain for some areas of stroke prevention and has been discussed passionately among international experts. As part of a worldwide survey, the purpose of this analysis was to provide an informative and comparative view of the current practice of leading experts in North America (NA) and Western Europe (WE), where most of the large prevention trials have been performed.

Methods—The survey was performed worldwide among 185 neurologists who are currently leading the discussions of stroke prevention practices. It contained questions on the use of antiplatelet agents, oral anticoagulation, and surgery for the prevention of ischemic stroke. The population of this present analysis is the two groups of experts from WE (n = 73) and NA (n = 48) exclusively.

Results—Of each group, >90% responded to the survey. Nearly all respondents reported prescribing aspirin in patients at risk of atherothrombotic stroke, but significant differences between NA and WE are shown by the recommended doses (P < .0001): aspirin doses of >500 mg daily are given exclusively by American participants (36%), whereas doses <200 mg are recommended only in Europe (51%). Eighty-six percent of American versus 59% of European respondents reported using ticlopidine as their second choice (P < .005), and 23% of respondents from WE used warfarin compared with 5% from NA (P < .05). The reported use of anticoagulants in patients with atrial fibrillation increased in accordance with the patient’s individual risk of stroke, but respondents from WE were more reluctant to use anticoagulants in patients older than 75 years. Relatively higher target international normalized ratio values were reported by European respondents. Nearly all participants recommend carotid endarterectomy in patients with symptomatic carotid stenosis. The use of carotid endarterectomy in asymptomatic patients was significantly more common among responding experts from NA (48% versus 28%; P < .05), particularly in patients with >95% stenosis (89% versus 53%; P < .0005).

Conclusions—This analysis shows significant differences in several areas of stroke prevention practices between leading experts from NA and WE. These differences may be explained partly by divergent results of trials from the two continents, but in some areas of controversy currently available trial data are not sufficient to form an international consensus to guide daily clinical practice. (Stroke. 1998;29:339-345.)

Key Words: aspirin ■ atrial fibrillation ■ carotid endarterectomy ■ North America ■ stroke prevention ■ ticlopidine ■ warfarin ■ Western Europe

During the last decade, many randomized multicenter trials have been performed in the field of stroke prevention, and spectacular results seemed to have answered important open questions. However, several of the available trial results are viewed controversially by leading experts, and there is an ongoing international discussion in different areas of stroke prevention, particularly in regard to the optimal dose of aspirin in patients with minor atherothrombotic stroke or TIA\(^5\)\(^\text{-}^6\) and the use of CEA in asymptomatic patients.\(^6\)\(^\text{-}^8\) Apparently, even results from large trials with a high level of significance do not inevitably lead to standardized recommendations for daily clinical practice.

We conducted a worldwide survey among leading international experts about their daily management of stroke-prone patients to evaluate the international acceptance of trial results and the need for further clinical studies to guide therapeutic decisions. The results of this survey have been published.\(^9\) Since most of the large stroke prevention studies have been performed in North America (NA) and Western Europe (WE), a direct comparison between experts from the two continents is of particular interest, and the number of participants from WE and NA was sufficient to perform a detailed statistical analysis. The purpose of this present analysis is to provide an informative and comparative view of the current practice of leading experts in NA and WE.
Subjects and Methods

The complete survey was performed worldwide among 185 experts of stroke therapy and prevention, ie, neurologists who had published articles on clinical aspects of this topic in peer-reviewed journals indexed in Medline and Current Contents and are thereby leading the international or regional discussions. Of these 185 neurologists, 73 were residents of WE (including Northern, Western, and Southern Europe but excluding Eastern Europe), 48 were practicing in North America, and the remaining 64 were from South America, Eastern Europe, Africa, Australia, or Asia. The results of the survey have been published for the entire population. This present study is a comparative analysis between the two groups of experts from WE (n = 73) and NA (n = 48) exclusively.

The questionnaire experts were identified in two ways: (1) members of the editorial and advisory boards of peer-reviewed journals were chosen if they had published articles primarily focusing on clinical aspects of stroke therapy indexed in Medline and Current Contents; and (2) a Medline search was used to identify the national experts for all countries by selecting all clinical articles on stroke published between 1983 and February 15, 1996, that had been written by authors of the respective countries. The authors whose articles were predominantly centered on stroke prevention or therapy rather than on general or pathophysiological aspects were chosen as national experts. If more than one eligible expert was traced to the same institution, we chose the one with the higher number of clinical articles, presuming that prevention practice is homogeneous among physicians of one clinical center.

The data were collected between February and August 1996. A questionnaire was designed for use in a mail survey. It contained 21 questions on the general use of different treatment strategies and was divided into four sections: (1) use of antithrombotic agents in patients with a past history of TIA or minor ischemic stroke of noncardiogenic origin; questions focused on the choice of agents, the preferred daily doses, duration of therapy, procedures in case of inefficacy, and different treatments for women/patients with major stroke; (2) treatment of patients with nonvalvular AF according to their age and risk profile; (3) general indications for surgery to prevent stroke in patients with asymptomatic or symptomatic arteriosclerotic disease of major extracranial arteries; and (4) questions to determine the factors that have been important to the physician for developing her/his therapeutic concept. The questionnaire can be reviewed on the Internet (http://www.ukrw.de/ch/neuro/quest.html).

The survey started on February 15, 1996. Nonrespondents were sent two additional mailings of the questionnaire. All physicians who had not answered by July 1 were contacted by telephone and were sent a last questionnaire by fax. The data collection process ended on August 15, 1996.

The frequency distributions of the different reported treatment strategies were analyzed for both groups separately. The given percentages of participants who reported using a certain therapy are related to the number of valid answers (n) to the specific question. If a question had been omitted or was answered vaguely or if more than one answer was given, it was regarded as invalid data and did not enter the statistical analysis. Differences in frequency distribution of reported therapies between both groups were statistically tested for significance. The statistical analyses included cross-tabulations, the Mann-Whitney U and Wilcoxon rank tests, and the χ² test.

Results

Overall, 92% of questioned NA neurologists (n = 44) and 93% of questioned WE neurologists (n = 68) responded to the survey in time and formed the basis for frequency analysis. Two questionnaires from Europe arrived after the deadline and could not be considered.

Antithrombotic Therapy

Almost all participating experts in both NA (n = 44) and WE (n = 65) reported prescribing aspirin as their first-choice antiplatelet agent for the prevention of atherothrombotic stroke in patients with a past history of TIA or minor ischemic stroke of noncardiogenic origin (96% and 94%, respectively). In NA, two participants (4%) reported using warfarin in these patients. In WE, three respondents (4%) reported prescribing aspirin combined with dipyridamole, and one reported prescribing ticlopidine.

Asked for their second-choice agent if contraindications, adverse effects, or recurrent attacks demanded an alternative treatment, 86% of American (n = 43) and 59% of European respondents (n = 65) reported using ticlopidine, whereas 7% and 12%, respectively, reported prescribing a combination therapy of aspirin and dipyridamole. Warfarin was the reported second choice of 23% of WE participants compared with 5% of responding experts from NA. The overall difference concerning the reported second-choice agents was significant at P < .01. The comparison of the frequencies of reported use of the single agents showed significant differences for ticlopidine (P < .005) and for coumarin (P < .05).

Regarding the third-choice agent, 78% of NA participants (n = 37) named warfarin, 11% ticlopidine, and 5% aspirin in combination with dipyridamole. In WE (n = 57), 49% of participants reported using warfarin as third choice, 25% aspirin and dipyridamole combined, 16% ticlopidine, and 9% dipyridamole alone. This difference was significant (P < .01) for the entire spectrum of agents. The comparison of the frequencies of reported use of the single agents showed significant differences (P < .05) for coumarin and for the combination of aspirin and dipyridamole. Aspirin in combination with warfarin or ticlopidine, and low-dose heparin were named only once.

The reported aspirin doses ranged from 30 to 1300 mg per day. Fig 1 shows the frequency distribution of the reported use of low (30 to 175 mg), medium (200 to 400 mg), and high (500 to 1300 mg) daily aspirin doses among American and European respondents. In NA (n = 44), medium doses of aspirin was reported by 61%, high doses by 36%, and low doses by 2% of responding experts. Of 68 Western European participants, 51% recommend low-dose aspirin, 47% medium-dose aspirin, and 2% high-dose aspirin. This difference in frequency distribution was significant (P < .0001). Of all respondents, 10 American experts (23%) reported using aspirin doses > 800 mg per day. Of these, 5 experts reported prescribing a dose of 1300 mg daily, and the other 5 preferred doses between 975 and 1200 mg. The highest dose found among European participants was 500 mg daily, which was reported by 1 expert. Doses of ≤ 60 mg per day were found among 7 European experts (10%); 4 of 5 Dutch experts preferred 30 mg daily. Of 8 European participants who reported using 75 mg of aspirin per day, 5 were from Sweden and 2 from Great Britain.

Selected Abbreviations and Acronyms

ACAS = Asymptomatic Carotid Atherosclerotic Study
AF = atrial fibrillation
CEA = carotid endarterectomy
INR = international normalized ratio
NA = North America
TIA = transient ischemic attack
WE = Western Europe
One American respondent reported a dose of <300 mg daily (81 mg). The most commonly reported dose was 300 to 350 mg per day in both NA and WE (61% and 38%, respectively). In WE, nearly one third (29%) prescribed doses of 100 to 175 mg daily.

Regarding the duration of prophylactic treatment, 100% of American (n=43) and 85% of European (n=66) respondents reported prescribing their first-choice agent indefinitely, and 14% of European experts reported prescribing their first-choice agent for 2 to 3 years. Asked for the treatment of patients who suffered from a major stroke, approximately two thirds of responding experts in both NA (n=44) and WE (n=67) said they would not choose a different treatment regimen than in patients with minor strokes or TIA (68% and 66%, respectively). There was a statistically significant difference (P<.005) between the two groups regarding the treatment of women: 25% of American (n=44) and 6% of European (n=68) respondents do treat women and men differently. Of the 25% Americans, 73% used ticlopidine in women.

In case of recurrence of cerebral ischemia despite treatment, approximately one third of responding experts from both NA (n=44) and WE (n=67) reported increasing the dose of their favorite agent first (36% and 57%, respectively), whereas 57% and 61%, respectively, immediately proceed with their second-choice agent. Respectively, 40% and 37% reported combining different drugs at some time in the search for an effective therapy, especially aspirin with warfarin or ticlopidine.

Atrial Fibrillation
The Table shows the frequency distribution of the use of warfarin and aspirin according to the patient’s clinical characteristics. In both groups of participants, the reported use of warfarin generally increased with the increase of the patient’s risk of stroke (AF plus no additional risk; AF plus concomitant risk factors; AF plus history of cardioembolism), whereas the frequency of the use of aspirin decreased in the same direction.

The reported frequencies of use of warfarin and aspirin in patients younger than 75 years show no significant difference between NA and WE.

Concerning the treatment of patients older than 75 years, the reported frequency of use of warfarin is higher among respondents from NA, whereas more European respondents reported using aspirin in these patients. This difference was significant at P<.05 for patients of this age with AF only and for patients with cardioembolism as well as AF.

Respondents from NA recommended target INR values between 1.75 and 3.0. Of these, 65% reported a target INR between 2.0 and 3.0, 17% reported a target INR of ≤2.0, and 18% reported a target INR of 3.0. Among WE participants, INR values between 1.75 and 3.5 were recommended; 46%

### Percentages of Participants Reporting Use of Warfarin and Aspirin in Patients With Nonvalvular AF

<table>
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<tr>
<th>Patient’s Age, y</th>
<th>Additional Risk Factors*</th>
<th>Cardioembolic Event</th>
<th>Warfarin NA</th>
<th>Warfarin WE</th>
<th>Aspirin NA</th>
<th>Aspirin WE</th>
<th>No Treatment NA</th>
<th>No Treatment WE</th>
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<td>No</td>
<td>65</td>
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NA indicates the percentage of participants from North America who reported using the respective treatment; WE, percentage of participants from Western Europe who reported using the respective treatment.

* Risk factors such as hypertension, diabetes, or cardiac disease.
reported a target INR of $\geq 3.0$, 46% reported a target INR between 2.0 and 3.0, and 8% reported a target INR of $\leq 2.0$.

**Vascular Surgery**

All participants from NA ($n=44$) and nearly all of their European colleagues ($n=67$) (99%) reported recommending CEA for patients with a symptomatic stenosis of the extracranial portion of the internal carotid artery. In both NA and WE, the majority of respondents (84% and 78%, respectively) reported suggesting CEA if the degree of stenosis is $\geq 70\%$; 7% and 10%, respectively, recommend the procedure for patients with $>80\%$ stenosis, and again 7% and 10% use it for patients with $>60\%$ stenosis. One European participant does not operate at all, and one American participant waits for a $>90\%$ stenosis. The vast majority of both groups (approximately 98% each) reported that they also recommend surgery for patients with an additional stenosis of the contralateral carotid artery.

The reported use of CEA in asymptomatic patients is summarized in Fig 2. Of all American respondents ($n=44$), 48% reported recommending CEA in asymptomatic patients, while 28% of their European colleagues ($n=67$) do so. This difference was significant at $P<.05$. Within Europe, considerable regional variations were found: 71% of participants from Southern European countries ($n=17$) reported using CEA in asymptomatic patients, whereas only 7% of experts from Northern European countries ($n=15$) do so. For the majority of experts from both continents who recommended an operation to asymptomatic patients, a $>80\%$ stenosis is an indication for surgery (70% of 21 in NA and 63% of 19 in WE). Twenty percent of the 21 American experts and 16% of the 19 experts from WE reported operating on patients with $>70\%$ stenosis, and 10% and 21%, respectively, reported operating on patients with $>60\%$ stenosis.

The reported frequencies of use of CEA in asymptomatic patients changed according to concomitant characteristics of the disease. Asked for their management of patients with an asymptomatic high-grade ($>95\%$) stenosis, 89% of participants from NA and 53% of WE respondents reported using CEA. This difference was significant ($P<.0005$). The fast progression of the disease was a criterion for operation for more than half of all respondents from both continents (55% and 58%, respectively). Forty percent of responding American experts and 24% of their European colleagues reported recommending surgery in the case of detected vessel-wall ulceration (not significant at $P>5$).

The majority of experts from both continents (nearly 90% each) agree in prescribing aspirin for those asymptomatic patients who do not undergo surgery; the remaining respondents administer warfarin, ticlopidine, or no treatment.

Asked for their management of patients with a stenosis of the vertebral artery, 30% of responding experts from NA and 15% of participants from WE reported considering vascular surgery or percutaneous transluminal angioplasty. Reported indications were proximal stenosis of the vertebral artery, particularly bilateral, vascular malformations, and proven embolism in the vertebrobasilar area.

Concerning extracranial-intracranial arterial bypass surgery, 26% of the participating American experts and 14% of their European colleagues reported using this therapy in a few exceptional cases.

**Discussion**

The results of this survey demonstrate differences in several areas of medical and surgical stroke prevention between participating leading neurologists from NA and WE. Although aspirin was the first-choice antplatelet agent in patients with a recent TIA or minor stroke in both groups, recommended doses varied significantly. Whereas responding European experts only exceptionally (2%) prescribe aspirin doses $\geq 500\text{ mg}$, 36% of American participants prefer a dose of $\geq 500\text{ mg}$. In contrast, doses $<200\text{ mg}$ daily are used by 51% of European respondents but by only 2% of their American colleagues. This dissent in dosing policies is substantial and differs from the results of the only survey among leading experts that has been published thus far: Hennerici$^{10}$ reported a "secret consensus" in favor of low and very low aspirin doses among 44 members of the Advisory/Editorial Boards of Cerebrovascular Diseases. Only two experts reported preferring a daily dose of $\geq 500\text{ mg}$, whereas 42 (95%) recommended doses of $\leq 325\text{ mg}$ and 9 experts (20%) recommended a dose of $\leq 100\text{ mg}$. However, this survey did not examine regional differences, and the consensus might be due to a smaller number of participants from NA.
Our results reflect the ongoing dispute regarding optimal aspirin dose between some European and American experts published in several articles and editorials.\(^1,^4\) Whereas several neurologists from WE follow the results of low-dose aspirin trials and argue that these doses are as effective as high doses but cause fewer side effects,\(^3,^5\) Barnett et al\(^4\) point to the smaller risk reduction achieved in low-dose trials (7% to 18%) compared with high-dose trials (25% to 42%), and Dyken et al\(^6\) emphasize that the increase in side effects is small and does not contraindicate higher doses if they are more effective. The reported use of lower aspirin doses among European respondents in our survey might be influenced by the fact that all low-dose trials have been performed in Europe.\(^1,^11-^13\) Regional differences exist even within the continent itself: the use of very low doses (30 to 75 mg) was mainly reported by respondents from the Scandinavian and Benelux countries, where the corresponding trials have been performed.\(^12,^13\)

The arguments presented in these “aspirin wars” are largely based on indirect and selective comparisons of different trial data, mini-meta-analyses, or subgroup analyses of individual studies, and it appears that available trial data are not sufficient to form an international consensus, although the large meta-analysis of the Antiplatelet Trialists’ Collaboration found “no appreciable evidence that either a higher aspirin dose or any other antiplatelet regimen was more effective than medium dose aspirin in preventing vascular events.”\(^1,^14\) Our survey confirms the need for a randomized trial to settle the ongoing aspirin wars and to determine the optimal aspirin dose against which any new antiplatelet agent must be tested to obtain indisputable results.

Although a majority of responding experts from both continents reported using ticlopidine as their second-choice agent if recurrent attacks occur, the survey shows a significant difference in the use of anticoagulants. Almost one fourth of all participating European neurologists prefer warfarin as second choice compared with only 5% from NA. This result is surprising because the effectiveness of anticoagulants in patients with TIA or minor stroke of noncardioembolic origin is still not proven. Since participants were not asked to explain why they prefer a certain therapeutic regimen, it can only be suspected that respondents from WE are more likely to switch to a different therapeutic principle rather than to try a different antiplatelet agent. The majority of responding American neurologists consider warfarin as the third option if patients do not respond to aspirin and ticlopidine.

A combination of aspirin and dipyridamole was more frequently found among responding European experts, but this difference was not significant. Since the now published results of the Second European Stroke Prevention Study\(^15\) had only been reported to a congress when this survey was performed,\(^16\) an increased use of aspirin and dipyridamole by European experts may be seen in the future.

There is no clear scientific evidence that recurrent attacks of cerebral ischemia necessitate a change of medical treatment, although this may be common clinical practice. However, one third of participating experts in both groups reported increasing the dose, and two thirds reported changing to their second-choice agent if recurrent cerebral ischemic events occur. The implications of these results should be viewed critically. The question of whether to continue the initial antiplatelet agent or switch to a second antiplatelet drug or even to anticoagulants cannot be answered from the available published trials. The fact that only one participant from WE reported continuing the initially chosen treatment may be due to the fact that “continuation of treatment” was not explicitly named as a possible answer. We asked the participants how they would proceed if the chosen therapy was ineffective, and possible answers included “increase dose,” “change to second choice,” “combine different agents,” and “others.” The phrasing of the possible answers may have been suggestive, so that a change from the initial therapy was anticipated.

In this survey, significantly more American respondents (25% versus only 6% in WE) reported using ticlopidine in women, thereby questioning the equal efficacy of aspirin for stroke prevention in both sexes. This difference may be due to the fact that thus far only three European trials found a significant benefit of aspirin in female patients with previous TIA or minor stroke,\(^12,^15,^17\) whereas women did not benefit in two other studies.\(^11,^18\) On the other hand, ticlopidine was effective in men and women in both American ticlopidine trials.\(^19,^20\) The large meta-analysis of the Antiplatelet Trialists’ Collaboration,\(^1\) which found no difference for aspirin between the two sexes, appears to have settled this question.

The reported practices of stroke prevention in patients with nonvalvular AF depended on the patient’s age, on concomitant risk factors (such as hypertension, diabetes, or cardiac disease), and primarily on the patient’s history of cardioembolic events. Several randomized trials have shown that anticoagulants can reduce the risk of cardioembolic stroke by approximately 70%, whereas the prophylactic efficacy of aspirin is equivocal.\(^21-^23\) Consequently, the reported use of warfarin generally increased with the increase of the patient’s risk of stroke, whereas the frequency of the use of aspirin decreased in the same direction, with no difference for patients younger than 75 years. In patients older than 75 years, respondents from WE were less likely to prescribe anticoagulants, even for high-risk patients with a previous cardioembolic event. This difference is probably due to concerns about the safety of anticoagulants in this age group, which are based on results from Stroke Prevention in Atrial Fibrillation II. In this trial, a significant increase of bleeding complications, particularly intracranial hemorrhages, occurred with warfarin but not with aspirin in patients older than 75 years.\(^24\) However, several participants emphasized that the patient’s age is not the main criterion for the decision to use warfarin, but that other factors such as a history of falls or bleeds, the patient’s competency and mental state, and monitoring facilities are more crucial.

Overall, responding experts from WE recommended higher intensities of anticoagulation for all given clinical settings. The highest target INR value reported by American neurologists was 3.0 and 83% use a target value between 1.75 and 3.0, whereas nearly 50% of the responding experts from WE reported target INR values \(\geq 3.0.\) This different practice corresponds to recommendations in the respective continents: the Fourth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy recommended target INR values of 2.0 to 3.0,\(^24\) whereas the European Atrial

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Fibrillation Trial study group proposed an optimal oral anticoagulation between 2.0 and 3.9.25

There was a clear consensus among both groups to recommend CEA for patients with a severe symptomatic stenosis of the internal carotid artery. However, we did not explicitly ask for the method of measurement of the degree of stenosis (North American Symptomatic Carotid Endarterectomy Trial or European Carotid Surgery Trial), and the results show a trend rather than a particular comparable degree of stenosis for which CEA is recommended.

This clear unanimity was not found for asymptomatic patients. Almost 50% of all participating experts from NA reported the use of CEA compared with 28% from WE (P<.05). This difference was even more impressive concerning the management of asymptomatic patients with a nearly occluded internal carotid artery: 89% of American and 53% of European respondents recommended CEA in these patients (P<.0005). These numbers reflect the contrary view of the ACAS results by several experts from NA and WE. The American ACAS trial showed a significant benefit of CEA in asymptomatic patients with a carotid stenosis ≥60% and a surgical risk <3%.26 In view of these results, a Multidisciplinary Consensus Statement from the American Heart Association recommended CEA for asymptomatic patients, whereas some European experts point to the little absolute risk reduction achieved by CEA for asymptomatic carotid stenosis and its lack of cost-effectiveness and recommend caution in the interpretation of ACAS results.8

In this survey, participating experts from NA were generally more likely to use surgical measures for stroke prevention in patients with a stenosis of either the carotid or the vertebral artery than their colleagues from WE.

The experts questioned in our survey have access to the same published clinical studies, and most of them attend the same international meetings where the results of these trials are discussed and interpreted. In a scientific discipline, one would therefore expect a high level of agreement in the interpretation of these studies and conclusions for clinical practice. We did not investigate several factors such as the age of the investigator, site of training, size of clinical practice, or the number of patients actually seen by the experts during the last year, and we cannot exclude that those factors may have influenced the divergent treatment recommendations of experts from both continents. However, it seems unlikely that the significant differences found in the survey, eg, the different aspirin dosing policies, are sufficiently explained by those factors. Indeed, if such factors were of major importance for the reported differences, one would expect a random distribution of the divergent treatment recommendations among the experts from both continents. It may be assumed that the recommended lower aspirin doses in WE and the more frequent use of carotid surgery in asymptomatic subjects in NA are at least partly explained by the location where the respective studies have been performed.

The results of this survey do not report the actual clinical practice of general practitioners or of primary or secondary health care centers but report the treatment recommendations of opinion leaders who define the “dogma” of medical treatment in the field of stroke prevention. It can be assumed that actual clinical practice may be further influenced by additional factors such as the physician’s medical specialty, budget issues, and the availability of medical facilities. Hence, a definite conclusion about the practice cannot be drawn.

In conclusion, the results of this study do not show the real use of different pharmacological agents for stroke prevention or the real frequency of CEA for asymptomatic carotid artery stenosis in both continents but rather reflect the medical dogma in the field of stroke prevention set by experts in NA and WE.

Appendix

List of Participants


References


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