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Adherence to Secondary Stroke Prevention Strategies – Results from the German Stroke Data Bank

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Secondary stroke prevention · Adherence to medication · Aspirin · Clopidogrel · Oral anticoagulation

Abstract
Only very limited data are available concerning patient adherence to antithrombotic medication intended to prevent a recurrent stroke. Reduced adherence and compliance could significantly influence the effects of any stroke prevention strategies. This study from a large stroke data bank provides representative data concerning the rate of stroke victims adhering to their recommended preventive medication. During a 2-year period beginning January 1, 1998, all patients with acute stroke or TIA in 23 neurological departments with an acute stroke unit were included in the German Stroke Data Bank. Data were collected prospectively, reviewed, validated and processed in a central data management unit. Only 12 centers with a follow-up rate of 80% or higher were included in this evaluation. 3,420 patients were followed up after 3 months, and 2,640 patients were followed up one year after their stroke. After one year, 96% of all patients reported still adhere to at least one medical stroke prevention strategy. Of the patients receiving aspirin at discharge, 92.6% reported to use that medication after 3 months and 84% after one year, while 81.6 and 61.6% were the respective figures for clopidogrel, and 85.2 and 77.4% for oral anticoagulation. Most patients who changed medication switched from aspirin to clopidogrel. Under the conditions of this observational study, adherence to stroke prevention strategies is excellent. The highest adherence rate is noticed for aspirin and oral anticoagulation. After one year, very few patients stopped taking stroke preventive medication.

Various drugs are currently used for secondary stroke prevention, e.g. aspirin, clopidogrel, ticlopidine and aspirin plus dipyridamole [1]. Current conventions and forums focus on the best strategies for stroke prevention [2–5]. Recommendations from various experts are based on small to moderate differences between various drugs. These differences result from large-scale trials sponsored by pharmaceutical companies (e.g. CAPRIE, ESPS-2) [6, 7]. Very few data on patient adherence are available for secondary stroke preventive medication. In 1994, Ko-

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miya et al. reported the results of a study in 159 outpatients and 79 inpatients [8]. Seventeen outpatients (about 10%) had inadequate thrombocyte aggregation inhibition and were considered non-compliant. Adherence to antiplatelet drugs, as well as to antihypertensive and lipid lowering drugs, is subject of numerous studies [9–16]. While 80% adherence to antihypertensive drugs after one year is considered satisfactory, reductions up to 50% after one year are reported [17]. In the Aspirin Myocardial Infarction Study, 85% of the patients taking aspirin and 78% treated with a placebo kept their medication [18]. A major risk factor for recurring vascular events or death is nonadherence to medication. This also causes major economic problems. Non-compliance accounted for more than half of the drug failures under antihypertensive treatment [19]. Adherence to a prescribed drug, moreover, is perhaps related to other factors such as patient's education and attitude to disease [20], perceived or experienced side effects [21, 22], patient specific reminders [23], medical regimen with a convenient intake frequency [24], adherence control and physician's attitude regarding therapy [23]. Major problems also include potential side effects and the patient's non-verbalized anxiety towards any chemical agent [23]. Also, cerebrovascular disease-related cognitive impairment can reduce the ability to adhere to a specific medication [26]. Finally, physicians, too, reliant upon the limited means of the German health care system, cannot always afford to prescribe costly new drugs, like the thienopyridines.

Various methods to detect adherence to a given drug were implemented, e.g. direct measurement of the drugs or their metabolites in blood, urine or saliva, count of remaining and distributed pills, record of drug prescription, and self-reports of the physicians or patients [27]. Recently, new computerized containers were additionally used for drug adherence control [17, 28]. Self-reports could overestimate drug adherence when compared to more objective methods such as drug inventory or plasma levels [29]. This study, planned as a part of the German Stroke Data Bank, interviewed patients by telephone to detect their drug adherence. We present the data on stroke preventive strategies as self-reported after 3 months and 1 year following an index stroke event.

Patients and Methods

Data were collected prospectively within the German Stroke Data Bank of the Stiftung Deutsche Schlaganfall-Hilfe in 23 neurological departments during a 2-year period beginning January 1, 1998. All hospitals have an acute stroke unit and in most cases also a neurological intensive care unit. They serve areas of 100,000 to 1 million inhabitants and are the principle health care providers for stroke patients in their regions. Cranial CT or MRI, extra- and transcranial Doppler sonography and/or angiography of brain-supplying arteries (including CT or MR angiography), ECG and/or ECG monitoring, basic blood tests and additional laboratory investigations were performed in all patients. The majority of patients was examined by transthoracic or transesophageal echocardiography. Local review boards approved the protocol of the Stroke Data Bank, and most patients consented that, apart from the medical data, their personal records be transferred and kept in the central data management center. In accordance with extensive guidelines, the data collected included age, sex, time of event and admission, risk factors, vascular comorbidities, prior medication, baseline neurological impairments, as rated on the National Institute of Health Stroke Scale (NIH-SS), functional independence pre-stroke and after admission, as rated on the Barthel Index and modified Rankin Scale, results of ancillary tests, morphology and localization of infarction, TOAST classification of ischemic stroke, acute therapy, onset and severity of medical plus neurological complications, secondary prevention, and neurological impairments as well as functional independence at discharge. The outcome, assessed twice, first at 3 and later at 12 months, included causes of death, recurrent stroke, compliance with secondary prevention, risk factor modification, and functional independence, as rated on the Barthel Index and modified Rankin Scale.

All data were collected on a standardized questionnaire by the local neurologists. Scores were quantified by local researchers who were familiar with the NIH-SS from other clinical trials or from the NIH-SS training video.

Between 1998 and 1999, a total of 8,200 patients with ischemic stroke or TIA were entered into the data bank. In order to assure accurate data, only patients from such centers were considered that had followed-up more than 80 % of their patients. 12 centers – Minden, München-Harlaching, Essen, Heidelberg, Leipzig, Benjamin Franklin Berlin, Bonn, München-Grosshadern, Frechen, Jena and Bielefeld – met these criteria and registered a total of 5,219 patients. 215 patients (4.1%) died in the admitting hospital and 219 (4.2%) had no data available on secondary prevention at discharge. Of the remaining 4,785 patients, secondary prevention could be assessed at first follow-up (within 70–180 days after the initial event) in 3,420 patients (71.5%), while 204 patients (4.3%) had died since discharge from the hospital and 1,161 patients (24.3%) were either unable to be reached or unable to provide any information on their secondary prevention (see fig. 1).

Of the 3,420 patients with information available at the first follow-up, the secondary prevention could be assessed in 2,640 (77.2%) at a second follow-up (within 330 and 450 days after the event). 155 patients (4.5%) had died since the first follow-up, and 625 patients (18.3%) could not be reached during this time or could provide no information on their secondary prevention (see fig. 1).

Data Evaluation and Statistics

After a final consistency check with the source data at site, the questionnaires were sent to the data management centers at the University of Essen and the Stiftung Deutsche Schlaganfall-Hilfe, Gütersloh, where they were rechecked by two physicians for accuracy and entered into the data bank by trained personnel. Missing or questionable data were reinvestigated by the local neurologist. Monthly reports and clinical site visits further ensured data quality.

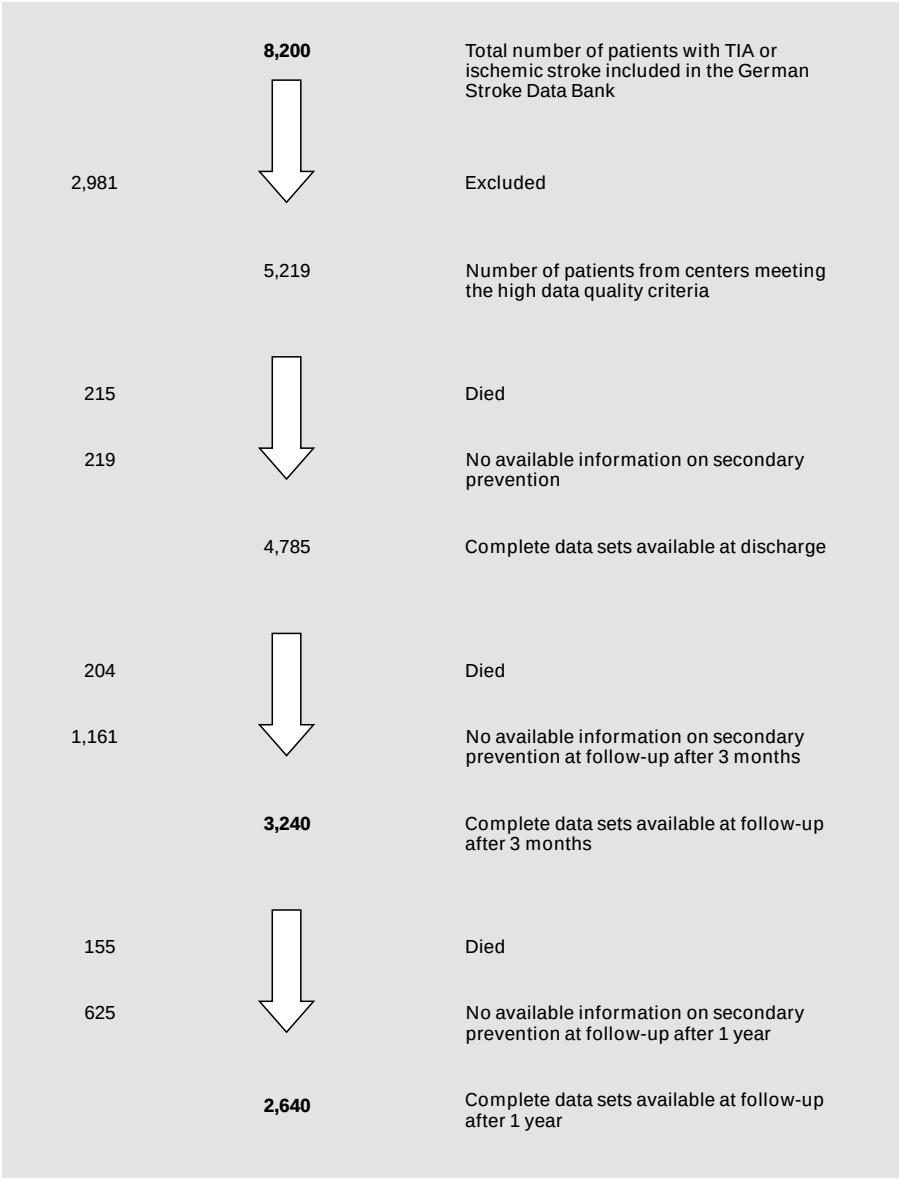

Fig. 1. Patients in the German Stroke Data Bank included in this study.

If the patient did not consent to submission of his personal data, the participating center forwarded only anonymous data to the data management center, and performed the follow-up interview on site upon bimonthly request. Otherwise, the follow-up at 3 and 12 months was performed by central telephone interview. If the patient could not be reached via telephone or his physician, a follow-up letter was sent. If no information on patient outcome could still be obtained, the citizen registry was checked for current address or death.

Categorical variables are presented as percentages. Comparisons of categorical variables between different medications were performed with the χ^2 test, according to Pearson, with 1 degree of freedom. Statistical analyses were performed using the program package SPSS version 9.0.

Results

According to the distribution of secondary stroke preventive strategies at discharge from hospital, only 117 patients (2.5%) had no medication to prevent stroke recurrence. Antiplatelet drugs were used in the majority of patients (3,429 patients = 71.7%). Various forms of anticoagulation (i.v. heparin, s.c. heparin or oral anticoagulation) were used in 1,239 patients (25.9%).

After 3 months, at first follow-up, complete data sets were available for 3,420 patients. Only 60 patients (1.6%) received no secondary prevention treatment. The majori-

Table 1. Adherence to aspirin in patients 3 months after the initial event, changes to secondary medications

	Patients	Percent
Still on aspirin	1,617	92.6
Changed to		
Clopidogrel	78	4.5
Oral anticoagulation	50	2.8
Ticlopidine	29	1.7
No secondary prevention	23	1.3
Total	1,744[a]	

Some patients were using several secondary preventive strategies simultaneously, therefore the total percentage exceeds 100%.
[a] On aspirin at discharge from hospital and followed-up after 3 months.

Table 2. Adherence to aspirin in patients 1 year after the initial event, changes to secondary medications

	Patients	Percent
Still on aspirin	1,134	84
Changed to		
Clopidogrel	103	7.6
Oral anticoagulation	53	3.9
Ticlopidine	22	1.6
No secondary prevention	61	4.5
Total	1,350[a]	

Some patients were using several secondary preventive strategies simultaneously, therefore the total percentage exceeds 100%.
[a] On aspirin at discharge from hospital and followed-up after 3 and 12 months.

ty of patients was still using aspirin. Of 1,747 patients treated at discharge with aspirin in doses between 80 and 325 mg, according to the recommendations of the American Heart Association (AHA), 1,617 patients (92.6%) were still taking aspirin after 3 months. Table 1 shows the change in secondary prevention for all patients receiving aspirin at discharge from the index hospital stay.

Of 262 patients discharged on ticlopidine, only 183 patients (69.8%) were still taking ticlopidine after 3 months, while 65 patients (24.8%) had switched to aspirin and 14 patients (5.3%) to clopidogrel.

Of 553 patients discharged on clopidogrel, 452 patients (81.6%) were still taking this medication after 3 months, and 120 patients (21.7%) were on aspirin. (The numbers may exceed 100% due to some cases using more than one preventive medication simultaneously, for example the combination of aspirin and clopidogrel).

647 patients took oral anticoagulation at discharge, and 551 patients (85.2%) were still taking anticoagulants after 3 months. Only 65 patients (10%) had changed to an antiplatelet agent, while both strategies were used in 28 patients (4.3%).

Of 46 patients without any secondary stroke prevention at discharge, 24 patients took an antiplatelet agent after 3 months and 2 patients were on oral anticoagulants.

A total of 2,640 patients could be followed up after 1 year. At this time, only 116 patients (4.4%) did not take any medication for stroke prevention. The majority of 1,968 patients (74.5%) was on antiplatelet agents and 532 patients (20.2%) were on oral anticoagulation.

Of 1,350 patients on aspirin, the largest group on a single medication at discharge, 1,184 patients (84%) were still taking aspirin after one year. Table 2 depicts the changes from aspirin to other strategies, especially emphasizing clopidogrel as an alternative medication.

Of 197 patients initially discharged on ticlopidine, 104 patients (52.8%) were still taking this medication after one year, while 70 patients (35,5%) had changed to aspirin and 26 patients (13,2%) to clopidogrel. In the clopidogrel group, 261 of 424 patients (61.6%) were still on clopidogrel, while 132 (31.1%) had changed to aspirin and 25 (5.9%) to oral anticoagulation.

Unexpectedly, 401 of 518 patients (77.4%) discharged on oral anticoagulation were still on this medication after one year, and 86 (16.6%) had switched to aspirin as the main alternative.

During the study period, the German drug administration authority did not approve the combination of aspirin plus dipyridamole.

The causes of death were defined in 204 patients who died at 3 months: 67 (32.8%) died from their initial stroke or a recurrent cerebrovascular event, 7 (3.4%) died following an intracerebral bleeding, 35 (17.2%) died from another vascular event, 51 (25%) died from a non-vascular disease, and in 44 (21.6%) patients the cause of death was unknown.

Another 40 patients (25.8%) died between 3 months and one year from the cerebrovascular disease: 3 (1.9%) from an intracerebral haemorrhage, 26 (16.8%) from a vascular event, 56 (36.1%) from a nonvascular disease and in 30 patients (19.4%) the underlying cause of death was unknown.

The group of the patients which were followed for the whole study period (non-dropout group) and those who could not be followed (dropout group) differed significantly by the initial NIHSS (4.7 vs. 6.5, $p < 0.05$) and the gender distribution (male 76.1% vs. female 73.1%, $p < 0.05$), the age distribution was similar.

The stroke recurrence rate in the adherent group was 6.8% in patients without a change in their secondary prevention regimen.

Discussion

This evaluation of the German Stroke Data Bank revealed an unexpectedly high adherence to secondary stroke prevention. 2,460 patients were surveyed until one year after their stroke, and only 4% did not use any kind of antithrombotic medication for secondary stroke prevention.

Compared to other fields in cardiovascular medicine where the rate of adherence was reported as substantially lower [30], 96% adherence for any stroke prevention is an extremely high rate. How can this be explained?

First, the German Stroke Data Bank includes only patients from the leading stroke care centers. Most patients were briefed extensively on the disease, its underlying causes, the importance of stroke prevention and the disastrous results of non-adherence. Providing ongoing health care, from the acute care facility to the rehabilitation center and the primary physician, is standard practice in Germany. These possible reasons would increase the demand for excellent stroke management. This would also suggest, moreover, further evidence for the correlation between low-adherence and sub-optimal patient care [23, 31–33].

Second, our method of self-reporting adherence could overestimate the actual adherence. Interviewing patients by telephone, a frequently used indirect method, has a low accuracy [34]. Other indirect methods in use are therapeutic outcome, pill count, and computerized compliance monitoring [17, 27, 28, 35, 36]. More sophisticated methods such as electronic distribution devices, physician or patient records, and inventories appear advantageous compared to simple self-report or interview technique [29, 36]. Objective methods, such as plasma level determination of a drug, detection of metabolites in urine, saliva or blood, and detection of effects caused by the drug under investigation [37, 38] proved to be the most reliable monitoring of drug adherence [10, 34]. However, it was suggested that a satisfactory data quality on adherence can be expected when patients are personally interviewed or called by telephone [39, 40]. No rigorous comparison between indirect methods, like that used in our study, and objective methods are available yet. In large scale studies, like the German Stroke Data Bank, interviews or self-reports are the only workable adherence detection methods, since objective methods are too costly. Other inexpensive methods like online information from local pharmacies and/or general practitioners are prohibited by law in Germany or impossible with aspirin as a free over the counter medication. Taking into account a 10% error margin on telephone interviews, an 85% adherence rate still reflects the upper range of reports on patient adherence [11].

Third, the relative high loss of patients at the two follow-up steps may also be responsible for the high adherence, since the adherence in non-reporting patients may be much weaker than in the patient group still participating in the follow-up. The two groups of patient (dropout and non-dropout) did not differ in age, but the dropout group had slightly more females and more severe initial NIHSS. How stroke severity affects adherence is not determined until now. The loss of patients at the different follow-up steps is high, but in large scale well-performed and well-controlled pharmaceutical trials, similar rates for non-compliance with very low dropout rates were reported [6, 7]. In CAPRIE [6] 21.2% (4,059 out of 19,185) of all patients stopped taking the trial medication, the loss of patients was 0.13% (49 patients). In ESPS-2 1,690 out of 7,054 patients stopped the continuous intake of the trial medication, 452 wrong entries were reported and 0.6% (42 patients) were lost, in total 31% of the patients which entered the initial study were not included in the final data analysis [7].

The reported adherence implies that the patient is still taking the respective medication, but not every single dose. In studies on drug adherence using electronic records, only 50–60% of all patients took exactly the prescribed medication, while 5–10 % did not take any medication. Approximately 30–45% experienced setbacks, but took most of the medication [41]. Data concerning the daily adherence to medication used for secondary stroke prevention cannot be provided.

Besides compliance to medication, adherence is a term, implying many other different components. Non-compliance may be a major cause of non-adherence, but other complex medical, psychological and social influences may also result in non-adherence. We are of course not able to differentiate between the various variables in this large-scale study. Therefore, we need specific

observational studies with limited numbers of participants to further clarify the influences on adherence, and to quantify the impact of non-compliance as a cause of non-adherence in stroke prevention. The stroke recurrence rate was 6.8% in the first year after the initial stroke and at the lower margin of an expected rate.

The results of this study concerning individual drugs prove especially important for three medication regimens: aspirin, thienopyridines and oral anticoagulation.

Adherence to aspirin is favorable and higher than to any other drug used for secondary stroke prevention in Germany. While this reflects most recent scientific recommendation [4, 5, 42, 43], high aspirin adherence may also result from socioeconomic pressure, which hinders primary care physicians from using more expensive drugs like thienopyridines. The change pattern to other regimens gives some insight into the reasons for non-adherence. Patients who switched to clopidogrel, ticlopidin or oral anticoagulation experienced either new cerebral events or side effects from aspirin therapy (in total 13.1% after one year). Only 4.5% were thought to be non-compliant and stopped any secondary prevention. Non-adherence to aspirin after one year can therefore basically explained by medical reasons in 75% of patients, while only approximately 25% of patients appeared non-compliant.

Adherence to clopidogrel and ticlopidin as typical thienopyridines was much weaker than adherence to aspirin, but most patients who changed their medication switched to aspirin. Therefore, non-adherence to thienopyridines is most likely not the effect of non-compliance. Medical reasons, side effects, and also socioeconomic problems may account for the high rate of patients who changed to less expensive aspirin.

Oral anticoagulation is thought to be potentially more harmful and also less convenient for patients because of the need for frequent coagulation controls. When patients were discharged on oral anticoagulants from the primary stroke care center [44], adherence was high and even after one year close to 80%, second after aspirin. This might be explained by the common scientific consensus, that anticoagulants are first choice in atrial fibrillation and cardioembolism, and therefore are less likely to be changed by the treating primary care physician.

Data concerning other secondary stroke prevention strategies like blood pressure control, smoking cessation, and treatment of lipid metabolism disorders from the German Stroke Data Bank are in preparation to be reported.

Conclusions

In summary, our study provides adherence data to stroke preventive medication in a large cohort of stroke patients in Germany. It demonstrates that a surprisingly high number of patients is adherent to any form of medical stroke prevention after one year. Aspirin is most widely used and best adhered to after 3 months and one year. Almost 85% of patients who initially received the drug are still taking it one year later. Oral anticoagulation adherence is similar to aspirin adherence, while the thienopyridines depict a reduced adherence of about 60% after one year. Limited financial resources may account for this finding. In general, non-adherence may be linked to various social, medical, and personal factors. Although adherence to secondary stroke prevention strategies in our study seems high, further research needs to clarify the underlying factors responsible for non-adherence.

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