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Clopidogrel plus acetylsalicylic acid in acute coronary syndrome[1]

Executive Summary

[1] Translation of the executive summary of the final report "Clopidogrel plus Acetylsalicylsäure bei akutem Koronarsyndrom" (Version 1.0; Status: 28.01.2009). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Executive summary

Background

The Institute for Quality and Efficiency in Health Care (IQWiG) was commissioned by the Federal Joint Committee to assess the benefit of clopidogrel plus acetylsalicylic acid (ASA) combination therapy versus ASA monotherapy in the treatment of acute coronary syndrome.

Research question

The aim of this research was to assess the benefit of clopidogrel plus ASA combination therapy versus ASA monotherapy in patients with acute coronary syndrome (acute coronary syndrome without ST-segment elevation [NSTE-ACS] or ST-segment elevation myocardial infarction [STEMI]). The focus of the assessment was on patient-relevant therapy goals.

Methods

The assessment methods were specified in advance in a report plan (Version 1.0, 9 September 2005). Two amendments were made to this report plan and published. After the publication of the second amendment on 27 June 2007, a hearing was held. Written comments could be submitted from 27 June 2007 to 25 July 2007. Unclear aspects of these written comments were discussed in a scientific debate on 21 August 2007. The report plan was subsequently revised (Version 2.0, 13 March 2008) and published on the Internet, together with the documentation and evaluation of the comments received on the report plan (Version 1.0, 13 March 2008), on 26 March 2008.

The assessment was conducted on the basis of randomized controlled trials (RCTs) on the research questions outlined above. The assessment was made separately for the 2 disease entities NSTE-ACS and STEMI. To identify relevant studies, a systematic search for literature (coverage up to January 2008) was conducted in the databases MEDLINE, EMBASE, and CENTRAL. In addition, reference lists of relevant secondary publications (systematic reviews, HTA reports) were searched, as well as study registries, study results registries, and publicly accessible regulatory documents. Furthermore, relevant published and unpublished studies were requested from the manufacturer of clopidogrel (Sanofi-Aventis).

A preliminary report (Version 1.0, 22 September 2008) was prepared based on the methods formulated in the report plan 2.0, and was published on the Internet on 23 September 2008. Interested persons and parties were invited to submit written comments (hearing) up to 22 October 2008. Unclear aspects of the written comments were discussed with those submitting comments on 26 November 2008 in a scientific debate. In addition, an external review of the preliminary report was performed.

After the hearing had been conducted, the present final report was produced. The comments received on the preliminary report and the minutes of the scientific debate were documented separately (“Documentation and evaluation of comments on the preliminary report”).

Results

Results of the literature search

The literature search identified a total of 7 RCTs examining the effect of clopidogrel plus ASA combination therapy versus ASA monotherapy in patients with acute coronary syndrome, and focussing on patient-relevant outcomes.

Two studies included insufficient information and could not be considered in the benefit assessment. One of these studies, the CREDO study, had been sponsored by Sanofi-Aventis, who did not supply the clinical study report (CSR), despite a request. However, due to the size and design of both studies, it can be assumed that they would not greatly influence the conclusion of the IQWiG report.

Of the remaining 5 studies, one (the manufacturer-sponsored CURE study) referred to acute coronary syndrome without ST-segment elevation (NSTE-ACS), i.e., unstable angina pectoris and non-ST-segment elevation myocardial infarction (NSTEMI). The other 4 studies investigated patients with STEMI. Two of these 4 studies were sponsored by Sanofi-Aventis (COMMIT and CLARITY).

Extensive information was publicly available for all 5 studies considered in the assessment. The CSRs were supplied by Sanofi-Aventis for the 3 manufacturer-sponsored studies.

Results – Acute coronary syndrome without ST-segment elevation (NSTE-ACS)

The CURE study (>12 500 patients) was the only study included in the assessment that investigated ACS without ST-segment elevation. Clopidogrel plus ASA or ASA plus placebo were given for a minimum of 3 and a maximum of 12 months (mean observation period: 9 months). Regarding study conduct, the CURE study showed no serious methodological deficiencies that would have relevantly affected the interpretation of results.

The CURE study provides no proof that clopidogrel plus ASA combination therapy affects cardiovascular mortality or all-cause mortality rates when compared with ASA monotherapy. However, it provides proof that combination therapy over a period of up to 12 months reduces the rate of a composite outcome of cardiovascular mortality, myocardial infarction (MI) and stroke (with or without consideration of refractory ischaemia). Regarding the individual components of the primary outcomes, there is only proof of a risk reduction through combination therapy for the MI rate, especially the rate of ST-segment elevation MI. A comparison of the absolute reduction of the MI rate (1.5%) with the absolute reduction of the rate of the CURE composite primary outcomes (2.1% and 2.3%) illustrates that the former is mainly responsible for the therapy effect (risk reduction in vascular events) shown in the co-primary outcomes. There is no proof that combination therapy reduces the stroke rate.

In addition, the CURE study provides an indication that clopidogrel plus ASA combination therapy reduces the rate of coronary ischaemia of any severity (including angina pectoris symptoms) and of heart failure during initial hospitalization, but not subsequently. The same applies to coronary revascularization. For the complete observation period, the rate of mechanical coronary revascularization was largely identical in both treatment groups,

indicating that in patients using combination therapy, this intervention only becomes necessary at a later point in time.

The CURE study provides proof that bleeding complications occur more frequently with clopidogrel plus ASA than with ASA monotherapy. This applies both to major bleeding and bleeding leading to the discontinuation of study medication (minor bleeding). However, there is no proof that life-threatening or fatal bleeding occurs more frequently with combination therapy. In general, patients using combination therapy experienced more serious adverse events and more study discontinuations due to adverse events; this was especially due to the higher rate of bleeding complications. The data provide no indications that other (non-bleeding related) serious adverse events occur more frequently with combination therapy.

The sources available did not contain any useful information on some relevant outcomes. This was especially the case for the rates of recurrence of acute coronary syndrome, cardiac arrhythmia in need of treatment, transitory ischaemic attacks, revascularization due to symptomatic cerebrovascular disease, overall hospitalizations, as well as for health-related quality of life, treatment satisfaction, dependence on assistance from third parties or need for care, physical endurance, coping with daily activities, and the maintenance or restoration of the capacity to work.

It can be inferred from the analyses of time progression that the reduced risk of vascular events can particularly be explained by the early treatment phase (up to Day 90). Moreover, in the early treatment phase, the reduced risk of vascular events considerably outweighed the increased risk of bleeding complications. On the other hand, in the late phase (after Day 90), the change in risk difference for bleeding complications (regarded purely numerically) was greater than the change in risk difference for cardiovascular events. However, the ideal duration of combination therapy in the sense of an optimized benefit-harm balance remains unclear, as valid studies designed to investigate this research question are lacking.

Sub-group analyses provide an indication that the reduced risk of vascular events is less pronounced both in women and older patients (≥ 65 years). There is, however, no proof that the harmful effects of combination therapy differ between men and women or older and younger patients. In addition, the data provide an indication that the reduced risk of vascular events is particularly pronounced in smokers (including ex-smokers); however, the CURE study did not show a benefit of combination therapy for non-smokers. Due to a lack of data, it remains unclear whether smoker-status has an influence on the harmful effects of combination therapy.

The data provide no indication of a qualitative change in the results referring to the beneficial and harmful effects of combination therapy if a secondary (early elective) coronary intervention is performed. No studies were available on combination therapy in patients who underwent a primary percutaneous coronary intervention (PCI). The results of the PCI-CURE study (a sub-study of the CURE study) support the hypothesis that vascular events are primarily prevented by pre-treatment with combination therapy before a coronary intervention and in a subsequent interval of up to 30 days, and that it is less likely to be successful after this period.

Finally, the data provide no indication that the reduced risk of vascular events or the increased risk of bleeding complications is dependent on the ASA dose used. However, they do provide indications of a positive association between an increase in ASA dose and the overall number of major bleeding complications, independent of whether ASA is used as monotherapy or in combination with clopidogrel.

Results – Acute coronary syndrome with ST-segment elevation myocardial infarction (STEMI)

A total of 4 relevant studies on STEMI were identified and were all included in the benefit assessment. The main information sources were the CLARITY study (nearly 3500 patients) and the COMMIT study (more than 45 000 patients). Publicly accessible publications (including those on study design) and the CSRs were available for both studies. The 2 other studies (Dogan 2005 and Sulimov 2006) hardly played a role, as they included only about 80 and 100 patients respectively. No conclusions drawn from the CLARITY and COMMIT studies were affected by the results of these 2 studies.

The CLARITY study and the COMMIT study followed treatment strategies for STEMI that excluded primary intervention therapy with PCI (with or without stenting). Whereas the CLARITY study required a thrombolysis as primary treatment for STEMI (which was then provided for 99.7% of patients) according to the protocol of the COMMIT study, a planned thrombolysis therapy was not a precondition for study participation, and in fact was only performed in 55% of patients. However, the sub-group analysis of the primary outcome of the COMMIT study provides no indication of an interaction with regard to the factor "thrombolysis". In the CLARITY study, a coronary intervention was carried out in about two-thirds of patients up to 30 days after the start of the study. No information on this issue was presented in the COMMIT study. Another difference compared with the COMMIT study was that all patients in the CLARITY study had suffered a STEMI, whereas in the COMMIT study only the suspicion of an acute MI was the inclusion criterion. Nevertheless, a STEMI was diagnosed in the majority of patients (approx. 87%), so that this difference is of minor relevance for the IQWiG report.

In the CLARITY study, after the initial loading dose clopidogrel was administered for up to 8 days. In the COMMIT study, it was administered for up to 28 days without a loading dose. In both cases, the administration of the study drug (clopidogrel plus ASA vs. ASA plus placebo) was limited to inpatient treatment within the framework of the index event. The studies thus do not answer the question as to whether combination therapy beyond primary hospitalization causes more benefit than harm, or vice versa.

Neither study showed serious methodological deficiencies that would have affected the interpretation of the results. However, some results varied greatly, which raises the question, among other things, about the validity of the results of the individual studies for the German health care context.

On the whole, the studies provide proof that clopidogrel plus ASA combination therapy reduces the rate of repeated MI versus ASA monotherapy. In addition, they provide an indication that urgent coronary revascularization is less frequently necessary with clopidogrel plus ASA combination therapy, but that elective revascularization is performed more

frequently. There is no indication that combination therapy leads to fewer overall coronary revascularizations. Nor is there any indication that repeated coronary ischaemia (different from MI) re-occurs less frequently with clopidogrel plus ASA combination therapy than with ASA monotherapy.

Although the meta-analytical summary of study results showed a statistically significant effect on all-cause mortality, the results in the 2 major studies were inconsistent. It is unclear whether this was caused by differences in the study setting and/or study design. In summary, IQWiG evaluated this as an indication of a benefit. Similarly, the data provide an indication of a benefit for the combined outcome "death, repeated MI or stroke". As the deaths that occurred were practically exclusively of a cardiovascular nature, this also applies to cardiovascular mortality.

The data also provide an indication that the risk of stroke is reduced by combination therapy. They provide no indication of an advantage of combination therapy with regard to cardiac arrhythmia in need of treatment, the occurrence of heart failure, and the risk of cardiogenic shock.

Confirmed bleeding complications occurred more frequently with clopidogrel plus ASA combination therapy than with ASA monotherapy. This was due to the more frequent occurrence of minor bleeding complications. There was no indication that fatal, cerebral or other major bleeding complications occurred more often; nor did other (non-bleeding related) adverse drug reactions occur more often.

The sources available did not have usable information on some relevant outcomes. This was the case for health-related quality of life, treatment satisfaction, physical endurance, the capacity of patients to work, dependence on third-party assistance or the need for care, and the ability of patients to cope appropriately with daily activities; nor was the issue of (repeated) hospitalizations addressed in the studies.

Further analyses provide an indication that the effect of clopidogrel plus ASA combination therapy depends on the latency period between the occurrence of symptoms and the start of therapy. The effect of combination therapy was at least less pronounced if treatment started 6 or more hours after symptom occurrence. The data provide no indication that the effect in certain subgroups is different from that in the overall group; this especially applies to age, gender, and concomitant diseases.

The data provide no indication of a qualitative change in the results for the beneficial and harmful effects of combination therapy if a secondary (early elective) coronary intervention is performed. There were no studies on combination therapy in patients with primary PCI.

Conclusion

Acute coronary syndrome without ST-segment elevation

The data provide proof of a benefit of clopidogrel plus ASA combination therapy versus ASA monotherapy in the treatment of ACS without ST-segment elevation over a treatment period of up to 12 months (observation period 3-12 months). This is inferred from a reduction of the rate of a composite outcome of cardiovascular mortality, MI, and stroke, with or without

consideration of refractory ischaemia. Regarding the individual components of this composite outcome, only a benefit for the MI rate is proven. This is countered by proof of harm, resulting from the more frequent occurrence of bleeding complications with combination therapy; this applies both to major and minor bleeding complications. Purely numerically, the rate of prevented vascular events outweighs the rate of provoked bleeding complications. There is no proof available that combination therapy reduces all-cause mortality.

It can be inferred from the analyses of time progression that the reduced risk of vascular events can in particular be explained by the early phase of treatment (up to Day 90). During initial hospitalization, the rates of all levels of severity of coronary ischaemia (including angina pectoris symptoms), coronary revascularization, and heart failure were reduced, but not subsequently. In addition, in the early treatment phase, the reduced risk of vascular events clearly outweighed the increased risk of bleeding complications. In contrast, in the late phase (from Day 90), the change in the risk difference for bleeding complications was greater than the change in the risk difference for cardiovascular events (regarded purely numerically). Overall, the optimal duration of therapy in the sense of an optimized benefit-harm balance is unclear, as valid studies designed to investigate this question are lacking.

For some specific patient groups, conclusions can be drawn that deviate from the overall result. The data provide an indication that there is also a reduced risk of vascular events in women and older patients (≥ 65 years); it is, however, less pronounced. No proof is available that this also applies to bleeding complications. The data also provide an indication that the reduced risk of vascular events especially refers to smokers. It is not proven that combination therapy reduces the risk in non-smokers. Due to a lack of data, it remains unclear whether smoker-status has an influence on the harmful effects of combination therapy.

The data provide no indication that the beneficial and harmful effects of combination therapy versus ASA monotherapy are dependent on the ASA dose used. However, they do provide indications of a positive association between an increase in ASA dose and the overall number of major bleeding complications, independent of whether ASA is used as monotherapy or in combination with clopidogrel.

No studies were identified in which patients were primarily treated with a PCI. However, the data provide no indications that the conclusions on beneficial and harmful effects are any different for patients who underwent a secondary (early elective) coronary intervention.

Acute coronary syndrome with ST-segment elevation

The data provide proof of a benefit of clopidogrel plus ASA combination therapy in the context of inpatient treatment of ST-segment elevation MI; this results from a reduction in the rate of repeated MI. They also provide an indication of a benefit of combination therapy for the stroke rate. In addition, they provide an indication that urgent coronary revascularization is less frequently necessary with combination therapy, but that elective revascularization is performed more often. There is no indication that combination therapy leads to a reduction of the overall coronary revascularization rate.

The data provide an indication of a benefit of combination therapy for all-cause mortality. Although the meta-analysis of the study data showed a reduction in all-cause mortality with

combination therapy, the results of the available studies were inconsistent. There is also an indication of a benefit for the combined outcome “death, repeated MI or stroke”.

The benefit aspects described above are countered by proof of harm caused by combination therapy with regard to the occurrence of bleeding complications; however, this is due to the more frequent occurrence of minor bleeding complications. There is no indication that fatal, cerebral or other major bleeding complications occur more often.

The data provide an indication that the effect of combination therapy depends on the latency period between the occurrence of symptoms and the start of treatment. In addition, they provide an indication that there is either no effect or that the effect is less pronounced if treatment starts 6 or more hours after symptom occurrence.

As no studies were available comparing combination therapy with ASA monotherapy for long-term treatment after hospitalization, no proof is available that combination therapy has greater benefits than harms after a hospital stay when compared with ASA monotherapy.

No studies were identified in which patients were treated primarily with a PCI. However, the data provide no indications that the conclusions on the beneficial and harmful effects are any different for patients who underwent a secondary (early elective) coronary intervention.

Key words: clopidogrel; acetylsalicylic acid; acute coronary syndrome; benefit assessment; systematic review.