Antiplatelet agents – Clopidogrel (Plavix)

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This is a translation of version 1, published on October 29, 1999.
The latest version of this report is not available in English.

Published Jan 10, 2000
Version 1

Findings by SBU Alert

Clopidogrel is a recently approved drug which helps prevent the formation of blood clots in vascular diseases resulting from atherosclerosis. There is strong evidence that drugs which inhibit blood clots, eg, acetylsalicylic acid (ASA), have prophylactic effects in patients with atherosclerotic disease. The effects of clopidogrel have been compared to the effects of ASA in a randomized, controlled study involving over 19 000 patients. The diseases targeted for prevention were stroke, myocardial infarction, and fatal cardiovascular disease. After a followup of 1.9 years, the authors found a 0.5 per cent absolute difference favoring clopidogrel. Hence, 196 patients must be treated with clopidogrel for one year to prevent one additional case of the diseases listed above (beyond the number of cases prevented by ASA). The cost of preventing one case would be approximately 1.2 million SEK.

There is good* evidence on the short-term effects of treatment. The long-term results of treatment exceeding one to three years are not available, nor are published findings on the cost-effectiveness of treatment.

The annual cost per patient for clopidogrel is approximately 6 000 SEK higher than for ASA. A shift from ASA to clopidogrel would provide a marginal health benefit, but would substantially increase the costs for drugs.

*This assessment by SBU Alert uses a 4-point scale to grade the quality and evidence of the scientific documentation. The grades indicate: (1) good, (2) moderate, (3) poor, or (4) no scientific evidence on the subject. For further information please see “Grading of evidence”.

Alert is a joint effort by the Swedish Council on Technology Assessment in Health Care (SBU), the Medical Products Agency, the National Board of Health and Welfare, and the Federation of Swedish County Councils.

Technology

Cardiovascular diseases are accompanied by a risk for blood clot formation where platelets collect (thrombocyte aggregation). This can lead to vascular constriction or the release of small clots which follow the blood stream to the peripheral vessels. Blood clots may cause myocardial infarction, stroke, or occlusion of peripheral vessels. Clot formation can be counteracted by antiplatelet drugs. Scientific studies have shown that ASA has an antiplatelet effect. In recent years, other drugs with different active mechanisms have appeared on the market. Their effects on platelets are similar to ASA. The latest in the series of new antiplatelet agents is clopidogrel (Plavix).

Target group

Clopidogrel is registered for use against atherosclerotic events such as myocardial infarction, stroke, and death from vascular causes in patients with symptomatic atherosclerotic disease. The target groups for treatment are patients with ischemic stroke, TIA (Transitory Ischemic Attack, ie, temporary lack of oxygen to the brain), myocardial infarction, or established peripheral artery disease. There are no confirmed epidemiological data on the size of the target group. Acute myocardial infarction, chronic ischemic heart disease, and occlusion of the arteries in the brain are three common causes of death. In 1996, these disorders accounted for 28 per cent of male mortality and 24 per cent of female mortality in Sweden. Around 17 000 new cases of ischemic stroke and TIA per year are estimated to be candidates for secondary prophylaxis. The corresponding figure for myocardial infarction is approximately 25 000. The number of patients with peripheral artery disease (angina in the legs) may be similar in volume. Since patients may require treatment for several years, the size of the target group is several hundred thousand of individuals.

Relation to other technology

Clopidogrel has basically the same secondary prophylactic applications as ASA (Trombyl, Bamycor) and, to some extent, ticlopidine (Ticlid) and dipyridamol (Persantin Depot) with ASA (Asasantin Retard). Because of its superior safety profile, clopidogrel should replace ticlopidine when ASA cannot be used.

Patient benefits

The effects of clopidogrel were studied in a randomized trial, CAPRIE [1]. The study randomized patients either to treatment with 75 mg of clopidogrel once per day or 325 mg of ASA once per day. Patients with any of the following disorders were included in the study: ischemic stroke/TIA (≥1 week and ≤6 months before randomization); myocardial infarction (≤35 days before randomization); and peripheral atherosclerotic disease. Current or expected need for anticoagulants, other drugs which have antiplatelet effects, or NSAID were obstacles to participation. Oversensitivity to ASA was also a reason for exclusion.

In total, the study included 19 185 patients at 384 clinical centers in 16 countries. The average followup time was 1.9 years (arithmetic mean value). Primary outcome variables included any serious events such as ischemic stroke, myocardial infarction, or death from cardiovascular disease. When the study concluded, the following results were observed:

	Clopidogrel	**ASA**	
No. patients	9 599	9 586	
No. patient years	17 636	17 519	
No. disease events	939	1 021	
Incidence per year	5.3%	p=0.043,	5.8%

- Relative risk reduction 8.7 per cent (95 per cent confidence interval 0.3 per cent to 16.5 per cent)
- Absolute risk reduction 0,5 per cent (95 per cent confidence interval 0.02 per cent to 0.98 per cent)

For clopidogrel to prevent one more "serious event" than ASA, 196 patients must be treated for 1 year, where the actual number with 95 per cent probability lies between 102 and 4 178 patients.

Several secondary outcome variables were also analyzed in the study. The following were reported: ischemic stroke, myocardial infarction, vascular death or amputation; vascular death, death from stroke, infarction, or death from unexpected causes; death regardless of cause. None of the combinations of outcome variables showed statistically significant differences among the treatment groups.

Complications and side effects

The side effects reported in the 19 000 patients in the CAPRIE study [1] were few and relatively minor. Clopidogrel did not appear to be associated with an increased risk for neutropenia (reduced number of white blood cells) as with ticlopidine.

The following side effects were more common with clopidogrel than with ASA:

- Skin rash, 6 per cent with clopidogrel versus 5 per cent with ASA
- Diarrhea, 5 per cent with clopidogrel versus 3 per cent with ASA

The following side-effects were more common with ASA than with clopidogrel;

- Stomach problems and nausea, 18 per cent with ASA versus 15 per cent with clopidogrel
- Gastrointestinal bleeding, 2.7 per cent with ASA versus 2 per cent with clopidogrel
- Abnormal liver function, 3.2 per cent with ASA versus 3 per cent with clopidogrel

Costs and cost-effectiveness

In 1998, when clopidogrel was introduced, sales totaled 2.7 million SEK. During the first four months of 1999, sales reached 7.5 million SEK. The cost for entire group of antiplatelet agents in 1996 was 74 million SEK. In 1998, the cost was 103 million SEK. Based on sales during the first quarter of 1999, the prognosis for the year is 130 million SEK.

The cost for Trombyl, the ASA agent used most in Sweden for the indications mentioned, was nearly 52 million SEK in 1998. The treatment cost per day is normally 0.35 SEK. This converts into 148 million treatment days in 1998 for Trombyl. If clopidogrel had been used instead of Trombyl for 10 per cent of the treatment days, ie, 14.8 million days, the drug costs would have increased by 250 million SEK (14.8 million multiplied by 17 SEK).

One year of clopidogrel treatment costs around 6 200 SEK while the cost for ASA is around 200 SEK, ie, a difference of 6 000 SEK. The drug costs of avoiding one event for 1 year would be approximately 1.2 million SEK at NNT=196. A more comprehensive economic assessment should also consider the direct costs for care due to side effects, the savings from fewer events, and the indirect costs. The net costs should then be weighed against the potential health benefits.

A model analysis from Great Britain used the cost of a stroke event and data from the CAPRIE and ESPS-2 studies [1,2] to compare the cost-effectiveness of clopidogrel, ASA, and a combination of ASA and dipyridamol [3]. The findings show that combinations of ASA and dipyridamol, in comparison to ASA alone, result in extra costs between 8 000 and 11 000 GBP per prevented stroke. However, if one compares clopidogrel with ASA, the additional costs are 111 000 GBP (approximately 1.45 million SEK) per prevented stroke. The preliminary results of the study were presented at a convention, but the evidence is weak.

Structure and organization of health services

Clopidogrel treatment does not require a structural or organizational change in health services. However, an increase in the cost for new drugs would require resources to be redistributed within the total framework of health and medical care.

Ethical aspects

No ethical complications are foreseen.

Experts

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