Original articles

Safety and efficacy evaluation of clopidogrel compared to ticlopidine after stent implantation: an updated meta-analysis

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Clopidogrel; Meta-analysis; Stenting; Ticlopidine.

Background. **Combination therapy with aspirin plus ticlopidine has become the reference antithrombotic therapy after coronary stenting. However despite its effectiveness, ticlopidine is associated with a significant incidence of severe side effects. Thus, clopidogrel, a ticlopidine analogue with an excellent safety profile, has been introduced in clinical practice. To date only a few, underpowered studies comparing the clinical efficacy of clopidogrel and aspirin versus standard combination therapy after coronary stenting have been performed and the odds ratios (OR) vary substantially among them. The purpose of the present investigation was to update the data regarding this issue by means of a formal meta-analysis.**

Methods. **Ten studies were considered suitable for analysis. The OR were calculated for 30 days of follow-up in patients who had undergone successful coronary stenting. Primary endpoints were a composite of death and non-fatal myocardial infarction (MI) (efficacy endpoint) as well as a composite of major adverse side effects (safety endpoint) as considered in every single study. Secondary endpoints were a composite of major adverse cardiac events, according to single study definition, and individual cardiac events as well.**

Results. **Overall, 11 688 patients were included. At 30 days, the OR for death and non-fatal MI was 0.63 (95% confidence interval-CI 0.47 to 0.85, p = 0.003) in favor of patients treated with clopidogrel and aspirin. There was also a trend toward less major adverse cardiac events (OR 0.83, 95% CI 0.66 to 1.03, p = 0.1), less mortality (OR 0.70, 95% CI 0.40 to 1.25, p = 0.2), and less non-fatal MI (OR 0.76, 95% CI 0.54 to 1.07, p = 0.1). Furthermore, OR for major adverse side effects was 0.53 (95% CI 0.42 to 0.66, p < 0.00001) in favor of clopidogrel. Similarly, drug intolerance was significantly reduced by clopidogrel (OR 0.51, 95% CI 0.36 to 0.72, p < 0.0001). Fewer patients on clopidogrel developed neutropenia or thrombocytopenia (OR 0.58, 95% CI 0.18 to 1.81, p = 0.3), while the incidence of severe bleeding was similar in the two groups (OR 1.19, 95% CI 0.71 to 1.99, p = 0.5).**

Conclusions. **The present meta-analysis demonstrates that clopidogrel reduces the 30-day combined endpoint of death and non-fatal MI, thereby showing a superior clinical efficacy compared to ticlopidine in patients who had undergone successful coronary stenting. A significantly better safety profile than ticlopidine was also reported, confirming on a larger scale the findings of randomized comparative trials.**

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Introduction

The ticlopidine-aspirin combination has become the reference antithrombotic therapy after coronary stenting[1-5]. Despite its effectiveness, ticlopidine is associated with a small but not negligible incidence of severe side effects[6]. Clopidogrel, a new thienopyridine derivative recently approved for use in patients with atherosclerotic vascular disease[7,8], differs from ticlopidine in that it has an excellent safety profile[7].

To date, only a few, relatively small trials (a mixture of observational and randomized studies) comparing clopidogrel to ticlopidine on top of aspirin after coronary stenting have been published and results are controversial[9-19]. Therefore, we performed a meta-analysis of all the published studies comparing clopidogrel plus aspirin versus ticlopidine plus aspirin after coronary stenting.

Methods

We performed a Medline search to identify all the published, English-language

studies through December 2001 that compared clopidogrel plus aspirin versus ticlopidine plus aspirin after coronary stenting. The key words used were clopidogrel, ticlopidine and coronary stenting and their various combinations. We also conducted a manual search of the references cited in original and review articles. There were 8 published papers, 3 abstracts and 4 reviews or editorial articles. Three investigators reviewed manuscripts, and disagreements were resolved by consensus. The inclusion criteria used were 1) direct comparison of combination therapy with clopidogrel and aspirin versus the standard ticlopidine-aspirin combination after coronary stenting; 2) a clear description of the study methods; 3) the ability to extract data for different endpoints. The 10 studies identified as suitable to be included are reported in table I[9-19]. The three randomized trials[12,13,16] were the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS), which was the only double-blind study, the Ticlid or Plavix Post-Stent (TOPPS) trial and the study performed by Mueller et al. There were differences in the loading doses and length of therapy among these three trials (Table I). Besides, they also differed in their inclusion and exclusion criteria; in particular, the CLASSICS study enrolled a very low risk population. The seven registries[9-11,14,15,17,18] had the same differences in mode and length of therapy as the randomized ones, but overall they included a higher risk population. An additional potentially relevant study[19], published only as an abstract, was excluded because of our inability to extract sufficient data for the different endpoints. However, in this study clopidogrel was as effective as ticlopidine after coronary stenting. Methods for data abstracting have been previously described[20]. No attempts were made to contact the authors for information.

Study endpoints. *Efficacy evaluation.* The primary efficacy endpoint was a composite of death and non-fatal myocardial infarction (MI). It was selected for its consistency among randomized as well as registry studies, and was therefore the pre-specified outset of our analysis. The secondary endpoint was a composite of major adverse cardiac events (MACE), according to the definition used in the single studies. Although the definition of MACE differed among studies (Table I), it was mostly a combination of death, non-fatal MI, target vessel revascularization or subacute stent thrombosis. Thus, we accepted the definition of each individual study. In addition, the rates of death, MI, target vessel revascularization and subacute stent thrombosis, as defined in each trial, were pooled and analyzed as individual endpoints.

Safety evaluation. The primary safety endpoint was a composite of major adverse side effects as considered in every single study (mostly a combination of bone marrow suppression, drug intolerance due to non-cardiac side effects and major bleeding). In addition, the rates of major bleeding or drug intolerance, as defined in each trial, were pooled and analyzed as individual secondary endpoints.

Statistical analysis. Odd ratios (OR) were calculated using the RevMan software version 3.1 (Cochrane Collaboration)[21]. We used a fixed-effects model[22] that assumes identical treatment effects in the studies (homogeneity of the true treatment effect) and the variance of the mean depends on the size of each study. The Mantel and Haenszel results are reported as OR with variances calculated using the procedure described by Yusuf et al.[23]. Z values were calculated, and p values of < 0.05 were considered statistically significant. We searched for possible heterogeneity and, when found, the extent of heterogeneity in the trials was examined using Q statistics that approximated a χ^2 statistic test; this means that the null hypothesis in all the studies estimates the same true value[24].

Results

Efficacy analysis. A total of 11 688 patients were available for this analysis. We found that at 30 days, therapy with clopidogrel was associated with a significant decrease in the occurrence of death or non-fatal MI from 3.4 to 1.6% (OR 0.63, 95% CI 0.47 to 0.85, p = 0.003) (Fig. 1)[9-17]. There was a trend (OR 0.83, 95% CI 0.66 to 1.03, p = 0.1) toward less MACE in patients receiving clopidogrel (2.7%) instead of ticlopidine (3.8%). Pooled data of the individual cardiac endpoints (Table II) showed a reduced probability of death (OR 0.70, 95% CI 0.40 to 1.25, p = 0.2) and non-fatal MI (OR 0.76, 95% CI 0.54 to 1.07, p = 0.1) in favor of clopidogrel, while the incidence of target vessel revascularization (OR 1.16, 95% CI 0.77 to 1.77, p = 0.5) and subacute stent thrombosis (OR 1.08, 95% CI 0.66 to 1.77, p = 0.8) was equally distributed in both groups.

Safety analysis. A total of 7165 patients were suitable for this analysis. At 30 days there was a 47% reduction in the occurrence of major adverse side effects (OR 0.53, 95% CI 0.42 to 0.66, $p < 0.00001$) (Fig. 2) in patients treated with clopidogrel plus aspirin. Similarly, the incidence of drug intolerance was significantly reduced among patients on clopidogrel and aspirin (OR 0.51, 95% CI 0.36 to 0.72, $p < 0.0001$). Although not statistically significant, fewer patients treated with clopidogrel and aspirin developed neutropenia or thrombocytopenia (OR 0.58, 95% CI 0.18 to 1.81, p = 0.3) while the incidence of major bleeding was similar in the two groups (OR 1.19, 95% CI 0.71 to 1.99, p = 0.5).

Subgroup analysis. *Randomized versus registry studies.* When the analysis was limited to the three randomized clinical trials (Fig. 1, Table II), the percentage of patients who reached the primary endpoint in the clopidogrel group (19/1529; 1.2%) was similar to that

Table I. Description of trials included and excluded.

Author	Year	No. patients	Type of study	No. patients on clopidogrel	No. patients on ticlopidine	Reported outcomes	MACE definition	Major adverse side effect definition	Follow-up	Clopidogrel therapy
Trials included										
Moussa et al.[9]	1999	1689	Registry	283	1406	MACE, D, MI, SAT, CABG, safety	D, MI, TVR, SAT	N, Diar, R	30 days	300 mg × 1 plus 75 mg/day for 4 weeks
Mishkel et al.[10]	1999	875	Registry	514	361	MACE, D, MI, SAT, TVR, re-PTCA, CABG, safety	CD, MI, TVR	B, Dis	30 days	75 mg/day for 2 or 4 weeks
Berger et al.[11]	1999	1327	Registry	500	827	MACE, D, MI, SAT, TVR	D, MI, TVR, SAT	–	30 days	300 mg × 1 plus 75 mg/day for 14 days
Bertrand et al.[12]	2000	1020	Randomized	680	340	Safety, MACE	CD, MI, TVR	B, N, T, Dis	28 days	300 mg × 1 or no loading, plus 75 mg/day for 28 days
Mueller et al.[13]	2000	700	Randomized	355	345	MACE, D, CD, MI, SAT, TVR, safety	CD, MI, TVR, SAT	NCD, B, S, N, T, Dis	30 days	75 mg/day for 4 weeks
Calver et al.[14]	2000	361	Registry	171	190	MACE, D, MI, SAT, TVR	D, MI, TVR	B, N, T	30 days, > 30 days	150 mg × 2 plus 75 mg/day for 30 days
L'Allier et al.[15]*	2000	2369	Registry	652	1717	MACE, D, MI, TVR	D, MI, TVR	–	30 days	300 mg × 1 plus 75 mg/day for 30 days
Taniuchi et al.[16]	2001	1016	Randomized	494	522	Intolerance, SAT, MACE, CD	CD, MI, TVR, SAT	Dis	30 days	300 mg × 1 plus 75 mg/day for 14 days
Dangas et al.[17]	2001	827	Registry	395	432	MACE, D, MI, SAT, TVR	D, MI, TVR	–	30 days	300 mg × 1 or no loading, plus 75 mg/day for 4 weeks
Wang et al.[18]*	1999	1504	Registry	312	1192	MACE, SAT, safety	D, MI, CABG	Diar, BM, R	30 days	Mode of therapy not reported
Trial excluded										*Reason*
Plucinski et al.[19]*	2000	1378	Registry	240	1138	D, MI, TVR	–	–	30 days, 6 months	Insufficient data

B = bleeding; BM = bone marrow suppression; CABG = coronary artery bypass graft; CD = cardiac death; D = death; Diar = diarrhea; Dis = drug discontinuation; MACE = major adverse cardiac events; MI = myocardial infarction; N = neutropenia; NCD = non-cardiac death; PTCA = percutaneous transluminal coronary angioplasty; R = rash; S = stroke; SAT = subacute stent thrombosis; T = thrombocytopenia; TVR = target vessel revascularization. * studies published as abstracts.

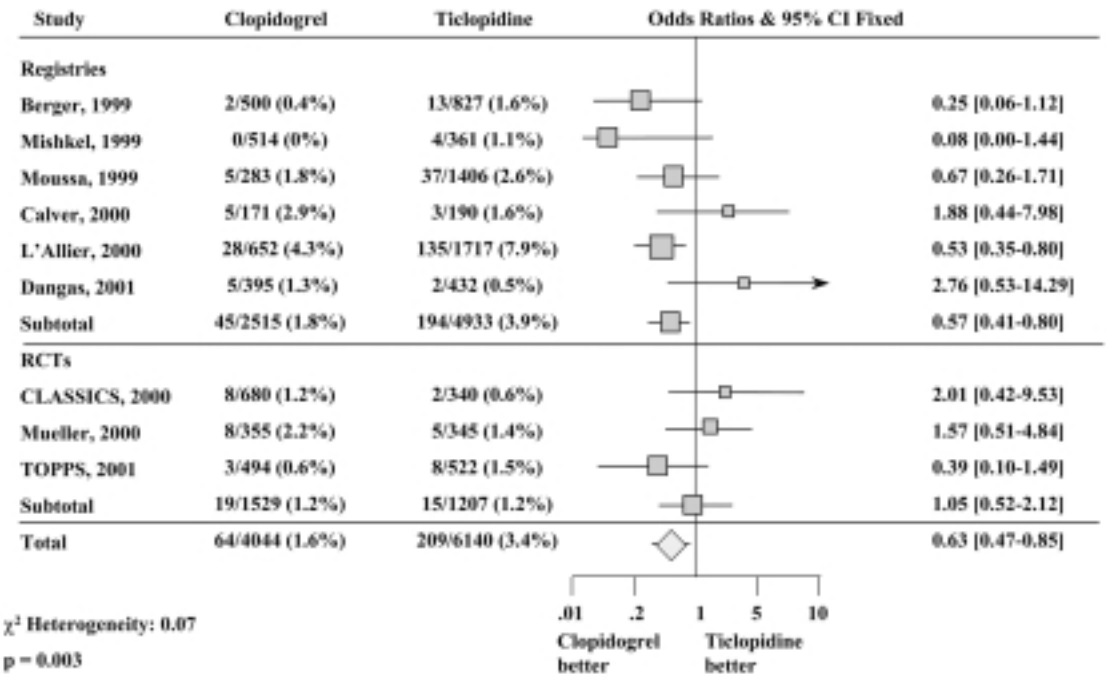

Figure 1. *The odds ratio plots together with the 95% confidence intervals (CI) for the rate of the 30-day composite endpoint (death and non-fatal myocardial infarction) for each of the registries and randomized clinical trials (RCTs), as well as for the pooled data. The* size of the boxes *corresponds to the number of patients in the trial.* Arrows *indicate that the limits of the CI extend beyond the graph.*

Table II. Meta-analysis of observed events in randomized and registry trials.

Outcome	No. events/no. enrolled (%)		Fixed OR	95% CI	p
	Clopidogrel	Ticlopidine			
Death					
Registries	16/2515 (0.6%)	51/4933 (1%)	0.66	0.39-1.13	0.1
RCTs	6/1529 (0.4%)	9/1207 (0.7%)	0.60	0.21-1.70	0.3
Total	22/4044 (0.5%)	60/6140 (1%)	0.70	0.40-1.25	0.2
Non-fatal MI					
Registries	40/2515 (1.6%)	143/4933 (2.9%)	0.71	0.51-0.99	0.04
RCTs	13/1035 (1.2%)	6/685 (0.9%)	1.63	0.61-4.36	0.3
Total	53/3550 (1.5%)	149/5618 (2.6%)	0.76	0.54-1.07	0.1
Target vessel revascularization (re-PTCA or CABG)					
Registries	20/2515 (0.8%)	41/4933 (0.8%)	1.04	0.60-1.82	0.9
RCTs	22/1529 (1.4%)	15/1207 (1.2%)	1.37	0.70-2.66	0.4
Total	42/4044 (1%)	56/6140 (0.9%)	1.16	0.77-1.77	0.5
MACE					
Registries	77/2827 (2.7%)	244/6125 (4%)	0.76	0.59-0.99	0.04
RCTs	39/1529 (2.5%)	33/1207 (2.7%)	1.09	0.68-1.76	0.7
Total	116/4356 (2.7%)	277/7332 (3.8%)	0.83	0.66-1.03	0.1
Subacute stent thrombosis					
Registries	14/2175 (0.6%)	43/4408 (1%)	0.87	0.47-1.61	0.7
RCTs	14/849 (1.6%)	9/867 (1%)	1.60	0.69-3.73	0.3
Total	28/3024 (0.9%)	52/5275 (1%)	1.08	0.66-1.77	0.8

CABG = coronary artery bypass graft; CI = confidence interval; MACE = major adverse cardiac events; MI = myocardial infarction; OR = odds ratio; PTCA = percutaneous transluminal coronary angioplasty; RCTs = randomized clinical trials.

of the ticlopidine group (15/1207; 1.2%) (OR 1.05, 95% CI 0.52 to 2.12, p = 0.9). However, there was a trend toward a lower death rate for patients treated with clopidogrel (6/1529; 0.4%) than for those treated with ticlopidine (9/1207; 0.7%) (OR 0.60, 95% CI 0.21 to 1.70, p = 0.3). Importantly, this datum was consistent with the death rate reported in the registries. Major adverse side effects were significantly less frequent (OR 0.46, 95% CI 0.32 to 0.66, p = 0.00002) among patients treated with clopidogrel plus aspirin than among those

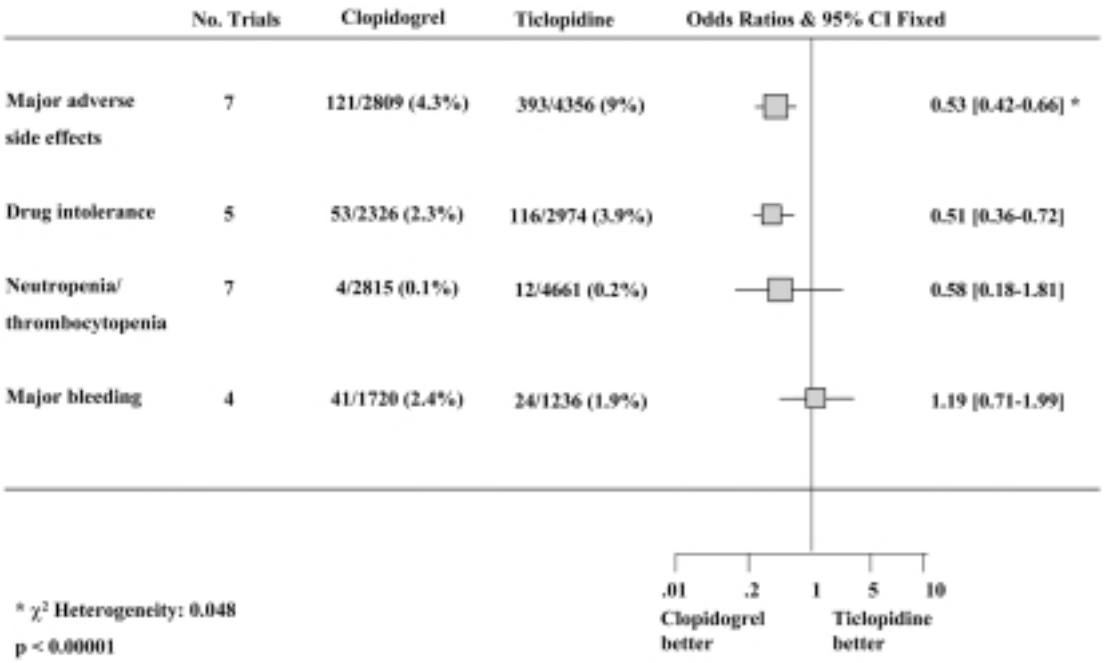

Figure 2. *The odds ratio plots together with the 95% confidence intervals (CI) for the rate of the 30-day observed major adverse side effects, drug intolerance, neutropenia and thrombocytopenia and major bleedings for the pooled data.* Boxes *and* arrows *with the same meaning as in figure 1.*

submitted to treatment with the standard association. Thus, the statistically superior clinical performance of clopidogrel in the pooled analysis was substantially influenced by the results of the large registries.

Loading versus no loading clopidogrel dose. Data were analyzed according to the utilization of a loading dose of clopidogrel (7 studies)[9,11,12,15-18] or not (4 studies)[10,12-14] (Table I). The CLASSICS study was a three-arm study comparing a loading dose versus no loading dose of clopidogrel versus standard ticlopidine. The published trial pooled both clopidogrel arms, but for the purpose of our analysis each arm was considered independently. When studies that used a loading dose of clopidogrel were separated from that without it, a significant advantage (Fig. 3) for all the endpoints em-

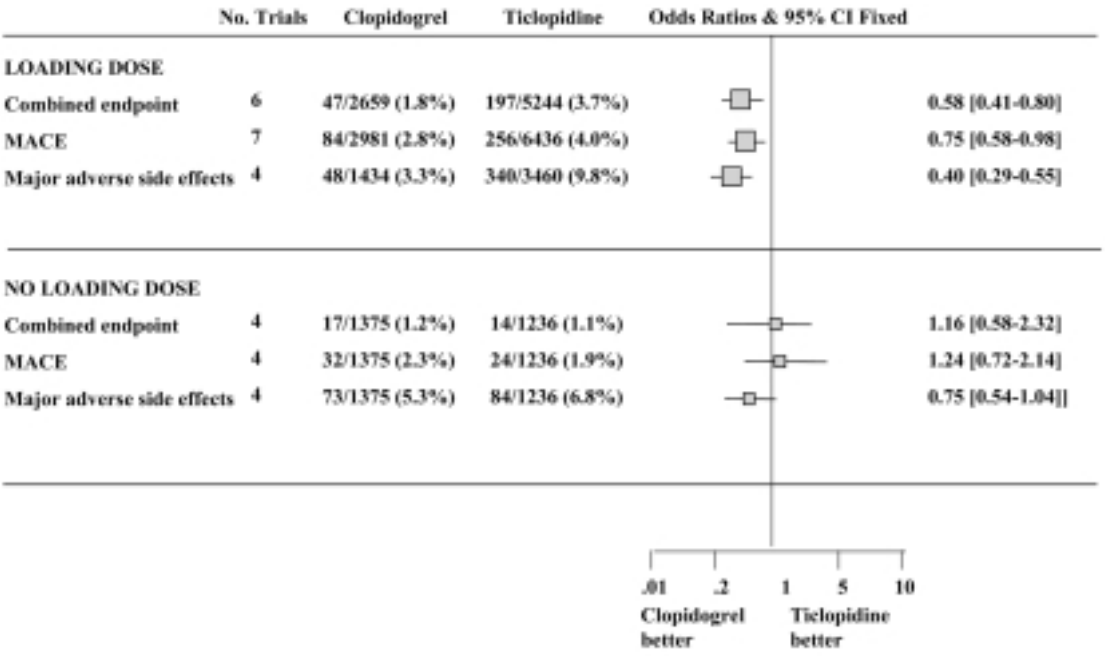

Figure 3. *The odds ratio plots together with the 95% confidence intervals (CI) for the rate of the 30-day observed combined endpoint, major adverse cardiac events (MACE), and major adverse side effects for the pooled studies divided according to the utilization of a clopidogrel loading dose or not.* Boxes *and* arrows *with the same meaning as in figure 1.*

erged with the former policy. Again, clopidogrel's statistically superior clinical performance in the pooled analysis was mostly determined by the data of the trials where a loading dose was used.

Heterogeneity analysis. The Q statistics revealed a significant degree of heterogeneity for the primary endpoint analysis. This could perhaps be due to some differences between registries and randomized trials in the patient populations included. Interestingly, this heterogeneity was not found when cardiac death and non-fatal MI were analyzed individually. On the other hand, the significant heterogeneity affecting the safety analysis should be clearly related to the much wider differences in the definitions of major side effects considered in each individual study (Table I).

Discussion

Since the introduction of the combination of ticlopidine with aspirin, a remarkable and unique progress has been made in antithrombotic and antiplatelet therapy following coronary stenting[1-3]. The latest progress in this field has been the utilization of the new thienopyridine derivative, clopidogrel. Interestingly, the substitution of clopidogrel for ticlopidine after stenting is rapidly gaining worldwide acceptance although the evidence for such a change is still low and recent long-term data cast doubts on it[25]. The infrequent but severe hematological toxicity of ticlopidine, along with its frequent "minor" side effects, are the only issues favoring such a switch to date[26]. The CLASSICS study was a safety study, with the primary endpoint consisting of major peripheral or bleeding complications, neutropenia, thrombocytopenia, or the early discontinuation of the study drug for non-cardiac adverse events[12]. The primary endpoint occurred more frequently among patients treated with ticlopidine (9.1%) than in the combined clopidogrel group (4.6%) ($p = 0.005$), supporting a superior safety profile of the latter drug. This could translate in a better clinical outcome since more patients would be able to benefit from a full course of an effective combination antiplatelet regimen, and the risk of subacute stent thrombosis caused by the early discontinuation of ticlopidine should be reduced. This could be very important in specific situations such as after brachytherapy and covered or drug-eluting stents, for which cases of late stent occlusions have been described. These favorable results of the CLASSICS trial are confirmed by the current meta-analysis too (Fig. 2).

In addition, our data are consistent with a previous meta-analysis[27] indicating a superior clinical efficacy of clopidogrel over ticlopidine after stenting. In fact, the use of clopidogrel was associated with a 37% reduction in the primary endpoint (death and non-fatal MI) rate from 3.4 to 1.6% ($p = 0.003$). Notably, this was consistent with the 30% relative reduction in the incidence of cardiac death, evident in both randomized and registry studies. In addition, a mild 17% reduction in the incidence of MACE was observed with clopidogrel. Unfortunately, these short-term advantages of clopidogrel as compared to ticlopidine have been recently counterbalanced by the higher mortality of patients initially treated with clopidogrel which emerged from the extended follow-up of the Mueller's study[25]. This negative effect has been attributed to a higher incidence of subacute stent thrombosis after the first month of therapy and to a potential inhibition of the antiplatelet activity of clopidogrel due to concomitant therapy with statins[28]. However, the worse performance of clopidogrel observed in that single study could be more logically attributed to the absence of a loading dose. In fact, the present meta-analysis as well as other studies confirms a clear advantage of starting treatment with a loading dose when clopidogrel is used[29].

Moreover, the subgroup analyses of the present study demonstrate that clopidogrel's superior performance is mainly driven by registries. This evidence could strongly bias our results since it is difficult to check patient selection and treatment in observational studies. However, even the three randomized trials have several structural limitations that could negatively affect their results. As we already discussed, the study by Mueller et al. is hampered by the absence of a loading dose. Besides, the TOPPS trial did not report the rate of non-fatal MI, thus leaving only two randomized trials suitable for the combined endpoint analysis. Additionally, in the CLASSICS trial both arms of the clopidogrel-treated patients were combined for the analysis (Fig. 1), thereby unbalancing the results in favor of ticlopidine. In fact, when the trial was analyzed in detail, each single clopidogrel arm showed no difference in the rate of death or non-fatal MI compared to ticlopidine (1.1 vs 0.6% for the no loading dose clopidogrel arm vs ticlopidine, $p = 0.7$, and 0.9 vs 0.6% for the loading dose clopidogrel arm vs ticlopidine, $p = 0.9$).

Limitations. Inherent to all meta-analyses and similar to the previous one[27], the included trials differed to some extent in design, inclusion criteria as well as mode and length of therapy. In fact, heterogeneity analysis, which provides information about the validity of pooling different trials, revealed a significant heterogeneity for the combined endpoint. However, this heterogeneity was neither evident for the individual endpoint (mortality and non-fatal MI) analysis nor for the subgroup analyses. Furthermore, although the choice to limit the meta-analysis to randomized clinical trials may have enhanced the quality of the data, it adds a further selection bias to it. In fact, the broader and higher risk populations included in well-designed registries do not overestimate the magnitude of the effects of treatment seen in randomized trials[28] and may better reflect

the "real world" situation. As opposed to the meta-analysis by Bhatt et al.[27], to avoid any further potential bias we chose not to supplement published data with unpublished cases[29]. In addition, MACE were not selected as primary endpoint in our analysis owing to the wide differences in the definition of some of the their components among studies. Thus, our pre-specified choice to combine "hard events" such as death and non-fatal MI into a primary endpoint should offer a sufficiently objective measure of clopidogrel efficacy through the entire set of studies.

In conclusion, the present meta-analysis demonstrates that in patients who have undergone successful coronary stenting, clopidogrel has a superior clinical efficacy compared to ticlopidine. In addition, a significantly better safety profile than ticlopidine was reported, confirming on a larger scale the findings of the randomized comparative trials. These additional benefits of clopidogrel compared to ticlopidine after stent deployment would overcome the extracost of such a substitution in several countries.

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