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Clopidogrel in acute coronary syndrome: when, how much, how long?

Clopidogrel bei akutem Koronarsyndrom: wann, wie viel, wie lange?

Zusammenfassung Wesentlicher Bestandteil des medikamentösen Behandlungsprinzips beim akuten Koronarsyndrom (ACS) ist die Thrombozytenaggregationhemmung. Während der Einsatz von Acetylsalicylsäure etabliert ist, wird inzwischen durch die Leitlinien der amerikanischen, europäischen und deutschen Gesellschaften für Kardiologie die additive Gabe von Clopidogrel bei ACS ohne persistierende ST-Hebung empfohlen. Bei konservativem Therapiemanagement soll die möglichst frühe Gabe von 75 mg Clopidogrel für die Dauer von einem (Empfehlung IA) bis zu neun Monaten (IB) erfolgen. Bei geplanter PTCA wird zusätzlich vorab eine „loading dose" von 300 mg Clopidogrel empfohlen.

Diese Empfehlungen beruhen hauptsächlich auf den Daten der CURE- und CREDO-Studie, die allerdings nicht alle Fragen beantworten. Die absolute Risikoreduktion durch Clopidogrel in diesen Studien betrug lediglich 2%. Dabei wurde nur die Inzidenz des kombinierten Endpunktes bestehend aus kardiovaskulärem Tod, Myokardinfarkt und Schlaganfall statistisch signifikant beeinflusst, wohingegen sich bei der Analyse der Endpunkte im Einzelnen kein Unterschied ergab. Auch die Empfehlung bezüglich der Dauer der Clopidogrelbehandlung beruht lediglich auf der mittleren Applikationszeit der beiden Studien. Aufgrund des erhöhten Blutungsrisiko unter Clopidogrel (schwere Blutungen ca. 1%) bleibt die Frage nach der Rationale für eine duale antiaggregatorischen Behandlung bei ACS damit nach wie vor nur teilweise beantwortet. Betrachtet man zudem die Kosten, die durch die Clopidogrelbehandlung entstehen, erscheint die Forderung nach weiteren Studien, die die Effektivität der dualen antiaggregatorischen Therapie weiter untermauern, gerechtfertigt. Bis dahin sind die auf den Leitlinien basierenden Behandlungsschemata unter besonderer Berücksichtigung des individuellen Risikos des Patienten anzuwenden.

Schlüsselwörter Akutes Koronarsyndrom – Clopidogrel – Thrombozytenhemmung

Summary An important part of the therapy management of acute coronary syndrome (ACS) consists of antiplatelet drugs. Whereas the administration of acetylsalicylic acid (ASA) is well established, the guidelines recommend the additive use of clopidogrel in patients with ACS without persisting ST-elevation. Clopidogrel should be added to ASA as soon as possible in patients with a non-invasive treatment strategy and continued for more than 1 month (class 1A) and up to 9 months (class 1B). In patients for whom a percutaneous coronary intervention (PCI) is planned, an additional loading-dose of 300 mg clopidogrel should be given on top of ASA (100 mg).

These recommendations are based on data recently published in the CURE and CREDO trials, which however should be critically discussed: In these trials, an absolute risk reduction of only

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2% could be documented by additive use of clopidogrel. The combined endpoint of cardiovascular death, myocardial infarction and stroke is significantly reduced, but there was no improvement taken the individual endpoints alone. In additional, the data for duration of clopidogrel therapy were determined by taken the mean follow-up of these studies. The efficacy of the dual antiplatelet therapy should be discussed in the context of an increased frequency of major bleedings (in total 1%) and should be considered against a reasonable cost effective background.

An adequate therapy with clopidogrel in patients presenting ACS should be confirmed by further trials. Until more detailed data are available, the guideline recommendations should be implemented based on of patient's individual risk.

Key words Acute coronary syndrome – clopidogrel – platelet inhibition

Introduction

The antiplatelet agent clopidogrel is a thienopyridine ADP receptor antagonist and inhibits platelet aggregation by blocking ADP binding to one of its three known receptors on the platelet surface named the P2Y12 receptors. Thereby, an ADP-mediated upregulation of the glycoprotein IIb/IIIa receptor with an amplification of platelet activation is inhibited. Clopidogrel is a prodrug and requires conversion to an active metabolite by the hepatic cytochrome P450-1A enzyme system [1]. Clopidogrel does not have an effect on the thromboxane pathway, which is inhibited by acetylsalicylic acid (ASA). Therefore this dual oral antiplatelet therapy should be superior in preventing major adverse cardiac events related to platelet activation in acute coronary syndrome (ACS) compared to treatment with ASA alone. However, antiplatelet drug resistance has previously been described to be 8% for ASA [2] and about 11% for clopidogrel [3].

What is the evidence?

The CURE trial (Clopidogrel in Unstable angina to prevent Recurrent Events) was designed to compare the efficacy and safety of the early and long-term use of clopidogrel plus ASA (75 mg to 325 mg). In total, 12,562 patients with ACS and non-ST segment elevation myocardial infarction were included. A loading dose of clopidogrel 300 mg or placebo was given on a double blind basis immediately after randomization followed by study medication (clopidogrel 75 mg per day or placebo) for 3 to 12 months with a mean duration of 9 months. Patients having received GPIIb/IIIa inhibitors within a period of three days were excluded. The primary outcome was the combined endpoint of death from cardiovascular causes, non-fatal myocardial infarction, and stroke. The secondary outcomes were severe ischemia, heart failure, and the need for target-vessel revascularization [4].

Clopidogrel in combination with ASA reduced the relative risk of the combined atherothrombotic endpoint of cardiovascular death, myocardial infarction or stroke by 20% (95% CI 0.72–0.90; $p<0.001$). This represents an absolute risk reduction of this composite endpoint by 2.1%. There was also a significant difference of the combined secondary endpoint in the placebo group compared with the clopidogrel group by 2.3% (RR 0.86, 95% CI, 0.79 to 0.94; $p<0.001$).

PCI-CURE as a prespecified substudy of the CURE trial tested the hypothesis whether pre-treatment with a loading dose of clopidogrel followed by long-term therapy after PCI is superior to a strategy of no pre-treatment and short-term therapy for only 4 weeks after PCI. A total of 2,658 patients of the CURE study population presenting with ACS and need for PCI were pre-treated with ASA and clopidogrel or placebo for a median of 6 days after enrollment. After PCI, all patients received an open-label thienopyridine (either clopidogrel or ticlopidine) in combination with ASA for 2–4 weeks. Thereafter study medication (clopidogrel 75 mg or placebo) was restarted for a mean duration of 8 months. The primary end point of the study was the composite of cardiovascular death, myocardial infarction, or urgent target vessel revascularisation within 30 days of PCI. Cardiovascular death or myocardial infarction from the time of PCI to the scheduled end of the trial was also assessed to determine the effects of continuing clopidogrel long-term after PCI.

In case of a high-risk profile and PCI therapy, the subanalysis PCI-CURE showed an absolute risk reduction of 1.9% regarding the composite endpoint. Events occurred in 4.5% in the clopidogrel group and in 6.4% of the placebo group (RR, 0.70 95% CI, 0.50 to 0.97; $p=0.03$). This statistically significant benefit was maintained through the end of the follow-up (RR, 0.75 95% CI, 0.56 to 1.00; $p=0.047$). The efficacy of clopidogrel compared with placebo

was evident before PCI, at 30 days of follow-up, and at the end of the study (mean duration of follow-up 8 months) [5].

The CREDO (Clopidogrel for the Reduction of Events During Observation) trial was not only designed to evaluate the benefit of long-term treatment (12-month) with clopidogrel after PCI but also the safety and efficacy of a 300 mg loading-dose before PCI. A total of 2,116 patients were included, if they had symptomatic coronary artery disease with objective evidence for ischemia and were referred for elective PCI. ST-elevation myocardial infarctions were excluded, but 52.8% of the study population presented with unstable angina. The primary one-year outcome was the composite of death and myocardial infarction in the intend-to-treat population. A prespecified secondary analysis included the individual components of the composite end point for administration of clopidogrel less than 6 hours or at least 6 hours before PCI [6].

The incidence for the combined endpoint of death, myocardial infarction and target lesion revascularization within 28 days showed a non-significant reduction (6.8 vs 8.3%) for patients treated with clopidogrel. At one year, the incidence of the primary end point of death, myocardial infarction, and stroke was significantly reduced in the group having continuously received clopidogrel treatment followed by up to 1 year, compared with the placebo group that received only 4 weeks of clopidogrel therapy after PCI (8.5 vs 11.5%; RR, 26.9%; 95% CI, 3.9 to 44.4; $p = 0.02$). This correlates with an absolute risk reduction of 3.0%. The degree of benefit was similar among all subgroup especially in patients presenting with ACS (RR 27.6%; 95% CI 47.8 to –0.40).

Both, the CREDO trial and the PCI-CURE trial examined safety and efficacy of a loading dose of 300 mg clopidogrel. In CREDO, the mean duration between loading dose and PCI was 9.8 hours. The pre-treatment with a loading dose was associated with a non-significant 18.5% relative reduction in the combined endpoint of death, myocardial infarction, or urgent target vessel revascularization at 28 days (6.8% pre-treatment vs 8.3% no pre-treatment; 95% CI, –14.2 to 41.8%; $p = 0.23$). An analysis of the prespecified time-to-treatment intervals of 3 to 6 hours, 6 to 12 hours, and 12 to 24 hours showed that patients in whom clopidogrel was administered at least 6 hours prior to PCI experienced a 38.6% relative reduction after 28 days in the combined end point, which was not statistically significant (95% CI, –1.6 to 62.9%; $p = 0.09$).

Current recommendations in guidelines

In the current guidelines, the European Society of Cardiology (ESC), the German Society of Cardiology (DGK) and the American Heart Association (AHA) recommend for antiplatelet treatment in patients with ACS without ST elevation that clopidogrel should be added to ASA as soon as possible in patients with a non-invasive treatment strategy and continued for more than 1 month (class 1A) and up to 9 months (class 1B); in patients for whom a percutaneous coronary intervention (PCI) is planned and who are not at high risk for bleeding, a loading-dose of 300 mg clopidogrel should be given on top of ASA (100 mg) and followed by 75 mg clopidogrel daily for more than 1 month (class 1A), respectively 9 months (class 1B) [7–9].

The recommendation level of class 1 implies that the experts are convinced that this treatment is beneficial. Evidence level B relates to the fact that the long term benefit is based on a single, albeit large trial. Despite this strong support by the guidelines, several questions are left open when this expensive treatment is translated to clinical practice.

CURE and CREDO challenged

The absolute difference in events of 2.1% prevented by clopidogrel is rather small, although the endpoints are hard ones. Statistical significance is reached because of the exceptionally large study size. The combined endpoint of cardiovascular death, myocardial infarction and stroke is significantly reduced, but there was no improvement taken the individual endpoints alone. Clopidogrel is simply not yet shown to be a life-saving drug. Particularly PCI-CURE results must be interpreted with caution, because this has only the value of an observation within CURE.

The concept of CURE favors a conservative management of ACS, which is not supported by current guidelines. Accordingly, rather low-risk patients were included as evidenced by the low event rate within the first few days. Related to this, another critical concern refers to the study concept of CURE that found little attention. After enrollment of the first 3000 patients it became obvious that the inclusion criteria as originally defined were not strict enough to meet the expectations with respect to events. Therefore, the steering committee had to change the inclusion criteria and allowed only patients with electrographic changes or elevation of cardiac enzymes to be enrolled. Patients at a higher risk for bleeding were excluded. Changing horses like this

during a running study may lead to overestimating the effect in patients at lower risk and underestimating the benefit in high-risk subsets.

The most limiting complication noted with the additional clopidogrel treatment was an increased risk of bleeding. In the CURE trial, the rate of major bleeding increased by an absolute rate of 1% nearly half of which were defined to be life-threatening. Moreover, the occurrence of minor bleedings was more than doubled when treated with clopidogrel. The necessity for transfusion after bleeding was significantly increased (2.8 vs 2.2%, $p = 0.02$). However, bleeding complications seem to be driven to a great extent by high doses of ASA. At doses of 100 mg or less, like commonly used in Europe, this issue loses importance. Perioperative bleedings, however, are a major shortcoming that may require postponing surgery by 5 days if the clinical condition allows this.

Khot et al. evaluated the efficacy and safety of clopidogrel therapy. Based on the CURE data it was calculated that 978 of 1000 patients taking clopidogrel derive no benefit from this drug, 15 non-fatal myocardial infarctions could be prevented by use of clopidogrel, 10 additional patients develop major bleedings and 69 additional patients have minor bleedings. All of this occurs without saving one life. Thus, the clinical benefit/risk ratio of clopidogrel is low, but the costs of the treatment are high. The absolute costs amount to approximately 8 to 16 billion Euro for approximately 11.5 to 22.7 million patients worldwide per year [10]. Compared to evidence-based therapy with ASA for the same number of patients, the costs for the additional clopidogrel treatment explode by approximately a factor of 100 [11].

Focussing on Germany, every year approximately 400,000 patients presenting with ACS are potential candidates for clopidogrel treatment according to the guidelines. On the basis of a nine month treatment and daily costs of € 2.50, the costs rise to € 270 million per year. Other pharmacological principles, like beta blockers, ACE inhibitors or statins, reduce mortality at much lower costs. For clopidogrel no subsets of patients could be identified with a more pronounced effect or a lack of benefit allowing stratification of treatment. Accordingly, due to costs, the CURE results can be implemented in clinical routine with some reservations.

Clopidogrel in clinical practice

When?

Clopidogrel has been shown to reduce complications during PCI on top of glycoprotein IIb/IIIa antagonists [12]. Guidelines recommend to load the patient with clopidogrel before PCI, if no bypass surgery is expected. This recommendation is not very helpful in daily practise, because who can predict this based on clinical findings? The German guidelines take a more practical approach when they advise to start the loading dose only when the antiplatelet effect is actually present at the time of the procedure. It is not advised to withhold PCI until the antiplatelet effect is reached, but the majority of patients will not undergo catheterization so urgently. Accordingly, clopidogrel should be given at earliest convenience. Only a minority of patients (~5%) will require immediate operative revascularization. The bleeding risk in these patients probably outweighs the benefit in the remaining patients undergoing PCI directly.

How much?

Although some early studies suggested that near maximal effects of clopidogrel could be achieved within 3 hours of a 300 mg loading dose, more recent published data show that 6 hours or longer are needed with this dose [13], or larger loading doses in the range of 450 to 600 mg may be necessary to achieve equipotent effects [14, 15]. A recent study reported that a loading dose of 300 mg clopidogrel failed to achieve sufficient platelet inhibition within 2.5 hours [16]. Accordingly, when time is an important factor like in ACS a loading dose of 600 mg may be preferred despite the lack of data from large randomised trials. Negative effects like increased bleeding complications have not yet been reported.

The observation that a loading dose with 600 mg of clopidogrel leads to a substantially greater degree of platelet inhibition than chronic treatment with 75 mg per day also suggests that higher daily clopidogrel doses might be necessary in chronic therapy to achieve a sufficient antiplatelet effect [17]. However, as yet there are no studies available comparing the efficacy of the antiplatelet effect and safety of different daily doses of clopidogrel. Therefore at this time, it seems reasonable to administer the traditional 75 mg dose daily. However, patients with a clopidogrel resistance may benefit from higher daily doses.

How long?

The 9 month treatment in patients after acute coronary syndrome is widely accepted, but appears rather by chance due to the CURE protocol. The efficacy of treatment with clopidogrel beyond the first month after PCI is rather weak, since there is no sig-

nificant advantage of active therapy over placebo in terms of the rates of cardiovascular death or non-fatal myocardial infarction (3.1 vs 4.0%, RR 0.78, CI 95%). A shorter length of, e.g., 6 months clopidogrel therapy may be considered in patients with a successfully stented single vessel disease. Up to now no studies about the efficacy and safety of an even longer treatment are available. Due to the lack of evidence, clopidogrel must only be given for 9 months until further data are available.

More open questions

Trials never give solutions to all treatment aspects in clinical routine. For the treatment with clopidogrel several critical questions remain open:

Do patients after ST-elevation acute myocardial infarction also need clopidogrel treatment? Since the pathophysiological mechanisms are rather similar, a benefit may be expected, particularly after successful fibrinolysis. Due to the lack of data, this may be decided individually.

What is the antiplatelet management in ACS patients after coronary artery bypass surgery? Bhatt et al. proposed an advantage of clopidogrel over ASA in patients having undergone cardiac surgery. However, this is only a subgroup analysis of the CAPRIE trial and was not prespecified [18].

Do all patients with a stented single vessel coronary artery disease require clopidogrel long-term treatment? *Is longer clopidogrel treatment necessary in ACS patients receiving a drug eluting stent?* Considering that the acute coronary syndrome is one of the most common reasons for hospitalization and that drug eluting stents will become common practise these questions must be addressed in the future.

Is clopidogrel necessary when obstructing coronary artery disease is angiographically excluded? Most likely no, when the coronaries appear completely normal. When wall irregularities are present, probably yes.

How to decide, when anticoagulation is required? Possibly on top of dicoumarol in patients with artificial valves or a history of embolism. In atrial fibrillation an individual risk/benefit evaluation should take place.

Conclusions

If clopidogrel would be available at the costs of ASA, many questions would never arise. The controversial discussion is mostly driven by cost issues. The resistance to reimburse this evidence based treatment by the public insurance companies in Germany should not be abused to question the benefit of dual antiplatelet treatment in ACS. There is a demand for more trials to clarify the above unresolved questions for the best use of clopidogrel. Some ongoing trials will provide more clarity. The COMMIT and CLARITY trials comparing dual antiplatelet therapy to that of ASA alone in patients presenting with ST elevation myocardial infarction are highly interesting. The ongoing CHARISMA trial investigates primary and secondary prevention in patients with high atherothrombotic risk by dual antiplatelet therapy. At the time being, clopidogrel should be given according to the recommendations in the guidelines complemented by individual decision making.

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