A CRITICAL APPRAISAL OF THE CURE TRIAL: ROLE OF CLOPIDOGREL IN NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROMES

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ABSTRACT

Background
A clinical study, the CURE trial, compared the use of clopidogrel/acetylsalicylic acid (ASA) to ASA alone in 12,562 patients with non-ST-segment elevation acute coronary syndromes (ACS). Results of the trial suggested a possible first-line role for the more expensive combination of clopidogrel/ASA.

Objective
To perform a critical appraisal of the CURE trial, to determine the efficacy and safety of the clopidogrel/ASA combination in the management of ACS patients and to describe the population most likely to benefit from this combination.

Methods
A critical appraisal of the CURE trial was conducted.

Results
The CURE trial was found to be of high quality (Jadad score 5/5). An absolute risk reduction (ARR) of 2.1% was seen for the clopidogrel/ASA combination for the first primary outcome (death from cardiovascular causes, non-fatal myocardial infarction (MI), or stroke), compared to ASA alone. A 2.3% ARR was seen for the clopidogrel/ASA combination for the second primary outcome, which included the first primary outcome or refractory ischemia. The clinical benefit appears to have mainly been driven by a reduction in the risk of non-fatal MI. A 1% absolute risk increase (ARI) was observed for major bleeding in the clopidogrel/ASA group. Also, 5.2% of subjects in the clopidogrel/ASA group discontinued their study medication for adverse events other than bleeding, thrombocytopenia or allergy, compared to 3.5% in the ASA group.

Conclusions
We established that the overall quality of the CURE trial was good. Compared to ASA, the clopidogrel/ASA combination reduces the risk of recurrent vascular ischemic events in non-ST elevation ACS patients. The main clinical benefit however appears to be limited to a reduction in the risk of non-fatal MI. This benefit needs to be interpreted in light of the associated increased bleeding risk. Given that the risk of MI is elevated in high-risk ACS patients, the benefit of clopidogrel/ASA combination is expected to outweigh the bleeding hazards for this population. As details of all adverse events were not reported, it was not possible to fully evaluate the safety of use of this intervention.

Key words: *Acetylsalicylic acid; acute coronary syndromes; bleeding; clopidogrel; myocardial infarction; platelet aggregation inhibitors*

Both unstable angina (UA) and myocardial infarction (MI) usually result from atherosclerotic plaque disruption and thrombotic occlusion of a coronary artery.[1] Non-ST-segment elevation MI and UA are often indistinguishable in the acute setting and are collectively referred to as non-ST elevation acute coronary syndromes (ACS).[2] Both conditions are initially managed similarly until a diagnosis of MI can be confirmed by an elevation in biochemical markers of myocardial injury. Patients with non-ST elevation ACS may be classified as being at high-, intermediate-, or low-risk of a subsequent cardiac complication (Table 1). The 30-day risk of fatal or non-fatal MI is 12% to 30% in the high-risk group, 4% to 8% in the intermediate group and less than 2% in the low-risk group.[1]

TABLE 1 Risk stratification of patients presenting with non-ST elevation ACS[1]

High-risk: Prolonged chest pain (> 20 min) or ongoing, with at least one high-risk feature such as:
- transient ST-segment elevation or depression, or sustained ST-segment depression
- positive biomedical markers (abnormal troponin/CK-MB serum levels)
- recurrent myocardial ischemia with ST-segment shift with or without chest pain
- acute MI in past four weeks
- hemodynamic compromises (heart failure or hypotension) with chest pain

Intermediate-risk: No high-risk features, but one or more of the following:
- ongoing chest pain but no high-risk features
- crescendo angina preceding rest pain
- borderline positive troponin serum levels
- previous intervention such as coronary artery bypass graft (CABG)
- increased baseline risk: diabetes, age

Low-risk: No high- or intermediate-risk features:
- single episode of chest pain at rest, or crescendo exertional angina
- normal or non-specific abnormalities or unchanged ECG from previous one

It has been estimated that plaque rupture and thrombosis is associated with 50%[3] to 85%[4] of ACS and MI cases. Other data from 44 hospitals in Ontario indicate that 40% of all MIs are non-ST elevation MIs (Chau Tran, Institute for Clinical Evaluative Sciences, Toronto: personal communication, 2002 June). Accordingly, it may be projected that approximately half of MIs are non-ST-segment elevation MIs.

Non-ST elevation ACS carries a high burden. In 1997, there were 5,315,000 visits to emergency rooms (ER) in the US for the evaluation of chest pain and related symptoms. In 1996, there were 1,433,000 hospitalizations in the US for non-ST elevation ACS.[5] In Canada, there were on average each year for the period 1989 to 1993, 200 hospital separations (end of hospital stay due to discharge or death) per 100,000 population attributable to MI.[6] This means that approximately 100 hospital separations per 100,000 population per year may be attributed to non-ST-segment elevation MIs in Canada.

Management of patients with non-ST elevation ACS is based on risk stratification. Acetylsalicyclic acid (ASA) monotherapy and investigation of MI over a six to eight hour observation period in the ER is recommended for the lower-risk group. ASA and antithrombin agents, along with possible consideration for cardiac catheterization, is recommended for the intermediate-risk group.[1] For the high-risk group, the combination of ASA and antithrombin agents, in conjunction with intravenous glycoprotein (GP) IIb/IIIa inhibitors, as well as early

cardiac catheterization, have been recommended.[1, 5]

Recently, Health Canada approved the antiplatelet medication, clopidogrel (in combination with ASA and other standard therapies) for the reduction of atherothrombotic events in patients with non-ST elevation ACS.[7] Clopidogrel belongs to a newer class of antiplatelet medications called thienopyridines that work differently than ASA.[2] This new indication was based on results of the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial.[8]

The purpose of the CURE trial was to evaluate the efficacy and safety of the clopidogrel/ASA combination, compared with ASA monotherapy; in 12,562 patients with non-ST elevation ACS.[8] Patients were eligible if they had been hospitalized within 24 hours after onset of symptoms. They were followed for three to 12 months (mean duration of treatment was nine months). The CURE trial reported a 20% relative risk reduction (RRR) in the rate of vascular events (defined as a composite outcome of cardiovascular death, non-fatal MI, or stroke) when the combination therapy was used, as opposed to patients treated with ASA alone.[8]

Results of the CURE trial suggest a possible first-line role for the more expensive clopidogrel/ASA combination. Prior to the CURE trial, ASA was recommended as the antiplatelet agent of choice for most patients with non ST-elevation ACS, while clopidogrel was considered as an alternative. This was partially based on the results of the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial released in 1996.[9] This trial recruited 19,185 patients at high-risk of recurrent vascular ischemic events (ischemic stroke, MI, atherosclerotic peripheral artery disease) and compared clopidogrel 75 mg daily with ASA 325 mg daily. A RRR in the composite outcome (stroke, MI, or vascular death) of 8.7% [95% confidence interval (CI): 0.3%-16.5%)] was reported in favor of clopidogrel. However, for the MI subgroup, randomization had to occur within 35 days of the onset of symptoms and only 17% of MI patients had UA as a qualifying event.[9] Accordingly, both the study population and the treatment strategies in the CAPRIE trial were somewhat different from those studied in the CURE trial.

Given that approximately half of all MIs may be non-ST elevation MIs, the potential population for clopidogrel/ASA combination therapy may be considered to be relatively large. We performed a critical appraisal of the CURE trial to determine the role of the clopidogrel/ASA combination in this clinical setting.

METHODS

The objective of this assessment was to evaluate the role of clopidogrel in the medical management of non-ST elevation ACS, excluding revascularization procedures. More specifically, we were interested in determining the efficacy and safety of the clopidogrel/ASA combination in this clinical setting and to identify the population most likely to benefit from this combination. To do so, a critical appraisal of the CURE trial was conducted.

However, to ensure that no other potentially relevant clinical studies that addressed the objective of our assessment were available, a literature search was also performed.

Literature search

Published literature was obtained by searching a number of databases on the DIALOG® system (BIOSIS Previews®, EMBASE®, MEDLINE®, PASCAL and ToxFile). Searches were performed and updated on the CD ROM version of The Cochrane Library. Grey literature was obtained through searching a number of clinical trial registries, as well as the web sites of health technology assessment and near-technology assessment agencies and their associated databases. Further information was sought by hand searching the bibliographies of selected papers.

Apart from CURE, no other completed clinical trials were identified which addressed the objective of our assessment. The CAPRIE trial and revascularization studies were excluded from our assessment, as the populations studied were not relevant to our

objective. The literature search identified one ongoing trial, the COMMIT trial. This trial is currently being carried out in China and is randomizing 30,000 participants to either ASA or a combination of ASA and clopidogrel.[2] The COMMIT trial is also known as the second Chinese Cardiac Study (CCS-2).[10, 11] The study aims to determine whether adding clopidogrel to ASA for up to four weeks in hospital after suspected acute MI further reduces the risk of major vascular events, compared with using ASA monotherapy. The trial began in July 1999 and is not completed.[10]

Quality assessment and critical appraisal

We performed an overall assessment of the quality of the CURE trial, using the Jadad scale. This scale is composed of three items related directly to the reduction of bias (randomization, double-blinding, study withdrawals and drop-outs). A score is given for each of the three items, for a maximum of five points. Allocation concealment is also considered in the assessment, with ratings of adequate, unclear or inadequate.[12]

To facilitate the interpretation of the results of the CURE trial, values for absolute risk reduction (ARR), absolute risk increase (ARI), number needed to treat (NNT) and number needed to harm (NNH), were calculated for statistically significant results. Consistent with current methodology, 95% CIs were also calculated for each of these values.[13, 14] These were calculated using the CIA statistical package (version 2.0.0) from Altman et al.[15]

In addition, Dr. Salim Yusuf (Professor of Medicine and Director, Division of Cardiology, McMaster University, Hamilton, Ontario), principal investigator of the CURE trial, was contacted. Finally, the most recent product monograph of clopidogrel (PlavixTM) was obtained from Sanofi-Synthelabo Canada Inc. and Bristol-Myers Squibb, who were also invited to submit relevant information that could assist us with our appraisal of the CURE trial.

RESULTS

Quality assessment

Study design

The Canadian Cardiovascular Collaboration Project Office located at McMaster University in Hamilton, Ontario coordinated the study. A steering committee consisting of national coordinators oversaw the study. Investigators were supported by a research grant from Sanofi-Synthelabo and Bristol-Myers Squibb.[8] Trial participants were recruited between December 1998 and September 2000 at 482 centres in 28 countries. The ethics review board of each institution approved the study.

The CURE trial compared the outcomes of patients with non-ST elevation ACS treated with either clopidogrel 75 mg daily or placebo, in addition to ASA (recommended dose, 75 to 325 mg daily), for three to 12 months (mean duration of treatment was nine months). At trial entry, patients assigned to the clopidogrel group were given a loading dose of 300 mg, followed by a maintenance dose of 75 mg daily. Patients assigned to the placebo group received a matching placebo for both loading and maintenance dose.

Randomization

The CURE trial was randomized, double-blind and placebo-controlled. We determined the randomization procedure was well described and appropriate. It was accomplished with a central, 24-hour, computerized randomization service. Permutated-block randomization, stratified according to clinical centers, was used. Double-blinding was maintained by using matching placebo for both the initial loading dose of 300 mg of clopidogrel and the daily maintenance dose of 75 mg.

Sample size

The initial sample size of 9,000 participants for this trial was calculated based on an expected rate of events for the control group of 12% to 14%. However, because the rate of events appeared to be lower than had originally been expected, the sample size of the study was increased after its initiation.

Sample size was recalculated assuming a 10% rate of events for the placebo/ASA group for the first primary outcome and a rate of 14% for the second primary outcome. This led to a new sample size of 12,500 patients, which provided 90% power to detect a 16.9% relative reduction in risk for the first primary outcome and 16.4% for the second primary outcome.

In addition to the recalculation of the sample size, a further modification of the study protocol occurred. Initially, patients older than 60 years of age with no new electrocardiographic (ECG) changes but with a history of coronary artery disease (CAD) were enrolled. However, after a review of the overall rate of events among the first 3,000 patients, the steering committee recommended that only patients with ECG changes and/or an elevation in biochemical markers be enrolled.

Outcomes

There were two co-primary outcomes. The first was a composite of death from cardiovascular causes, non-fatal MI, or stroke. The second was the composite of the first primary outcome or refractory ischemia. The secondary outcomes were in-hospital refractory or severe ischemia, heart failure, and the need for revascularization procedures.[8]

Safety

Information relating to adverse events was limited to bleeding complications and some hematological parameters.[8] Bleeding complications were categorized as life-threatening, major or minor. Major bleeding episodes were defined as substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least two units of blood.

Major bleeding was classified as life-threatening if:

1. the bleeding episode was fatal or led to a reduction in the hemoglobin level of at least five grams per deciliter or to substantial hypotension requiring the use of intravenous inotropic agents;
2. it necessitated a surgical intervention;
3. it was a symptomatic intracranial hemorrhage; or
4. it necessitated the transfusion of four or more units of blood.

Minor bleeding episodes included other hemorrhages that led to the discontinuation of the study medication.[8] Hematological parameters monitored during the trial were thrombocytopenia and neutropenia.[8]

Drop-outs and withdrawals

The analysis for all endpoints was appropriately based on the intent-to-treat (ITT) principle. It was reported in the statistical analysis section of the publication that six patients in the clopidogrel/ASA group and seven in the placebo/ASA group were lost to follow-up. Regarding withdrawals, it was reported that 21.1% of patients in the clopidogrel/ASA group and 18.8% in the control group permanently discontinued their study medication.[8]

The reasons for dropping out or withdrawing from the study were not specified in the manuscript. This information was, however, clarified as part of the current review via personal communication with Dr Salim Yusuf (2002 September). The main reason for drop-out was patient refusal to continue participation in the trial. Patient refusal was also the main reason for permanently discontinuing study medications. The next most common reason was adverse events.

Overall quality

Using the quality assessment tool, the Jadad scale, we assigned a quality rating of 5/5 for this trial. It was not possible to assess whether treatment allocation was concealed for all patients.

Critical appraisal

A review of the baseline characteristics of the CURE trial participants determined that both treatment groups were comparable.

Primary outcomes

The first primary outcome, which included death from cardiovascular causes, non-fatal MI, or stroke, occurred in 582 of the 6,259

patients (9.3%) in the clopidogrel/ASA group, compared with 719 of the 6,303 patients (11.4%) in the placebo/ASA group. This corresponded to a relative risk (RR) of 0.80 (95% CI, 0.72-0.90; p <0.001) for the clopidogrel/ASA combination.[8] This translates to an ARR of 2.1% (95% CI, 1%-3.2%), which corresponds to an NNT of 47 patients (95% CI, 32-96) to prevent one occurrence of the first primary outcome over an average period of nine months.

The incidence of the second primary outcome, which included either the first primary outcome or refractory ischemia, was also significantly lower in the group treated with the clopidogrel/ASA combination. The second primary outcome was observed in 1,035 patients in the clopidogrel/ASA group (16.5%) and in 1,187 patients (18.8%) in the placebo/ASA group. This corresponded to a RR of 0.86 (95% CI, 0.79-0.94; p <0.001) for the clopidogrel/ASA combination.[8] This translates to a 2.3% ARR (95% CI, 1%-3.6%) and an NNT of 44 patients (95% CI, 28-104) to prevent one occurrence of the second primary outcome over an average period of nine months.

The largest effect of the clopidogrel/ASA combination was observed for the MI outcome (RR 0.77; 95% CI, 0.67-0.89).[8] This corresponds to an ARR of 1.5% (95% CI, 0.6%-2.3%) and an NNT of 68 patients (95% CI, 44-155) to prevent one MI over an average period of nine months.

Because there were no significant differences between the two groups in the rates of cardiovascular death [RR: 0.93 (95%CI: 0.79-1.08)], the main benefit was a reduced risk of non-fatal MI [calculated RR: 0.72 (95% CI: 0.61 – 0.85)]. For the other individual components of the primary outcomes, there were no statistically significant differences between the clopidogrel/ASA and placebo/ASA groups. However, given that the CURE trial was not powered to detect differences between the two treatment groups for individual endpoints, one should be cautious when interpreting these results.

TABLE 2 CURE trial – incidence of secondary outcomes[8]

Outcome	Clopidogrel/ASA (% of patients)	ASA (% of patients)	RR, 95% CI (p value)
Severe ischemia	2.8	3.8	0.74, 0.61-0.90 (p= 0.003)
Recurrent angina	20.9	22.9	0.91, 0.85-0.98 (p = 0.01)
Revascularization procedures			
Entire study	36.0	36.9	N/A
Initial hospitalization	20.8	22.7	0.92, NA (p = 0.03)
HF	3.7	4.4	0.82, 0.69-0.98 (p = 0.03)

NA = not available HF=heart failure

Table 3 CURE trial – Incidence of bleeding complications[8]

Outcome	Clopidogrel/ASA (% of patients)	ASA (% of patients)	RR, 95% CI (p value)
Any bleeding complications	8.5	5.0	1.69, 1.48-1.94 (p < 0.001)
Minor bleeding	5.1	2.4	2.12, 1.75-2.56 (p < 0.001)
Major bleeding	3.7	2.7	1.38, 1.13-1.67 (p = 0.001)
Major bleeding requiring > 2 units of blood	2.8	2.2	1.30, 1.04-1.62 (p = 0.02)
Life-threatening bleeding	2.2	1.8	1.21, 0.95-1.56 (p = 0.13)

Secondary outcomes

Table 2 presents the incidence of secondary outcomes. As with the two co-primary outcomes, the incidence of secondary outcomes was significantly lower in the clopidogrel/ASA group.

Safety

Table 3 summarizes the bleeding complications observed in the CURE trial. There was no statistically significant difference in the number of life-threatening bleeding episodes in the clopidogrel/ASA group (2.2%) compared with the placebo/ASA group (1.8%; RR 1.21; 95% CI, 0.95-1.56). However, major bleeding episodes were significantly more common in the clopidogrel/ASA group (3.7%) compared with the placebo/ASA group (2.7%).[8] This corresponds to an ARI of 1% (95% CI, 0.4%-1.6%) for the clopidogrel/ASA group and a NNH of 99 patients (95% CI, 61-253).

If only those patients with major bleeding requiring a blood transfusion (two or more units) were considered, the incidence rates were 2.8% in the clopidogrel/ASA group and 2.2% in the placebo/ASA group, resulting in a significantly higher RR of 1.30 for patients receiving the clopidogrel/ASA combination.[8] This corresponds to an ARI of 0.7% (95% CI, 0.1%-1.2%) and a NNH of 153 patients (95% CI, 83-927) to cause one additional serious adverse bleeding event requiring the transfusion of two or more units of blood within an average of nine months.

The incidence of minor bleeding was also higher in the clopidogrel/ASA group (5.1%) compared with the placebo/ASA group (2.4%), leading to a significantly higher RR of 2.12.[8] This corresponds to an ARI of 2.7% (95% CI, 2.1%-3.4%) and a NNH of 37 patients (95% CI, 29-49) for the clopidogrel/ASA combination.

In total, 533 patients in the clopidogrel/ASA group (8.5%) and 317 patients in the placebo/ASA group (5%) suffered from a bleeding complication.[8] This corresponds to an ARI of 3.5% (95% CI, 2.6%-4.4%) and a NNH of 29 patients (95% CI, 23-38) for the clopidogrel/ASA combination.

Major bleeding complications were more frequently observed in patients undergoing coronary artery bypass graft (CABG) surgery if clopidogrel was not stopped at least five days before the procedure (9.6% in the clopidogrel/ASA group versus 6.3% in the placebo/ASA group; RR 1.53, p = 0.06). There was, however, no apparent excess in major bleeding within seven days after surgery in patients who interrupted their clopidogrel treatment more than five days before surgery (4.4% in the clopidogrel/ASA group versus 5.3% in the placebo/ASA group).[8]

Recently, CURE trial investigators reported on the effects of the dose of ASA, used either alone or in combination with clopidogrel. In this analysis, patients were divided into three ASA daily dose groups, 100 mg or less, 101 through 199 mg, and 200 mg or greater. Compared to the placebo/ASA group, the incidence of the first primary outcome was reduced by clopidogrel in all ASA dose groups; 10.5% vs. 8.6% for the first group (RR= 0.81, 95%CI, 0.68-0.97), 9.8% vs. 9.5% for the second group (RR=0.97, 95%CI, 0.77-1.22) and, 13.6% vs. 9.8% for the third group (RR=0.71, 95%CI, 0.59-0.85). The incidence of major bleeding increased with increasing ASA doses both for the placebo/ASA group (1.9%, 2.8%, and 3.7%, respectively, p=0.0001) and the clopidogrel/ASA group (3.0%, 3.4%, and 4.9%, respectively, p=0.009). However, these findings were based on post hoc analysis and should therefore only be considered explanatory.[16]

Finally, unpublished data from the CURE trial reveals that there were a higher number of patients in the clopidogrel/ASA combination group (5.2%) compared with the placebo/ASA group (3.5%) who permanently discontinued study medications because of adverse events other than bleeding, thrombocytopenia or allergy.

DISCUSSION

The rate of occurrence of most components of the primary outcomes tended to be lower in the clopidogrel/ASA group; however, an

apparent significant reduction in the RR was only observed for MIs.

The initial study protocol enrolled patients older than 60 years of age with no new ECG changes but with a history of CAD. This may have resulted in some patients being enrolled that did not have an ACS. This could increase the clinical heterogeneity of the trial population, and may reduce the internal validity of the results. On the other hand, this may have led to an underestimation of the potential efficacy of the clopidogrel/ASA combination, since patients who may not have had an ACS were exposed to similar risk while deriving less benefit from the intervention.

Fortunately, however, the entry criteria were revised relatively early in the trial, so that the remainder of the trial population was not affected by the initial more flexible selection criteria. In total, there were 624 patients out of 12,562 enrollees, who had normal ECGs, or less than five percent of the ITT study population.

It should be noted that not all ECG changes are necessarily compatible with high-risk ischemia. Nonetheless, 42% of patients had ST-segment depression and an additional 4% had ST-segment elevation. Also, about 25% of patients had cardiac enzyme elevation at study entry. A high proportion of subjects had independent risk factors in their medical history [heart failure (7-8%), revascularization procedures (18%), diabetes (22-23%), MI (32%), hypertension (58-60%), and smoking (61%)]. Finally, about 50% of subjects were over 65 years of age.[8]

Several of these factors have been identified as either high-risk or intermediate-risk criteria in the diagnosis of ACS.[1] Accordingly, we determined that the majority of the study population was moderate- to high-risk ACS patients.

The clinical benefit observed with the clopidogrel/ASA combination, needs to be interpreted in light of the associated increased bleeding risk. In particular, for every 99 patients treated with the clopidogrel/ASA combination, one patient suffered a major bleeding episode, when compared with the ASA group.

In a recent publication, Albers and Amarenco, combined major bleeding episodes and major vascular events into a single endpoint and found a RRR of 8%, favouring the clopidogrel/ASA combination over ASA.[17] This represents an absolute net benefit of 1.1% with combination therapy, with a calculated odds ratio of 1.10 (95% CI, 0.99-1.22) of a major bleed or vascular event with ASA alone.[17]

Another way of considering both the morbidity benefit and the bleeding complications of the clopidogrel/ASA combination, compared with ASA alone, is the following: about one non-ST elevation ACS patient in 50 (NNT: 47) will avoid a vascular event (cardiovascular death, non-fatal MI, or stroke).

However, about one in 100 (NNH: 99) will suffer a major bleeding episode. This means that for every two non-ST elevation ACS patients who will benefit from the clopidogrel/ASA combination, one will suffer a major bleeding episode. It may be concluded that the clopidogrel/ASA combination provides increased efficacy with respect to the prevention of vascular events compared with ASA alone, but this benefit is partly offset by an increased risk of bleeding. However, in making such a determination, it is important to also consider the clinical consequence of the bleeding complications.

The sites where a higher incidence of major bleeding was observed with the clopidogrel/ASA combination, compared with ASA, were gastrointestinal (1.3% vs. 0.7%), followed by arterial puncture sites (0.6% vs. 0.3%) and surgical sites (0.9% vs. 0.8%).[7] Although serious, these would be expected to be reversible and non-fatal in most cases. For example, upper gastrointestinal bleeding is generally associated with a mortality rate of 1% to 10% in the US and Europe.[18]

Another parameter to consider is the ASA dose. CURE trial investigators recently suggested that the optimal dose for ASA is between 75 and 100 mg per day, either alone or in combination with clopidogrel.[16]

Finally, bleeding complications may not be the only relevant safety parameter to be considered given there were 1.7% more

subjects in the clopidogrel/ASA group who permanently discontinued their study medications due to adverse events other than bleeding, thrombocytopenia or allergy, compared to the placebo/ASA group.

Further interpretation of this observation is however difficult because the nature of these adverse events could not be determined, which is unfortunate as information on all adverse events associated pharmacological treatment may be considered critical to fully determine the role of a pharmaceutical agent.

Although it was not the focus of our evaluation, the combined use of clopidogrel and ASA was also recently studied in ACS patients undergoing percutanous coronary intervention (PCI). A subgroup of the CURE trial population, comprised of 2658 patients in whom PCI was performed, were enrolled in the PCI-CURE trial. In this subgroup, 1313 patients were randomly assigned to double-blind treatment with clopidogrel and ASA while 1345 were in the placebo/ASA group.[19]

Patients received this regimen for six days (median) before PCI. After PCI, over 80% of subjects in both groups received an open-label thienopyridine (either clopidogrel or ticlopidine) in combination with ASA for two to four weeks, after which the initial study medication was restarted for three to 12 months (mean of 8 months).[19]

Most patients (82% and 81% in each group, respectively) received an intracoronary stent. The incidence of cardiovascular death, MI or urgent revascularization was lower in the clopidogrel/ASA group, compared to the placebo/ASA group, both at 30 days (4.5% vs. 6.4%, RR = 0.70, 95%CI, 0.50-0.97, p = 0.03) and at the end of follow-up (18.3% vs. 21.7%, RR = 0.83, 95%CI, 0.70-0.99, p = 0.03). As with the CURE trial, this effect was mainly driven by a reduction in non-fatal MI both at 30 days (2.1% vs. 3.8%, RR = 0.56, 95%CI, 0.35-0.89) and at the end of follow up (4.5% vs. 6.4%, RR = 0.71, 95%CI, 0.51-0.99). There was no difference in cardiovascular death between the two groups. [19]

From a safety perspective, there were no differences between groups in the incidence of major bleeding both at 30 days (1.6% vs. 1.4%, RR=1.13, 95%CI, 0.61-2.10, p=0.69) and at the end of follow up (2.7% vs. 2.5%, RR=1.12, 95%CI, 0.70-1.78, p=0.64). There was however more minor bleeding in the clopidogrel/ASA group at the end of the follow up period (3.5% vs. 2.1%, RR=1.68, 95%CI, 1.06-2.68, p=0.03), but not at 30 days (1.0% vs. 0.7%, RR=1.33, 95%CI, 0.59-3.03, p=0.49).[19]

It may be possible that the smaller sample size in the PCI-CURE trial explains these findings as the increase in bleeding risk was clearly observed in the broader CURE trial population. CURE trial investigators have also recently recognized the increased bleeding risks associated with the concurrent use of complex antiplatelet regimens (comprising ASA, clopidogrel, and GP IIb/IIIa receptor inhibitors) and antithrombin agents (heparin) during revascularization procedures.[16]

The Clopidogrel for the Reduction of Events During Observation (CREDO) study is another recent randomized, double-blind, placebo-controlled trial. It compared a regimen composed of a loading dose of clopidogrel (300 mg) administered before PCI followed by 12 months of clopidogrel 75 mg daily started after PCI, to a regimen limited to clopidogrel 75 mg daily for four weeks started after PCI. Both groups received ASA throughout the study. In total, 2116 patients were enrolled.[20]

The indication for PCI was unstable angina for over 50% of them. Randomization to long-term clopidogrel/ASA treatment was associated with a 26.9% RRR in the combined endpoint of death, MI or, stroke (95%CI, 3.9%-44.4%, p=0.02), corresponding to a 3% ARR. None of the individual components of that composite outcome were associated with a statistically significant RRR. Also, pre-treatment with a loading dose of clopidogrel did not significantly reduce the combined endpoint of death, MI or, urgent target vessel revascularization at 28 days (RRR=18.5%, 95%CI, -14.2% to 41.8%, p=0.23). Combination treatment with clopidogrel/ASA was associated with an increase in major bleeding, compared with the placebo/ASA group (8.8% vs. 6.7%, p=0.07).[20]

Overall, based on these two recent trials, although treatment with clopidogrel/ASA prior to PCI appears to be beneficial, there is no clear clinical benefit associated with the use of a loading dose of clopidogrel before PCI in patients with non ST-elevation ACS. After PCI, extending the combined use of clopidogrel and ASA beyond two to four weeks reduces cardiovascular morbidity, although this may be limited to a reduction in non-fatal MI. Such practice may however be associated with increased risk of bleeding complications.

TABLE 4 ACC/AHA recommendations for antiplatelet and anticoagulation therapy for patients with non-ST elevation ACS[5]

1. Antiplatelet therapy should be initiated promptly. ASA should be administered as soon as possible after presentation and continued indefinitely. (Level of Evidence: A*)
2. Clopidogrel should be administered to hospitalized patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance (Level of Evidence: A)
3. Clopidogrel should be added to ASA as soon as possible on admission in hospitalized patients in whom an early non-interventional approach is planned and maintained for at least one month (Level of Evidence: A) and for up to nine months (Level of Evidence: B†).
4. In patients for whom a PCI is planned, clopidogrel should be started and continued for at least one month (Level of Evidence: A) and up to nine months (Level of Evidence: B) in patients who are not at high risk for bleeding
5. In patients taking clopidogrel in whom CABG is planned, if possible the drug should be withheld for at least five days prior to the CABG procedure, and preferably seven days (Level of Evidence: B).
*High level of evidence (A) is based on data derived from multiple randomized clinical trials that involve large numbers of patients.
†Intermediate level of evidence (B) is based on data derived from a limited number of randomized trials that involved small numbers of patients or from careful analyses of non-randomized studies or observational registries.

The American College of Cardiology and the American Heart Association (ACC/AHA) guidelines for administration of antiplatelet therapy in patients with non-ST elevation ACS were revised in March 2002 (Table 4).[5]

The morbidity benefit as well as the bleeding concerns described above were apparently considered in these revised recommendations, which include the use of the clopidogrel/ASA combination early in the management of non ST-elevation ACS patients.

However, given that the 30-day risk of fatal and non-fatal MI is elevated (12% - 30%) in high-risk ACS patients, the additional benefit of the clopidogrel/ASA combination is expected to primarily outweigh the potential harm from bleeding complications in this specific population. Such favorable benefit/risk ratio could possibly extend to moderate-risk non ST-elevation ACS patients, although the risk of MI in this group is lower (4% - 8%).

Reserving use of combination therapy to higher risk patients is consistent with recent observations from the Antithrombotic Trialists'Collaboration.[21] In addition, patients with pre-existing bleeding risk (e.g. recent gastrointestinal bleed, concurrent use of long term anticoagulants or non-steroidal anti-inflammatory drugs), should probably not receive the clopidogrel/ASA combination, at least not on a long-term basis. If a clinician elects to use the antiplatelet combination, it may be prudent to limit its duration to one month only.

From an economic perspective, there is a substantial difference in the acquisition cost of the two drug regimens in Canada: one tablet of ASA 325 mg costs less than $0.01 if non-enteric coated and between $0.01 and $0.02 if enteric coated;[22] whereas, one tablet of clopidogrel (Plavix™) 75 mg costs $2.40.[23] An analysis of the Canadian data collected during the CURE trial found an incremental cost-effectiveness ratio of C$ 7,597 per first

primary event avoided, for patients taking the clopidogrel/ASA combination. The authors concluded that the cost per event avoided with clopidogrel in the CURE study is comparable to other cost-effective therapies in cardiovascular disease.[24]

Another recent cost-effectiveness analysis evaluated the use of antiplatelet agents for the secondary prevention of coronary events.[25] The purpose of this study was to perform an incremental cost-effectiveness analysis of the long-term use of ASA, clopidogrel, or both, for secondary prevention of cardiovascular events in patients with known CAD. Costs and benefits were projected over a 25-year period. The researchers reported a cost-effectiveness ratio varying from US $11,000 to US $130,000 per quality-adjusted year of life gained, depending on whether ASA was used alone or in combination with clopidogrel.[25]

Although a 25-year treatment time span would be encountered in practice, it is much longer than both the duration of treatment assessed in the CURE trial and the duration of treatment currently recommended for the management of ACS. This significantly increases the cost portion of the cost-effectiveness ratio for this treatment option. It may not therefore apply to the population studied in the CURE trial.

CONCLUSIONS

We established that the overall quality of the CURE trial was good. Compared to ASA, the clopidogrel/ASA combination reduces the risk of recurrent vascular ischemic events in non-ST elevation ACS patients. The main clinical benefit however appears to be limited to a reduction in the risk of non-fatal MI. This benefit needs to be interpreted in light of the associated increased bleeding risk.

Given that the risk of MI is elevated in high-risk ACS patients, the benefit of clopidogrel/ASA combination is expected to outweigh the bleeding hazards for this population. As details of all adverse events were not reported, it was not possible to fully evaluate the safety of use of this intervention.

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