Clopidogrel versus acetylsalicylic acid for the secondary prevention of vascular diseases[1]

- Final report -

[Commission No. A04-01A]

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Topic: Evaluation of the benefits and harms of clopidogrel versus acetylsalicylic acid for the secondary prevention of vascular diseases

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EXECUTIVE SUMMARY

Background

The Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* [IQWiG]) was commissioned by the Federal Joint Committee (*Gemeinsamer Bundesausschuss*) to evaluate the benefits and harms of clopidogrel versus acetylsalicylic acid (ASA) for the secondary prevention of vascular diseases.

Research question

The aims of this evaluation were:

- the comparative evaluation of the benefits and harms of clopidogrel and ASA as antiplatelet monotherapy for secondary prevention in patients with manifest ischaemic heart disease (IHD), ischaemic cerebrovascular disease (ICVD), or symptomatic peripheral arterial disease (PAD).

and

- the specific comparative evaluation of benefits and harms of a switch in therapy to clopidogrel versus continuation of existing ASA therapy for secondary prevention (as described above) in patients who had previously suffered an adverse event during ASA therapy (in particular a thromboembolic event or severe bleeding).

The focus of this evaluation was on patient-relevant therapy goals.

Methods

This evaluation was conducted on the basis of randomised controlled trials (RCTs) available on the research questions outlined above. For this purpose, a systematic search for literature published before October 2005 was conducted in the databases MEDLINE[2] (including Pre-MEDLINE), EMBASE,[3] and CENTRAL.[4] In addition, reference lists of relevant secondary publications (systematic reviews, HTA reports) were searched, as well as study registers, study results registers, and publicly accessible regulatory documents. Furthermore, queries

[2] Medical Literature Analysis and Retrieval System Online

[3] Excerpta Medica Database

[4] Cochrane Central Register of Controlled Trials

concerning relevant published and unpublished studies were sent to the manufacturer of clopidogrel.

The evaluation included RCTs that compared clopidogrel with ASA therapy in patients with vascular disease (IHD, ICVD, or PAD). The literature search was conducted by 2 reviewers independently of one another.

The evaluation of the study quality and study results (patient-relevant therapy goals and outcomes) was presented in a preliminary report, which was published on the IQWiG website (www.iqwig.de). Interested parties could submit written statements, which were discussed in a scientific hearing. The final report was subsequently produced.

Results

The literature search identified 5 published relevant studies and 1 additional unpublished, potentially relevant study. Of the published studies included in this evaluation, 3 showed major and 2 showed minor deficiencies with regard to the study and publication quality.

The CAPRIE trial (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; CAPRIE 1996), which included nearly 20 000 patients and had a mean follow-up of nearly 2 years, was the main source of information for most of the patient-relevant outcomes investigated in this report.

The Chan trial (Chan 2005) is particularly relevant with regard to patients with a history of ulcer bleeding under ASA, and for whom either a continuation or switch of therapy are potential treatment options.

The CAPRIE trial included a similar proportion of patients (approx. 6300-6450 in each group) with recent ischaemic stroke (likely to be of atherothrombotic origin), recent myocardial infarction (MI) (with at least 2 indications of ischaemia), or symptomatic PAD (with existing or history of intermittent claudication). In this review, these subgroups are referred to as the ICVD, IHD, and PAD subgroups, respectively. In the overall study population, a statistically significant difference for the predefined composite primary outcome (MI, ischaemic stroke, or vascular death) was shown in favour of clopidogrel. No significant differences were noted for the predefined secondary outcomes (including all-cause mortality). For the primary outcome, patients in the clopidogrel group had an average rate per year of 5.32%, compared with 5.83% in the ASA group (absolute risk difference: 0.51%). This difference was mainly caused by the subgroup of patients with symptomatic PAD. Under consideration of the statistically significant heterogeneity test (p=0.042), the results of the CAPRIE trial should be assessed differently for the 3 subgroups. In the IHD and ICVD subgroups, it cannot be determined with

any certainty whether clopidogrel had a slightly beneficial effect, no effect, or even a detrimental effect compared with ASA. In contrast, the evidence of the superiority of clopidogrel versus ASA in patients with symptomatic PAD for the composite primary outcome can be regarded as being sufficiently certain.

Several secondary analyses of the CAPRIE trial assessed the efficacy of clopidogrel versus ASA in patients with additional vascular risks. All of these secondary analyses showed major methodological deficiencies. None of these analyses provided sufficient evidence that in patients with these additional risks, the efficacy of clopidogrel versus ASA should be viewed differently than for the overall study population. The results of the CAPRIE trial have so far not been confirmed by a second, completely published study.

The other studies did not substantially contribute to the complex "vascular/thromboembolic events".

According to preliminary results of the additionally identified and so far unpublished WATCH trial (Warfarin and Antiplatelet Therapy in Chronic Heart Failure) in patients with (mainly ischaemic) heart failure, numerically more thromboembolic events occurred under clopidogrel than under ASA. Though repeatedly requested, no further results were provided by the organisation conducting the study, the sponsor (Sanofi-Aventis), or the principal investigator.

With regard to adverse effects, one needs to distinguish between studies including lower-dose (75-160 mg daily) and higher-dose (325 mg daily) ASA (which does not have a greater therapeutic effect), as bleeding complications in particular possibly occur less frequently under lower-dose ASA. Of the included studies, only the CAPRIE trial was conducted with a higher ASA dose not usually used in Germany for secondary prevention of vascular diseases. Therefore, its contribution is limited with regard to the comparison of the occurrence of adverse effects of ASA versus clopidogrel. Even under higher-dose ASA, intracranial haemorrhages were not statistically significantly more frequent than under clopidogrel. The data on the incidence of severe gastrointestinal bleeding were inconsistent. There was also no significant difference between treatment groups for all-cause mortality and study discontinuations due to adverse events.

Two trials (Chan 2005 and Ng 2004), using lower-dose ASA, were explicitly designed to evaluate safety aspects. The studies investigated whether, in patients with a history of symptomatic gastroduodenal ulcers/erosions under ASA (Chan 2005: bleeding; Ng 2004: bleeding or dyspepsia), a switch to clopidogrel reduced the risk of recurrent bleeding or increased the healing rate of ulcers. Due to major methodological deficiencies, no valid

conclusions can be drawn from the Ng trial. The Chan trial also showed major deficiencies. However, under consideration of the additional information supplied by the main author of the study publication, at least an indication was provided that in patients with a history of ulcer bleeding under ASA, a combination of lower-dose ASA plus the proton pump inhibitor (PPI) esomeprazole was more effective in preventing recurrent ulcer bleeding than a switch to clopidogrel therapy.

No relevant comparator studies on ASA and clopidogrel therapy were available in patients who had previously experienced a vascular event under ASA.

None of the studies included had the primary aim of investigating the effect of the treatment options on the quality of life or disease-related symptoms of patients. It could not be inferred from the studies investigated whether clopidogrel is more effective than ASA in reducing disease-related symptoms such as pain (when walking or resting) or angina pectoris symptoms, or in increasing physical capacity or the ability to perform daily activities.

Conclusion

Compared with ASA, long-term antiplatelet monotherapy with clopidogrel in patients with symptomatic PAD has an additional benefit with regard to the risk reduction for vascular/thromboembolic events. No such evidence is available with regard to the reduction of overall mortality. In patients with IHD or ICVD (in each case without co-existing symptomatic PAD), an additional benefit of clopidogrel therapy has not been demonstrated. There is no evidence available that the above conclusions differ for specific patient groups with an increased risk of thromboembolic events (e.g. patients with hypercholesterolaemia, diabetes mellitus, or manifestations of atherosclerosis in more than 1 vascular territory). There is no evidence available that in patients who experienced a gastrointestinal complication (symptomatic ulcers/erosions) under ASA, a switch of therapy to clopidogrel results in a patient-relevant additional benefit. In patients with prior gastrointestinal ulcer bleeding under ASA, indications exist that a continuation of treatment with lower-dose ASA combination therapy plus a PPI (esomeprazole) results in a higher patient-relevant benefit than a switch to clopidogrel.

There is no evidence available that in patients who experienced a vascular event under ASA, a switch to clopidogrel therapy results in an additional patient-relevant benefit.

Key words: clopidogrel; acetylsalicylic acid; antiplatelet drugs; ischaemic heart disease; ischaemic cerebrovascular disease; peripheral arterial disease; systematic review.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
ABI	Ankle brachial index
ACS	Acute coronary syndrome
ASA	Acetylsalicylic acid
ASCET	ASpirin non-responsiveness and Clopidogrel Endpoint Trial
CADET	Clopidogrel and Aspirin: Determination of the Effects on Thrombogenicity
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
DARE	Database of Abstracts of Reviews of Effects
EMBASE	Excerpta Medica Database
EMEA	European Medicines Agency
ESRS	Essen Stroke Risk Score
EUSI	European Stroke Initiative
FDA	Food and Drug Administration
HTA	Health technology assessment
ICVD	Ischaemic cerebrovascular disease
IHD	Ischaemic heart disease
INAHTA	International Network of Agencies for Health Technology Assessment
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	Intention-to-treat
MATCH	Management of ATherothrombosis with Clopidogrel in High-risk patients
MEDLINE	Medical Literature Analysis and Retrieval System Online
MI	Myocardial infarction
NSAID	Non-steroid anti-inflammatory drug
NSTEMI	Non-ST-segment elevation myocardial infarction
PAD	Peripheral arterial disease

Abbreviation	Meaning
PhRMA	Pharmaceutical Research and Manufacturers of America
PI	Platelet inhibitor
PP	Per protocol
PPI	Proton pump inhibitor
RCT	Randomised controlled trial
STEMI	ST-segment elevation myocardial infarction
TIA	Transient ischaemic attack
WATCH	Warfarin and Antiplatelet Therapy in Chronic Heart Failure

1. AIMS OF THE EVALUATION

The aims of this evaluation are:

- the comparative evaluation of the benefits and harms of clopidogrel and acetylsalicylic acid (ASA) as antiplatelet monotherapy for secondary prevention in patients with symptomatic ischaemic heart disease, symptomatic ischaemic cerebrovascular disease, or symptomatic peripheral arterial disease.

and

- the specific comparative evaluation of benefits and harms of a switch in therapy to clopidogrel versus continuation of existing ASA therapy for secondary prevention (as described above) in patients who had previously suffered an adverse event under ASA therapy (in particular a thromboembolic event or severe bleeding).

The focus of this evaluation was on patient-relevant therapy goals.

This evaluation was conducted on the basis of the comparison and weighing of desired and undesired effects of the respective drugs (weighing of benefits and harms).

2. BACKGROUND

Atherosclerosis and atherothrombosis

Atherothrombosis is characterised by the rupture of atherosclerotic vessel lesions and the subsequently induced formation of thrombi and/or arterio-arterial and/or cardio-arterial emboli. The development of atherosclerotic lesions is a diffuse process that starts in childhood and initially progresses asymptomatically during adulthood [1,2]. The chronic phase of atherothrombosis is distinguished from acute phases, which are normally triggered by the more or less complete occlusion of the vessel lumen, and which are accompanied by infarction of the dependent tissue.

Atherosclerosis and atherothrombosis can affect the whole arterial vascular system, with preferences, however, for particular vascular territories. The most common clinical manifestations are:

- Ischaemic heart disease
- Ischaemic cerebrovascular disease
- Peripheral arterial disease

These diseases show different clinical symptoms, but can be regarded as a single pathogenetic entity [3]. However, acute ischaemic heart disease events are mostly triggered by thrombi originating from the coronary arteries themselves, whereas the main cause of ischaemic cerebrovascular disease events is cerebral emboli originating from a carotid stenosis. Therefore, a mandatory relationship between the clinical manifestations of these diseases does not exist. In addition, different risk factors predominate in the progression of the diseases in the individual vascular territories [4]. For these reasons, it is conceivable that despite their pathogenetic entity, differences may exist in the therapeutic capacity to influence the course of the 3 diseases.

Ischaemic heart disease (IHD) mainly manifests itself as chronic stable angina pectoris, which can be triggered by physical activity or other stimuli (e.g. cold), and which is a sign of insufficient myocardial perfusion. The disease is usually caused by coronary stenosis, complicated in rare cases by coronary spasms. Myocardial ischaemia can also occur without typical angina pectoris symptoms (asymptomatic ischaemia) and can be the cause of ventricular arrhythmia to the point of sudden arrhythmic cardiac death. The quality of life and daily activities of affected patients can be severely restricted by angina pectoris symptoms.

An acute coronary syndrome (ACS) is an acute attack of myocardial ischaemia triggered by sudden atherothrombotic processes as a result of plaque rupture or erosion. It occurs as acute myocardial infarction (MI), unstable angina pectoris, or sudden arrhythmic cardiac death. The pre-existing coronary stenosis is not necessarily severe, i.e. the occurrence of an MI is also possible if the underlying IHD was previously asymptomatic [5]. In MI, non-ST-segment elevation infarctions (NSTEMI) are distinguished from ST-segment elevation infarctions (STEMI). Common to both is the elevation of specific cardiac enzyme levels (e.g. troponin), which is absent in unstable angina pectoris. In the latter, angina symptoms are of new onset, prolonged, or stronger than usual. In unstable angina pectoris, it is important to identify patients who have risk factors (and therefore a poor prognosis). International professional societies recommend treating these patients in the same way as patients with a NSTEMI [6-11].

Ischaemic cerebrovascular disease (ICVD) mainly manifests itself as a stroke or a transient ischaemic attack (TIA). Stroke is defined by the WHO as the "clinical syndrome of rapid onset of focal (..) cerebral deficit, lasting more than 24 h or leading to death, with no apparent cause other than a vascular one" [12]. About 80% of cases are ischaemic strokes, the others are intracerebral (15%) or subarachnoidal (5%) haemorrhages. Ischaemic events whose symptoms persist for less than 24 hours are referred to as TIAs. It is estimated that about 50% of all ischaemic strokes and TIAs are due to atherothrombotic disease of the larger extra- or intracranial vessels [12]. The triggers for these acute events are thrombotic processes with sudden occlusion or transposition of the lumen of these vessels or arterio-arterial thromboemboli, arising from ruptured plaques and ulcerations of atherosclerotic lesions. About 20% of all ischaemic strokes arise from emboli from the heart (e.g. from atrial fibrillation) or from ruptured atherotic plaques of the ascending thoracic aorta; about 25% are due to occlusion of one of the small, perforating cerebral arteries (lacunar infarcts) [12,13].

Atherothrombosis is also the most common cause of peripheral arterial disease (PAD) [3]. PAD is relatively seldom caused by arteriitis, aneurysms, or emboli. 70-80% of affected patients do not show clinical symptoms. The measurement of the ankle/brachial index (ABI) is a suitable method of diagnosis, particularly in daily clinical practice. The result of this test is also a good predictor of future coronary or cerebrovascular events and of overall mortality [14,15]. Imaging techniques serve mainly to clarify anatomical conditions before interventional measures. PAD symptoms are usually present in the form of intermittent claudication with a restriction in walking distance. Deterioration of a patient's condition, with a reduction in walking distance to the point of pain while resting, is mostly triggered by

emboli or acute thrombotic processes. PAD can progress to ischaemic gangrene and further to the necessity of amputation. Whether symptomatic or asymptomatic, PAD also has great significance as an indicator of general atherothrombosis, as it is frequently associated with IHD and/or ICVD [16]. Patients with (asymptomatic) PAD are often treated because of concomitant IHD or ICVD symptoms [17].

Clopidogrel preparations (Plavix® und Iscover®) are approved for the following indications (date of approval: 1998) [18,19].

The prevention of atherothrombotic events:

- In patients with MI (a few days up to 35 days previously), an ischaemic stroke (7 days up to 6 months previously), or with proven PAD;
- In combination with ASA: in patients with non-ST-elevation ACS (unstable angina pectoris or non-Q-wave MI).

Antiplatelet therapy is an established treatment to prevent vascular events in patients with atherosclerosis. In patients with previous MI, stroke or TIA who were treated for 2 years, antiplatelet therapy reduced the rate of vascular events (non-fatal MI, non-fatal stroke, or vascular death) by 3.6% (absolute reduction) compared with placebo. Among other high-risk patients (e.g. with pre-existing PAD or after an ACS) the rate was reduced by 2.2% (absolute reduction) [20].

In clinical studies, antiplatelet therapy with ASA has been studied most frequently and in the largest number of patients [20]. ASA reduces the activation and aggregation capacity of platelets by the irreversible inhibition of platelet thromboxane synthesis. Its antioxidant and anti-inflammatory effects may also be relevant factors with regard to vasoprotection [21]. Maximum inhibition of platelet aggregation is reached at the latest 30 minutes after oral intake of 160-325 mg of ASA. The effect is still detectable for 5-7 days after the end of therapy [22]. In patients with an increased vascular risk, ASA reduces the risk of severe vascular events by 23% (relative reduction). Recommendations on the daily ASA dose are inconsistent in current German guidelines and lie between 75 mg and 325 mg daily [6,23,24]. For patients with IHD, the Medicinal Commission of German Physicians *(Arzneimittelkommission der Deutschen Ärzteschaft)* primarily recommends 100 mg daily [25]. This recommendation is reflected in the German prescription numbers: in the vast majority of cases, antiplatelet ASA therapy is prescribed in a dosage of 100 mg daily [26].

Presumably there is no difference in benefit between daily doses of 75 mg and 325 mg ASA [20]. With regard to severe bleeding complications, the evidence from direct comparative studies is insufficient to postulate an equivalence of low (75 mg daily) and high (325 mg

daily) ASA dosages. In direct comparative studies, numerically fewer (statistically not significant) bleeding events occurred under ASA 75 mg daily compared with 325 mg ASA daily [20]. Indirect comparisons from placebo and active-controlled trials show a distinct increase in severe bleeding complications in doses above 325 mg daily [27]. In the particular clinical situation of patients with ACS, a difference with regard to the risk of bleeding was already shown for ASA dosages of 100 mg and 200 mg daily. However, this is not necessarily transferable to long-term therapy outside the acute situation [28].

Thienopyridines such as ticlopidine and its analogue clopidogrel also irreversibly inhibit platelet activation and aggregation, but with a different mode of action (by antagonism of the adenosine receptor). After initiation of therapy with the maintenance dose (75 mg clopidogrel daily), maximum inhibition of platelet aggregation is achieved only after 3-7 days. In contrast, if a loading dose is administered (300 mg or 600 mg clopidogrel) maximum inhibition is already achieved after 2 (600 mg) to 6 (300 mg) hours [29].

The common final pathway for the effect of thienopyridines and ASA is the reduced stimulation of the glycoprotein-IIb/IIIa-receptor as the key step in the activation of thrombocytes [30,31].

In platelet function tests, clopidogrel is more effective than ASA. In addition, on average 30% of patients show a so-called resistance to ASA; i.e. in laboratory experiments a decreased inhibition of platelet aggregation has been shown in these patients compared with so-called responders to ASA [32]. Cases of resistance have, however, also been reported under clopidogrel in rates of 5-30% of patients treated [33]. Opinions on the clinical relevance of platelet function tests are inconsistent [32,33]. It can only be clarified by suitable clinical trials whether differences between clopidogrel and ASA in this respect are reflected in a varying effect on patient-relevant outcomes of the most important manifestations of atherosclerosis. These trials should include outcomes such as the rates of vascular deaths, MIs, strokes, etc. The same applies to the tolerability of both substances. The well-known ulcerogenicity of ASA (also in a dose of 100 mg daily) could result, among other things, in an increased risk of gastrointestinal bleedings and ulcers compared with clopidogrel, especially as there is no evidence that the pharmacological effects of clopidogrel trigger or increase the risk of peptic ulcers [29]. However, a more favourable safety profile for clopidogrel cannot automatically be inferred from this. Suitable clinical trials are therefore also necessary to describe validly the potential of clopidogrel to induce adverse effects compared with low-dose ASA.

3. PROJECT PROCEDURES

3.1 Course of the project

The Federal Joint Committee (*Gemeinsamer Bundesausschuss*) commissioned IQWiG in writing on 15 December 2004 to evaluate the benefits and harms of clopidogrel in patients with cardiac and/or other vascular diseases. This also includes the evaluation of the benefits and harms of clopidogrel versus ASA as antiplatelet monotherapy for secondary prevention of vascular diseases.

The nature of this commission was specified by letter of 26 January 2005, as well as by the meeting of the Subcommittee "Pharmaceuticals" (*Unterausschuss Arzneimittel*) of the Federal Joint Committee on 2 February 2005.

External experts were involved in the commission, and contributed to the production of the report plan, the literature search and its evaluation, as well as to the production of the preliminary and final report.

Patient representatives were consulted with the aim of defining patient-relevant outcomes, also from the viewpoint of patients (on 12 May 2005: a representative of the Federal Association of PAD Self-help Groups [*AVK-Selbsthilfegruppen Bundesverband e.V.*]; on 8 June 2005: a representative of the Federal Association for the Rehabilitation of Aphasic Patients *[Bundesverband für die Rehabilitation der Aphasiker e.V.*]; on 10 June 2005: a representative of the Association of the Self-help Initiative HFI – Circulation and Metabolism [*Selbsthilfe-Initiative HFI e.V. - Kreislauf und Stoffwechsel*]).

The report plan (version: 12 July 2005) was published on the Internet on 28 July 2005. The preliminary report (version: 27 March 2006) was sent to the Board of Trustees of the Institute and the Federal Joint Committee on 28 March 2006, and published on the Internet on 4 April 2006. Until 25 April 2006, written statements from all interested private persons, patient representatives, professional societies, and commercial enterprises could be made in terms of a written hearing. In addition, an external review of the preliminary report was conducted. On 16 May 2006, a scientific hearing on the written statements was conducted at IQWiG. All persons who had made substantial statements, as well as external reviewers, were invited. Further participants were external experts and IQWiG employees. Following the scientific hearing, IQWiG produced the final report, which was published on the Internet 2 months after submission to the Federal Joint Committee. The link to the final (German) report, which also

includes the written statements, the list of participants, and the meeting minutes of the scientific hearing can be found in Appendices F and G.

3.2 Changes to the preliminary report following the scientific hearing

After the hearing, the following changes were made and included in the final report:

- In Sections 5.3.3.3 und 5.4, the reasons for the different assessment of the overall results of the CAPRIE trial (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; CAPRIE 1996) for the predefined subgroups are more clearly elaborated.
- In Section 5.3.5.1, as well as in the new Section 6 (Discussion), it is more clearly elaborated why the results of the Chan trial (Chan 2005), despite deficits in the publication, can be regarded as an indication of a benefit of combination therapy with ASA plus esomeprazole versus clopidogrel.
- In Section 5.3.5.1, a distinction is now made between the 2 constellations "ulcer bleeding as first event" and "recurrent bleeding after previous event under antiplatelet therapy".
- The discussion of the publication "Ringleb 2004" in Section 5.3.7.6 was revised; in addition, the interpretation of the results of this publication is again discussed in detail in Section 6.
- In Section 6, the concept of "cross risks" in PAD patients is discussed in detail.

New studies relevant to this evaluation were not presented within the framework of the written statements submitted on the preliminary report.

4. METHODS

The methods for producing the report were predefined in the report plan of 12 July 2005. Insofar as amendments in this regard were made during the course of the report production, they are presented in Section 4.5.

4.1 Criteria for the inclusion of studies in the evaluation

In the following, the criteria are stated that were prerequisites for inclusion of a trial in this report (inclusion criteria) or led to exclusion from further evaluation (exclusion criteria).

4.1.1 Population

Studies were considered that included patients with symptomatic IHD, symptomatic ICVD, or symptomatic PAD. No further restrictions were made with regard to the patients investigated in these studies.

4.1.2 Intervention and comparator treatment

The intervention to be investigated was treatment with clopidogrel (in any dosage). The comparator intervention investigated was treatment with ASA (in any dosage). Studies where additional drugs were administered which aimed primarily at influencing blood coagulation (e.g. other antiplatelet therapy) were not included.

4.1.3 Outcomes

The outcomes investigated in this evaluation were parameters that enabled an assessment of the following patient-relevant therapy goals:[5]

- Reduction of total mortality.
- Reduction of vascular mortality:
    - Fatal MI, sudden cardiac death, other cardiac deaths,
    - Fatal stroke,
    - Other vascular deaths (e.g. fatal haemorrhages).
- Reduction of vascular morbidity:
    - Non-fatal MI; stroke; ulcer, gangrene or amputation caused by ischaemia,
    - Revascularisation interventions due to ischaemia-related symptoms,

[5] 12.04.2007: original translation (“patient-relevant therapeutic therapy goals”) corrected

  - ACS, angina pectoris, symptomatic arrhythmia, TIA, intermittent claudication,
  - New occurrence of heart failure or deterioration of existing heart failure.
- Reduction of the hospitalisation rate:
  - Overall,
  - Hospitalisation due to vascular disease,
  - Hospitalisation due to adverse effects.
- Reduction of the incidence of adverse drug effects:
  - Bleeding,
  - Haematological changes (e.g. anaemia, leukopenia, thrombopenia),
  - Gastrointestinal symptoms (e.g. symptomatic ulcers),
  - Allergic reactions (e.g. dermatological symptoms),
  - Renal dysfunction,
  - Others.
- Improvement of disease-related quality of life.
- Avoidance of dependence on third parties/need of care.
- Improvement or maintenance of physical capacity.
- Extension of the pain-free walking distance (insofar as restrictions in this respect exist).
- Extension of the maximum walking distance (insofar as restrictions in this respect exist).
- Improvement or maintenance of capacity to cope with daily activities.
- Maintenance or restoration of capacity to work.
- Reduction of other disease-related symptoms.

4.1.4 Study types

Randomised controlled trials (RCTs) provide the most reliable results for the evaluation of the effects of a medical intervention as they are least prone to produce uncertainty of results, insofar as they have been conducted with appropriate methods and in accordance with the relevant research question.

An evaluation within the framework of RCTs is possible and feasible in practice for all therapy goals listed in Section 4.1.3 and the interventions listed in Section 4.1.2. Therefore, only RCTs were included in this evaluation as relevant scientific literature.

4.1.5 Other study characteristics

Limitations with regard to other study characteristics were not planned.

4.1.6 Overview of the inclusion and exclusion criteria

Studies that fulfilled all of the inclusion criteria and none of the exclusion criteria listed below were included in the evaluation.

Inclusion criteria	
I1	Patients with symptomatic IHD, ICVD, or PAD.
I2	Direct comparison of treatment with clopidogrel versus ASA as defined in Section 4.1.2.
I3	Evaluation of outcomes that can be inferred from the therapy goals formulated in Section 4.1.3.
I4	RCTs.
I5	Languages of publication: German, English, French, Dutch, Portuguese or Spanish, or other languages if an English title and abstract of these publications were available, indicating the relevance of the study.

Exclusion criteria	
E1	Studies in animals
E2	Duplicate publications without relevant additional information.
E3	No full-text publication available.[a]
a: In this context, full-text publications also include the non-confidential provision of clinical study reports to the Institute or the non-confidential provision of other reports on a study to the Institute that fulfil the CONSORT[6] criteria [34] and enable the evaluation of the study.	

[6] Consolidated Standards of Reporting Trials

4.2 Literature search

The aim of the literature search was to identify full-text published and unpublished clinical studies that provided relevant information on the evaluation of the benefits and harms of clopidogrel versus ASA for the secondary prevention of vascular diseases.

4.2.1 Literature sources

The literature search for relevant published studies[7] was conducted in the following sources:

- Bibliographic databases: MEDLINE,[8] EMBASE,[9] CENTRAL.[10]
- Reference lists of relevant secondary publications (systematic reviews, HTA[11] reports, meta-analyses).

The search strategies for the search in bibliographic databases can be found in Appendix C.

The search was conducted in 3 steps:

- First search: on 23 June 2005 for MEDLINE, EMBASE and CENTRAL; on 27 June 2005 for PRE-MEDLINE.
- First additional search after publication of the report plan: on 29 July 2005 for CENTRAL; on 3/4 August 2005 for MEDLINE and EMBASE.
- Second additional search during the process of the report production on 20/21 September 2005 for MEDLINE, PRE-MEDLINE, EMBASE, and CENTRAL.

The search for relevant secondary publications was conducted in MEDLINE and EMBASE parallel to the search for relevant primary literature by the appropriate formulation of the search strategy (see Appendix C).
In addition, parallel to the search in CENTRAL, a search was conducted in the specialised databases CDSR,[12] DARE,[13] and the HTA database.

[7] 12.04.2007: original translation ("unpublished studies") corrected

[8] Medical Literature Analysis and Retrieval System Online

[9] Excerpta Medica Database

[10] Cochrane Central Register of Controlled Trials

[11] Health technology assessment

[12] Cochrane Database of Systematic Reviews

4.2.2 Search for further published and unpublished studies

The following steps were taken in the search for published and unpublished studies:

- Queries to Sanofi-Synthelabo (now: Sanofi-Aventis) GmbH, Berlin (Plavix®) und Bristol-Myers Squibb GmbH & Co. KgaA, Munich (Iscover®).
- Search for study reports of completed studies in publicly accessible (via the Internet) clinical study results databases of the manufacturers of Iscover® and Plavix® (http://www.clinicalstudyresults.org; search term "clopidogrel"; access on 2 August 2005).
- Search for completed trials in the trial register ClinicalTrials.gov (http://www.clinicaltrials.gov; search term "clopidogrel"; access on 2 August 2005)
- Search on the website of the European Medicines Agency (EMEA, http://www.emea.eu.int, access on 1 August 2005) and the U.S. Food and Drug Administration (FDA, http://www.fda.gov, access on 1 August 2005).

4.2.3 Search for additional information on relevant studies

The documents retrieved by the procedures described in Section 4.2.2 were searched for references to studies not identified previously and for additional information on published studies already identified.

In addition, queries were made to the sponsors and/or authors on individual aspects of relevant studies. These were, in detail:

On the CAPRIE trial [35]:

- Query to Sanofi-Aventis and Bristol-Myers Squibb with regard to additional information on methodological aspects and additional evaluations for particular subgroups.
- Query to M. Gent as the representative of the Clinical Trials Methodology Group, Hamilton Civic Hospitals Research Centre, Canada, on methodological aspects and single results.
- Query to E. Topol, corresponding author, to clarify an outcome definition in the secondary publication "Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery" [36].

On the WATCH trial [37]:

[13] Database of Abstracts of Reviews of Effects

- Query to Sanofi-Aventis with regard to the results of the prematurely terminated WATCH trial (Warfarin and Antiplatelet Therapy in Chronic Heart Failure).
- Queries to B. Massie (Study Chairman of the WATCH trial) with regard to the results of the WATCH trial and various inconsistencies between the information in the database "ClinicalTrials.gov" and the publication by Massie 2004 [37].
- Query to J. Gough (Acting Director of Administration in VA's Office of Research and Development, Department of Veterans Affairs, USA) with a request for support concerning the query to B. Massie (the WATCH trial was supported and administered by the Department of Veterans Affairs).
- Query to D.A. Zarin (Director of ClinicalTrials.gov) with a request for support concerning the query to B. Massie.
- Additional query to Sanofi-Aventis and Bristol-Myers Squibb within the framework of the scientific hearing of the written statements.
- Additional query to B. Massie after his first response, requesting the clinical study report.

On the Chan trial [38]:

- Queries to F. Chan (main author of the publication "Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding") concerning methodological aspects and individual results.
- Query to A.J. Hui and W.K. Leung, co-authors of the Chan 2005 publication concerning methodological aspects and individual results.
- Query to J.M. Drazen (Editor-in-Chief, New England Journal of Medicine) with a request for support concerning the query to F. Chan.

On the ASCET trial (ASpirin non-responsiveness and Clopidogrel Endpoint Trial) [39]:

- Query to A. Pettersen (main author of the publication "Unstable angina, stroke, myocardial infarction and death in aspirin non-responders. A prospective, randomized trial. The ASCET design") concerning any available results of the ongoing ASCET trial.

4.2.4 Identification of relevant studies

Title and abstract screening of the retrievals from bibliographic databases

The citations identified in bibliographic databases were evaluated with regard to their relevance by 2 reviewers independently of each other on the basis of their titles, and, if available, their abstracts. Publications viewed by both reviewers as potentially relevant were perused with regard to their relevance using the full text. All citations that were regarded by at least 1 reviewer as potentially relevant and that could not definitely be excluded in this step were included in the pool of potentially relevant studies.

Assessment of potentially relevant full texts

The assessment of the relevance of the publications on the basis of the full text was also performed independently by 2 reviewers. After this step, studies assessed as relevant for this report were defined as:

- Studies that were assessed as relevant by both reviewers.
- Studies that were initially assessed as relevant by only 1 reviewer, but after subsequent discussion were assessed as relevant by both reviewers.

Search in reference lists of relevant secondary publications

Reference lists of relevant secondary publications were searched in order to identify any further primary publications. The full texts of the publications identified in these reviews were assessed for their relevance by 2 reviewers, as described above.

Documents of the Federal Joint Committee

In the Federal Joint Committee's letter of 26 January 2005 specifying this commission, the question of the relevance of the MATCH trial (Management of ATherothrombosis with Clopidogrel in High-risk patients) [40] was raised. In the MATCH trial, no antiplatelet monotherapy, but a combined inhibition of platelet aggregation with clopidogrel plus ASA was investigated. The results of the MATCH trial, which were not considered in this evaluation, are outlined in Appendix E.

4.3 Evaluation of information

The evaluation of the studies included was conducted on the basis of the information available and was therefore strongly dependent on the quality of the relevant publications and the additional sources of information.

The evaluation was conducted in 3 steps:

- Data extraction,
- Evaluation of the consistency of data within the publication itself and between the publication and other sources of information (e.g. information provided in the publication and in regulatory documents).
- Evaluation of the quality of the studies and publications.

Data extraction

Data extraction from published studies was conducted by 1 reviewer with standardised data extraction forms. The second reviewer checked the data extraction. Any discrepancies were resolved by discussion between the reviewers. Both reviewers then prepared a mutually agreed data extraction form for each trial.

Details on the following aspects of study quality were systematically extracted:

- Randomisation process, allocation concealment,
- Blinding of treating staff, patients, and evaluators,
- Sample size planning,
- Study discontinuations,
- Definition and implementation of the intention-to-treat (ITT) analysis.

Assessment of data consistency

Following the data extraction, where appropriate, a comparison took place between these data and the data obtained by the additional searches for published studies described in 4.2.2 and 4.2.3.

Insofar as discrepancies were detected (also discrepancies between multiple data provided on a topic within the publication itself) that may have had a substantial effect on the study results or on their interpretation, this is presented in the corresponding parts of the results section.

Evaluation of the study and publication quality

Furthermore, an overall evaluation of the study and publication quality was conducted by means of a 4-graded scale (biometric quality) under consideration of the aspects stated above.

Possible grades were:

- No identifiable deficiencies,
- Minor deficiencies,
- Major deficiencies,

- Unclear.

The grades were predefined as follows: “minor deficiencies”: it is assumed that their correction will not substantially influence the results and the overall conclusion of the study; “major deficiencies”: the overall conclusion of the study is to be questioned, as a correction of the deficiencies may possibly lead to different conclusions.

4.4 Synthesis and analysis of information

Aspects of study design, study quality, and study results are presented as a summary for the total study pool.

4.4.1 Meta-analysis

An evaluation of data by means of meta-analysis following the Institute’s methods was to be conducted, provided that this was seen as a meaningful methodological and textual procedure; this was not the case for any of the outcomes investigated.

4.4.2 Sensitivity analysis

Sensitivity analyses were preplanned:

- For the biometric evaluation of quality on the basis of the ordinal classification specified in the extraction form (see Section 4.3);
- If possible, for the per-protocol (PP) evaluations (versus the ITT evaluations) presented in the publications;
- For a (statistical) model with fixed effects (vs. a model with random effects), if a meta-analysis was to be conducted.

4.4.3 Subgroup analysis

The data were primarily to be evaluated separately according to the 3 diseases IHD, ICVD, and PAD (corresponding to the qualifying event).

Subgroup analyses were planned for the following characteristics, if possible and meaningful:

- Gender;
- Age groups;
- Different concomitant diseases or vascular risk factors (hyperlipoproteinaemia, diabetes mellitus, smoking, hypertension, condition after coronary bypass operation);
- Previous antiplatelet therapy;

- Qualifying disease (IHD, ICVD, PAD) in combination with pre-existing atherosclerotic/thrombotic diseases with explicit initial naming of the qualifying event;
- Organisation according to anamnestic predictors (pre-existing vascular diseases):

Qualifying event	**Possibilities**
IHD, with or without pre-existing vascular disease	2
ICVD, with or without pre-existing vascular disease	2
PAD, with or without pre-existing vascular disease	2
Sum of possibilities (= subgroups)	6

- Time span between qualifying event and start of intervention;
- If applicable, for characteristics that were responsible for relevant heterogeneity.

4.5 Changes from the report plan

During the production of the report, some changes in the methodology predefined in the report plan were made. These changes refer on the one hand to the necessity of a specification or clarification of an issue (without substantial changes to the preplanned methodological procedure) and on the other, to the methodological procedure itself. The most relevant changes are listed below.

4.5.1 Changes made during the production of the preliminary report

Changes of content compared with the preplanned procedure

- No additional search for HTA reports on the INAHTA[14] website, as the search for these reports had been conducted via the HTA database.
- No queries to German and US professional societies with regard to unpublished studies; the search for unpublished studies had already been conducted via study registers, clinical study results data bases, and queries to the pharmaceutical industry.

Changes without consequences with regard to content

- Specification of the aims of this evaluation (see Section 1) (the wording was previously unclear).

[14] International Network of Agencies for Health Technology Assessment

4.5.2 Changes after the publication of the preliminary report

No methodological changes were made after the publication of the preliminary report.

5. RESULTS

In the following, first the results of the literature search are presented, i.e. the search for published and unpublished studies, as well as for additional information on these studies from other sources, followed by a summary of the relevant studies. Subsequently, the results of predefined subgroup analyses are presented.

5.1 Studies available

5.1.1 Results of the literature search

The results of the search for published trials via bibliographic databases, manual searches in the reference lists of systematic reviews and HTA reports, and queries to manufacturers are presented in Figure 1.

After exclusion of 314 duplicates, a total of 1366 hits were initially identified. Of these hits, 305 were assessed by at least 1 reviewer as potentially relevant on the basis of the respective abstract or, if none was available, of the title. Of these 305 publications, 12 were classified as relevant after perusal of the full text. Ten publications were classified as relevant by immediate agreement of both reviewers, 2 others were classified as relevant by consensus after discussion. The citations of the excluded studies are listed in Appendix A.

The search for relevant secondary literature produced a total of 39 systematic reviews or HTA reports (Appendix B). A total of 17 publications were identified from the corresponding reference lists on the basis of their titles. These publications appeared to be potentially relevant and had not yet been identified in the systematic search of databases. After perusal of the full texts, all 17 publications were excluded unanimously by both reviewers. The citations of these full-text publications and the reasons for exclusion are also listed in Appendix A.

One of the relevant publications (Massie 2004; WATCH trial) was the protocol of a 3-arm trial comparing warfarin, ASA, and clopidogrel for chronic (mainly ischaemic) heart failure. According to the authors, this study was prematurely terminated due to insufficient recruitment. Up to this point, 1587 patients were included, 524 of them in the clopidogrel group and 523 in the ASA group. The WATCH trial was registered in advance in the study database “ClinicalTrials.gov”, (Registration No.: NCT00007683). This was confirmed by the manufacturer of clopidogrel and co-sponsor of the WATCH trial (Sanofi-Aventis) by e-mail of 19 November 2005. In the information provided on the WATCH trial in ClinicalTrials.gov in November 2005, it was stated that recruitment of a total of 1500 patients was planned (therefore complete recruitment had taken place). The study was referred to as “completed”,

not as “prematurely terminated”. It was also noticeable that information on sample size planning (85% power and an estimated relative difference of 30% between treatment groups) in ClinicalTrials.gov (November 2005) differed from the information provided in Massie 2004 (power: 90%, relative difference: 20%). According to Sanofi-Aventis, a full-text publication of the results of the WATCH trial is still not available (e-mail of 28 October 2005). In the same e-mail, Sanofi-Aventis stated that they had no direct access to the data and therefore could not provide them. Initially, the study chairman of the WATCH trial, B. Massie, did not respond to repeated queries from the Institute. IQWiG also contacted the directors of ClinicalTrials.gov and the Department of Veterans Affairs (this Department supported and administered the WATCH trial). During the scientific hearing on the written statements and the preliminary report, representatives of Sanofi-Aventis and Bristol-Myers Squibb were again requested to provide the results of the trial. The company representatives stated that they could not provide the data on the WATCH trial, despite their sponsorship. It was however agreed that they would ask B. Massie to forward the study results. B. Massie subsequently responded by e-mail on the 9 June 2006. He stated that the manuscript of the WATCH trial would be submitted for publication shortly, but did not provide results. In the meantime, the information in ClinicalTrials.gov had been amended. It was stated (Status: 20 January 2006) that the sample size planning had been changed during the course of the study and that this was included in an amendment to the study protocol. This means that 3 different statements have been published with regard to a central point of the WATCH trial. It can be assumed that the discrepancies will finally be resolved only by the clinical study report on the WATCH trial. B. Massie was therefore asked to provide the study report. Up to the completion of the final report, this query had not been answered. The WATCH trial, due to its design and the outcomes investigated, may contribute relevant data on clopidogrel versus ASA therapy in patients with IHD. Some partial results of the trial were reported within the framework of congress reports (Congress of the American College of Cardiology, 2004 [41]). A numerical disadvantage under clopidogrel for the combined outcome “death, myocardial infarction, stroke” was reported (21.8% under clopidogrel versus 20.5% under ASA) [41].

The citations of full-text publications that were not considered relevant and the reasons for exclusion are listed in Appendix A. Of these, 2 publications of study protocols merit special attention:

The ASCET publication (Pettersen 2004) refers to the protocol of a trial which, for a planned sample size of 1000 patients who experienced an ischaemic event under ASA therapy, compares the continuation of treatment with ASA with a switch to clopidogrel therapy.

Completely published results for this trial are not yet available. The outcomes investigated may contribute clinically relevant data on the question as to whether patients with an ischaemic event under ASA therapy profit from a switch to clopidogrel. According to an e-mail from the main author, Pettersen, published results cannot be expected before 2008.

The CHARISMA publication (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; Bhatt 2004) refers to the protocol of a study including more than 15 000 patients suffering from symptomatic atherosclerosis or a greatly increased risk of ischaemic vascular events. ASA monotherapy is compared with combination therapy (ASA plus clopidogrel). Clinically relevant outcomes are investigated, so that the result of this trial might well be relevant for an evaluation of combined antiplatelet therapy with clopidogrel and ASS. However, antiplatelet combination therapy is not the subject of this report.

The results of the study have meanwhile been published. The manuscript was published after the second additional literature search for this report was conducted.

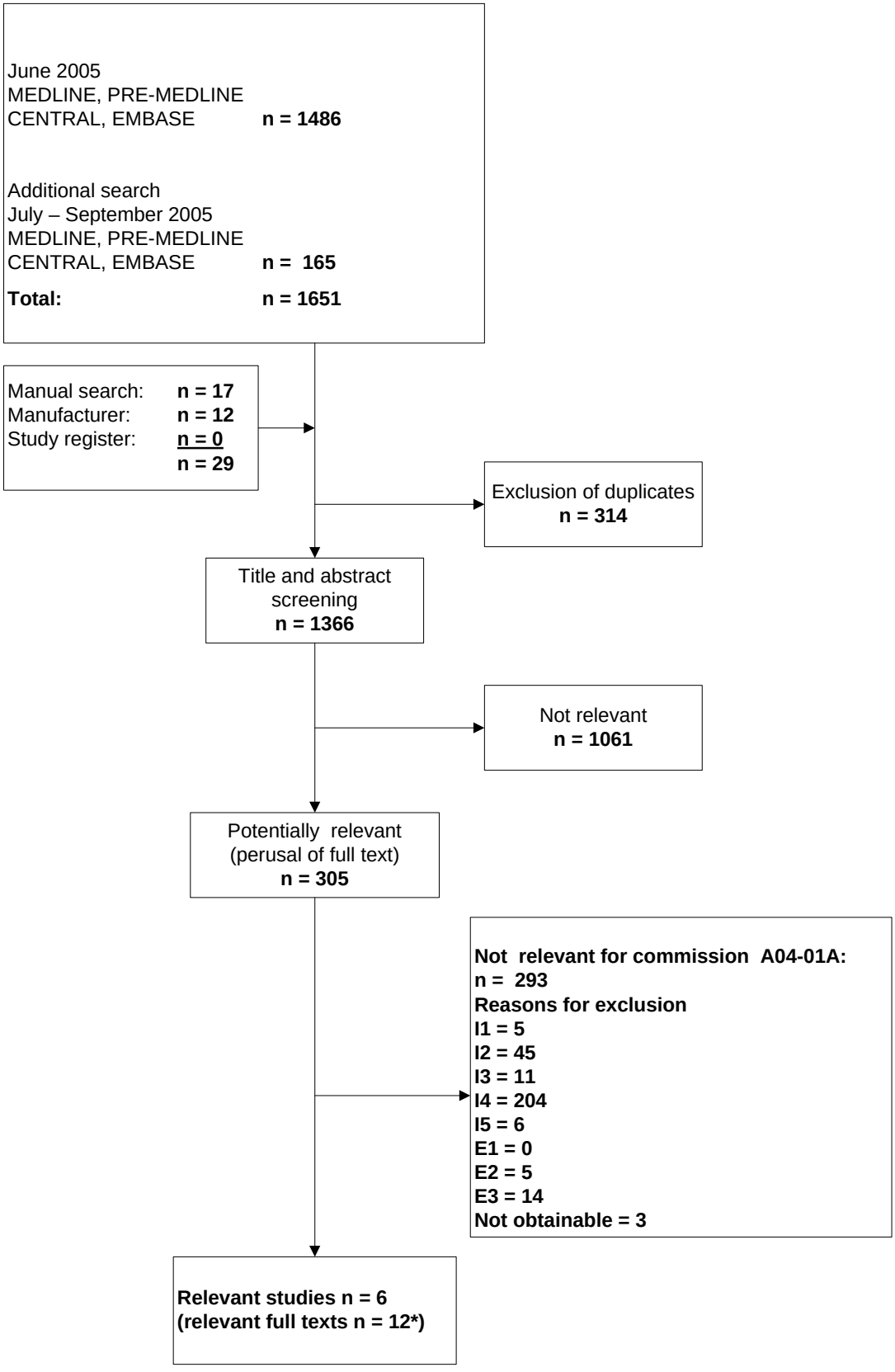

Figure 1: Flow chart of the literature search

* In addition to the primary publication, 6 additional relevant publications on the CAPRIE trial were identified.

5.1.2 Study register and study results data bases

No additional relevant information was found in the study results database http://www.clinicalstudyresults.org.

The following relevant information was found under: http://www.clinicaltrials.gov/:

- Reference to the WATCH trial completed in June 2003.

5.1.3 Publicly accessible documents from regulatory authorities

No references to further relevant trials for this report were found under http://www.emea.eu.int/ and http://www.fda.gov/.

5.1.4 Responses to queries to manufacturers

Bristol-Myers Squibb (Iscover®) and Sanofi-Aventis (Plavix®) provided the following relevant information:

- Reference list on clopidogrel (349 publications) including the quoted original literature as hardcopies; no additional relevant publications resulted from this list.
- Overview of ongoing studies on clopidogrel (none relevant for the research questions posed in this report).
- A table including health economic publications.

In addition, on request, further documentation on methodological aspects and results of the CAPRIE trial was provided by Sanofi-Aventis (see below in the corresponding results section). The responses from Sanofi-Aventis and Bristol-Myers Squibb concerning queries about the WATCH trial are presented in Section 5.1.1.

5.1.5 Responses to queries to authors or other persons involved in relevant studies (see also Appendix D)

CAPRIE trial

On 27 September 2005, R. Roberts replied on behalf of M. Gent to queries about the methodological aspects and results of the CAPRIE trial (see below in the corresponding results section).

D. Bhatt replied on behalf of E. Topol to an inquiry regarding the definition of a combined outcome in the Bhatt 2001 publication [36].

Chan 2005

The author F. Chan replied to the third query after intervention of the editor-in-chief of the New England Journal of Medicine. However, only 1 of the 3 questions posed was answered (on the issue of "lost to follow-up"), forwarding an email from J. Ching, the statistician responsible [38].

WATCH trial

At first, neither B. Massie (Study Chairman of the WATCH trial) nor J. Gough (Acting Director of Administration in VA's Office of Research and Development, Department of Veterans Affairs) responded to queries concerning the WATCH trial. After intervention by Sanofi-Aventis, B. Massie informed the Institute that the manuscript of the WATCH trial would shortly be submitted for publication. Further results were not provided.

D. Zarin, Director of ClinicalTrials.gov, answered with regard to the WATCH trial that the responsibility for the correctness of information in their database lies in the hands of the responsible principal investigator.

5.1.6 Study pool

Table 1 shows the relevant study pool resulting from the various search steps.

Table 1: Study pool

Study	Relevant	Published	Inclusion in report
CAPRIE[a] [35,36,42-46]	yes	yes	yes
Chan 2005 [38]	yes	yes	yes
Ng 2004 [47]	yes	yes	yes
CADET (Woodward 2004) [48]	yes	yes	yes
Jagroop 2004 [49]	yes	yes	yes
WATCH [37]	yes	no[b]	no

a: The original publication [35] and 6 additional publications on subgroup analyses and further analyses of the CAPRIE trial were included in this report.
b: Only protocol on the study design available, as well as congress publications on partial results.

All studies were included in this evaluation that, firstly, were identified by the search strategy, secondly, were assessed by the reviewers as relevant, at least in part (e.g. with regard to adverse effects), and thirdly, were available as full publications.

In the following text, the studies investigated are referred to as follows: CAPRIE trial [35,36,42-46], Chan trial [38], Ng trial [47], CADET trial (Clopidogrel and Aspirin: Determination of the Effects on Thrombogenicity; [48]), Jagroop trial [49], and WATCH trial [37].

At the request of the Federal Joint Committee, the MATCH trial is presented separately in Appendix E (see also Section 4.2.4); the results were not considered in this evaluation.

The CAPRIE trial, whose results were published in 1996, represents the largest relevant trial for the primary research questions of this report [35]. A previously published protocol on the CAPRIE trial could not be identified and was not available for evaluation. Six secondary analyses of the CAPRIE trial were included in this report [36,42-46]. One publication reported data on adverse events that went beyond the information provided in the original CAPRIE publication and was therefore included (Harker 1999, [46]). Five publications referred to other relevant secondary analyses [36,42-45]. Further secondary publications on the CAPRIE trial identified by the literature search were either irrelevant or not available as full-text publications and were therefore not taken into account.

Two of the publications included (Chan 2005, Ng 2004) primarily investigated the gastrointestinal tolerability of clopidogrel versus ASA. Two further trials primarily investigated surrogate parameters (markers of platelet aggregation/function), which were not relevant for this report. However, the publications included additional information on adverse events (CADET trial [Woodward 2004] [48]; Jagroop 2004 [49]), and in order to assess these events, the respective publications were included in the report.

Details on the potentially relevant, previously unpublished WATCH trial can be found in Section 5.1.1.

5.2 Characteristics of the studies included in the evaluation

5.2.1 Study design and population

The study design and population of the 5 trials included, whose publications contained results on the outcomes investigated in this report, are presented in Tables 2-4. Specific aspects of the secondary publications on the CAPRIE trial are outlined in the corresponding parts of the results section. (Therapy goals: “reduction of hospitalisation rate” and “reduction of stroke

rate" [44], "reduction of adverse event rate" [46], and "reduction of MI rate" [44,45]; subgroup analyses [36,42,43].)

The double-blind, randomised, parallel-group CAPRIE trial compared clopidogrel 75 mg (once daily, p.o.) and ASA 325 mg (once daily, p.o.) in patients with recent ischaemic stroke, recent ischaemic MI, or symptomatic PAD. In this review, these subgroups are referred to as the ICVD, IHD, and PAD subgroups. The study was designed to include roughly equal proportions of patients in these 3 subgroups. The total study population included 19 185 patients. A predefined allocation to subgroups was conducted (and a subsequent subgroup evaluation), depending on the vascular territory affected by the qualifying event. Stratified randomisation was performed according to these subgroups. Four non-fatal outcome events (ischaemic stroke, MI, primary intracranial haemorrhage, and leg amputation) and 5 fatal outcomes (deaths classified as due to ischaemic stroke, MI, haemorrhage, other vascular causes, or non-vascular causes) were evaluated by an independent, blinded central validation committee. The primary outcome of the study was the first event of a composite outcome (MI, ischaemic stroke, or vascular death). Four secondary (single or composite) outcomes were also predefined in the study protocol, and validated by the central validation committee. In addition, 3 secondary publications were identified, in which details on "need for hospitalisation" and "stroke" (Bhatt 2000), "rate of MI" (Cannon 2002), and "adverse events" (Harker 1999) were reported for the overall study population in CAPRIE. The information provided in these publications is, however, of little evidential value due to the methodology applied, i.e., how the events were documented and verified (especially inclusion of outcomes not predefined, and/or events based on self-reported medical history, or missing validation of the reported events by an independent validation committee). The planned follow-up in the CAPRIE trial was 1-3 years, the mean follow-up was 1.9 years (the treatment period was 1.6 years). The mean age of the total study population was 63 years. Patients in the IHD subgroup were on average about 6 years younger than patients in the ICVD and the PAD subgroup. Many patients had a history of vascular disease before the occurrence of the qualifying event (ICVD subgroup: mostly cerebrovascular events; IHD and PAD subgroups: mostly coronary events). The distribution of other vascular risk factors was similar between the clopidogrel and the ASA groups, also within the predefined subgroups. No information was provided on previous and concomitant medication; however, presumably a large proportion of patients had been pre-treated with ASA for pre-existing diseases.

Both the Chan and Ng trials primarily investigated gastrointestinal tolerability of clopidogrel versus ASA. In both studies, a specific population was investigated, only including patients

with a history of a gastrointestinal adverse event (symptomatic ulcers/erosions) under low-dose ASA (antiplatelet) therapy. Both trials had a noticeably smaller sample size and were shorter than the CAPRIE trial (Chan: 1 year; Ng: 8 weeks).

The 12-month, double-blind, randomised Chan trial included 320 patients with a history of endoscopically confirmed ulcer bleeding under low-dose ASA, who experienced ulcer healing within 8 weeks (with concomitant proton pump inhibitor [PPI] therapy and, if necessary, *H. pylori* eradication therapy). The rate of recurrent ulcer bleeding (defined according to prespecified clinical, laboratory, and endoscopic criteria) was compared between treatment groups. Patients received either ASA 80 mg (once daily p.o.) plus esomeprazole (a PPI) 20 mg (twice daily p.o.) or clopidogrel 75 mg (once daily p.o.) plus placebo (twice daily p.o.).

The Ng trial 2004 included 139 patients who had a history of symptomatic gastroduodenal ulcers/erosions under ASS therapy, but who no longer had active major bleeding. The study was conducted in a single-blind manner (blinding of the endoscoper) and investigated a surrogate parameter (the endoscopic healing rate of ulcers and erosions after 8 weeks of treatment). Patients either received ASA p.o. in the previous dosage or were switched to clopidogrel 75 mg (once daily, p.o.). All patients additionally received 20 mg omeprazole (PPI) once daily p.o.

The Jagroop trial and the CADET trial differ from the studies above, as they primarily investigated the effects of clopidogrel and ASA on surrogate markers of platelet aggregation (e.g. fibrinogen), which were not relevant for this report. However, they also provided information on adverse effects. The open-label Jagroop trial included 20 patients (10 per group) with known PAD, who were treated with clopidogrel 75 mg/day or ASA 75 mg/day for 8 days. They subsequently participated in a second study period lasting 8 more days, in which all patients were treated with a combination therapy of ASA and clopidogrel.

The 6-month, double-blind, randomised CADET trial included 184 patients with acute MI within the previous 3-7 days. Patients received clopidogrel 75 mg (once daily, p.o.) or ASA (75 mg once daily p.o.) The patient-relevant outcomes investigated in this report were exclusively documented within the framework of the safety evaluation as adverse events.

Table 2: Overview of studies

Study	Study design	Hypothesis	Study period	N	ASA (mg/day)	Study location	Main outcomes[1]
Objective: evaluate efficacy in secondary prevention							
CAPRIE 1996	RCT, parallel, double-blind	Demonstrate superiority	1.91 years[2]	9599 [C] 9586 [A]	325	Europe, North America, Australia	Primary outcome: composite outcome: ischaemic stroke, myocardial infarction, or vascular death. Secondary outcomes: composite outcome: primary outcome plus "amputation"; vascular death; composite outcome: any stroke, death from any cause, myocardial infarction; all-cause mortality. Other outcomes: adverse events,[3] myocardial infarction,[4] stroke,[5] need for hospitalisation.[5]
Objective: evaluate gastrointestinal tolerance / complications							
Chan 2005	RCT, parallel, double-blind	Demonstrate non-inferiority	12 months (median) 0.3-12 months (range)	161 [C+P] 159 [A+E]	80	Hong Kong (single centre)	Primary outcome: recurrent ulcer bleeding. Secondary outcome: lower gastrointestinal bleeding. In addition, other types of bleeding were documented (without specified diagnostic criteria): extra gastrointestinal bleeding (intracranial bleeding; other bleeding disorders leading to hospitalisation, hypotension, the need for transfusion, or the need to discontinue study medication).
Ng 2004	RCT, parallel, single-blind	Demonstrate superiority	8 weeks	randomised 74 [C+O] 65 [A+O] evaluated: 69 [C+O] 60 [A+O]	80-160	Hong Kong	Primary outcome: healing rate of ulcers/erosions at the eighth week (control endoscopy). Secondary outcomes: not explicitly stated. However, dyspeptic symptoms were recorded systematically and regularly like a secondary outcome (4-point scale: 0-1-2-3).
Objective: evaluate surrogate parameters (blood coagulation). The publications also included additional information on adverse events.							
CADET (Woodward 2004)	RCT, parallel, double-blind	unclear	6 months[6]	94 [C] 90 [A]	75	Great Britain	Primary outcome: reduction in Clauss fibrinogen. Other outcomes: other surrogate parameters, adverse events.
Jagroop 2004	RCT, parallel, open	unclear	8 days[7]	10 [C] 10 [A]	75	England	Primary outcome: unclear, several platelet function indices. Other outcomes: adverse events.

continued

Table 2: Overview of studies (continued)

1: Primary outcome and other patient-relevant outcomes.
2: Mean follow-up (treatment period: 1.6 years).
3: Harker 1999.
4: Cannon 2002.
5: Bhatt 2000.
6: Planned minimum follow up, achieved by 82% of patients.
7: Subsequently 8 more days, in which all patients were treated with clopidogrel + ASA.
[C]: Clopidogrel; [A]: Acetylsalicylic acid; [E]: Esomeprazole; [O]: Omeprazole; [P]: Placebo.

Table 3: Inclusion and exclusion criteria

Study	Patient population and diagnosis of qualifying disease	Main inclusion and exclusion criteria
Objective: evaluation of efficacy in secondary prevention		
CAPRIE 1996	**Patients with recent ischaemic stroke (ischaemic cerebrovascular disease), recent ischaemic myocardial infarction (ischaemic heart disease) or symptomatic peripheral arterial disease** **Ischaemic stroke:** Neurological signs persisting ≥ 1 week from stroke onset (CT or MRI ruling out haemorrhage). **Recent myocardial infarction:** Characteristic ischaemic pain ≥ 20 min.; typical ECG changes; elevation of cardiac enzymes to 2x upper limit of laboratory normal (at least 2 of these 3 criteria). **Peripheral arterial disease:** Typical intermittent claudication (pain disappearing in <10 min on standing) and ankle/arm systolic BP ratio < 0.85 or history of intermittent claudication with previous leg amputation or vascular surgery.	I: Ischaemic stroke ≥ 1 week and ≤ 6 months before randomisation; myocardial infarction ≤ 35 days before randomisation; symptomatic peripheral arterial disease. E: Carotid endarterectomy after qualifying stroke, severe comorbidity likely to limit patient's life expectancy to less than 3 years; long-term anti-coagulation necessary; probable dependency on third person as a result of the qualifying event; (history of) haemostatic disorder or systematic bleeding; severe renal or hepatic insufficiency; uncontrolled hypertension; history of aspirin sensitivity.
Objective: evaluation of gastrointestinal tolerance / complications		
Chan 2005	Upper gastrointestinal bleeding under ASA (≤ 325 mg/d) and endoscopic confirmation of the diagnosis "ulcer bleeding". Anticipated regular use of antiplatelet therapy.	I: Patients with a history of ulcer bleeding under ASA (confirmed by endoscopy), and endoscopically confirmed ulcer healing after 8 weeks. Negative results for the *H. pylori* test or successful eradication of *H. pylori*. Continuing indication for use of low-dose ASS (< 325 mg/d). E: Concomitant use of nonsteroid anti-inflammatory drugs, cyclooxygenase-2 inhibitors, anticoagulant agents, other antiplatelet drugs, or corticosteroids; a history of gastric surgery other than a patch repair; the presence of gastric-outlet obstruction; erosive oesophagitis or severe illness.
Ng 2004	Dyspeptic symptoms or gastrointestinal bleeding under low-dose ASA (80-160 mg/d) and confirmation of the diagnosis "ulcer" or "erosions" by upper endoscopy. Requirement of continuous antiplatelet therapy for secondary prevention of cerebrovascular disease, ischaemic heart disease, or peripheral vascular disease.	I: Patients with ischaemic heart disease, peripheral vascular disease, ischaemic stroke or transient ischaemic attacks who, under ASA therapy (80-160 mg/d) for secondary prevention, developed ulcers ≥ 3 mm in diameter or more than 10 erosions in the stomach or duodenum. E: Oesophagitis, pyloric stenosis, major active gastrointestinal bleeding (including ulcer with adherent clot [Forrest IIb], and visible vessels [Forrest IIa]), coagulopathy, antiplatelet-free period of more than 7 days.

continued

Table 3: Inclusion and exclusion criteria (continued)

Study	Patient population and diagnosis of qualifying disease	Main inclusion and exclusion criteria
Objective: evaluation of surrogate parameters (blood coagulation). The publications included additional information on adverse events.		
CADET (Woodward 2004)	Patients with recent myocardial infarction (acc. to WHO criteria; with or without ST-segment elevation).	I: Myocardial infarction within 3-7 days of study entry. E: Uncontrolled hypertension, being scheduled for major surgery (including coronary artery bypass grafting), concomitant use of hormone replacement therapy.
Jagroop 2004	Patients with peripheral vascular disease.	I: Intermittent claudication. E: No recent cardiac or cerebral events; no recent surgery or angioplasty.
CT: computer tomography; MRT: magnetic resonance tomography; I: inclusion criteria; E: exclusion criteria.		

Table 4: Baseline characteristics

Study	**N (total)** study discontinuations[1]	**Age[2]** [years]	**Gender** f [%]	 m [%]	**Vascular and cardiac diseases/risk factors[3] ([C%] / [A%])**	**Other characteristics ([C%] / [A%])**
Objective evaluation of the efficacy in secondary prevention						
CAPRIE 1996	9599 [C] 9586 [A] 4059 patients (21.2%) prematurely terminated the intake of study medication (21.3% [C]; 21.1% [A])	63 (± 11)	28	72	Previous ischaemic stroke[3] (9/9) Previous transient ischaemic attack[3] (10/10) Previous myocardial infarction[3] (17/16) Stable angina pectoris (22/22) Unstable angina pectoris (9/9) Symptomatic PAD (5/4) Atrial fibrillation (4/4) Congestive heart failure (6/5) Hypertension (52/51) Diabetes mellitus (20/20) Hypercholesterolaemia (41/41) Current smoker (29/30) Ex-smoker (49/49)	-
Objective: evaluation of gastrointestinal tolerance / complications						
Chan 2005	161 [C+P] 159 [A+E] 3 patients with incomplete follow-up. Premature study termination: - overall: 8.8% [A+E] vs. 11.8% [C+P] - due to adverse events: 1.9% [A+E] vs. 4.3 [C+P]	72 (± 10) 73 (± 10)	33 35	67 65	Ischaemic heart disease (55/49) Cerebrovascular insufficiency (34/42) Peripheral arterial disease (5/4) Multiple ischaemic diseases (6/6) Current smoker (13/8)	*Source of bleeding:* Gastric ulcer (58/47) Duodenal ulcer (30/38) Gastric and duodenal ulcer (6/11) Ulcer with signs of bleeding (28/34) Ulcer ≥ 2cm (12/13) Transfusion required (48/56) *H. pylori* infection (46/47)
Ng 2004	74 [C+O] 65 [A+O] In each treatment group, 5 patients were not evaluated by endoscopy. Data on dyspeptic symptoms were available for 5 of these patients (3 [C]; 2 [A]). Data were not available for the other 5 patients.	75 (± 9) 71 (± 13)	39 35	61 65	Ischaemic heart disease (83/83) Ischaemic stroke (32/23) Peripheral arterial disease (3/0) Current smoker (7/10)	*Source of bleeding:* Gastric ulcer (41/40) Duodenal ulcer (10/12) Gastric and duodenal ulcer (6/3) Ulcer with active bleeding (0/0) Ulcer ≥ 2cm (0/3) Transfusion necessary (17/8) *H. pylori* infection (45/55) History of ulcers (12/15)

continued

Table 4: Baseline characteristics (continued)

Study	**N (total)** Study discontinuations[1]	**Age[2]** [years]	**Gender** f[%]	 m[%]	**Vascular and cardiac diseases / risk factors[3] ([C%] / [A%])**	**Other characteristics ([C%] / [A%])**
Objective: evaluation of surrogate parameters (blood coagulation). The publications included additional information on adverse events.						
CADET (Woodward 2004)	94 [C] 90 [A] 25 (13%); 10 under clopidogrel and 15 under ASA.	63 (± 10) 62 (± 13)	19 19	81 81	Angina pectoris (17/17) Congestive heart failure (19/10) Hypertension (4/2) Current smoker (34/37) Ex-smoker (45/33)	-
Jagroop 2004	10 [C] 10 [A] No study discontinuations	70 (range, 58-77)[4]	30	70[4]	Type 2 diabetes mellitus (30%) Hypertension (60%) Known ischaemic heart disease (40%)	-

1: Excluding deaths.
2: Mean values (± standard deviation, if reported).
3: Concomitant illnesses before the qualifying event.
4: Total study population; no separate data according to treatment groups provided.
[C]=Clopidogrel; [A]=ASA; [P]=Placebo; [E]=Esomeprazole; [O]=Omeprazole.

5.2.2 Study and publication quality

An overview of the criteria for the study and publication quality is presented in Table 5.

CAPRIE 1996

Some deficiencies were identified in the primary publication of the CAPRIE trial which may possibly be due to deficits in the quality of the publication, but not necessarily of the study itself. Allocation concealment was poorly described. The same applies to the description of how the independent central validation committee functioned; its blinding with regard to the allocation of study medication was not explicitly noted. A further deficit of the publication was the lack of specification of the study setting, particularly with regard to details on the screening and selection process of patients before randomisation and study entry. With regard to baseline characteristics, details were missing on previous and concomitant medication. Furthermore, it was unclear which statistical method was used to determine the p-value for the primary outcome. This was not clearly described in the methods and results section. It also remains unclear whether adjustment techniques were used for the primary outcome analyses.

Above all, the information provided on the number of patients under risk in the Kaplan-Meier curve for the primary outcome was inconsistent. With a predefined minimum follow-up of 12 months, the information provided does not seem consistent with an ITT analysis: according to the published data, after the first year of follow-up, details on about 1800 patients are missing.

The responses from the manufacturer of clopidogrel and the authors of the CAPRIE trial contributed to the clarification of these open issues and are described in the following:

- The screening process in CAPRIE was not documented.
- All decisions in the central validation committee with regard to events were made without knowledge of study treatment (study drug or control). Events were reported by local investigators. The event dossier was transferred to the central validation committee secretariat, which then organised the central validation committee review process. Information about the treatment of individual patients was known only to the external safety and efficacy monitoring committee, and the third-party drug packaging company. Blinding of the evaluators with regard to patient allocation was therefore given.
- The information provided by the authors and sponsors invalidated the suspicion that patients may have been dropped from the evaluation without providing reasons. A relevant number of patients did not complete the study exactly at the planned time of 12 months after study entry, because the operations manual specified an allowable window

for any 4-month follow-up of ± 14 days. The 12-month Kaplan-Meier curve for the primary outcome in the publication considers only those patients who had their follow-up on or after day 366 (8087 in the ASA group and 8131 in the clopidogrel group). In the ASA and in the clopidogrel group, 827 and 864 patients, respectively, had a follow-up of 366 days. A total of 609 primary and 63 competing events (non-cardiovascular deaths or deaths due to bleeding) occurred in the ASA group; 533 primary and 71 competing events occurred in the clopidogrel group. Summing up the events or patients with a follow-up of less than 366 days results in exactly the total number of patients in the ASA group (9586) and clopidogrel group (9599). It can therefore be assumed that planned ITT analysis was not violated.

Therefore, it can be concluded that the CAPRIE trial only showed "minor deficiencies".

Chan 2005

The publication investigating rates of recurrent ulcer bleeding (Chan 2005) showed major deficiencies. The study was planned and conducted to show the non-inferiority of clopidogrel versus ASA plus esomeprazole. The non-inferiority limit was predefined: clopidogrel (test drug) would not be inferior to combination therapy including ASA and esomeprazole (active control) if the upper limit of the 95% confidence interval (CI) for the difference in recurrent ulcer bleeding rates did not exceed 4% after 12 months. Non-inferiority was not demonstrated, as the upper limit (12.4%) of the (2-sided) 95% CI (3.4% to 12.4%) for the difference between event rates exceeded the non-inferiority limit. As the lower limit (3.4%) of the 95% CI was greater than zero, the authors concluded a superiority of ASA plus esomeprazole. It may be assumed that the authors changed the study hypothesis post hoc and tested the superiority of ASA plus esomeprazole versus clopidogrel. There is no indication in the publication that, besides the non-inferiority test, further predefined hypotheses were formulated. Despite several queries, the main author, F. Chan, did not address this issue.

The main deficit of the publication was the discrepancy with regard to the number of patients who were prematurely discontinued from the primary outcome evaluation (in particular, lost to follow-up patients). It was read off Figure 1, Chan 2005 (numbers at risk, Kaplan Meier curve for the primary outcome), that 27 patients in the clopidogrel group and 20 patients in the ASA group were censored within the follow-up period of 12 months. Overall, 13 events occurred in the clopidogrel group and 1 event in ASA group. It is also stated in the text that a total of 3 patients were "lost to follow-up" (all in the ASA group). Furthermore, 8 patients in the clopidogrel and 4 patients in the ASA group died. If one assumes that all patients who

died were prematurely censored, i.e. no recurrent gastrointestinal bleeding had occurred beforehand (conservative approach), and they were legitimately prematurely censored due to the competing event "death", then the premature termination of follow-up in 21 patients in the clopidogrel group and 8 patients in the ASA group can be explained (clopidogrel: 13 events, 8 deaths; ASA: 1 event, 4 deaths, 3 lost to follow-up). From this it follows that for 6 patients in the clopidogrel group and 12 patients in the ASA group it remains unclear why the follow-up with regard to the primary outcome was prematurely terminated (i.e. before the end of the planned follow-up of 12 months).

If one assumes in a "worst case scenario" that, of these patients, as well as of the "lost to follow-up" patients, all patients in the ASA group (n=15) and none in the clopidogrel group experienced a primary event, then the observed difference between the treatment groups is equalised. On the basis of the publication, the results of the study were initially classified as "not robust" and of questionable validity.

The inconsistencies were at least partially clarified by F. Chan and the statistician responsible, J. Ching. On the one hand, 2 of the 8 patients, who according to the publication, died during the study, were not censored at the time point of death, but had experienced a gastrointestinal event (as a primary outcome) beforehand. On the other hand, patients were prematurely censored who had experienced a different event than "death" or a primary outcome, namely "lower gastrointestinal bleeding" (7 patients in both groups), bleeding from a malignant tumour (clopidogrel: 1 patient; ASA: 3 patients), or unclear anaemia (2 patients in the ASA group). The allocation of the 6 patients in the clopidogrel group and the 12 patients in the ASA group who were prematurely censored without a primary outcome event is therefore clarified. However, the above procedures were not described in the publication and are also not comprehensible: a follow-up with regard to upper gastrointestinal bleeding would, for example, still have been meaningful and possible after the diagnosis of "unclear anaemia" or "lower gastrointestinal bleeding" was reported. If one regards the events listed by J. Ching, as well as the deaths, as primary events (in the sense of a balanced analysis for both treatment groups) and one still assumes that the "lost to follow-up" patients in the ASA group also experienced a primary event (worst case scenario for ASA), then one can assume that 27 patients in the clopidogrel group and 20 patients in the ASA group experienced a primary event (compared with 13 vs. 1 event as reported in the publication). It is unclear whether this difference remains significant in the survival analysis. However, in this analysis the numerical advantage for ASA still remains and therefore the results for the primary outcome are robust. Under consideration of the additional information provided by the authors, the initial

classification as a publication with "major deficiencies" (Chan 2005) with regard to the results of the primary outcome must therefore be qualified.

Ng 2004

"Major deficiencies" were also identified in the Ng trial. The study was described as a single-blind trial, which refers to the blinding of the endoscopist (page 361 of the publication). No details were provided on the randomisation process and on whether and how allocation concealment was ensured. In this context, the noticeable mean age difference between groups may indicate a potential selection bias. This must be regarded as a serious issue, also because of the lack of blinding of patients and physicians. Details were also not available on the screening procedure. The evaluation was described as an ITT analysis. However, the principles of such an analysis seem to have been violated several times. The data provided on the number of randomised and/or evaluated patients were inconsistent with regard to the text and tables. Furthermore, with the rate of ulcer healing (confirmed by endoscopy), the study primarily investigated a surrogate parameter of unclear relevance for patients. This study is therefore seen as only suitable to generate a hypothesis with regard to gastrointestinal complications under clopidogrel or ASA. For these reasons, the authors of the publication were not contacted.

CADET (Woodward 2004) and Jagroop 2004

In the publication on the double-blind CADET trial, no details were provided on whether and if yes, how allocation concealment was ensured. Other serious deficits were not found.

In the publication on the Jagroop trial, no information was provided on the randomisation procedure, including allocation concealment. In an open-label study, this must be regarded as a major deficit. The authors of the publication were not contacted, as in both studies the outcomes that were relevant for this report were exclusively determined within the framework of the safety evaluation and were not specifically validated.

Table 5: Study and publication quality

Study	Randomisation / concealment appropriate	Blinding	Sample size planning	Study discontinuations / reasons for discontinuation reported	Appropriate ITT analysis	Consistency of information[1]	Study and publication quality
CAPRIE 1996	yes / yes	double-blind	yes	yes	yes	no[2]	minor deficiencies
Chan 2005	yes / yes	double-blind	yes	yes	no[3]	no[3]	major deficiencies[4]
Ng 2004	unclear / unclear	single-blind[5]	yes	yes	no	no	major deficiencies[6]
CADET (Woodward 2004)	yes / unclear	double-blind	yes	yes	yes[7]	yes	minor deficiencies
Jagroop 2004	unclear / unclear	open	no	yes	yes[7]	yes	major deficiencies[8]

1: Consistency of all information provided (within and between publications, including information provided by the authors and sponsors).
2: Differences in the statements on statistical significance for single adverse events between CAPRIE 1996 and Harker 1999. See also Section 5.3.5.
3: The inconsistencies in the publication with regard to patients who were prematurely discontinued from the evaluation were clarified by the additional information provided by the authors. See also previous text.
4: "Major deficiencies" generally due to discrepant information between text and tables in the publication, inappropriate ITT analysis, unclear procedure when changing the hypothesis. With regard to the evaluation of the results for the primary outcome, these major deficiencies are, however, qualified by the subsequent details provided by the authors. See also previous text.
5: Blinding of the endoscopist.
6: "Major deficiencies" due to unclear randomisation procedure/allocation concealment and potential selection bias, as well as inappropriate ITT analysis and inconsistency of information.
7: With regard to adverse events.
8: "Major deficiencies" due to unclear randomisation procedure/allocation concealment in an open-label study design; no sample size planning conducted.

5.3 Results on patient-relevant therapy goals

The patient-relevant therapy goals outlined in Section 4.1.3 can mainly be classified into 3 major categories:

1. Reduction of the rate of thromboembolic events,
2. Reduction of the rate of adverse events,
3. Improvement of quality of life (including the reduction of disease-related symptoms).

In addition, "all-cause mortality" is to be seen as an overall criterion including the first 2 categories, insofar as it concerns fatal events in these categories.

The information pool on "thromboembolic events" mainly originated from the CAPRIE trial and the corresponding secondary publications.

The 5 secondary publications on efficacy in part included composite outcomes that were not listed in the primary publication (CAPRIE 1996); one may therefore assume that they were defined post hoc. The results for these composite outcomes are not presented because of their questionable validity. In contrast, single results for secondary outcomes are presented in this report, even if they were not defined in the primary CAPRIE publication, but represented a disease entity (e.g. MI, stroke), and were evaluated by the validation committee; i.e., the corresponding results can therefore to some extent be regarded as valid [50]. In the remaining studies, data on thromboembolic events were provided, if at all, only within the framework of the safety evaluation.

Two studies were available which primarily investigated the reduction in the rate of gastrointestinal adverse events of clopidogrel and ASA (Chan 2005 and Ng 2004). The 3 other studies also reported adverse events occurring under these treatment options. Again, the CAPRIE trial is the main contributor to the information pool due to its sample size and duration. However, because of the comparatively high ASA dose, the results can only be transferred to a limited extent to the German health care setting.

Few data on "quality of life / disease-related symptoms" were provided in all studies. With the exception of the Ng trial (2004), which systematically documented dyspeptic symptoms, no study investigated events of this category as predefined primary or secondary outcomes.

Information on all-cause mortality was provided in all studies. Again, the CAPRIE trial is relevant for the evaluation in this regard, as all-cause mortality was a predefined outcome, and the CAPRIE trial was the largest and longest study included.

The presentation of results is organised as follows:

1. All-cause mortality,
2. Thromboembolic events,
   - fatal events
   - non-fatal events
   - composite outcomes
3. Adverse events
4. Quality of life / symptoms

If available, results for specific subgroups are subsequently presented. This also includes the predefined subgroups of the CAPRIE trial, (patients with recent ischaemic stroke [ICVD subgroup], recent ischaemic MI [IHD subgroup], or symptomatic PAD [PAD subgroup]). If relevant, single results for these predefined subgroups are also described within the framework of the presentation of overall results of the CAPRIE trial.

5.3.1 All-cause mortality

None of the studies included was designed to evaluate a benefit of clopidogrel versus ASA with regard to "all-cause mortality" as a primary outcome.

In the CAPRIE trial (1996), "all-cause mortality" was 1 of 4 predefined validated secondary outcomes. With a mean follow-up of 1.91 years, in the 9599 patients at risk in the clopidogrel group, 560 deaths occurred in 18 377 years under risk; this corresponds to an overall rate of 5.83% and an event rate per year of 3.05%. In the 9586 patients at risk in the ASA group, 571 deaths occurred in 18 354 years under risk. This corresponds to an overall rate of 5.96% and an event rate per year of 3.11%. The difference between treatment groups was not statistically significant.

The other studies, with a total of 21 deaths (14 under clopidogrel, 7 under ASA), which were all documented within the framework of the safety evaluation, contributed little information to this outcome. Because of the heterogeneous study designs (design, research question, duration of follow-up) a meta-analysis of results did not seem meaningful.

An overview of all-cause mortality is shown in Table 6; there was no evidence of a difference between treatment groups with regard to all-cause mortality.

Table 6: Outcome "All-cause mortality"

Study	Study duration	Patients (N)	Events		Relative risk (95% CI)	Type of documentation	Outcome validated[1]
			Clopidogrel (N [%])	ASA (N [%])			
CAPRIE 1996	1.91 years	9599 [C] 9586 [A]	560 (5.83%)	571 (5.96%)	0.98 (0.87-1.10)[2]	secondary outcome	yes
Chan 2005	1 year	161 [C+P] 159 [A+E]	8 (5.0%)	4 (2.5%)	n.d.	within the framework of the safety evaluation	no
Ng 2004	8 weeks	74 [C+O] 65 [A+O]	1 (1.4%)	0 (0%)	n.d.	within the framework of the safety evaluation	no
CADET (Woodward 2004)	6 months	94 [C] 90 [A]	5 (5.3%)	3 (3.3%)	n.d.	within the framework of the safety evaluation	no
Jagroop 2004	8 days	10 [C] 10 [A]	0	0	n.d.	within the framework of the safety evaluation	no

1: Information on whether the validation of the outcomes was conducted by a blinded validation committee. If this information was not explicitly provided in the publication, the outcome is evaluated as "non-validated".
2: Derived from the information on the relative risk reduction for the yearly event rate from CAPRIE 1996, rounded off.
[C]: Clopidogrel; [A]: ASA; [P]: Placebo; [E]: Esomeprazole; [O]: Omeprazole; 95% CI: 95% confidence interval; n.d.: no details provided.

5.3.2 Vascular death

Vascular death is defined as follows: cardiac death (fatal MI, sudden cardiac death, and other cardiac deaths, insofar as they are not specifically of non-vascular origin); cerebral death (fatal stroke, fatal cerebral haemorrhage); fatal haemorrhage, as well as all other deaths where a vascular cause cannot be excluded.

None of the studies included was designed to evaluate a benefit of clopidogrel versus ASA with regard to the reduction of vascular death rates as a primary outcome.

In the CAPRIE trial, vascular death corresponded with the above definition (i.e. also including fatal cerebral haemorrhages or other fatal haemorrhages) and was predefined as 1 of the 4 secondary outcomes. It was also a component of the composite primary outcome. All fatal events (including vascular death) were evaluated by the central validation committee. With a mean follow-up of 1.91 years in both groups, in the 9599 patients in the clopidogrel group, 350 vascular deaths occurred in 18 377 patient years under risk (not 17 482 years, as stated in the publication; this is probably due to a confusion of numbers); this corresponds to an overall rate of 3.65% and an event rate per year of 1.90%. In the 9586 patients in the ASA group, 378 vascular deaths occurred in 18 354 patient years under risk. This corresponds to an overall rate of 3.94% and an event per year of 2.06%. The (statistically non-significant) difference between treatment groups is mainly due to the difference concerning the component “fatal MI”. Overall, 53 fatal MIs occurred under clopidogrel (overall rate: 0.55%) and 75 occurred under ASA (overall rate: 0.78%). Only a small difference between treatment groups was shown for fatal ischaemic stroke (37 vs. 42 events within the framework of the composite primary outcome).

As “vascular death“ was a component of the primary outcome of the CAPRIE trial, details in this regard were available for the 3 predefined subgroups of patients with recent ischaemic stroke, recent ischaemic MI, or symptomatic PAD as a qualifying disease (ICVD, IHD, and PAD subgroups). For vascular death, opposite trends were observed in the IHD and PAD subgroups (with a comparable follow-up period of approx. 11 500 patient years). In the IHD subgroup, 111 vascular deaths occurred under clopidogrel and 97 under ASA; in the PAD subgroup, 95 vascular deaths occurred under clopidogrel and 122 under ASA. In the ICVD group, 102 vascular deaths occurred in both the clopidogrel and ASA groups. Only vascular deaths were counted that occurred as a first event of the primary outcome.

In both studies on gastrointestinal tolerability, vascular deaths were documented within the framework of the safety evaluation as adverse events. In the Chan trial, 1 fatal MI and 1 fatal

cerebral haemorrhage were reported under clopidogrel (1.2%); 1 fatal MI and 1 fatal "cerebrovascular insufficiency" were reported under ASA (1.3%).

The Ng trial reported a fatal MI under clopidogrel (1.4%). No vascular deaths were reported under ASA. The study only lasted 8 weeks.

The CADET trial reported 3 deaths in patients in the ASA group and 5 deaths in the clopidogrel group (no information was provided on how many of these cases were due to vascular death).

In the Jagroop trial, no deaths (and therefore no cases of vascular death) were reported.

In summary (Table 7), no advantage for either treatment option (clopidogrel vs. ASA) for vascular death was shown.

In the CAPRIE trial, opposite effects were shown in the IHD and PAD subgroups with a numerical disadvantage for clopidogrel in the subgroup of IHD patients and a numerical advantage for clopidogrel in the subgroup of PAD patients.

Table 7: Outcome "Vascular mortality"

Study	Study duration	Patients (N)	Events		Relative risk (95% CI)	Type of documentation	Outcome validated[1]
			Clopidogrel (N [%])	ASA (N [%])			
CAPRIE 1996	1.91 years	9599 [C] 9586 [A]	350 (3.65%)	378 (3.94%)	0.92 (0.80-1.07)[2]	secondary outcome	yes
Chan 2005	1 year (median)	161 [C+P] 159 [A+E]	2 (1.2%)	2 (1.3%)	n.d.	within the framework of the safety evaluation	no
Ng 2004	8 weeks	74 [C+O] 65 [A+O]	1 (1.4%)	0 (0%)	n.d.	within the framework of the safety evaluation	no
CADET (Woodward 2004)	6 months	94 [C] 90 [A]	n.d.	n.d.			
Jagroop 2004	8 days	10 [C] 10 [A]	0 (0%)	0 (0%)	n.d.	within the framework of the safety evaluation	no

1: Information on whether the validation of the outcomes was conducted by a blinded validation committee. If this information was not explicitly provided in the publication, the outcome is evaluated as "non-validated".
2: From the information on the relative risk reduction from the proportional hazard model from CAPRIE 1996, rounded off.
[C]: Clopidogrel; [A]: ASA; [P]: Placebo; [E]: Esomeprazole; [O]: Omeprazole; 95% CI: 95% confidence interval; n.d.: no details provided.

5.3.3 Vascular morbidity

This report investigated the following outcomes with regard to the therapy goal "vascular morbidity":

- Non-fatal MI,
- Non-fatal stroke,
- Ulcer, gangrene, or amputation due to ischaemia,
- Revascularisation procedure due to ischaemic symptoms,
- ACS, angina pectoris, symptomatic arrhythmia, TIA, intermittent claudication,
- New occurrence of heart failure or deterioration of pre-existing heart failure.

None of the outcomes defined above were defined as primary or secondary outcomes in the studies included. However, some of the outcomes defined above were components of the composite primary and/or composite secondary outcome of the CAPRIE trial, and were reported in the CAPRIE publication (1996) and/or one of its secondary publications. In addition, information was found on single outcomes reported within the framework of the safety evaluation of both the CAPRIE trial and the other studies included. The corresponding results are presented in the following sections.

5.3.3.1 Myocardial infarction

In the CAPRIE trial, the outcome "non-fatal MI" was a component of the composite primary outcome, as well as of a composite secondary outcome, and was also described in a secondary publication (Cannon, 2002). The evaluation of this outcome in the CAPRIE trial can be described as valid, as a central validation committee was involved.

A total of 308 MIs (255 non-fatal and 53 fatal) occurred under clopidogrel (3.21 MIs per 100 patients); 376 MIs occurred under ASA (301 non-fatal and 75 fatal; 3.92 MIs per 100 patients). This also includes reinfarctions, so on the basis of the CAPRIE trial data it remains unclear exactly how many patients experienced at least 1 MI during the study period. The (numerical) difference of 68 MIs was mainly due to the difference in the PAD subgroup (68 MIs under clopidogrel vs. 108 under ASA). A comparative statistical analysis of the MI rates under clopidogrel and ASA was not conducted in the CAPRIE trial.

The relative risk for the MI rate in the CAPRIE trial (including the 95% CI, see also Table 8) could be read off Figure 2 in a secondary publication (Bhatt, 2000); the relative MI risk was significantly reduced under clopidogrel versus ASA (by about 22%). Details on the number of

MIs in both treatment groups and/or which MIs were analysed (first events within the framework of the primary outcome of CAPRIE 1996, total number of MIs, or only first MIs) were not provided in this publication. In addition, the analysis was not an ITT analysis but a modified PP analysis. Its evidential value concerning the MI rate under clopidogrel compared with ASA is therefore limited.

Data on the frequency of MIs in the CAPRIE trial were also available in the secondary analysis presented in the Cannon publication (2002), where it is reported that of the 19 185 patients in the CAPRIE trial, a new acute MI occurred in 617 patients. However, it is unclear from the publication which types of MIs were evaluated (e.g. it is unclear whether reinfarctions were considered). In addition, the reported rates of 4.2% (clopidogrel) and 5.04% (ASA) (relative risk reduction: 19.2%, p=0.008), differ from the rates which can be calculated from the CAPRIE 1996 publication. No reasons for this are provided in the Cannon 2002 publication; therefore these data are of limited evidential value due to their unclear validity.

In the Chan trial, 1 MI was documented as an adverse event in both the clopidogrel and ASA groups. In the Ng trial, 1 MI occurred in the clopidogrel group, and no MI occurred in the ASA group. In the CADET trial, an MI was reported as an adverse event in 1 (1.1%) of 94 patients in the clopidogrel group and 6 (6.7%) of 90 patients in the ASS group. No MIs were reported in the Jagroop trial in either treatment group.

The results are summarised in Table 8.

Table 8: Outcome "Myocardial infarction"

Study	**Study duration**	**Patients (N)**	**Events**		**Relative risk (95% CI)**	**Type of documentation**	**Outcome validated**[1]
			Clopidogrel (N)	**ASA** (N)			
CAPRIE 1996	1.91 years	9599 [C] 9586 [A]	308 (including 53 fatal events)	376 (including 75 fatal events)	0.78 (0.68-0.94)[2]	as a component of the composite primary and a composite secondary outcome	yes
Chan 2005	1 year (median)	161 [C+P] 159 [A+E]	1 (fatal)	1 (fatal)	n.d.	within the framework of the safety evaluation	no
Ng 2004	8 weeks	74 [C+O] 65 [A+O]	1 (fatal)	0	n.d.	within the framework of the safety evaluation	no
CADET (Woodward 2004)	6 months	94 [C] 90 [A]	1 (fatal: n.d.).	6 (fatal: n.d.)	n.d., p>0.05	within the framework of the safety evaluation	no
Jagroop 2004	8 days	10 [C] 10 [A]	0	0		within the framework of the safety evaluation	no

1: Information on whether the validation of the outcomes was conducted by a blinded validation committee. If this information was not explicitly provided in the publication, the outcome is evaluated as "non-validated".
2: Read off Figure 2, Bhatt 2000. Discrepant information in Cannon 2002; see previous text.
[C]: Clopidogrel; [A]: ASA; [P]: Placebo; [E]: Esomeprazole; [O]: Omeprazole; 95% CI: 95% confidence interval; n.d.: no details provided.

5.3.3.2 Stroke

In the CAPRIE 1996 publication, validated data were provided on non-fatal stroke of any cause (486 under clopidogrel; 528 under ASA); however, data were not provided on the overall rate of stroke of any cause, including fatal stroke of any cause. The reported cases were mainly cases of ischaemic stroke. Fatal and non-fatal ischaemic stroke were validated outcomes. A total of 509 out of the 9599 patients in the clopidogrel group experienced an ischaemic stroke (472 non fatal; 37 fatal) during the study; in the 9586 patients in the ASA group, 546 patients experienced an ischaemic stroke (504 non-fatal, 42 fatal). Ischaemic stroke occurred as a first event (as a component of the primary outcome of CAPRIE 1996) in 438 patients (including 33 fatal events) in the clopidogrel group and in 462 patients (including 32 fatal events) in the ASA group. No comparative statistical analysis was conducted between treatment groups.

The relative risk (including the 95% CI) of a stroke could be read off Figure 2, Bhatt 2000. It was about 6% (non-significantly) lower in the clopidogrel group vs. ASA. Details were not provided in the publication on the number of strokes in each treatment group and/or on which type of strokes were analysed (ischaemic or also non-ischaemic, first events as a component of the composite primary outcome of CAPRIE 1996, total number of strokes, or only first strokes). In addition, this was not an ITT analysis, but a modified PP analysis. The evidential value of the data provided in Bhatt 2000 on the stroke rate under clopidogrel versus ASA is therefore limited.

Two cases of “cerebrovascular insufficiency” (not further defined) were reported as an adverse event under clopidogrel in the Chan trial; 3 cases were reported under ASA. No information on cerebrovascular events under clopidogrel or ASA was provided in the Ng and CADET publications.

No adverse events (and therefore no cases of stroke) occurred in the Jagroop trial (2004).

The results of the single studies are summarised in Table 9 (limited to ischaemic stroke, the main type of stroke that occurred).

Table 9: Outcome "Ischaemic stroke"

Study	Study period	Patients (N)	Events		Relative risk (95% CI)	Type of documentation	Outcome validated[1]
			Clopidogrel (N)	**ASA** (N)			
CAPRIE 1996	1.91 years	9599 [C] 9586 [A]	509 (including 37 fatal events)	546 (including 42 fatal events)	0.94 (0.82-1.08)[2]	as a component of the composite primary outcome and a composite secondary outcome	yes
Chan 2005	1 year (median)	161 [C+P] 159 [A+E]	2[3]	3[3]	n.d.	within the framework of the safety evaluation	no
Ng 2004	8 weeks	74 [C+O] 65 [A+O]	n.d.	n.d.			
CADET (Woodward 2004)	6 months	94 [C] 90 [A]	n.d.	n.d.			
Jagroop 2004	8 days	10 [C] 10 [A]	0	0		within the framework of the safety evaluation	no

1: Information on whether the validation of the outcomes was conducted by a blinded validation committee. If this information was not explicitly provided in the publication, the outcome is evaluated as "non-validated".
2: Read off Figure 2, Bhatt 2000.
3: "Cerebrovascular insufficiency"; no further details provided.
[C]: Clopidogrel; [A]: ASA; [P]: Placebo; [E]: Esomeprazole; [O]: Omeprazole; 95% CI: 95% confidence interval; n.d.: no details provided.

5.3.3.3 Composite primary outcome (CAPRIE trial): Vascular death, myocardial infarction, or stroke

The composite primary outcome of the CAPRIE trial was the first occurrence of an event of ischaemic stroke, MI, or vascular death. The CAPRIE trial included 19 185 patients. The primary outcome occurred in 1960 patients. There were 939 events in the clopidogrel group - an average rate per year of 5.32%. There were 1021 events in the ASA group - an average rate per year of 5.83%. The (statistically significant) relative risk reduction was 8.7% (relative risk: 0.913; 95% CI: 0.835 to 0.997; p=0.043).

The preplanned subgroup analysis of the ICVD, IHD, and PAD patients showed different effects of clopidogrel in these 3 populations. The corresponding heterogeneity test was statistically significant (p=0.042). Due to the limited power of the individual subgroup analyses, the results are only relevant in association with the heterogeneity test. The relative risk reduction was particularly noticeable in the PAD subgroup, although comparatively few events occurred (relative risk reduction: 23.8%; 95% CI: 8.9% to 36.2%; p=0.0028). The event rate per year was 3.71% and 4.86% in the clopidogrel group and ASA group, respectively. At 8.9%, the lower limit of the 95% CI lay slightly above the relative risk reduction with clopidogrel therapy for the total study population of the CAPRIE trial (8.7%). Numerically more patients in the IHD subgroup experienced an event under clopidogrel than under ASA (relative risk increase: 3.7%; 95% CI: 22.1% to –12.0%, p=0.66). The event rate per year (5.03% vs. 4.84%) was lower than that of the total study population, but higher than the overall event rate of the PAD subgroup.

In the ICVD subgroup, the primary outcome occurred numerically less often under clopidogrel than under ASA. At 7.3% (95% CI: -5.7% to 18.7%; p=0.26) the relative risk reduction was slightly below that of the total study population, the event rate being comparatively high (event rate per year: 7.15% [clopidogrel] vs. 7.71% [ASA]).

The CI of the ICVD subgroup strongly overlaps the CIs of both the IHD and the PAD groups, whereas the CIs of the IHD and the PAD subgroups hardly overlap.

In summary, the results of the CAPRIE trial for the primary outcome can be evaluated as follows:

- A superiority of clopidogrel was demonstrated in the subgroup of PAD patients.
- Under consideration of the results of the heterogeneity test, this finding was not demonstrated for the IHD and ICVD subgroups. The results in these groups could be compatible with a positive effect of clopidogrel versus ASS (although less marked

than in the PAD subgroup), with no effect, as well as with a negative effect. The results in the IHD subgroup do not seem to indicate a favourable effect of clopidogrel in this subgroup. The results in the ICVD subgroup could be compatible with the effects in both the IHD and the PAD subgroups.

No adverse events (and therefore no event of this composite outcome) occurred in the Jagroop trial.

In the other studies included, the composite outcome of the CAPRIE trial was not a predefined outcome.

The results are summarised in Table 10.

Table 10: Primary outcome of the CAPRIE trial: "Vascular death, myocardial infarction, ischaemic stroke"

Study	**Study duration**	**Patients (N)**	**Events**		**Relative risk (95% CI)**	**Type of documentation**	**Outcome validated[1]**
			Clopidogrel (N)	**ASA** (N)			
CAPRIE 1996	1.91 years	9599 [C] 9586 [A]	939 (5.32%)[2]	1021 (5.83%)[2]	0.913 (0.835-0.997)[3]	primary outcome	yes
Chan 2005	1 year (median)	161 [C+P] 159 [A+E]	n.d.	n.d.			
Ng 2004	8 weeks	74 [C+O] 65 [A+O]	n.d.	n.d.			
CADET (Woodward 2004)	6 months	94 [C] 90 [A]	n.d.	n.d.			
Jagroop 2004	8 days	10 [C] 10 [A]	0	0		within the framework of the safety evaluation	no

1: Information on whether the validation of the outcomes was conducted by a blinded validation committee. If this information was not explicitly provided in the publication, the outcome is evaluated as "non-validated".
2: Event rates per year in brackets.
3: Derived from the information on the relative risk reduction from the proportional hazard model in CAPRIE 1996.
[C]: Clopidogrel; [A]: ASA; [P]: Placebo; [E]: Esomeprazole; [O]: Omeprazole; 95% CI: 95% confidence interval; n.d.: no details provided.

5.3.3.4 Ischaemic ulcer, gangrene, and amputation

Amputations were only documented in the CAPRIE trial, namely as a validated component of a composite secondary outcome. A total of 52 events occurred in the clopidogrel group, compared with 47 in the ASA group. A statistical comparison of these rates was not conducted.

No details on the number or rate of ischaemic ulcers or gangrene were provided in the publications included, neither as documented outcomes nor as adverse events.

5.3.3.5 Revascularisation procedures due to ischaemic symptoms

Little information on revascularisation procedures was provided in the studies included.

In the CADET trial, it was reported that an angiography was performed in 7 out of 94 patients in the clopidogrel group. This procedure was conducted in 6 of the 90 patients in the ASA group. Details on the type of angiography and whether and how often it was combined with a revascularisation procedure were not provided in the publication.

5.3.3.6 Acute coronary syndrome, angina pectoris, symptomatic arrhythmia, transient ischaemic attacks, intermittent claudication

Information on the above outcomes was only provided within the framework of adverse event reporting. As a validation of these events was not conducted by a central validation committee, the respective results are of little evidential value. The following information was provided in the publications:

Acute coronary syndrome (including unstable angina pectoris), stable angina pectoris

In the Ng trial, 1 case of unstable angina pectoris was reported in both treatment groups that led to study discontinuation.

In the Chan trial, unstable angina pectoris was reported in 6 (clopidogrel) and 7 (ASA) patients.

In the CADET trial, angina pectoris was reported in 9 out of 94 patients (9.6%) and 11 out of 90 patients (12.2%); in the clopidogrel and ASA groups, respectively; no information was provided on whether these were cases of stable or unstable angina. Of these cases, 3 (clopidogrel) and 6 (ASA) were classified as “serious occurrences” (serious adverse events).

In the CAPRIE trial, no information on angina pectoris was provided in the primary publication (CAPRIE 1996) nor in the safety publication (Harker 1999).
In the Jagroop trial, no adverse events occurred.

Symptomatic arrhythmia

Only the safety evaluation of the CAPRIE trial (Harker 1999) included information on the overall incidence of heart rate and rhythm events. Such events were more frequently reported under ASA than under clopidogrel (5.0% vs. 4.3%; p=0.011). No information was provided on the type of disorders and whether they were symptomatic or life-threatening. The relevance of this finding for patients is therefore unclear. In addition, due to the lack of a predefined hypothesis (documentation of events only within the framework of the safety evaluation) these results are only of limited value.

Transient ischaemic attacks, intermittent claudication

The rate of TIAs or intermittent claudication under clopidogrel versus ASA was not reported in any of the relevant publications.

5.3.3.7 New occurrence of heart failure or deterioration of pre-existing heart failure

The rate of newly occurring heart failure or deterioration of pre-existing heart failure under clopidogrel versus ASA was not reported in any of the relevant publications.

5.3.4 Rate of hospitalisations

The hospitalisation rate was not a predefined outcome in any study.
The Bhatt 2000 publication (CAPRIE trial) included details on hospitalisation rates under clopidogrel and ASA; however, these were only recorded within the framework of the safety evaluation and are therefore not validated.
Details were found on reasons for hospitalisation, for example, due to ischaemic or bleeding events. Due to the post-hoc character of the evaluation of data, the post-hoc definition of outcomes on hospitalisation rates and the lack of outcome validation by an independent validation committee, at best the outcome “hospitalisation for any cause” gives a certain indication for a comparison between treatment groups. The choice of reasons for

hospitalisation (e.g., due to specific ischaemic events or bleeding events) seems arbitrary and is therefore not presented here.

According to Bhatt 2000, 3500 (36.6%) of the 9553 patients in the clopidogrel group and 3573 (37.4%) of the 9546 patients in the ASA group were hospitalised (only patients with at least 1 dosage of study drug were evaluated). The difference was not statistically significant.

The other publications did not include any (or any validated) information on the overall hospitalisation rate.

5.3.5 Adverse events

Of the 5 trials included, 2 (Chan 2005 und Ng 2004) primarily investigated the comparison between treatment options with regard to safety aspects (gastrointestinal bleeding / complications).

The other 3 studies also evaluated safety aspects; however, these were secondary objectives. Of these studies, in particular the CAPRIE trial, due to its size and duration, was relevant for the safety evaluation. The Harker 1999 publication is a separate publication on adverse events in the CAPRIE trial. The reported events were documented within the framework of the safety evaluation and were only evaluated by the validation committee in exceptional cases (if the investigator thought that an event within the framework of the efficacy evaluation was possible). Furthermore, in the Harker 1999 publication, there was no adjustment for multiple testing. The significant differences between treatment groups for single adverse events reported in Harker 1999 are therefore primarily to be seen as an indication, but not as evidence of a difference between treatment groups. Furthermore, in the CAPRIE trial, a comparatively high dose of ASA was used, which per se limits the evidential value of results on specific adverse events.

As 2 trials primarily evaluated the prevention of gastrointestinal complications under clopidogrel and ASA, the respective results are presented separately. Then a presentation of the adverse events listed in Section 4.1.3 follows (only adverse events classified as “severe”), as their documentation within the framework of the safety evaluation can largely be seen as reliable and such events can be regarded as relevant to patients. Finally, further patient-relevant outcomes that are important indications of the damage potential of the substances are presented (“serious adverse events [overall]”, “study discontinuation due to adverse events”).

5.3.5.1 Gastrointestinal complications

From a clinical point of view, 2 types of gastrointestinal complications should be distinguished:

1. Specific gastrointestinal tolerability of clopidogrel or ASA in patients with a history of gastrointestinal complications, in particular, bleeding.
2. General gastrointestinal tolerability of clopidogrel or ASA in patients with no history of gastrointestinal complications.

Both trials where the evaluation of gastrointestinal complications was the primary objective (Chan 2005 und Ng 2004) refer to the first point, i.e. to patients who, due to a prior gastrointestinal event (symptomatic ulcers/erosions [Chan 2005: bleeding; Ng 2004: bleeding or dyspepsia]), had a high risk of a recurrent gastrointestinal complication. In the other 3 studies, patients with a history of gastrointestinal complications were neither the specific target population nor were they excluded from the study. Subgroup analyses for this population were also not available; therefore no conclusions with regard to patients with or without a history of gastrointestinal complications can be made from the other studies.

Gastrointestinal bleeding and ulcers

Both publications with the primary objective of evaluating gastrointestinal complications showed major deficits (see Section 5.2.2). In the Ng trial, which had the character of a pilot study (primary outcome: surrogate parameter “endoscopic confirmation of ulcer healing; open-label design; study duration: 8 weeks), this had no decisive effect on the overall evidential value (which was anyway limited). These deficits are, however, relevant in order to classify the study results of the Chan trial; see Section 5.2.2.

In the Ng trial, only small differences between treatment groups were shown with regard to treatment success (healing of pre-existing gastroduodenal ulcers/erosions: 90% under clopidogrel vs. 95% under ASA [ITT analysis: p=0.337]). No cases of ulcer bleeding were reported in either treatment group during an 8-week period. In contrast, statistically significantly more cases of recurrent ulcer bleeding were reported under clopidogrel than under ASA plus esomeprazole in the Chan trial (8.6% vs. 0.7%; p=0.001; Kaplan-Meier estimate). The rate of lower gastrointestinal bleeding was identical in both treatment groups (4.6%). The explanations presented by F. Chan concerning the discrepancies with regard to patients who were prematurely censored leave open the possibility that the advantage reported in the publication for ASA may be smaller than reported or, indeed, may not exist at all. However, this does not affect the conclusion by the authors that the non-inferiority of

clopidogrel versus ASA and esomeprazole with regard to recurrent ulcer bleeding was not demonstrated.

The results on gastrointestinal bleeding in the CAPRIE trial (Harker 1999) are shown in Table 11. In addition, the respective results of the CADET trial and Jagroop trial are presented.

Only the CAPRIE trial made a relevant contribution to the information pool. More cases of gastrointestinal bleeding occurred under 325 mg ASA compared with clopidogrel (2.66% vs. 1.99%; $p<0.002$).

According to Table 3 in Harker 1999, the difference in the rate of severe gastrointestinal bleeding was not statistically significant (0.71% under ASA vs. 0.49% under clopidogrel); however, according to the abstract in this publication, this difference was statistically significant. In CAPRIE 1996, this difference was also reported to be statistically significant. The respective event rates reported in Harker 1999 and CAPRIE 1996 were identical.

Lower gastrointestinal bleeding mainly contributed to the overall rate of gastrointestinal bleeding in both groups ("rectal haemorrhage" or "melena", possibly including positive tests for occult blood testing or self-reported blood in stool without objective confirmation). The rate of upper haemorrhagic ulcers was low and comparable between groups (25 [0.26%] under clopidogrel vs. 26 [0.27%] under ASA; including 17 severe events in both groups).

Fewer peptic gastric and duodenal ulcers were reported under clopidogrel than under 325 mg ASA (0.68% vs. 1.15%, $p<0.001$; Harker 1999). It is unclear how the diagnosis "ulcer" was made. The rate of ulcers classified as severe was similar between treatment groups (0.25% vs. 0.38%; $p>0.05$). In the CADET trial, gastric and duodenal ulcers were reported in 5 out of 94 patients in the clopidogrel group and 5 out of 90 patients in the ASA group. None of these events was reported to be severe. It remains unclear whether gastrointestinal ulcer bleedings occurred. Table 11 shows the results of the individual studies.

In summary, the following statements can be made on the rate of gastrointestinal bleeding in the relevant studies:

1. In patients with a high risk of gastrointestinal ulcer bleeding due to a history of symptomatic ulcers/erosions, no study is available that shows that treatment with clopidogrel versus low-dose ASA (with or without PPIs in both groups) leads to a lower rate of recurrent ulcer bleeding. (This also applies to patients with a history of symptomatic ulcers/erosions under ASA therapy.) One study (Chan 2005) is available that shows that in patients who had a history of gastrointestinal bleeding under ASA (up to 325 mg daily), further therapy with ASA (80 mg daily) plus a PPI (esomeprazole) leads to fewer cases of recurrent bleeding compared with clopidogrel

(without a PPI). As the publication showed major deficits, which could only in part be resolved with additional information provided by the authors, the results of this study cannot be regarded as evidence of the superiority of ASA plus esomeprazole vs. clopidogrel (without a PPI) in this regard, but only as an indication hereof.

2. Insufficient data are available to compare the long-term gastrointestinal tolerability of treatment with clopidogrel versus ASA. The only large long-term trial (CAPRIE), included treatment with a comparatively high dose of ASA, which is hardly used in Germany for secondary prevention. Therefore, no reliable conclusion for the German setting can be made on the basis of the reported results, irrespective of other methodological limitations.

Gastrointestinal complications (excluding bleeding)

The Ng trial was the only trial included that investigated dyspeptic symptoms (abdominal pain, heart burn, nausea, vomiting, abdominal bloating) as a predefined (non-primary) outcome. After 8 weeks of therapy, 1 (1.4%) of 69 patients in the clopidogrel group and 1 (1.7%) of the 60 patients in the ASA group experienced moderate or severe dyspeptic symptoms (grade $\geq$ 2 on a scale of 0-3). It was not reported whether this scale was validated.

In the CAPRIE trial, severe gastrointestinal complications such as indigestion, nausea, and vomiting was relatively common in both groups. Differences between treatment groups were not significant (ASA: 118 [1.23%]; clopidogrel: 93 [0.97%]; $p > 0.05$). However, significantly more patients discontinued the study under ASA compared with clopidogrel because of such gastrointestinal symptoms (2.41% vs. 1.90%; $p<0.05$). No information on this type of symptoms was provided in the other studies.

“Severe dyspepsia” was reported as an adverse event for 0.19% of clopidogrel patients and 0.25% of ASA patients ($p>0.05$), (Harker 1999). In the Chan trial, dyspepsia was reported in 7.5% of clopidogrel patients and 2.5% of ASA patients (no details were provided on severity).

In the CAPRIE trial, severe diarrhoea did not occur statistically significantly more frequently under clopidogrel than under ASA (22 [0.23%] vs. 11 [0.11%]). In the CADET trial, this adverse event occurred in 1 patient treated with clopidogrel (1.06%); no patient treated with ASA was affected.

In summary, insufficient data are available on the long-term effects of treatment with clopidogrel or ASA with regard to gastrointestinal complications (excluding bleeding). This is mainly due to the comparatively high dose of ASA used in the CAPRIE trial.

Table 11: Gastrointestinal bleeding / complications

Study	Study duration	Proton pump inhibitor	ASA dosage (mg/day)	GI bleeding	
				Upper GI tract	Lower GI tract
Objective: evaluation of gastrointestinal tolerance / complications					
Chan 2005	12 months	yes, only in the ASA group	80	13 (8.6%) [C+P] 1 (0.7%) [A+E] p = 0.001[1]	7 (4.6%) [C+P] 7 (4.6%) [A+E] p = 0.98[1]
Ng 2004	8 weeks	yes, in both groups	80-160	no events	no events
Other studies					
CAPRIE 1996 (also Harker 1999)	1.91 years	no	325	47 (0.49%) [C] 68 (0.71%) [A] p-value unclear[2]	
CADET (Woodward 2004)	6 months	no	75	n.d.	n.d.
Jagroop 2004	8 days	no	75	no events	no events

1: Kaplan-Meier estimate; the results are of questionable validity (see previous text).
2: Severe gastrointestinal bleeding; for total bleeding events, see text. No definite separation between upper and lower GI bleeding possible based on the information provided. P-value unclear, as inconsistent between publications.
GI: gastrointestinal; [C]: Clopidogrel; [A]: ASA; [P]: Placebo; [E]: Esomeprazole; n.d.: no details provided.

5.3.5.2 Other severe bleeding complications

The rates of other severe bleeding complications (including intracranial haemorrhages) were comparable between treatment groups. The results are presented in Table 12. In Harker 1999, a rate of fatal intracranial haemorrhages of 0.17% was reported in both the clopidogrel and ASA groups. Fatal bleeding events (overall) occurred in 0.24% of patients in the clopidogrel group and in 0.28% of patients in the ASA group (fatal events, including fatal bleeding events were validated by a validation committee in CAPRIE 1996). In the Chan trial, 1 patient died of an intracranial haemorrhage. No other fatal bleeding events occurred in the other studies.

5.3.5.3 Haematological changes

In the CAPRIE trial, severe haematological changes were rare (neutropenia) or uncommon (thrombocytopenia). No significant difference was shown between treatment groups for either adverse event. In the other studies; no severe haematological changes occurred. The results are presented in Table 13.

5.3.5.4 Allergic reactions

Severe allergic reactions were rare in the CAPRIE trial, and rates were similar between groups (Harker 1999). “Severe rash” (which seemingly was not necessarily associated with an allergic reaction) was more common in the clopidogrel group than in the ASA group (0.26% vs. 0.1%; p-value unclear; inconsistent information between CAPRIE 1996 and Harker 1999). In the Chan trial, allergic reactions occurred in 1.9% of patients in both treatment groups. No details were provided on severity. In the other studies no information was found on allergic reactions. The results are summarised in Table 14.

5.3.5.5 Renal dysfunction

Data on the therapy goal “reduction of renal dysfunction rates” were scarce. According to Harker 1999, this adverse event occurred in 1.9% of all patients (0.2% of all patients had a severe event) in the CAPRIE trial. Separate data for the treatment groups were not provided.

Table 12: Other severe bleeding complications including intracranial bleeding

Study	Study duration	ASA dosage (mg/day)	Severe bleeding complications (total)	Severe intracranial haemorrhage
CAPRIE 1996 (also Harker 1999)	1.91 years	325	132 (1.38%) [C][1] 149 (1.55%) [A][1] p > 0.05	30 (0.31%) [C] 41 (0.43%) [A] p > 0,05
Chan 2005	12 months	80	3 (1.9%) [C+P][2] 0 (0%) [A+E][2] p: n.d.	2 (1.2%) [C+P][3] 0 (0%) [A+E][3] p: n.d.
Ng 2004	8 weeks	80-160	no events	no events
CADET (Woodward 2004)	6 months	75	n.d.	n.d.
Jagroop 2004	8 days	75	no events	no events

1: Including gastrointestinal bleeding.
2: Extra-gastrointestinal bleedings only: 2 intracranial haemorrhages (no information on whether severe or not), 1 severe case of haematuria (transfusion required); gastrointestinal bleedings: see Table 11.
3: No information on whether severe or not.
[C]: Clopidogrel; [A]: ASA; [P]: Placebo; [E]: Esomeprazole; n.d.: no details provided.

Table 13: Severe haematological changes

Study	**Study duration**	**ASA dosage (mg /day)**	**Neutropenia (< 0.45 / µl)**	**Thrombopenia (< 80 000 / µl)**
CAPRIE 1996 (also Harker 1999)	1.91 years	325	5 (0.05%) [C] 4 (0.04%) [A] p > 0.05	18 (0.19%) [C] 10 (0.10%) [A] p > 0.05
Chan 2005	12 months	80	no events	no events
Ng 2004	8 weeks	80-160	no events	no events
CADET (Woodward 2004)	6 months	75	n.d.	n.d.
Jagroop 2004	8 days	75	no events	no events

[C]: Clopidogrel; [A]: ASA; n.d.: no details provided.

Table 14: Severe allergic reactions, including rash

Study	Study duration	ASA dosage (mg /d)	Severe allergic reaction	Severe rash
CAPRIE 1996 (also Harker 1999)	1.91 years	325	0.08% [C] 0.11% [A] p > 0.05	0.26% [C] 0.10% [A] p unclear[1]
Chan 2005	12 months	80	1.9% [C+P][2] 1.9% [A+E][2] p: n.d.	n.d.
Ng 2004	8 weeks	80-160	no events	no events
CADET (Woodward 2004)	6 months	75	no events	no events
Jagroop 2004	8 days	75	no events	no events

1: Inconsistent information between CAPRIE 1996 and Harker 1999
2: No information on whether severe or not.
[C]: Clopidogrel; [A]: ASA; [P]: Placebo; [E]: Esomeprazole; n.d.: no details provided.

5.3.5.6 Serious adverse events

Data on the overall rate of "serious adverse events" were insufficient to provide a valid overview of the damage potential of the investigated treatment options.

In the CADET trial, serious adverse events (drug related or otherwise) occurred in 25 (27.8%) patients in the ASA-group and 20 (21.3%) patients in the clopidogrel group. As serious adverse events related to study drug were not separately reported, this category included drug-related events, as well as thromboembolic events due to the underlying disease (e.g. cardiovascular disease).

No adverse events (and therefore no serious adverse events) occurred in the Jagroop trial.

In the Ng and Chan trials, it is unclear whether serious adverse events (overall) were documented within the framework of the safety evaluation.

In the CAPRIE trial, the severity of single adverse events is reported (the results are presented in the previous sections of this report). However, details on serious adverse events are lacking.

5.3.5.7 Study discontinuations due to adverse events

In the CAPRIE trial, 11.94% of patients in the clopidogrel group and 11.92% of patients in the ASA group discontinued the study due to adverse events (Harker publication; CAPRIE: 11.4% in both groups). In this respect, no difference was shown between treatment with clopidogrel and treatment with ASA in a comparatively high dose (325 mg daily). However, study discontinuations due to gastrointestinal symptoms were less common under clopidogrel (3.21% vs. 4.02%, $p<0.01$), whereas study discontinuations due to dermatological symptoms were more common (1.52% vs. 0.76%, $p<0.001$).

Study discontinuations due to fatal events occurred in 4.15% of patients in the clopidogrel group and 4.39% of patients in the ASS group ($p>0.05$). The difference in fatal events with a reported causal relationship to treatment was not significant (clopidogrel vs. ASA: 0.11% vs. 0.14%; $p>0.05$).

In the studies including low-dose ASA, there was a tendency towards a higher rate of study discontinuations due to adverse events in the clopidogrel group. The respective rates were 4.3% (clopidogrel) and 1.9% (ASA) in the Chan trial, and 4.3% (clopidogrel) vs. 1.7% (ASA) in the Ng trial.

In the CADET trial, only the overall rate of study discontinuations was reported (14 patients, [7.6%]), no separate data were available for treatment groups. No patients prematurely discontinued the study in the Jagroop trial.

5.3.6 Other outcomes, including quality of life

None of the relevant studies evaluated the effects of treatment on quality of life. Information on how and to what extent the 2 treatment options had an effect on disease-related symptoms was scarce and only provided on cardiovascular outcomes listed under Section 5.3.3.6 (e.g. angina pectoris). Additional information, in particular on physical capacity, pain-free walking distance in PAD patients, maintenance of activities of daily life, capacity to work, or prevention of the need for care was not provided.

5.3.7 Subgroup analyses

In the following it is presented whether and if yes, which differentiated statements can be made on individual predefined subgroups (see Section 4.4.3) on the basis of the relevant publications.

5.3.7.1 Gender

All studies included more men than women (1.5 – 4 times more).

However, there were no indications that this was intentional, so the unequal distribution is presumably primarily due to the actual difference between genders concerning the prevalence of the underlying diseases. Relevant subgroup analyses according to gender were only available for the CAPRIE trial for the outcome “MI” (Cannon 2002). No interaction can be inferred from Figure 3; however, an interaction test was not conducted.

Overall, there was no indication of gender specific differences.

5.3.7.2 Age

Subgroup analyses according to age were only available for the CAPRIE trial and only in the Cannon 2002 publication for the outcome MI, which was defined post hoc (subgroups: < 65 years and ≥ 65 years). No indications of any interaction were shown. However, as for “gender”, no interaction test was conducted.

5.3.7.3 Concomitant diseases

Hyperlipoproteinaemia

Separate data for patients with or without hyperlipoproteinaemia were only available for the CAPRIE trial (for patients with or without hypercholesterolaemia). A subgroup evaluation was only presented in the Cannon 2002 publication for the outcome "MI", defined post hoc (which was validated by the validation committee). Certain indications for interaction were evident according to Figure 3 (proportion of patients with hypercholesterolaemia: 41%; without hypercholesterolaemia: 59%). The relative risks were estimated from Figure 3: In patients without hypercholesterolaemia there was little difference in the MI rate between treatment groups (relative risk: 0.9 [95% CI: 0.75 to 1.15]); in patients with hypercholesterolaemia, a statistically significant difference concerning the relative risk in favour of clopidogrel was shown (relative risk: 0.65 [95% CI: 0.5 to 0.85]). An interaction test was not conducted.

As the subgroup of patients with hypercholesterolaemia was not predefined, and the outcome "MI" was also only defined post-hoc, and no interaction tests or adjustments for multiple testing were conducted, the results cannot be seen as sufficient evidence that clopidogrel generally has a more favourable effect on patient-relevant outcomes in patients with hypercholesterolaemia than ASA.

Diabetes mellitus

Patients with diabetes mellitus were not explicitly excluded from any of the relevant studies. Information on the proportion of diabetes patients was only provided in the CAPRIE trial (20% in the overall study population and in both treatment arms) as well as in the Jagroop trial (approx. 30% of the study population).

Relevant subgroup evaluations were only provided in the CAPRIE trial; however, the subgroup of diabetic patients was defined post hoc on the basis of the medical history provided at study entry (diabetes was defined by each investigator without using specific diagnostic criteria).

Evaluations were provided in a separate publication (Bhatt 2002) and also in Cannon 2002, within the framework of the subgroup analysis for the outcome "MI", defined post hoc for patients with or without diabetes mellitus.

In Bhatt 2002, the primary analysis was the rate of vascular death, all-cause stroke, MIs, rehospitalisation due to an ischaemic event (angina pectoris, TIA, or limb ischaemia) or

bleeding in diabetic patients who participated in the CAPRIE trial. This composite outcome was defined post hoc (not predefined in the CAPRIE trial). Furthermore, this composite outcome included validated (vascular death, all-cause stroke, MI) and non-validated outcomes (rehospitalisation for ischaemia or bleeding) of the CAPRIE trial. In patients with diabetes, the event rate per year was 15.6% in the clopidogrel group and 17.7% in the ASA group, with a (statistically significant) absolute risk reduction of 2.1% (p=0.042). In patients without diabetes, the respective rates were 11.8% (clopidogrel) and 12.7% (ASA). This difference was not statistically significant (p=0.096). For this composite outcome, the relative risk reduction achieved with clopidogrel (versus ASA) was not significantly different between diabetics and non-diabetic patients (12.5% vs. 6.1%; interaction test: p=0.36). For this outcome defined post hoc, the analyses in Bhatt 2002 therefore do not provide evidence that clopidogrel is more effective in patients with diabetes than in patients without diabetes. The same applies to all further validated (composite) outcomes evaluated in Bhatt 2002. There were no significant differences between patients with or without diabetes.

There was a noticeable discrepancy between the Bhatt 2002 and Cannon 2002 publications with regard to the relative risk reduction of the MI rate under clopidogrel. Whereas the reduction in Bhatt 2002 (read off Figure 2) was approx. 32%, the rate was substantially lower in the Cannon 2002 (approx. 10%; read off Figure 3). An explanation for this discrepancy was not provided in any of the 2 publications.

In summary, the subgroup of patients with diabetes was not predefined, the criteria for diabetes diagnosis were not clearly defined, the outcomes in the respective publications that reported results for diabetic patients in the CAPRIE trial were defined post hoc, and not all of their components were validated by a validation committee. Furthermore, the results of the publications were in part contrary or inconsistent. Therefore, the findings presented do not provide evidence that, in patients with diabetes mellitus, clopidogrel has a more favourable effect on patient-relevant outcomes than ASA.

Hypertension

Baseline data on the proportion of patients with hypertension (overall study population and subgroups) were reported in the primary CAPRIE 1996 publication (clopidogrel: 52%; ASA: 51%); in Bhatt 2002 (clopidogrel: 68%; ASA: 64%); in Bhatt 2001 (clopidogrel: 64%; ASA: 55%); in Ringleb 2004 (clopidogrel: 62%; ASA: 61%); and in Woodward 2004 (CADET; clopidogrel: 2%; ASS: 4%).

A subgroup analysis for patients with and without hypertension with regard to the patient-relevant outcomes investigated in this report was not available.

Previous coronary bypass operation

In the Bhatt 2001 and Cannon 2002 publications on the CAPRIE trial, information was available on patients with prior cardiac surgery. However, this subgroup was defined post hoc solely on the basis of patients' medical history. The type or the time of the respective cardiac surgery was not reported. Separate analyses for the subgroup of patients without a history of valvular heart disease were planned, but not presented (in order to identify the population that with a high probability had undergone coronary bypass operation and not valve surgery).

In Bhatt 2001, in the subgroup of patients with prior cardiac surgery of any type, a significant reduction of the primary outcome of the CAPRIE trial (vascular death, ischaemic stroke, MI) was shown under clopidogrel (775 patients) versus ASA (705 patients), (event rate per year for clopidogrel versus ASA: 9.1% vs. 5.8%; p=0.004). The relative risk reduction under clopidogrel for this outcome (36.3%; 95% CI: 13.4% to 53.1%) was higher in this subgroup than in the main CAPRIE trial (relative risk reduction: 8.7%; 95% CI: 0.3% to 16.5%). This finding was not supported by an interaction test.

On the basis of this finding, the hypothesis may be derived that in a specific group of patients with prior cardiac surgery, clopidogrel has a greater benefit than in patients with no prior cardiac surgery. However, these findings do not provide sufficient evidence of the superiority of clopidogrel versus ASA in patients with prior cardiac surgery: the subgroup was not predefined, and its identification was based on patients' reports of their medical history. In addition, the type of surgery was not clearly defined. Furthermore, the results were not adjusted for multiple testing, and interaction tests for the relative risk reduction under clopidogrel and ASA in patients with and without prior cardiac surgery were not conducted.

Smokers

No subgroup analysis for smokers/non-smokers was performed in the relevant studies.

5.3.7.4 Pretreatment with antiplatelet drugs

The conclusions from the safety trials (Chan and Ng) only apply to patients who had a history of symptomatic gastrointestinal ulcers/erosions under low-dose ASA.

On the basis of the data published to date, the question as to whether patients who experienced an ischaemic event under ASA would profit from a switch to clopidogrel therapy instead of a continuation of ASA therapy cannot be answered with sufficient certainty.
The protocol of a trial investigating this question and including a planned number of 1000 patients is published (ASCET, Pettersen 2004). On the basis of the outcomes investigated, clinically relevant data are to be expected with regard to the question as to whether patients with a prior ischaemic event under ASA could profit from a switch to clopidogrel. According to the main author (Pettersen), the results of this trial will not be available before 2008.
Further specific conclusions concerning the effect of pre-treatment with antiplatelet therapy on the outcomes investigated in this report cannot be made on the basis of the data currently available.

5.3.7.5 Qualifying disease

Only the CAPRIE trial provided information on whether differences with regard to the outcomes investigated in this report were shown in patients with IHD, ICVD, or PAD; if this was the case, this information has been presented in the corresponding sections.

5.3.7.6 Atherosclerosis in more than 1 vessel territory or previous ischaemic event

Only the CAPRIE trial provided detailed data on manifestations of atherosclerosis in more than 1 vessel territory or on prior ischaemic events occurring before the qualifying event that led to study entry. A previous ischaemic stroke/TIA, MI, or intermittent claudication was reported in 19%, 17%, and 5% of patients, respectively. In the CAPRIE primary publication, and in the secondary publications by Ringleb 2004 und Cannon 2002, separate results on the efficacy of clopidogrel in the respective subgroups are reported.
In the other publications, only Chan 2005 reported data on patients with manifestations of atherosclerosis in more than 1 vessel territory (clopidogrel: 6.2%; ASA plus esomeprazole: 5.7%). A separate analysis of these patients was not conducted.
According to CAPRIE 1996, a post-hoc analysis was conducted in patients in the ICVD and PAD subgroups who had a previous history of myocardial infarction (2144 patients), which showed a significant relative risk reduction of 22.7% (95% CI: 4.9% to 37.2%) in favour of clopidogrel for the primary outcome (vascular death, ischaemic insult, MI). In contrast, the risk reduction for the primary outcome in a subgroup of patients defined post hoc as patients with “any previous MI” (8446 patients) was not significantly different (risk reduction: 7.4%;

95% CI: 5.2% to 18.6%). The existence of symptomatic PAD in a large number of patients in the above analysis of 2144 patients may have been responsible for the statistically significant differences described between clopidogrel and ASA. In cannot be inferred from these 2 post-hoc analyses that the efficacy of clopidogrel in patients with manifestations of atherosclerosis in more than 1 vascular territory is generally higher than in patients where only 1 territory (cardiovascular) is known to be affected.

In the Ringleb 2004 publication, results were available for patients of the CAPRIE trial who had pre-existing atherosclerotic disease (defined post-hoc by self-reported history of ischaemic stroke and/or MI) before the occurrence of the qualifying event (overall: 23.4%; previous ischaemic stroke: 8.8%; previous MI: 16.7%). Using the CAPRIE database, multivariate analyses for these subgroups were performed (search for predictors of a high event rate).

The baseline data provided in Ringleb 2004 shows that in this subgroup the predefined CAPRIE subgroups (patients with recent ischaemic MI [IHD subgroup], recent ischaemic stroke [ICVD subgroup], or symptomatic PAD [PAD subgroup]) were not equally distributed. In particular, the IHD subgroup, with a proportion of 25%, was underrepresented (the IHD subgroup had experienced [numerically] more events under clopidogrel than under ASA in CAPRIE 1996). In patients with a prior ischaemic event, the 1-year event rates for the primary outcome of CAPRIE were 8.8% for clopidogrel and 10.2% for ASA. In the publication and abstract, the relative risk reduction, at 14.9% (95% CI: 0.3% to 27.3%) is reported to be statistically significant. However, in the footnote of the corresponding table (Table 3), it is reported that for the analysis stratified by qualifying event (described in CAPRIE 1996 as the planned analysis), there was no significant difference between treatment groups (p=0.054).

The results of the second composite outcome reported in Ringleb 2004 are of insufficient evidential value, as this outcome was not predefined and included components which were not validated by the validation committee. Even disregarding the fact that results of a subgroup analysis where the subgroup was defined posthoc can per se only be of limited value, and that the distribution of the stratified subgroups was unequal, no evidence is provided that in patients with a history of ischaemic events, treatment with clopidogrel results in fewer events than treatment with ASA.

In Cannon 2002, separate results were reported for the reduction of the MI rate under clopidogrel versus ASA in patients who had or had not experienced a prior MI (unclear whether as a first event or a recurrent event). The relative risk reduction for MI under

clopidogrel was lower in patients with a prior MI than in those who had not experienced a prior MI (prior MI: approx. 17.5%, 95% CI: 0% to 30%; no prior MI: 25%, 95% CI: 2% to 45% [estimated from Figure 3 of the publication]).

In summary, these findings did not provide evidence that the efficacy of clopidogrel is greater in patients with manifestation of atherosclerosis in more than 1 vascular territory or more than 1 ischaemic event than in patients with only 1 affected vascular territory or patients with a first ischaemic event.

5.3.7.7 Time between qualifying event and start of intervention

On the basis of the available data, no conclusion could be made on whether the time span between the qualifying event and study entry had an effect on results in patients treated with clopidogrel versus ASA.

5.4 Summary

A systematic literature search identified 6 studies in which the effects of clopidogrel therapy versus ASA therapy with regard to patient-relevant therapy goals were investigated. The search was conducted in bibliographic databases, references lists of relevant reviews, study results registers, and publicly accessible sources of international regulatory authorities. In addition, queries were sent to study sponsors (e.g. pharmaceutical companies). Publicly accessible, detailed information was available for 5 of these studies, which were therefore included in the evaluation. No complete results were available for the sixth study, the WATCH trial.

The CAPRIE trial, which included nearly 20 000 patients and had a mean follow-up of nearly 2 years, was the main source of information for most of the predefined patient-relevant outcomes investigated in this report. The relevance of the CAPRIE trial concerning the criterion “adverse events” is substantially limited by the comparatively high dosage of ASA (325 mg) administered.

The Chan trial (Chan 2005) is of particular relevance for patients with a history of gastrointestinal bleeding under ASA, as a switch to clopidogrel or continuation of ASA are possible treatment options in these patients.

About a third of participants in the CAPRIE trial were in each case patients with recent MI (with at least 2 indications of ischaemia), recent stroke (likely to be of atherothrombotic origin), and patients with symptomatic PAD (IHD, ICVD, and PAD subgroups). In the overall study population, a statistically significant difference in favour of the clopidogrel group was

shown for the composite primary outcome (MI, ischaemic stroke, or vascular death), but not for the predefined secondary outcomes. The absolute risk difference for the predefined primary outcome, with an event rate per year of 5.32% under clopidogrel and 5.83% under ASS, was 0.51%. The preplanned subgroup analyses for the IHD, ICVD, and PAD subgroups showed that this difference was mainly caused by the subgroup of patients with symptomatic PAD (who had a comparatively low event rate). The statistically significant heterogeneity test (p=0.042), which showed an association between subgroups (IHD, ICVD, PAD) and therapy effect, provides evidence that the results of the CAPRIE trial in these 3 subgroups should be assessed differently. However, it cannot be certainly determined whether in the ICVD and IHD subgroups, clopidogrel had a slightly beneficial effect, no effect, or even a detrimental effect compared with ASA. In contrast, the evidence of the superiority of clopidogrel versus ASA in patients with symptomatic PAD for the composite primary outcome can be regarded as being sufficiently certain.

Various secondary analyses of the CAPRIE trial assessed the efficacy of clopidogrel versus ASA in patients with additional risks such as diabetes mellitus, hypercholesterolaemia, prior cardiac surgery, clinical manifestation of atherosclerosis in more than 1 vascular territory, or a history of ischaemic events. All of these secondary analyses showed major methodological deficiencies. In particular, this refers to the lack of a predefinition of patient subgroups, the definition of subgroups by means of self-reported medical history without validation, as well as in part to the use of composite outcomes defined post hoc, often seemingly in an arbitrary manner. None of the secondary analyses of the CAPRIE trial provided sufficient evidence that the efficacy of clopidogrel compared with ASA in patients with the stated additional risks should be assessed differently than for the total study population.

No significant differences were shown between treatment groups (clopidogrel versus ASA) for both the outcomes “all-cause mortality” and “vascular death”. Individual outcomes such as “stroke” or “MI” were not predefined, but were in part presented besides other outcomes in secondary publications. In these publications, various other composite outcomes that were not predefined in the CAPRIE 1996 publication were evaluated. The relevance of the results of these additional publications is therefore substantially limited.

In the CAPRIE trial, evidence of the superiority of clopidogrel versus ASA was only shown for the predefined composite primary outcome in patients with PAD. A significant difference between treatment groups for all-cause mortality was not shown. The results of the CAPRIE trial have so far not been confirmed by a second, completely published study.

The other studies investigated did not substantially contribute to the complex "vascular/thromboembolic events".

No detailed information on the WATCH trial was provided by the organisations conducting the study, the sponsor (Sanofi-Aventis), or the principal investigator. According to the preliminary results, there is a tendency towards inferior results under clopidogrel compared with ASA with regard to thromboembolic events.

In respect of adverse effects, one needs to distinguish between studies including lower-dose (75-160 mg daily) ASA and higher-dose (325 mg daily) ASA (which does not have a greater therapeutic effect), as bleeding complications in particular may occur less frequently under lower-dose ASA [20,27,51]. Of the studies included, only the CAPRIE trial was conducted with a higher ASA dose not usually administered in Germany for secondary prevention of vascular diseases. Therefore, its contribution is limited with regard to the comparison of the occurrence of adverse effects under clopidogrel and ASA in the German health care setting. According to Harker 1999, even under higher-dose ASA, the overall incidence of bleeding events, as well as intracranial haemorrhages was not statistically significantly more frequent than under clopidogrel. The same applies to study discontinuations or death due to adverse events. The data provided on severe gastrointestinal bleeding events in the CAPRIE trial were inconsistent.

Two trials (Chan 2005 und Ng 2004) were specifically designed to evaluate safety aspects. In these studies, patients received lower-dose ASA. These studies investigated whether in patients with previous symptomatic gastrointestinal ulcers/erosions under ASA (Chan 2005: bleeding; Ng 2004: bleeding or dyspepsia), a switch to clopidogrel reduced the risk of recurrent bleeding or accelerated ulcer healing. Due to major methodological deficits, no valid conclusions can be drawn from the Ng trial. The Chan trial also showed major deficits. However, under consideration of the additional information provided by the main author, an indication at least was provided that in patients who had previously experienced an ulcer bleeding under ASA, the combination of lower-dose ASA and a PPI (esomeprazole) was more effective in preventing recurrent bleeding than a switch to clopidogrel monotherapy.

No relevant comparator trials on ASA and clopidogrel therapy were available in patients who had previously experienced a vascular event under ASA. It remains unclear, whether such patients would profit from a switch to clopidogrel therapy or not.

None of the studies included had the primary aim of investigating the effect of the treatment options on the quality of life or disease-related symptoms of patients. It could not be inferred from the studies whether clopidogrel is superior to ASA in reducing disease-related symptoms

such as pain when walking or resting, or angina pectoris symptoms, or in increasing patients' physical capacity, including the ability to perform daily activities.

6. DISCUSSION

Three major aspects can be highlighted in the evaluation of the relevant literature. This was also reflected in the written statements submitted on the preliminary report.

1. Should the overall result of the CAPRIE trial be assessed differently for the 3 predefined subgroups (patients with recent ischaemic MI [IHD subgroup], recent ischaemic stroke [ICVD subgroup], or symptomatic PAD [PAD subgroup])?
2. What is the relevance of the secondary publications on the CAPRIE trial for the research questions of this report?
3. What conclusions can be inferred from the Chan trial?

The different assessment of the overall results of the CAPRIE trial for the 3 predefined subgroups was addressed in nearly all of the written statements, as well as in the discussion within the framework of the scientific hearing. It is correct that the lack of statistical significance in the results of the IHD and ICVD subgroups is not equivalent to the non-existence of an additional benefit of clopidogrel in these patients; nor is this the conclusion of this report. However, in summary, the results of the heterogeneity test and the results in the individual subgroups show that the therapeutic effects observed in this trial should be assessed differently with regard to the 3 subgroups. In this context, the observed therapeutic effect of clopidogrel in the PAD subgroup can be regarded as valid and therefore as sufficient evidence of an additional benefit of clopidogrel in this group of patients. The conclusion is based on the fact that the PAD subgroup (as well as the IHD and ICVD subgroups) was a predefined subgroup and the respective diagnostic criteria were predefined. In addition, the subgroup analysis of the 3 predefined subgroups was preplanned. Furthermore, despite the insufficient power of the PAD subgroup analysis, the result observed is statistically significant, with a 95% CI of the relative risk reduction, whose lower limit is still above the effect observed in the overall study population. The result of the (statistically significant) heterogeneity test provides evidence that the therapeutic effects of clopidogrel should be assessed differently and that under consideration of the results in the subgroups, the effect of clopidogrel in the IHD and ICVD subgroups was less distinct than in the PAD subgroup.

This allows the following constellations for patients with IHD or ICVD:

1. Clopidogrel has an additional benefit versus ASA; however, this benefit is less pronounced than in patients with symptomatic PAD.
2. Clopidogrel has no additional benefit compared with ASA.

3. Clopidogrel has less benefit than ASA.

It is unclear which of these possibilities applies for patients with IHD or ICVD. The lack of statistical significance in the subgroup analyses is not equivalent to the lack of an additional benefit of clopidogrel. However, it also cannot be excluded that clopidogrel has less benefit in these patients than ASA. Whereas the results in the IHD subgroup do not seem to indicate a beneficial effect of clopidogrel, the results in the ICVD subgroup may be compatible with both the effects in the IHD subgroup and the effects in the PAD subgroup. Ultimately, in this regard, all participants at the scientific hearing were in agreement, including representatives of the pharmaceutical industry.

In this context, it is a major failing concerning all those involved in the WATCH trial, including the sponsor, that its results have still not been completely published, even though the study was concluded more than 2 years ago. Important results are being withheld from the scientific public, patients, and decision-makers in the health care system, thereby possibly condoning inappropriate care for the patients affected. The information available to date, which shows a numerically higher event rate under clopidogrel compared with ASA in the specific group of patients with (mainly ischaemic) heart failure, supports the conclusions inferred from the CAPRIE trial for patients with IHD. Under consideration of the (statistically non-significantly) higher event rate under clopidogrel in this group of patients observed in the CAPRIE trial, it cannot be excluded that an aggregation from data of the WATCH trial and the CAPRIE trial may provide evidence of a greater benefit of ASA versus clopidogrel for antiplatelet monotherapy in patients with IHD. Such an analysis would at any rate be meaningful after the publication of the results of the WATCH trial.

It should be noted that the different assessment of the overall results of the CAPRIE trial for the predefined subgroups does not mean that, in patients with IHD or ICVD, no evidence of an additional benefit of clopidogrel can in general be assumed. However, such an additional benefit can currently be assumed only if these patients also have s*ymptomatic* PAD. In contrast to comments in some of the written statements submitted, symptomatic IHD or ICVD is in most cases not associated with symptomatic PAD. This can be concluded from data provided in the CAPRIE trial itself: only about 6% and 8% of patients who were included in the study because of a recent ischaemic MI (IHD subgroup) or recent ischaemic stroke (ICVD subgroup), respectively, had co-existing symptomatic PAD (intermittent claudication). This is consistent with data from the REACH register provided by representatives of the pharmaceutical industry: whereas 61.2% of all registered patients either had IHD or ICVD disease exclusively, only 7.5% of patients additionally had symptomatic PAD.

In several statements submitted, the fear was expressed that by the differentiated conclusions made in this report on the IHD, ICVD, and PAD subgroups in the CAPRIE trial, a therapy with proven efficacy could be withheld from high-risk patients. In addition, it was commented that in patients with IHD or ICVD, PAD was often not diagnosed, as ABI measurements had not been performed. Even under the assumption that ABI measurements are rarely performed, as stated by the persons submitting statements, this does not mean that an underprovision or incorrect provision of care with regard to the choice of the type of antiplatelet therapy thereby takes place. In the CAPRIE trial, evidence of a benefit of clopidogrel was exclusively shown for patients with *symptomatic* PAD, not for patients with solely a low ABI. Symptomatic PAD, as defined in the CAPRIE trial, can be determined by recording a precise medical history, supported by suitable diagnostic techniques where appropriate. Some persons who submitted statements noted that ABI is an indicator in high-risk patients, as it identifies patients with generalised atherosclerosis. Referring to the CAPRIE trial, it was also stated that PAD patients in particular, because of a high cardiovascular "cross risk", would substantially profit from treatment with clopidogrel. Following this line of argument, it could hypothetically be inferred that the ABI is suitable to identify a subgroup of patients who may expect an additional benefit from clopidogrel therapy. This assumption is however not supported by data from the CAPRIE trial. In contrast, the CAPRIE trial refutes the assumption of particularly high efficacy of clopidogrel in high-risk patients. The group which evidently profited in particular from clopidogrel therapy were those who experienced comparatively few events during the study (the symptomatic PAD subgroup), whereas, for the IHD and ICVD subgroups, evidence of an additional benefit of clopidogrel was not provided, and even the inferiority of clopidogrel compared with ASA could not be excluded. In this context, it is also unclear whether, as assumed in some statements, the application of the "Essen Stroke Risk Score" (ESRS) could identify patients who would profit in particular from clopidogrel therapy [24,52,53]. To provide this evidence, corresponding prospective intervention studies are necessary, which also of course applies to assessment of the relevance of the ABI.

Several persons who submitted statements on the one hand queried the validity and the consideration of the (predefined and preplanned) subgroup analyses in the IHD, ICVD, and PAD subgroups, and on the other hand emphasised the importance of various analyses of the CAPRIE trial that were conducted post hoc. This line of argument is not plausible and in itself inconsistent. In this context, statements were made that in part could not be inferred from the publications or were not consistent with information provided in the publications. For

example, concerning the Ringleb 2004 publication, when applying an analysis that conforms with the original analysis in CAPRIE 1996, there was no statistically significant difference in absolute risk reduction between treatment groups for the primary CAPRIE outcome (neither after 1, nor after 3 years), nor in the relative risk reduction. Furthermore, the recommendations of the European Stroke Initiative (EUSI) of 2003, are not, as claimed, based on the results of Ringleb 2004 – this publication was not quoted in these recommendations and was published only after the completion of the EUSI recommendations [54]. It was noticeable that in the written statements reference was made exclusively to subgroup analyses in which patient groups were identified for whom a specific benefit of clopidogrel therapy was apparently demonstrated. Analyses identifying subgroups that might possibly *not* profit from clopidogrel therapy were not addressed or presented. However, such post-hoc analyses, which did not show statistically significant differences between clopidogrel and ASA therapy in selected subgroups, have evidently been conducted: congress abstracts on these analyses were identified in the literature search [55,56]. However, due to their methodology and largely insufficient power, they did not provide clear evidence of a potential benefit or a lack of a benefit of clopidogrel therapy (just as little as did the retrospective analyses that showed the alleged "positive" effects of clopidogrel).

Some statements noted that no direct treatment recommendations could be inferred from the Chan trial due to its major deficits, which were also described by IQWiG, and that evidence of the superiority of a combination therapy of ASA plus esomeprazole versus clopidogrel was not provided. This was supported by another written statement stating that the Chan trial had further relevant deficits.

In particular the following points were noted:

- that the study medication was administered in capsules, possibly resulting in a mainly enteral resorption of ASA and therefore a reduction in gastrotoxicity [57,58];
- that the esomeprazole dose of "2 x 40 mg" was extremely high, in particular considering the high proportion of "poor metabolizers" (14%-15%) in the Asian study population investigated [59-63];
- that differences in baseline characteristics, as well as concomitant medication with NSAIDs in 2 patients, had possibly affected the results to the disadvantage of clopidogrel [64];
- that the high rate of recurrent bleeding of the primary lesion in the clopidogrel group indicated that the primary lesion may not have been completely healed at the start of clopidogrel therapy.

IQWiG responds to these statements as follows:

The statements on the effects of the administration of capsules are speculative; furthermore, in the scientific hearing, evidence of these effects could not be provided by the persons who submitted statements. The statement that "2 x 40 mg" esomeprazole was administered in the Chan trial is incorrect; the dosage was 2 x 20 mg. It is unclear whether the expected proportion of approx. 10% more "poor metabolizers" in the Chan trial, compared with the German population, had a substantial effect on the study results. With regard to the differences in baseline characteristics, 2 criteria were noted in the written statements that seemingly resulted in a disadvantage for the clopidogrel group, whereas other criteria, which may have resulted in an advantage for the clopidogrel group, were not mentioned (e.g. occurrence of multiple lesions, visible blood vessels in the primary lesion, necessity of a transfusion). In summary, due also to the transparent description of the appropriate randomisation process, there is no indication of a relevant difference between treatment groups explaining the different therapeutic effects of clopidogrel and ASA. The reference to the fact that 2 patients in the clopidogrel group were also treated with NSAIDs is justified; however, this does not change the interpretation of the overall results. On the one hand, it cannot be excluded that patients in the ASA group took other NSAIDs during the study, but did not develop bleeding. On the other, even if the bleeding events of these 2 patients in the clopidogrel group were excluded from the overall result, the difference in favour of ASA plus esomeprazole would still be noticeable. Finally, it was ensured by the methodology of the study that only patients with healed primary lesions (confirmed by endoscopy) were included in the study.

In summary, no decisive new arguments for or against the relevance of the Chan trial were presented in the written statements. This does not mean that the Chan trial does not have deficits; on the contrary, these deficits have already been described in detail in the preliminary report. The Chan trial does not therefore provide convincing evidence of the superiority of ASS plus esomeprazole versus clopidogrel. It is important to note that the additional information provided by the authors, similarly to the CAPRIE trial, at least in part resolved the discrepancies, so that consequently indications exist that in patients with a history of gastrointestinal bleeding under ASA therapy, treatment with lower-dose ASA plus a PPI (esomeprazole) prevents recurrent ulcer bleeding more effectively than a switch from ASA to clopidogrel. It is unclear whether a switch to a combination therapy of clopidogrel plus a PPI further reduces this risk [65]. Studies that provide reliable evidence on this issue were neither identified in the literature search nor presented by the persons who submitted written statements.

Finally, with regard to the incidence of adverse events under antiplatelet therapy, it should be noted that the CAPRIE trial is suited to assess the effect of clopidogrel versus ASA on the incidence of vascular events. However, it is not suited as a conclusive weighing of benefits and harms, as the ASA dosage (325 mg daily) used in the study was comparatively high and only plays a minor role in secondary prevention in Germany. This may possibly have led to an overestimation of adverse events under ASA. Particularly with regard to the gastrointestinal tolerability of clopidogrel and ASA, no valid conclusion for the German health care setting can be made on the basis of the CAPRIE trial. For this reason, the study by Fork 2000 [66], which had already been identified in the literature search and also presented in the written statements, is only of subordinate relevance (comparison of clopidogrel 75 mg daily versus ASA 325 mg daily); furthermore, it was conducted with healthy participants.

7. CONCLUSION

Long-term antiplatelet monotherapy with clopidogrel (versus ASA) in patients with symptomatic PAD has an additional benefit with regard to the risk reduction for vascular/thromboembolic events. No such evidence is available with regard to the reduction of all-cause mortality. In patients with ischaemic heart or ischaemic cerebrovascular disease (in each case without co-existing symptomatic PAD), an additional benefit of clopidogrel therapy has not been demonstrated.

There is no evidence available that the above conclusions differ for specific patient groups who have an increased risk of thromboembolic events (e.g. patients with hypercholesterolaemia, diabetes mellitus, or manifestations of atherosclerosis in more than 1 vascular territory). There is no evidence available that in patients with a history of gastrointestinal complications (symptomatic ulcers/erosions) under ASA, a switch of therapy to clopidogrel results in a patient-relevant additional benefit. However, in these patients indications exist that a continuation of treatment with lower-dose ASA plus a PPI (esomeprazole) results in a higher patient-relevant benefit than a switch to clopidogrel (without a PPI).

There is no evidence available that in patients who experienced a vascular event under ASA, a switch to clopidogrel results in an additional patient-relevant benefit.

8. LIST OF RELEVANT STUDIES

CAPRIE

- CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348(9038): 1329-1339.
- Bhatt DL, Chew DP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. Circulation 2001; 103(3): 363-368.
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- Bhatt DL, Marso SP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. Am J Cardiol 2002; 90(6): 625-628.
- Cannon CP. Effectiveness of clopidogrel versus aspirin in preventing acute myocardial infarction in patients with symptomatic atherothrombosis (CAPRIE trial). Am J Cardiol 2002; 90(7): 760-762.
- Harker LA, Boissel JP, Pilgrim AJ, Gent M. Comparative safety and tolerability of clopidogrel and aspirin. Results from CAPRIE. Drug Saf 1999; 21(4): 325-335.
- Ringleb PA, Bhatt DL, Hirsch AT, Topol EJ, Hacke W. Benefit of clopidogrel over aspirin is amplified in patients with a history of ischemic events. Stroke 2004; 35(2): 528-532.

Chan 2005

- Chan FK, Ching JY, Hung LC, Wong VW, Leung VK, Kung NN, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med 2005; 352(3): 238-244.

Ng 2004

- Ng FH, Wong BCY, Wong SY, Chen WH, Chang CM. Clopidogrel plus omeprazole compared with aspirin plus omeprazole for aspirin-induced symptomatic peptic ulcers/erosions with low to moderate bleeding/re-bleeding risk - A single-blind, randomized controlled study. Aliment Pharmacol Ther 2004; 19(3): 359-365.

Woodward 2004 (CADET trial)

- Woodward M, Lowe GDO, Francis LMA, Rumley A, Cobbe SM, Bain R, et al. A randomized comparison of the effects of aspirin and clopidogrel on thrombotic risk factors and C-reactive protein following myocardial infarction: The CADET trial. J Thromb Haemost 2004; 2(11): 1934-1940.

Jagroop 2004

- Jagroop IA, Matsagas MI, Geroulakos G, Mikhailidis DP. The effect of clopidogrel, aspirin and both antiplatelet drugs on platelet function in patients with peripheral arterial disease. Platelets 2004; 15(2): 117-125.

WATCH[15]

- Massie BM, Krol WF, Ammon SE, Armstrong PW, Cleland JG, Collins JF, et al. The Warfarin and Antiplatelet Therapy in Heart Failure trial (WATCH): Rationale, design, and baseline patient characteristics. J Card Fail 2004; 10(2): 101-112.

[15] The WATCH trial was relevant. However, no full-text publication was available, and it was therefore not included in the evaluation.

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Appendix A: non-relevant publications (reviewed in full text)

Reason for exclusion: I1

1. Cadroy Y, Bossavy JP, Thalamas C, Sagnard L, Sakariassen K, Boneu B. Early potent antithrombotic effect with combined aspirin and a loading dose of clopidogrel on experimental arterial thrombogenesis in humans. Circulation 2000; 101(24): 2823-2828.

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Reason for exclusion: I2

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Appendix B: Systematic Reviews, meta-analyses, and HTA reports

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Appendix C: Search strategies

The following search dates refer to the date of the primary search. Additional searches were also conducted using the search strategies described.[17]

Thema: **RCTs on ASA and clopidogrel**
Search date: 23 June 2005
Search mask: PubMed
Database: MEDLINE

#	**Query**
1	"Aspirin"[MeSH]
2	Aspirin[Substance Name]
3	Aspirin*
4	"Acetylsalicylic Acid"
5	ASS
6	("acetylsalicylic acid lysinate"[Substance Name] OR "acetylsalicylic acid lysinate")
7	asprin
8	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9	"clopidogrel"[Substance Name]
10	Clopidogrel
11	Plavix
12	Iscover
13	Clopivas
14	Flusan
15	Noklot
16	Terotrom
17	Artevil
18	Tisten

[17] Changes compared with the preliminary report are due to a copying error in the production of the preliminary report. The search strategies presented in the final report are the strategies that were actually applied.

19	Cloflow
20	Zyllt
21	Nefazan
22	SR 25990
23	SR 25990 C
24	DV 7314
25	PCR 4099
26	SR 25989 C
27	113665-84-2
28	Clopod
29	Clopact
30	9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29
31	8 AND 30
32	"Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials"[MeSH]
33	"Controlled Clinical Trial"[Publication Type]
34	"Clinical Trial, Phase I"[Publication Type] OR "Clinical Trial, Phase II"[Publication Type] "Clinical Trial, Phase III"[Publication Type] OR "Clinical Trial, Phase IV"[Publication Type] OR "Clinical Trials"[MeSH] OR "Clinical Trial"[Publication Type]
35	"Multicenter Studies"[MeSH]
36	"Comparative Study"[MeSH]
37	"Meta-Analysis"[MeSH]
38	"Statistics"[MeSH] OR "Statistics, Nonparametric"[MeSH]
39	"statistics AND numerical data"[Subheading]
40	"Follow-Up Studies"[MeSH]
41	32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40
42	(#31) AND (#41)

Topic: **RCTs on ASA and clopidogrel**

Search date: 23 June 2005

Search mask: Ovid

Database: EMBASE <1980 to 2005 Week 25>

#	**Query**
1	acetyl?salicyl$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
2	acetyl$ salicyl$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
3	exp Acetylsalicylic Acid/
4	aspirin$.ab,ot,tn,tw,ti.
5	asprin.ab,ot,tn,tw,ti.
6	ass.ab,ot,tn,sh,tw,ti.
7	exp Lysine Acetylsalicylate/
8	acetylsalicylic lysinate.mp. or acetylsalicylic acid lysinate/
9	50-78-2.rn.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	exp CLOPIDOGREL/
12	clopidogrel.ab,ot,tn,tw,ti.
13	plavix.mp.
14	iscover.mp.
15	14 not 11
16	13 not 11
17	clopivas/
18	Flusan.ab,ot,sh,ti,hw.
19	Noklot.mp.
20	19 not 11
21	Terotrom.ab,ot,tn,sh,tw,ti,hw.
22	Artevil.ab,ot,dv,tn,tw,ti.
23	Tisten.ab,ot,tw,ti.
24	Cloflow.ab,ot,tn,tw,ti.
25	Zyllt.ab,ot,tn,tw,ti.

26	Nefazan.mp.
27	SR 25990.mp.
28	SR 25990 C.mp.
29	SR 25990 C.ot,tn,sh,tw,ti,hw.
30	DV 7314.ab,cd,ot,tn,sh,tw,ti,hw.
31	PCR 4099.cd,ot,tn,sh,tw,ti,hw.
32	SR 25989 C.cd,ot,tn,sh,tw,ti,hw.
33	113665-84-2.rn,cd,ot,tn,sh,tw,fs,ti,hw.
34	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	Randomized Controlled Trial/
36	Multicenter Study/
37	Comparative Study/
38	Confidence Interval/
39	RANDOMIZATION/
40	Statistical Significance/
41	35 or 36 or 37 or 38 or 39 or 40
42	(confidence interval or randomization or statistical significance).mp.
43	(double and blind$).tw.
44	placebo$.tw.
45	42 or 43 or 44
46	(confidence interval or randomi?ation).mp.
47	41 or 45
48	47 or 46
49	10 and 34
50	49 and 48

Topic: **RCTs on ASA and clopidogrel**

Search date: 23 June 2005

Search mask: Cochrane

Database: CENTRAL

#	**Query**
1	aspirin in Keywords
2	aspirine in All Fields
3	asprin in All Fields
4	acetysalicylic acid in All Fields
5	ASS in All Fields in all products
6	#1 or #2 or #3 or #4 or #5
7	clopidogrel in All Fields
8	plavix in All Fields
9	iscover in All Fields in all products
10	#7 or #8 or #9
11	(#6 and #10)

Topic: **Clopidogrel**

Search date: 27 July 2005

Search mask: Cochrane Library via DIMDI

Databases: Cochrane Reviews, DARE, HTA

#	**Query**
1	clopidogrel in All Fields

Topic: **RCTs on ASA und Clopidogrel**

Search date: 27 June 2005

Search mask: Ovid

Database: PRE-MEDLINE (MEDLINE(R) In-Process & Other Non-Indexed Citations)

#	**Query**
1	clopidogrel.ab,ot,tw,ti.
2	plavix.mp.
3	iscover.mp.
4	clopivas.mp. (0)
5	Flusan.ab,ot,ti,. (0)
6	Noklot.mp. (0)
7	Terotrom.ab,ot,tw,ti,. (0)
8	Artevil.ab,ot,dv,tw,ti. (0)
9	Tisten.ab,ot,tw,ti. (0)
10	Cloflow.ab,ot,tw,ti. (0)
11	Clopact.ab,ot,tw,ti. (0)
12	Zyllt.ab,ot,tw,ti. (0)
13	Clopod$.ab,ot,tw,ti. (0)
14	Nefazan.mp. (0)
15	SR 25990.mp. (0)
16	SR 25990 C.mp. (0)
17	SR 25990 C.ot,tw,ti,. (0)
18	DV 7314.ab,cd,ot,tw,ti,. (0)
19	PCR 4099.cd,ot,tw,ti,. (0)
20	SR 25989 C.cd,ot,tw,ti,. (0)
21	#1 or #2 or #3
22	acetyl?salicyl$.mp. [mp=title, original title, abstract, name of substance word]
23	acetyl$ salicyl$.mp. [mp=title, original title, abstract, name of substance word]
24	Acetylsalicyl$ Acid.mp. [mp=title, original title, abstract, name of substance word]
25	aspirin$.ab,ot,tw,ti.
26	asprin.ab,ot,tw,ti.

27	ass.ab,ot,tw,ti.
28	Lysine Acetylsalicyl$.mp. [mp=title, original title, abstract, name of substance word]
29	(acetylsalicylic lysinate or acetylsalicylic acid lysinate).mp.
30	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31	21 and 30

Topic: **RCTs on ASA and clopidogrel**

Search date: 27 June 2005

Search mask: Pubmed

Database: PRE-MEDLINE (non-indexed data sets from the Pubmed-PRE-MEDLINE-database)

#	**Query**
1	Aspirin
2	Asprin
3	acetylsalicylic acid lysinate
4	Acetylsalicylic Acid
5	Acetyl*salicyl*
6	Acetyl AND salicyl*
7	Acetyl*-salicyl*
8	ASS
9	Lysine Acetylsalicylate
10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
11	Clopidogrel[Text Word])
12	("clopidogrel"[TIAB] NOT Medline[SB])
13	Plavix[Text Word]))
14	(SR[All Fields] AND 25990[All Fields])
15	(SR[All Fields] AND 25990[All Fields] AND C[All Fields])
16	(DV[All Fields] AND 7314[All Fields]))
17	("clopidogrel"[TIAB] NOT Medline[SB])
18	PCR 4099[Text Word]))
19	("clopidogrel"[TIAB] NOT Medline[SB])
20	(SR 25989[Text Word]) AND C[All Fields])
21	113665-84-2[All Fields]
22	Iscover[Text Word]
23	Clopivas[Text Word]
24	Flusan[Text Word]
25	Noklot[Text Word]
26	Terotrom[Text Word]

27	Artevil[Text Word]
28	Tisten[Text Word]
29	Cloflow[Text Word]
30	Clopact[Text Word]
31	Zyllt[Text Word]
32	Clopod$[Text Word]
33	Nefazan[Text Word]
34	11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21OR 22 OR 23 OR 24 OR 25 OR 26 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33
35	10 AND 34
36	(35 (premedline[sb]))

Topic: **Systematic reviews**

Search date: 04 August 2005

Search mask: PubMed

Database: MEDLINE

#	**Query**
1	"Aspirin"[MeSH]
2	Aspirin[Substance Name]
3	"Acetylsalicylic Acid"
4	ASS
5	("acetylsalicylic acid lysinate"[Substance Name] OR "acetylsalicylic acid lysinate")
6	asprin
7	1 OR 2 OR 3 OR 4 OR 5 OR 6
8	"clopidogrel"[Substance Name]
9	Clopidogrel
10	Plavix
11	Iscover
12	Clopivas
13	Flusan
14	Noklot
15	Terotrom
16	Artevil
17	Tisten
18	Cloflow
19	Zyllt
20	Nefazan
21	SR 25990
22	SR 25990 C
23	DV 7314
24	PCR 4099
25	SR 25989 C
26	113665-84-2

27	Clopod
28	Clopact
29	8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28
30	7 AND 29
31	random*[Title/Abstract]
32	random allocation[MeSH Terms]
33	therapeutic use[MeSH Subheading]
34	(clinical[Title/Abstract] AND trial[Title/Abstract])
35	(clinical trials[MeSH Terms] OR clinical trial[Publication Type])
36	31 OR 32 OR 33 OR 34 OR 35
37	("review"[Publication Type] OR "review"[Text Word])
38	systematic[sb]
39	36 AND 37
40	36 AND 38
41	39 OR 40
42	41 AND 30

Topic: **Systematic reviews**

Search date: 04 August 2005

Search mask: Ovid

Database: EMBASE

#	**Query**
1	acetyl?salicyl$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
2	acetyl$ salicyl$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
3	exp Acetylsalicylic Acid/
4	aspirin$.ab,ot,tn,tw,ti.
5	asprin.ab,ot,tn,tw,ti.
6	ass.ab,ot,tn,sh,tw,ti.
7	exp Lysine Acetylsalicylate/
8	acetylsalicylic lysinate.mp. or acetylsalicylic acid lysinate/
9	50-78-2.rn.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	exp CLOPIDOGREL/
12	clopidogrel.ab,ot,tn,tw,ti.
13	plavix.mp.
14	iscover.mp.
15	clopivas/
16	Flusan.ab,ot,sh,ti,.
17	Noklot.mp.
18	Terotrom.ab,ot,tn,sh,tw,ti,.
19	Artevil.ab,ot,dv,tn,tw,ti.
20	Tisten.ab,ot,tw,ti.
21	Cloflow.ab,ot,tn,tw,ti.
22	Zyllt.ab,ot,tn,tw,ti.
23	Nefazan.mp.
24	SR 25990.mp.
25	SR 25990 C.mp.

26	SR 25990 C.ot,tn,sh,tw,ti,.
27	DV 7314.ab,cd,ot,tn,sh,tw,ti,.
28	PCR 4099.cd,ot,tn,sh,tw,ti,.
29	SR 25989 C.cd,ot,tn,sh,tw,ti,hw.
30	113665-84-2.rn,cd,ot,tn,sh,tw,fs,ti,hw.
31	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	10 and 31
33	Randomized Controlled Trial/
34	Multicenter Study/
35	Comparative Study/
36	Confidence Interval/
37	RANDOMIZATION/
38	Statistical Significance/
39	(confidence interval or randomization or statistical significance).mp.
40	(double and blind$).tw.
41	placebo$.tw.
42	drug therapy/ or emergency treatment/ or intensive care/ or patient care/
43	random allocation.mp.
44	systematic.mp.
45	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46	(double or random$ or study or trial or placebo or signifi$).ti.
47	(implicatio$ or overview or analysis or meta or review or systematic).ti.
48	exp "review"/
49	review.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
50	45 and (46 or 47)
51	50 and (48 or 49)
52	32 and 51
53	46 or 47
54	45 and 53
55	32 and 54
56	limit 55 to "review"

57	52 or 56

Appendix D: Queries to authors/other parties and responses

Table D.1: Queries to authors/other parties and responses

Study Date of query	**Name of addressee**	**Response (date/content)**
CAPRIE 1996		
01 August 2005	Gent	no
20 August 2005 (reminder)	Gent	27 September 2005, Roberts: Information on the CAPRIE trial (see original response in Appendix D.1)
Bhatt 2001 (additional publication on the CAPRIE trial)		
10 October 2005	Topol	10 October 2005, Bhatt: specification of the definition "stroke"
Chan 2005		
19 August 2005	Chan	no
05 October 2005 (reminder)	Chan and co-authors	no
12 January 2006	Dr. Drazen (Editor-in-Chief, New England Journal of Medicine, NEJM)	12 January 2006, Mary B. Hamel, Deputy Editor, NEJM,: Letter to F. Chan, requesting to answer queries (see original response in Appendix D.2)
	Chan	18 January 2006, Chan: Data cannot be provided as the statistician is not available.
19 January 2006	Chan	09 February 2006, Chan: response to 1 of 3 questions on the issue of patients lost to follow-up (see original response in Appendix D.3)
WATCH		
19 October 2005	Massie	no
28 October 2005 (reminder)	Massie	no
12 January 2006	Massie	no
	Gough (Acting Director, Department of Veterans Affairs)	no
	Zarin, Director of ClinicalTrials.gov	13 January 2006, Zarin: The study coordinator is responsible for the data (see original response in appendix D.4)
16 May 2006	Massie (via Sanofi Aventis)	09 June 2006, Massie: Manuscript on the WATCH trial will be published shortly (see original response in Appendix D.5)
14 June 2006 (Study report requested)	Massie	no
ASCET		
09 November 2005	Pettersen	14 November 2005, Pettersen: Results of the ASCET trial are expected in 2008.

Appendix D.1: Response from R. Roberts (CAPRIE trial)

From: Robin Roberts
Professor Emeritus,
Dept. Clinical Epidemiology & Biostatistics
McMaster University

Subject: CAPRIE Questions

Dear …,

My colleague Michael Gent, passed your enquiry about CAPRIE on to me. I will do my best to answer your questions although it's a long time since we finished the study!

1. Screening

We did not document the screening process in CAPRIE, patients entered the data base only at the point of randomization. The design of this study pre-dated CONSORT by a number of years. With such a large study and no "natural denominator" for PAD patients, the expense of data collection during screening was not thought to be justified. Just as we were publishing CAPRIE, Lancet adopted the first CONSORT recommendations and asked us to comply by including Figure 2, even though we had to include the numbers of patients screened and not eligible/randomized as unknown.

2. Central Validation Committee (CVC)

CAPRIE was a collaboration between academic trialists and a commercial sponsor (Sanofi). The study's organization included a Steering Committee (SC) with representation from both academia and the Sponsor, and a Coordinating and Methods Centre (CMC) at McMaster University. The CVC was appointed by the SC with a membership of academically-based clinicians with expertise in stroke, MI, and vascular disease; the committee's co-chairs were both academically-based members of the SC. The CVC was required to review all outcome

events (ischemic stroke, MI, death, primary intra-cranial hemorrhage, and above ankle amputation) reported by the local investigators during follow-up. For non-fatal events, the CVC determined whether the evidence supporting an event met study criteria; for deaths the committee classified the cause as being due to ischemic stroke, MI, other vascular, hemorrhage, or non-vascular. Outcome events were recorded in the study's case report forms (CRFs) and supported by additional documentation (clinical notes, discharge summaries, laboratory results, CTs, ECGs, death certificates, autopsies, etc.). Initial responsibility for ensuring the completeness of the event documentation and it's collection in the form of a "dossier" was with local study representatives, typically study monitors who were either employed by, or contracted by, the Sponsor. The CVC was operated through a "secretariat" located in the CMC. Once the event dossier was considered complete it was transferred to the CVC secretariat who then organized the CVC review process and resolution of disagreements. The secretariat maintained a separate data base to manage the process of adjudication and to record the ultimate decisions of the CVC. All CVC decisions were made without knowledge of study treatment. During the course of the study, individual patient treatment information was known only by the External Safety and Efficacy Monitoring Committee (actually the Independent Statistical Centre, an academically-based subgroup who prepared Safety Reports for the ESEMC) and the third-party drug packaging company. The Sponsor, SC, CMC, CVC had no access to the randomization until after the final data base closure. At this point the CRF data and adjudication data were combined by the CMC and a copy provided to the ESEMC in exchange for the study randomization. I conducted the end of study analysis in the CMC and reported the results to the SC about 2 weeks later. At this meeting, a member of the ESEMC verified that they had independently achieved an identical primary analysis. If I recall correctly, it was at this point that a copy of the combined data base was transferred to the Sponsor. The results were first presented a couple of months later at the annual AHA meeting with simultaneous publication in Lancet.

3. Numbers at Risk

The "potential" minimum follow-up was one year but non-vascular and hemorrhagic deaths are a competing risk and would have censored some patients before this time with respect to the primary outcome of ischemic stroke, MI, or vascular death. However, the vast majority of the "missing" patients in your calculations are due to the fact that patients do not return for follow-up exactly on their one-year randomization anniversary. The figures at the bottom of

Figure 3 are taken directly from the Kaplan-Meier output and are those still at risk on a particular day. So the 12 month figure,for example, is those still at risk at the end of day 365, ie. were event free for the primary event, had not died prior to that time from non-vascular causes, and had their last follow-up on or after day 366. The operations manual specified an allowable window for any 4-month follow-up of ± 14 days and so the number at risk around a scheduled follow-up point is very sensitive to the actual day chosen. For example about 300 patients attended for follow-up on their 365th day so if the number at risk was reported as of one day earlier than the current figure 3 it would already be 300 patients more. Moving the "at risk day" back to the start of the 28-day window increases the number at risk to 17,782 or 1,564 more than appears in the figure at 12 months (just 14 days later). Although we specified a ± 14 day window, centres don't always comply of course and some patients were brought in for their 12 month visit somewhat earlier, especially in the final push to get all follow-up data in just before the study closed. If a centre designated a visit to be the 12 month follow-up, even though it may have been done prior to the start of the official window, we still counted this as a completed follow-up. If this happened to be the patient's end-of-study visit they were considered a normal closeout and not lost-to-follow-up. We stand by the figure of 42 as those lost to follow-up; these are patients whose last completed follow-up was before the final planned follow-up and for whom this final planned follow-up never occurred. The low number of patients actually reaching the 36 month point is also due to the effect of the follow-up window and competing non-vascular death.

4. Statistical Methods

The p-value for the primary outcome of 0.043 is derived from a Mantel-Haenszel test stratified for clinical subgroup (stroke, MI, PAD). The randomization was stratified for clinical subgroup and thus the primary test was also pre-specified to be stratified by this factor. At the time I was using the BMDP package for analysis. This p-value was calculated with BMDP.1L and is labeled as Savage (Mantel-Cox) in the output. We used the Cox model to produce treatment effect estimates (hazard ratios) and corresponding 95% confidence intervals. These Cox models incorporated clinical subgroup as a stratification variable to allow for potentially different hazards for stroke, MI, and PAD patients but a common superimposed hazard ratio for treatment. There was also a secondary analysis with additional adjustment (as covariates) for pre-specified baseline variables. These results are not included in the publication other than a statement on page 1333 that these left treatment effect

estimates "virtually unchanged". All treatment effects for efficacy outcomes cited in the paper are thus estimated from Cox models with stratification for clinical subgroup.

7. Clinical Subgroup Survival Curves

I'm afraid I don't have easily to hand electronic copies of the individual Kaplan-Meier survival curves for the 3 clinical subgroups. As far as I remember, the stroke patient experienced the highest risk which was roughly constant with time with a consistently lower cumulative risk with clopidogrel. However, with the smaller N the formal test is non-significant. The PAD patients experienced a somewhat lower overall risk but very constant over time. The 2 PAD curves show good separation and the PAD specific treatment effect is strongly significant in its own right. The K-M curves for the MI patients showed higher early hazard which diminished with time thus flattening the cumulative risk curves. The ASA and clopidogrel curves crossed over at a couple of points but finished up at 3-years essentially equal. Our MI patients experienced a much lower risk that we expected and caused us to increase the sample size beyond the original 15,000 planned. As a SC, we did not believe that the heterogeneity in treatment effect was real and that we simply experienced bad luck with our MI patients. It is my belief that subsequent studies of clopidogrel in coronary patients supports our contention that clopidogrel works equally well with coronary patients and that the 8.7% RRR with respect to aspirin applies to all 3 types of atherosclerotic patient.

I hope this helps you in your deliberations.

Appendix D.2: Response from M. Hamel for J. Drazen (Chan 2005)

Dear …

I write to let you know that we received your correspondence. As I'm sure you can understand, your questions will need to be answered by Dr. Chan, the corresponding author on the manuscript. I have written to him to encourage him to address the questions you have raised.

Sincerely,

Mary Beth Hamel, MD, MPH
Deputy Editor

Appendix D.3: Response from F. Chan (Chan 2005)

Dear colleagues

Please refer to the response of my biostatistician to your query. In essence, we do not find any error in the results of the randomized trial published in the New England Journal of Medicine.

Best regards
Francis Chan

****
****
Francis K.L. Chan, *MBChB(Hons), MD(CUHK), FRCP(Lond, Edin, Irel), FACG, FHKCP, FHKAM(Med)*
Professor of Medicine
Assistant Dean (General Affairs)
Department of Medicine & Therapeutics
The Chinese University of Hong Kong
Tel (852) 2632 3126
Fax (852) 2647 6923
****
****

-------- Original Message --------
Subject: Re: Re: 2006-01-06_Bf-Chan-Clopidogrel.pdf]]
Date: Fri, 3 Feb 2006 12:37:02 +0800
From: Jessica Ching
To: <fklchan@cuhk.edu.hk>
References: <43DFBEB2.6030004@cuhk.edu.hk>

Dear Dr. Chan,

After re-examining the database, I do not find any error in the results published in the New England Journal of Medicine. You may wish to forward the following summary to …:
In Clopidogrel group: 13 patients had upper GI events, 7 had lower GI events, 1 rebled due to cancer and 6 died (total = 27)
In Aspirin group: 1 patient had upper GI event, 7 had lower GI events, 2 had anaemia that was not due to gastrointestinal blood loss, 3 rebled due to cancer, 3 were lost to follow up and 4 died (total = 20)

The no. of patients at risk stated in Figure 1 was correct. I believe Dr. … misinterpreted the no. of patients at risk for 2 reasons. First, as stated in the paper that "Patients who discontinued the study drugs prematurely were followed until the end of the study, to determine whether gastrointestinal events had occurred." Second, 2 patients in the Clopidogrel group died a few months after GI events had occurred. These cases were censored at the time of GI events but not at the time of death.

Since most of the outcomes could be explained, I don't think analysis based on "worst-case scenario" is applicable in this study.

Regards,
Jessica

Appendix D.4: Response from D. Zarin (WATCH trial)

Thank you for your query. We are not in a position to investigate issues such as those that you raised. However, it would be important for you to understand that the information in the public site, ClinicalTrials.gov, can be changed as the trial changes. Therefore, it is possible that the number of subjects was changed in the registry to reflect the actual number—this is not necessarily what was originally registered. You can see on the bottom of the record that it was last updated in December, 2005. In the near future we will have the ability to also provide the original record, and all subsequent revisions, but this is not easily done now.

Deborah A. Zarin, M.D.
Assistant Director for Clinical Research Projects
Director, ClinicalTrials.gov
Lister Hill National Center for Biomedical Communications, National Library of Medicine
301-451-4634
dzarin@mail.nih.gov

Appendix D.5: Response from B. Massie (WATCH trial)

June 8, 2006
Dear Drs. …:

I was recently asked by Sanofi-Aventis Pharmaceuticals to provide information to your office about the VA Cooperative Study 442 (the Warfarin and Antiplatelet Trial in Chronic Heart Failure, or WATCH). As study Chairman, I am writing to provide you with an update on this trial. I was told that IQWiG had made previous attempts to contact me. However, I have no record of any queries to me either via the post or in my stored e-mails, which date back to January 2004.

WATCH was designed in 1997-1998 and enrolled 1,587 of the 4,500 planned patients in 1999-2002. The protocol was designed by the VA Cooperative Studies Program, with funding provided by the Department of Veterans Affairs, supplemented by unrestricted grants from Dupont Pharmaceuticals, Bristol Myers Squibb, and Sanofi-Synthelabo Pharmaceuticals (the company names at that time). Unfortunately, in 2002 the VA Cooperative Study Program elected to terminate the study prematurely because of poor enrollment, without review of the data. Recruitment was discontinued in 2002 and follow-up ended in 2003. The results were presented in 2004 at the Scientific Sessions of the American College of Cardiology, but because of complexities with the data and turnover among the personnel in the VA Coordinating Center, the primary publication is only now being finalized and is not yet publicly available.

To assist you in evaluating the data, I am attaching the design paper published in the *Journal of Cardiac Failure*. This manuscript clearly states the reason for the early termination of the trial and provides the baseline data. I am also attaching a manuscript published in the *European Journal of Heart Failure* which accurately summarizes the results presented in the late-breaking trial session of the American College of Cardiology meeting in 2004. Further analyses have not resulted in any substantial changes in the principal findings presented at that meeting. We expect the manuscript to be submitted for publication in the next 60 days after review by all the interested parties.

Please feel free to contact me if you require any additional information.

Sincerely yours,

Barry M. Massie, M.D.
Professor of Medicine
University of California, San Francisco

Appendix E: MATCH trial

The MATCH trial was not included in the evaluation and needs to be assessed separately, as this trial was not designed to answer the research questions posed in this report (comparison of antiplatelet monotherapy: clopidogrel versus ASA). The MATCH trial compared clopidogrel (75 mg/day, p.o.) plus ASA (75 mg/day, p.o.) with clopidogrel (75 mg/day, p.o.) plus placebo in patients with recent (within the previous 3 months) ischaemic stroke or transient ischaemic attack and at least one of 5 additional vascular risk factors (previous ischaemic stroke, previous myocardial infarction, angina pectoris, diabetes mellitus, or symptomatic peripheral arterial disease). Patients in both groups received open-label clopidogrel and were randomised to receive either ASA or placebo in a double-blind manner. The primary outcome was the first occurrence of an event in the composite of ischaemic stroke, myocardial infarction, vascular death (including haemorrhagic death of any origin), or rehospitalisation for an acute ischaemic event (including unstable angina pectoris, worsening of peripheral arterial disease requiring therapeutic intervention or urgent revascularisation, or transient ischaemic attack). The planned follow-up was 18 months. No significant difference for the primary outcome was shown between treatment groups: the corresponding event rates were 15.7% in the group receiving ASA plus clopidogrel, compared with 16.7% in the group receiving clopidogrel alone (relative risk reduction 6.4%, 95% CI –4.6 to 16.3, p=0.244). Bleeding adverse events were more common in patients receiving combination therapy than in patients receiving clopidogrel alone. This applied to minor bleeding (3.2% vs. 1.0%; p<0.0001), major bleeding (1.9% vs. 0.6%, p<0.0001), as well as to life-threatening bleeding (2.6% vs. 1.3%; p<0.0001). Primary intracranial haemorrhage was also more common under combination therapy (0.85% vs. 0.45%).

A negative benefit-risk ratio for combined antiplatelet therapy with ASA plus clopidogrel compared with clopidogrel monotherapy can be inferred from the MATCH trial in patients with a recent cerebrovascular event.

Appendix F: Protocol of the scientific hearing

The (German-language) protocol can be found in the German final report on the Institute's website under:

http://www.iqwig.de/index.download.35a0460451885df0360ad2f66ac971b7.pdf

Appendix G: Statements in writing

The (German-language) statements can be found in the German final report on the Institute's website under:

http://www.iqwig.de/index.download.35a0460451885df0360ad2f66ac971b7.pdf