Platelet aggregation inhibitors in primary and secondary prevention of ischemic stroke
Gorenoi V, Kulp W, Greiner W, Graf von der Schulenburg JM

Background

The ischaemic stroke (IS) is an acute focal neurological deficit due to insufficient blood circulation in the brain, which is caused itself by at least temporary closure of arterial vessels. IS is one of the most frequent cause of death in Germany. Approximately 255 strokes per 100000 occur in Germany every year.

Many drug-based therapies in addition to non-drug interventions are used to prevent the first or recurrent IS (primary or secondary prevention of IS), - among them the use of thrombocyte aggregation inhibitors (or thrombocyte function inhibitors, TAI).

The main action mechanism of TAI is to inhibit the contact of thrombocytes with vessel endothelium, thrombocytes as well as with other blood cells. This mechanism is associated with main side effect of these substances - bleeding from the internal or external cerebral vessels. For the classic prevention (through a long-term therapy) oral TAI are of predominant importance. The daily therapy costs for the most important oral TAI (acetylsalicylic acid - ASA, ticlopidine, clopidogrel and combination of ASA with dipryidamole) range from 0.03 € (ASA) to 2.30 € (ticlopidine).

Objectives

The medical evaluation addresses questions on the medical efficacy of the TAI administration in the prevention of IS as compared to the management of risk factors alone as well as to the administration of anticoagulant drugs. From an economical point of view, the cost-effectiveness of the use of TAI in the primary and secondary prevention of IS as well as their impact on health-related quality of life are of outstanding importance.

Medical evaluation
Methods

The literature search for articles published after 1997 was conducted in December 2003 in the most important medical databases. The analysis was performed on the basis of the most up-to-date meta-analyses of randomised controlled trials (RCT) as well as of new RCT. The data for stroke, bleeding complications as well as for the combined endpoint “severe vascular events” (SVE: death or stroke or myocardial infarction) were extracted from the studies.

The results of the studies were checked on methodical quality, heterogeneity and then summarised in the meta-analyses. Estimates of avoided and additional events per 1000 assigned patients were calculated at a 95 % confidence interval.
Results

The medical analysis included data from 184 RCT (vs. placebo) and from 22 RCT (vs. anticoagulant drugs).

- **The comparison of TAI with the management of risk factors alone and the comparison of different TAI regimes.**

1. In primary as well as in secondary prevention of IS the administration of TAI reduces the rate of IS by 20 to 35 % (relative risk reduction) compared to the management of risk factors alone (absolute risks 4.8 % vs. 6.6 %; p < 0.00001). This risk reduction is associated with a relative reduction in the rate of SVE (death or stroke or myocardial infarction) by 16 to 26 % (absolute risks 10.0 % vs. 12.4 %; p < 0.00001) and with a relative increase in the rate of bleeding complications by 45 to 93 % (absolute risks 1.6 % vs. 0.9 %; p < 0.00001). The calculated effect estimates may be generally applied to all patients’ categories and subcategories investigated. The absolute reductions in IS and SVE are definitely higher than the absolute increase in bleeding complications in all patients’ categories and subcategories, however they are relatively similar to this absolute increase in a subpopulation with a low risk of IS and SVE.

The present analysis revealed the efficacy in the reduction of SVE-rates for the following TAI: acetylsalicylic acid (ASA, over 75 mg/day), dipyridamole, ticlopidine, picotamid, trapidil, cilostazol as well as for the combination of ASA with dipyridamole. The reduction in the rate of stroke was yielded only for ASA (over 150 mg/day), dipyridamole, cilostazol as well as for the combination of ASA with dipyridamole.

2. No differences could be identified between any of the various applied ASA doses.

3. In comparison to ASA an advantage was yielded for clopidogrel (as well as for thienopyridines in general) with regard to the reduction in the rate of SVE in patients with a previous thrombotic event (IS, MI or peripheral arterial obstructive disease), for ridogrel regarding the rate of stroke in patients after MI as well as for ticlopidin, triflusal and sulfipyrazon regarding the rate of major bleedings (in the case of triflusal only for patients after IS or TIA).

4. The combination of dipyridamole retard with ASA reduced the rate of stroke compared to ASA alone in patients after a previous stroke or TIA. The combination of clopidogrel with ASA showed an advantage compared to ASA alone in the reduction of SVE in patients after acute coronary syndrome without ST-segment elevation in EKG or in patients after percutaneous coronary intervention, however, it was associated with additional bleeding complications. By the combination of oral GB IIb / IIIa-antagonists orbifiban or lotrafiban with ASA an increase in the rate of major bleedings without benefit in efficacy was yielded.

- **TAI in comparison with the use of anticoagulants**

1. The anticoagulants showed better efficacy than TAI in patients with atrial fibrillation with regard to the rate of IS and in patients after acute cardiovascular events with regard to the rate of all SVE (at least for warfarin in comparison to ASA). Especially pronounced is the preventive effect in patients with atrial fibrillation. In contrast, the administration of ASA after acute or previous stroke or TIA compared to high-dosed anticoagulants is safer with regard to the rate of bleedings, haemorrhagic strokes and all recurrent strokes.

2. In patients with atrial fibrillation the pure warfarin anticoagulation (INR = 2.3-2.4) is more effective as compared to the combined low-dosed combination therapy of warfarin plus ASA (INR = 1.1-1.3) with regard to the rate of IS without a significant increase in major bleedings. In patients after acute
myocardial infarction the combined 75 to 81 mg/day ASS plus warfarin regimes (INR = 2.2-2.4) obtained similar results to those of pure warfarin anticoagulation (INR = 2.8-3.2), but showed a significant increase in the rate of major bleedings in comparison to the use of ASS in a high dose (160 mg/day) alone.

Discussion

Despite potential study biases the definite impact of individual factors could not be settled. Therefore, the study results were considered as valid for the populations and technology modifications investigated (intern validity). The transferability of the results from the studies to other populations and technology modifications (extern validity) is limited. The most up-to date publications evaluated only a part of the studies included in the present analysis. They show, however, quite similar results to those of the present report.

Economical evaluation

Methods

An extensive literature search was conducted in medical and health-economic data bases. Moreover, relevant health-economic journals were hand searched for studies related to the objectives of the HTA report. The articles should have been published between 1997 and 2003. Additionally, websites of respective neurological societies were reviewed for important information and pharmaceutical manufactures of TAI were contacted in order to obtain unpublished studies.

To be included in the analysis, the study should deal with costs, cost-effectiveness or cost-benefit aspects of the primary or secondary prevention of IS. Publications on acute treatment of IS and on exclusively prevention of myocardial infarction were excluded. Only publications in German, English, French and Spanish were considered. The evaluation of the identified studies was based on a 25 item criteria catalogue for methodical quality of health-economic studies. Results are presented in a descriptive way.

Results

Only three methodologically appropriate studies were identified. For four other studies this was not the case, especially due to a high degree of intransparency in pharmacoeconomical modeling. The identified studies address the use of ASA, clopidogrel as well as the combination of dipyridamole with ASA in the primary and secondary prevention of IS.

Based on identified studies, the administration of ASA in primary prevention of IS (no previous IS) appears to be cost-effective only in high-risk patients after previous myocardial infarction. The cost-savings in this patient group by the use of ASA are expected from a societal perspective. In the secondary prevention of IS the administration of ASA is associated with cost-savings in all patients without ASA intolerance. This statement is somewhat limited because of only one identified study for the endpoint IS. From the economic point of view new studies on this issue are desirable due to the political importance of IS prevention.

The use of clopidogrel is not cost-effective owing to the lack of data on beneficial medical efficacy as compared to ASA with regard to IS. Due to substantially higher costs of clopidogrel, ASA possesses a higher cost-effectiveness. Therefore, clopidogrel should be administered in the case of
ASA ineffectacy or intolerance.
The administration of the combination of ASA with dipyridamole in the secondary prevention of IS may be a cost-effective alternative as compared to ASA alone. The following cost-effectiveness ratios were determined:
- £ 3200 (€ 4800) / Life-year with functional restrictions,
- £ 1800 (€ 2700) / Life-year without functional restrictions,
- £ 1900 / (€ 2900) per avoided stroke,
- £ 600 / (€ 900) stroke-free life-year.

Discussion

While interpreting the results of economic analysis it should be considered that the applied models in the studies were not constructed for the German context. However, these results seem to be generally transferable as the costs and resource used are relatively similar in Germany. Pharmacoeconomic studies for the German context are desirable not only because of IS epidemiological importance.

Summarising discussion of all results

The exclusive consideration of stroke prevention is limited, as physicians expect to avoid all thrombotic events by administration of TAI. The importance of non-drug interventions has to be emphasized in the primary prevention of IS.

Conclusions

From a medical point of view TAI may be recommended for primary and secondary prevention of IS in patients with a high risk of severe vascular events and with a low risk of bleeding complications. At the same time, a reduction of all SVE and an increase in bleedings may be expected. The absolute reduction of thrombotic events is in general definitely higher than an absolute increase in bleeding complications. In patients with a low risk of SVE (patients without previous stroke or myocardial infarction) the difference between avoided events in relation to additional bleedings is lower, making the use of TAI in these patients less reasonable or not reasonable at all.

Generally, ASA in a dose over 75 mg/day should be administered. Other TAI such as dipyridamole, ticlopidin or clopidogrel and (due to limited data only for definite patient groups) picotamid, trapidil, cilostazol, triflusal, ridogrel or sulfinpyrazon as substitutes as well as dipyridamole or clopidogrel as additional drugs to ASA may be given. The use of ticlopidin, sulfinpyrazon and triflusal is beneficial as compared to ASA with regard to bleeding complications. Clopidogrel has an advantage in comparison to ASA in patients with previous thrombotic event with regard to the risk of all SVE without influencing the risk of stroke. The combination of ASA with oral GPII / IIIa-antagonists should only be administered in special indications due to increased risk of bleeding complications.

In patients with atrial fibrillation, ASA is definitely less efficient than anticoagulation and should only be administered in the case of increased risk of bleeding complications. In patients with acute coronary syndrome without ST-segment elevation in EKG and in patients after percutaneous coronary intervention, a combination of ASA with clopidogrel should be preferred after consideration of the risk of major bleeding. In patients after acute myocardial infarction the ASA is less effective than oral anticoagulants, however it may be used in combination with a low-dose warfarin or alone in patients with a higher risk of bleeding complications.
After stroke or TIA, ASA should be preferred instead of high-dosed anticoagulants due to fewer bleeding complications. Especially in these patients the combination of ASA with dipyridamole retard is advantageous with regard to the rate of recurrent strokes over ASA administration alone.

The use of TAI, especially of low-dosed ASA in secondary prevention and also for some indications in primary prevention, may be cost-saving both from the statutory health insurance as well as from the societal perspective. This conclusion is limited as it is based on one pharmacoeconomic study only. The clinical input data of this study, which were generated in a meta-analysis, however possess a high degree of validity.