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Meta-Analysis of Randomized and Registry Comparisons of Ticlopidine With Clopidogrel After Stenting

Deepak L. Bhatt, MD,* Michel E. Bertrand, MD, FACC,† Peter B. Berger, MD, FACC,‡ Philippe L. L'Allier, MD,§ Issam Moussa, MD, FACC,‖ Jeffrey W. Moses, MD, FACC,‖ George Dangas, MD, PHD, FACC,‖ Megumi Taniuchi, MD, FACC,¶ John M. Lasala, MD, FACC,¶ David R. Holmes, MD, FACC,‡ Stephen G. Ellis, MD, FACC,* Eric J. Topol, MD, FACC*

Cleveland, Ohio; Lille, France; Rochester, Minnesota; Montreal, Canada; New York, New York; and St. Louis, Missouri

OBJECTIVES We sought to determine whether clopidogrel is at least as efficacious as ticlopidine.

BACKGROUND Several trials have supported the enhanced safety and tolerability of clopidogrel compared with ticlopidine after coronary stent deployment. However, none of these individual trials were powered to detect possible differences in the efficacy for reducing ischemic end points.

METHODS Published data from trials and registries that compared clopidogrel with ticlopidine in patients receiving coronary stents were pooled, and a formal meta-analysis was performed. The rate of 30-day major adverse cardiac events (MACE), as defined in each trial, was used as the primary end point.

RESULTS There were a total of 13,955 patients. The pooled rate of major adverse cardiac events was 2.10% in the clopidogrel group and 4.04% in the ticlopidine group. After adjustment for heterogeneity in the trials, the odds ratio (OR) of having an ischemic event with clopidogrel, as compared with ticlopidine, was 0.72 (95% confidence interval [CI] 0.59 to 0.89, p = 0.002). Mortality was also lower in the clopidogrel group compared with the ticlopidine group—0.48% versus 1.09% (OR 0.55, 95% CI 0.37 to 0.82; p = 0.003).

CONCLUSIONS Based on all available evidence from randomized clinical trials or registries, clopidogrel, in addition to better tolerability and fewer side effects, is at least as efficacious as ticlopidine in reducing MACE. This finding may be due to the more rapid onset of an antiplatelet effect seen with the loading dose of clopidogrel, which was used in most of these studies, or to better patient compliance with clopidogrel therapy. Therefore, clopidogrel plus aspirin should replace ticlopidine plus aspirin as the standard antiplatelet regimen after stent deployment. (J Am Coll Cardiol 2002;39:9–14) © 2002 by the American College of Cardiology

The preferred method of percutaneous coronary revascularization is stenting. Compared with balloon angioplasty, coronary stenting has been proven to decrease rates of target vessel revascularization for a broad variety of lesion types (1–10). However, there is a risk created by placing a foreign object in the coronary vasculature—namely, stent thrombosis.

Antiplatelet therapy with aspirin plus the adenosine diphosphate (ADP) antagonist ticlopidine has been shown to be superior to either aspirin alone or aspirin plus anticoagulation with warfarin after coronary stent deployment (11). However, ticlopidine is associated with up to a 2.4% rate of neutropenia (white blood cell count <1,200/mm^3), which can be a life-threatening complication (11). In addition, thrombotic thrombocytopenic purpura (TTP) is estimated to occur in ~1 in 4,800 treated patients (12).

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study demonstrated that the newer ADP antagonist clopidogrel was more efficacious than aspirin in preventing ischemic events in patients with established atherosclerosis (13). This benefit is amplified further in high-risk subgroups (14). Clopidogrel is much safer than ticlopidine; neutropenia is no more likely to occur in patients taking clopidogrel than in those taking aspirin, with a 0.10% rate of neutropenia (neutrophils <1,200/mm^3) observed in CAPRIE (13). In addition, clopidogrel is better tolerated; the onset of action is more rapid; and the once-a-day dosing regimen is more convenient. Furthermore, in the U.S., clopidogrel is ~20% less expensive than ticlopidine, although this cost differential may vary in other parts of the world. These facts have led many interventional cardiologists to switch from ticlopidine plus aspirin to clopidogrel plus aspirin after stenting, although some have remained critical of this substitution in the absence of a large comparative data set demonstrating equivalent efficacy (15–17).

Despite the existence of multiple, randomized clinical trials and single-center registries comparing clopidogrel plus aspirin versus ticlopidine plus aspirin, none was individually powered to assess the comparative efficacy of clopidogrel

From the *Department of Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, Ohio; †Hopital Cardiologique, Lille, France; ‡Mayo Clinic, Rochester, Minnesota; §Montreal Heart Institute, Montreal, Canada; ‖Lenox Hill Heart and Vascular Institute, New York, New York; and ¶Washington University, St. Louis, Missouri.

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Abbreviations and Acronyms

ADP	= adenosine diphosphate
CI	= confidence interval
CLASSICS	= CLopidogrel ASpirin Stent International Cooperative Study
MACE	= major adverse cardiac events
MI	= myocardial infarction
OR	= odds ratio
SAST	= subacute stent thrombosis
TOPPS	= Ticlid Or Plavix Post-Stent
TTP	= thrombotic thrombocytopenic purpura
TVR	= target vessel revascularization

versus ticlopidine. Therefore, by aggregating all trial and registry data, we sought to determine whether clopidogrel plus aspirin would be at least as effective as ticlopidine plus aspirin in reducing ischemic events in patients receiving coronary stents.

METHODS

A MEDLINE search was performed to identify all published, English-language studies through December 2000 that compared clopidogrel plus aspirin versus ticlopidine plus aspirin. The medical subject headings and key words used were clopidogrel, ticlopidine and stents. In addition, relevant abstracts and presentations from the annual meetings in 1999 and 2000 of the American Heart Association, the American College of Cardiology, the European Society of Cardiology and Transcatheter Cardiovascular Therapeutics were identified. Three randomized clinical trials and seven single-center registries comparing clopidogrel plus aspirin versus ticlopidine plus aspirin have been presented or published. When the results were published only in abstract form or presented orally or in a poster, the data were verified with the primary investigator.

The three randomized trials (18–20) were the CLopidogrel ASpirin Stent International Cooperative Study (CLASSICS), the Ticlid Or Plavix Post-Stent (TOPPS) trial and the trial performed by Müller et al. There were differences in loading doses and length of therapy among these three trials. CLASSICS, which was the only double-blinded evaluation, utilized a loading dose of clopidogrel in one arm of the study, and therapy was administered within 6 h of completion of the procedure and lasted for 28 days. The TOPPS trial used loading doses of both ticlopidine and clopidogrel, given after the procedure, with therapy continued for 14 days. Müller et al. (18) used a 500-mg loading dose for the ticlopidine arm only, and therapy was commenced immediately after the procedure and continued for 28 days.

The seven single-center registries were from the Cleveland Clinic Foundation, the Lenox Hill Heart and Vascular Institute, the Mayo Clinic, North Memorial Hospital, Southern Illinois University, the Washington Hospital Center and the Wessex Cardiothoracic Centre (21–27). There were differences among the registries (and sometimes within the registries) as to whether patients were pretreated with a thienopyridine before the procedure, whether loading doses were administered and whether the length of therapy was 14 or 28 days.

The results from these 10 studies were pooled. Thirty-day major adverse cardiac events (MACE), as defined in each trial, served as the prespecified primary end point, and all-cause mortality was the prespecified secondary end point. The MACE consisted of death, myocardial infarction (MI), target vessel revascularization (TVR) or subacute stent thrombosis (SAST) in all studies except CLASSICS and those performed at the Cleveland Clinic and North Memorial Hospital, which did not report SAST. For MACE, there was no double counting of events. In addition, the rates of MI, TVR and SAST, as defined in each trial, were pooled, and Pearson chi-square values were calculated for each of these individual end points. For MACE and mortality, to address the heterogeneity among the trials and registries, a formal meta-analysis was performed by combining the numbers of observed and expected events from each trial using the Mantel-Haenszel test, as expressed by Yusuf et al. (28). A fixed-effects model was used for this tabular meta-analysis.

RESULTS

The majority of the trials and registries found a reduction in the 30-day rate of MACE, as defined by each trial, with clopidogrel versus ticlopidine. Figure 1 depicts the odds ratio (OR) plot, with 95% confidence intervals (CIs) for the rate of MACE. Overall, the pooled data from 13,955 patients showed an OR of 0.51 in favor of clopidogrel (95% CI 0.42 to 0.63). This 50% risk reduction in the MACE rate in those patients receiving clopidogrel plus aspirin versus ticlopidine plus aspirin (2.10% vs. 4.04%) was statistically significant ($p = 0.001$). The reduction in the MACE rate was seen in both the randomized clinical trial and the registry data, but was only substantial and statistically significant in the registries. The OR in favor of clopidogrel in the randomized clinical trials was 0.90 (95% CI 0.57 to 1.44). The OR in favor of clopidogrel in the larger numbers of patients in the registries was 0.45 (95% CI 0.36 to 0.57, $p = 0.001$).

Mortality. The majority of patients in the trials showed a reduction in all-cause mortality with clopidogrel versus ticlopidine (Fig. 2). The OR in favor of clopidogrel was 0.44 (95% CI 0.29 to 0.67). This 56% reduction in mortality in those patients treated with clopidogrel and aspirin instead of ticlopidine and aspirin (0.48% versus 1.09%) was statistically significant ($p = 0.001$). When confining the analysis to the three randomized clinical trials, the OR in favor of clopidogrel was 0.47 (95% CI 0.17 to 1.30, $p = 0.14$). The registry data produced an OR of 0.45 in favor of clopidogrel (95% CI 0.28 to 0.70, $p = 0.001$).

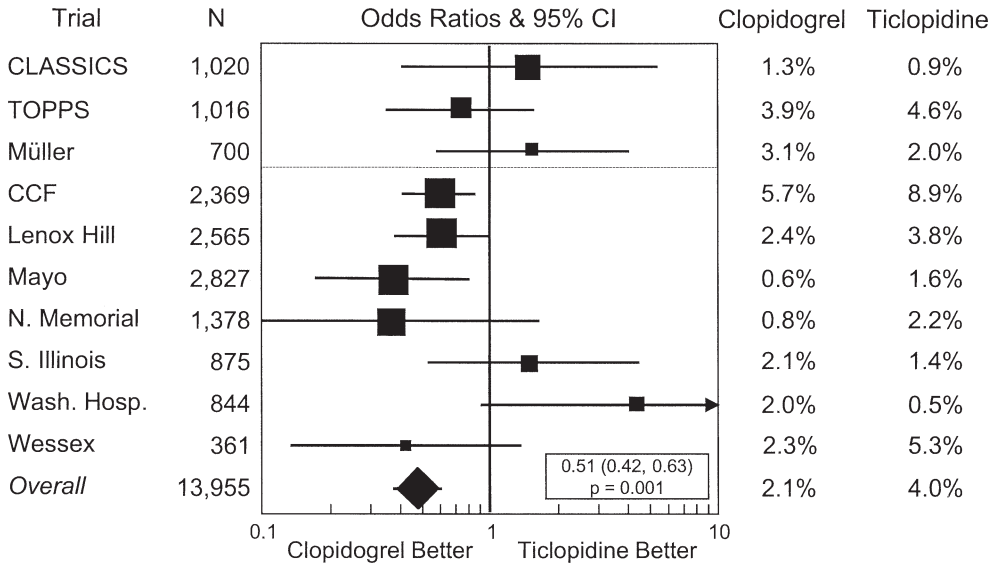

Figure 1. The odds ratio (OR) plots with 95% confidence intervals (CIs) for the rate of 30-day major adverse cardiac events (MACE) for each of the trials individually, as well as for the pooled data. Estimates to the left of the centerline reflect that clopidogrel was more effective; those to the right of the centerline indicate that ticlopidine was more effective. The size of the boxes corresponds to the number of patients in the trial. **Arrows** indicate that the limits of the CI extend beyond the graph. CCF = Cleveland Clinic Foundation; CLASSICS = CLopidogrel ASpirin Stent International Cooperative Study; TOPPS = Ticlid Or Plavix Post-Stent.

Individual end points. Myocardial infarction, TVR and SAST data were defined differently for the trials included, and not all trials collected data for each of these end points. Thus, the actual numbers of patients available for analysis for these particular end points were smaller than the number of patients for the overall analysis. Nevertheless, all the components of the MACE rate appeared to be affected favorably by clopidogrel instead of ticlopidine (Fig. 3).

Meta-analysis. Using a technique of formal meta-analysis to attempt to adjust for the heterogeneity among the trials included, a reduction in the event rate was still evident for both MACE and mortality. The OR for the rate of MACE for clopidogrel was 0.72 (95% CI 0.59 to 0.89, p = 0.002), as compared with ticlopidine. The OR for the rate of mortality was 0.55 in favor of clopidogrel (95% CI 0.37 to 0.82, p = 0.003).

DISCUSSION

Stent deployment has been a major advance in interventional cardiology. Few surgical procedures have undergone as rigorous clinical evaluation as coronary stenting. The

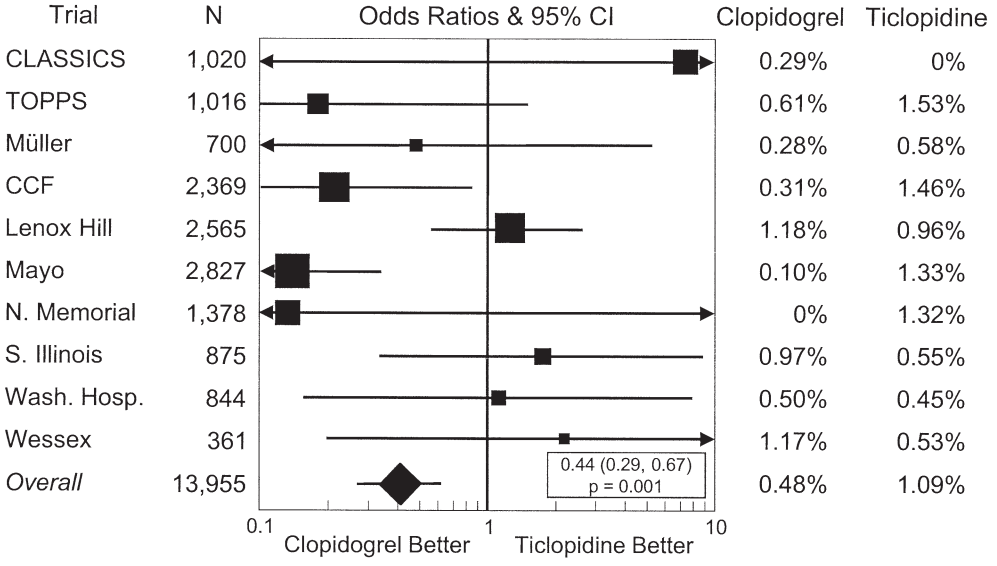

Figure 2. The odds ratio (OR) plots with 95% confidence interval (CIs) for the rate of 30-day mortality. The boxes for the CLopidogrel ASpirin Stent International Cooperative Study (CLASSICS) and North Memorial studies reflect directionality and sample size, but true ORs cannot be determined, because both trials had an arm with a point estimate of zero. **Arrows** indicate that the limits of the CI extend beyond the graph. CCF = Cleveland Clinic Foundation; TOPPS = Ticlid Or Plavix Post-Stent.

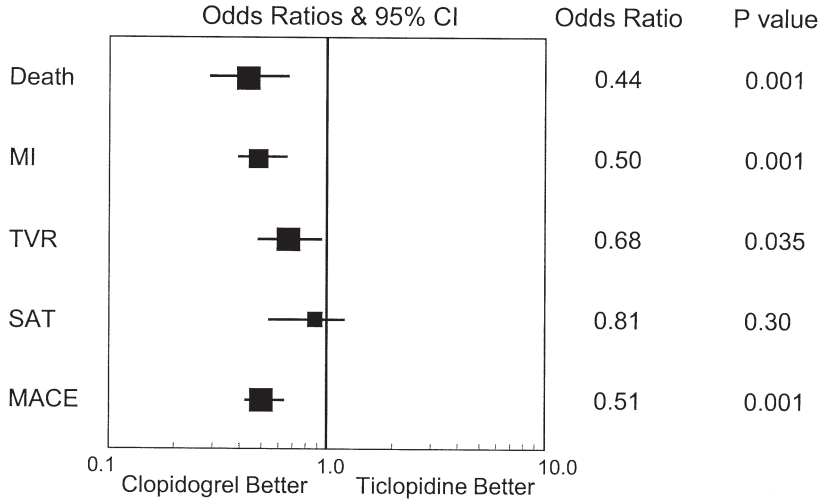

Figure 3. The odds ratio plots with 95% confidence intervals (CIs) for the rates of the individual components of the composite end point. MACE = major adverse cardiac events; MI = myocardial infarction; SAT = subacute stent thrombosis; TVR = target vessel revascularization.

results of numerous randomized clinical trials have demonstrated conclusively the benefits of stenting in reducing both urgent and elective TVR (1–10,29). This benefit in reducing TVR during one-year follow-up extends across a broad variety of lesion types.

Nevertheless, stent thrombosis is a major risk after coronary stenting. Initial attempts to decrease stent thrombosis through pharmacologic means often involved complex regimens of aspirin, heparin, dextran and warfarin, with high rates of bleeding and extended hospital stays. The use of high-pressure stent deployment and antiplatelet therapy with aspirin and ticlopidine has dramatically reduced the incidence of stent thrombosis (30,31). Aspirin plus ticlopidine has been demonstrated to reduce MACE significantly more than aspirin plus warfarin, with a decreased incidence of bleeding. However, when stent thrombosis does occur, it is typically accompanied by MI or death (32). Thus, any measure to decrease stent thrombosis is warranted.

Risks of ticlopidine. Although ticlopidine plus aspirin is clearly efficacious after coronary artery stenting, issues of safety hamper the use of ticlopidine. Neutropenia, which can be life threatening, can occur and necessitates periodic measurement of the white blood cell count. In addition, TTP rarely occurs with ticlopidine and, unless recognized and treated promptly, may lead to death. Clopidogrel, though also an ADP receptor antagonist, differs from ticlopidine in its chemical structure, with an additional methyl group. Furthermore, clopidogrel and ticlopidine share no known common metabolites. The CAPRIE trial demonstrated that the rate of neutropenia ($<$1,200/mm^3) was negligible and was no higher with clopidogrel than with aspirin (0.10% vs. 0.17%) (13). Although a recent case series described 11 cases of TTP in patients receiving medications, including clopidogrel, a true causal relationship could not be established with certainty (33). Regardless, even if the cases were due to clopidogrel, the incidence of TTP would still be at least an order of magnitude less than that seen with ticlopidine, with perhaps the same incidence as seen in the general population.

The randomized CLASSICS trial showed that the primary safety end point favored clopidogrel over ticlopidine (19). Clopidogrel was associated with less bleeding, fewer hematologic complications and fewer cases of drug discontinuation. However, CLASSICS was neither designed nor powered to look at differences in efficacy. Nevertheless, given the better safety and tolerability of clopidogrel, most interventional cardiologists in the U.S. switched to a regimen of clopidogrel plus aspirin after coronary stenting, often for a period of 30 days.

Clopidogrel versus ticlopidine. However, in this era of evidence-based medicine, there was a level of uncertainty regarding the comparative efficacy of clopidogrel versus ticlopidine (15–17). None of the individual trials or registries comparing clopidogrel with ticlopidine was large enough to conclusively demonstrate that clopidogrel was equivalent to ticlopidine in efficacy. In addition, investigations of warfarin plus aspirin after coronary stenting continue, despite the accumulated randomized data supporting ticlopidine plus aspirin (34). Thus, there was no consensus in the worldwide interventional community regarding the optimal antithrombotic regimen after stenting.

The present analysis demonstrates that compared with aspirin plus ticlopidine, a regimen of aspirin plus clopidogrel is associated with a decreased rate of MACE at 30 days. There was a reduction in each of the individual components of MACE. Most notable was a significant reduction in the rate of all-cause mortality, evident in both the randomized and registry data. Importantly, the decrease in death was proportionate and consistent with the reduction in MI. Although there was some heterogeneity between the randomized trials and registries for the rate of MACE, perhaps due to patient selection criteria in clinical trials, the magnitude of reduction in mortality was similar for both types of studies. Furthermore, the reduction in MACE and mortal-

ity rates persists even after adjustment for heterogeneity among the different trials and registries included.

Although the goal of this analysis was to demonstrate similar efficacy between clopidogrel and ticlopidine, the results strongly suggest superior efficacy of clopidogrel over ticlopidine. In part, this finding may be due to better patient compliance with clopidogrel, as demonstrated in the randomized CLASSICS data. Likely, this effect is even larger in clinical practice, outside the confines of a closely monitored clinical trial. Due to nausea and vomiting, up to 20% of patients have required discontinuation of ticlopidine in placebo-controlled trials. In addition, ticlopidine's onset of action is longer than that of a loading dose of clopidogrel. Previous work has shown that some cases of stent thrombosis occur early after the initiation of ticlopidine, presumably before its full antiplatelet activity has been achieved (35). Furthermore, the use of ticlopidine is sometimes limited to only two weeks after coronary artery stenting, whereas clopidogrel is often used for four weeks, perhaps providing further protection against ischemic events. The Clopidogrel for Reduction of Events During Observation trial will determine the incremental benefits of a more prolonged duration of therapy with clopidogrel after coronary artery stenting. Selection of the optimal dual-antiplatelet regimen has particular relevance now that vascular brachytherapy is widely available. In this setting, dual-antiplatelet therapy will be required for an extended time, particularly if a new stent is placed. The subset of patients from the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events trial who underwent stenting will provide further information on the safety and utility of an extended duration of clopidogrel therapy (36).

Study limitations. There are certain limitations to the present analysis. Registry data were often not concurrent, in that the data on patients taking ticlopidine were sometimes obtained in a period before the collected data on patients taking clopidogrel. In addition, registry data, due to its nonrandomized nature, can be subject to confounding variables, such as different rates of glycoprotein IIb/IIIa inhibitor or device use. Thus, this analysis may overestimate the treatment benefit seen with clopidogrel over ticlopidine. Nevertheless, registry data do give an impression of the applicability of clinical trial data in the "real world." There were different loading dose regimens used in the studies, and this can potentially affect the results obtained with either clopidogrel or ticlopidine. In addition, it was not known which patients may have been pretreated with a thienopyridine for a period of time. The definitions of some of the components of MACE—namely, MI, TVR and SAST—differed, and not all of these data were collected for each trial. For example, not all trials collected routine post-procedural creatine phosphokinase levels, and definitions of stent thrombosis varied somewhat. Of course, all-cause mortality was the one end point that was consistent among trials and was therefore prespecified at the outset of this analysis.

Conclusions. Compared with ticlopidine, clopidogrel is associated with a decreased rate of 30-day MACE, including all-cause mortality. In addition, clopidogrel is known to be safer, better tolerated and more conveniently dosed than ticlopidine and is also less expensive. Furthermore, the comparatively favorable hematologic profile of clopidogrel makes the possibility of its long-term use in secondary prevention more acceptable than long-term ticlopidine therapy. The beneficial effect of clopidogrel observed in this analysis may be due to the more rapid onset of an antiplatelet effect seen with the loading dose of clopidogrel used in most of these studies, or to better patient compliance with clopidogrel therapy. Based on this data set of almost 14,000 patients, it can be reasonably concluded that clopidogrel plus aspirin is at least as effective as ticlopidine plus aspirin in reducing adverse ischemic events, and, in fact, in addition to its known better safety profile, clopidogrel appears to be more efficacious than ticlopidine. Unless new, large and definitive randomized clinical trials are performed, clopidogrel plus aspirin should be regarded as the standard of care for patients who have received coronary stents.

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Reprint requests and correspondence: Dr. Eric J. Topol, Department of Cardiovascular Medicine, F25, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195. E-mail: topole@ccf.org.

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