Effect of Addition of Clopidogrel to Aspirin on Mortality
Systematic Review of Randomized Trials

Santiago Palacio, MD; Robert G. Hart, MD; Lesly A. Pearce, MS; Oscar R. Benavente, MD

Background and Purpose—In the Secondary Prevention of Small Subcortical Strokes (SPS3) trial, addition of clopidogrel to aspirin was associated with an unexpected increase in mortality in patients with lacunar strokes. We assessed the effect of the addition of clopidogrel to aspirin on mortality in a meta-analysis of published randomized trials.

Methods—Randomized trials in which clopidogrel was added to aspirin in subjects with vascular disease or vascular risk factors were identified. Trials were restricted to those with a mean follow-up of ≥14 days in which both the combination of aspirin and clopidogrel was tested and mortality was reported.

Results—Twelve trials included 90,934 participants (mean age, 63 years; 70% men; median follow-up, 1 year) with 6,849 observed deaths. There was no significant increase in mortality with the combination therapy either in 4 short-term (14 days–3 months; OR, 0.93; 95% CI, 0.87–0.99) or in 7 long-term (>3 months; hazard ratio, 0.97; 95% CI, 0.91–1.04) trials after 1 long-term trial (the SPS3 trial) was excluded because of heterogeneity. Addition of clopidogrel was associated with an increase in fatal hemorrhage (OR, 1.35; 95% CI, 0.97–1.90) and a reduction in myocardial infarction (OR, 0.82; 95% CI, 0.74–0.91).

Conclusions—The addition of clopidogrel to aspirin has no overall effect on mortality. The SPS3 trial results are outliers, possibly because of a lower prevalence of coronary artery ischemia. Addition of clopidogrel to aspirin increases fatal bleeding and reduces myocardial infarction.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00059306.

Key Words: clopidogrel ■ antiplatelet therapy ■ clinical trials ■ mortality ■ lacunar stroke

Dual antiplatelet therapy of clopidogrel combined with aspirin is standard antithrombotic therapy after coronary and carotid arteries stent placement and for patients with acute coronary syndromes. In the Secondary Prevention of Small Subcortical Strokes (SPS3) trial involving patients with recent lacunar strokes, the addition of clopidogrel 75 mg daily to aspirin 325 mg daily was associated with an unexpected increase in all-cause mortality (hazard ratio, 1.5; \( P = 0.005 \)).

We sought to determine the effect of addition of clopidogrel to aspirin on mortality in patients with a wide spectrum of vascular disease; we conducted systematic identification of all randomized trials comparing these agents and meta-analysis of their results. To understand further the effects on mortality, we examined the effects of addition of clopidogrel on vascular versus nonvascular death, fatal bleeding, and myocardial infarction. Adverse mortality effects of combining clopidogrel with aspirin are relevant to ongoing randomized trials testing this combination.2,3

Methods

Search and Selection Process
Randomized trials in which clopidogrel in any dosage was added to aspirin in any dosage and in which all-cause mortality was reported were included. Trials were excluded if follow-up averaged <14 days or if published only in abstract. Trials were identified by computerized search of the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov Web site, and Pubmed using the keywords of clopidogrel plus aspirin combined with clinical trial; inquiry to the manufacturer of Plavix brand of clopidogrel was also made.

Data Extraction
Two physician reviewers (S.P., R.G.H.) independently extracted the following from published sources: data on methodological features; number of patients treated; total follow-up exposure; and occurrence of all-cause mortality, causes of death, death caused by hemorrhage, myocardial infarction, and intracranial hemorrhage. Disagreements were resolved by joint review and consensus. If the years of exposure for each treatment arm were not provided, they were estimated from the number of primary events divided by the annualized event rate; if the overall mortality rate was not provided, then the mean

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Table 1. Design Features and Baseline Characteristics Participants

| Study | N | Age, y | Men % | DM % | Previous Stroke/TIA % | Previous Infarction % | Main Inclusion | Primary Outcome | ASA Dose, mg/d | CPD Dose, mg/d | Average Follow-Up | % Lost to Follow-Up |
|-------|---|--------|-------|------|------------------------|------------------------|-----------------|----------------|----------------|----------------|-----------------|-------------------|---------------------|
| **Short-Term Trials**<br>(14 d–3 mo) | | | | | | | | | | | | | |
| SP32 | 249 | 59 | 83 | 40 | 5 | Elective CABG | Graft occlusion at 3 mo | 100 | 75 | 3 mo | 3.6 |
| CHARISMA | 15 603 | 64 | 70 | 42 | 25 | CV disease or multiple risk factors | Stroke, MI, and vascular death | 75–162 | 75 | 2.3 y | <1 |
| CURE | 12 562 | 64 | 62 | 23 | 4 | Acute coronary syndrome | Stroke, MI, and vascular death | 75–325 | 300 × 1 | then 75 | 9 mo | <1 |
| ACTIVE | 7554 | 71 | 58 | 19 | 13 | AF + 1 risk factor | Stroke, MI, and vascular death | 96%: 75–100 | 3.5%: >100 | 75 | 3.6 y | <1 |
| CASCADE | 113 | 67 | 89 | 29 | NR | CABG with saphenous vein graft | Graft hyperplasia at 1 y | 162 | 75 | 1 y | none |
| CREDO | 2116 | 62 | 71 | 26 | 7 | Elective PCI | All death, stroke, MI | 325 × 28; then 81–325 | 300 × 1 | then 75 | 1 y | 4 |
| REAL-LATE/ZEST-LATE | 2701 | 62 | 70 | 26 | 4 | Drug-eluting stents for 12 mo | MI or death from cardiac causes | 100–200 | 75 | 1.6 y | <1 |
| CASP3AR | 851 | 66 | 76 | 38 | NR | Bypass for PVD | Graft occlusion or revascularization, amputation or death | 75–100 | 75 | 1 y | 2 |
| All trials | 90 934 | 63 | 70 | . . . | . . . | . . . | . . . | . . . | 75 | . . . | . . . | . . . |

DM indicates diabetes mellitus; TIA, transient ischemic attack; ASA, aspirin; CPD, clopidogrel; CAD, coronary artery disease; CABG, coronary artery bypass graft; NR, not reported; MI, myocardial infarction; CV, cardiovascular; AF, atrial fibrillation; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

follow-up multiplied by the number of participants was used. The biostatistician reviewer (L.A.P.) extracted available data on hazard ratios (HR) and their 95% CIs for the long-term trials.

Outcomes

We accepted the definitions of vascular versus nonvascular causes of death as reported in the individual clinical trials. For these analyses, deaths categorized as of unknown cause were combined with vascular deaths (ie, vascular deaths included all deaths that were not determined to be nonvascular). We accepted the diagnosis of myocardial infarction as reported in individual trials.

Data Synthesis

Intention-to-treat results were used for the analyses when available (and footnoted when not available). Meta-analyses of the trial results are presented as ORs comparing dual antiplatelet versus aspirin, with the exception of all-cause mortality results for longer-term trials, in which the HR was estimated instead. (Meta-analysis of other long-term trial results as an HR was not performed, as data were less available.) Each meta-analysis OR was computed assuming a random effects model, and the assumption of statistical homogeneity of the treatment effect (across trials) was tested using the $Q_e$ statistic for the relative odds scale. If the count in 1 or more of the cells for a trial was 0, then 0.5 was added to each of the 4 cells. The meta-analysis HR for all-cause mortality in longer-term trials was computed using a generic inverse variance method for continuous data. The log (HR) and standard error for each trial result were calculated from the published HR and 95% CI. For 1 trial (CURE), HR data for overall mortality were not reported, so OR data were used; and for a relatively small trial (CASCADE), total deaths numbered 1, so data were excluded. Heterogeneity across trials was evaluated using the $I^2$ index (percentage of the total variability in a set of effect sizes because of between-studies variability) and the $\chi^2$ test for heterogeneity. All tests and CIs are 2-sided. Software used for meta-analysis of ORs and HRs were MedCalc for Windows, version 12.1.4.0 (MedCalc Software) and RevMan 5.0 (the Cochrane Collaboration), respectively.

Results

Twelve randomized trials published between 2001 and 2012 were included, with a total of 90 934 randomized participants with a mean age of 63 years, a mean follow-up of 1 year per patient, and 6849 total deaths.1,6–16 (Table 1) Numbers of participants ranged from 113 to 45 852 and average follow-up from 15 days to 2.3 years. Trial cohorts mainly included patients with vascular diseases (acute coronary syndromes, coronary artery bypass grafting, peripheral vascular revascularization, atrial fibrillation, recent lacunar stroke), but 1 trial (CHARISMA) also included patients with vascular risk factors without clinically manifest vascular disease10 (Table 1). In the 8 trials in which follow-up averaged >3 months, clopidogrel versus placebo were administered double-blind.
Mortality

Four trials with short duration of follow-up (14 days–3 months) included 46,414 participants with 3,572 deaths, and were dominated by the large COMMIT trial.9 (Table 2) Meta-analysis of these trials showed all-cause mortality was reduced by dual antiplatelet therapy versus aspirin alone (OR, 0.93; 95% CI, 0.87–0.99; I² index, 0%; P = 0.94 for heterogeneity).

Eight trials with longer duration of average follow-up (>3 months) included 44,520 participants with 3,467 deaths (Table 2). Meta-analysis of these trials showed no effect on mortality of dual antiplatelet therapy versus aspirin alone (HR, 1.03; 95% CI, 0.91–1.16; Table 2); however, there was moderate heterogeneity among the results (I² index, 48%; P = 0.07 for heterogeneity). After excluding the SPS3 trial, meta-analysis of the remaining 7 trials showed no effect of dual antiplatelet therapy versus aspirin alone on mortality (HR, 0.97; 95% CI, 0.91–1.04) with no indication of heterogeneity of results across trials (I² index, 0%; P = 0.56 for heterogeneity; Figure 1).

Cause of death was reported as vascular versus nonvascular in 6 longer-term follow-up trials. (Table 3) The OR by meta-analysis for vascular death by dual antiplatelet therapy versus aspirin alone was 1.05 (95% CI 0.91–1.20); however, there was moderate heterogeneity among the trial results (I² index, 43%; P = 0.12 for heterogeneity). Excluding the SPS3 trial (OR, 1.61, 95% CI, 1.11–2.36), the OR estimate was 0.99 (95% CI, 0.91–1.08; I² index, 0%; P = 0.61 for heterogeneity). There was no evidence of heterogeneity across the trials for nonvascular death, and the OR estimate by meta-analysis was 0.95 (95% CI 0.83–1.09; I² index, 0%; P = 0.83 for heterogeneity).

Fatal Bleeding

Six longer-term follow-up trials reported the number of fatal hemorrhages (Table 4). Results for SPS3 were not available. The OR by meta-analysis for fatal hemorrhage among patients assigned to dual antiplatelet therapy was 1.35 (95% CI, 0.97–1.90; I² index, 0%; P = 0.57 for heterogeneity).
Myocardial Infarction

Myocardial infarctions were significantly reduced (OR, 0.82; 95% CI, 0.74–0.91; I² index, 2%; P = 0.41 for heterogeneity) when clopidogrel was added to aspirin based on meta-analysis of 7 longer-term follow-up trials (Table 5). The effect was of similar magnitude, but no longer significant when 3 trials involving patients with acute coronary syndromes was of similar magnitude, but no longer significant when 3 trials involving patients with acute coronary syndromes (CURE) or undergoing coronary stent placement (CREDO, REAL–LATE/ZEST-LATE) were excluded (OR, 0.87; 95% CI, 0.67–3.91; P = 0.66).

Excluded Trials

Trials that were excluded from these analyses and the reasons for exclusion are given in Appendix I (online data). For example, in 1 trial involving participants with acute myocardial infarction, 30-day mortality data are available, but randomly assigned clopidogrel versus aspirin was given only for the initial 2 to 4 days before coronary intervention was undertaken. A small trial involving 392 patients with acute transient ischemic attack or minor ischemic stroke followed for 90 days did not report total mortality.

Discussion

Based on analysis of all published randomized trials, addition of clopidogrel to aspirin does not affect overall mortality. In trials with long-term follow-up, a trend toward an increase in fatal hemorrhage with dual antiplatelet therapy (35%; 95% CI, −3% to 90%) was offset by a significant reduction in myocardial infarction (18%; 95% CI, 9%–26%). There was no impact on vascular death as reported in a subset of the trials (50% increase (P = 0.005) in mortality associated with addition of clopidogrel to aspirin in the SPS3 trial involving patients with recent lacunar stroke was an outlier when considered in the context of the other randomized trials.

Several subgroup analyses dealing with mortality from the large CHARISMA (2002–2006) trial have been published and may shed light on the aberrant mortality results reported from the SPS3 trial. The CHARISMA trial included 15 603 patients with vascular disease or multiple vascular risk factors randomized to aspirin (dose range, 75–162 mg daily) alone versus combined with clopidogrel 75 mg daily, administered double-blind. There was no difference in all-cause mortality (371 deaths with dual antiplatelet therapy versus 374 deaths...
with aspirin alone, 2.0%/pt-yr versus 2.1%/pt-yr; HR, 0.99) during the mean follow-up of 2.3 years. The investigators published 3 subsequent secondary analyses addressing the issue of clopidogrel added to aspirin and mortality. Wang et al reported mortality rates according to whether participants enrolled with asymptomatic (n=3284) versus symptomatic vascular disease (n=12 153) and found an unanticipated interaction (P for interaction=0.02) between symptom status and effect of addition of clopidogrel on all-cause mortality: all-cause mortality was increased in asymptomatic patients by dual antiplatelet therapy (HR, 1.4; P=0.04) versus decreased in those with symptoms (HR, 0.91 P=0.27). Asymptomatic participants were much more often diabetic (83%) than were symptomatic patients (31%); fatal bleeding did not account for the excess in deaths among asymptomatic patients. A second post hoc analysis considered diabetes and diabetic nephropathy (microalbuminuria ≥30 μg/mL as reported by local investigators) and concluded that patients having diabetic nephropathy was related to increased mortality in patients assigned to clopidogrel. A third analysis examined bleeding complications and found a strong independent relationship between moderate bleeding and all-cause mortality (HR, 2.9; P<0.0001).

The aspirin dosage (325 mg daily, enteric-coated) used in SPS3 is higher than that used in most other randomized trials testing dual antiplatelet therapy. Higher aspirin doses have been associated with increased rates of life-threatening bleeding when combined with clopidogrel. However, in a large trial involving 12 566 patients with acute coronary syndromes, participants randomly assigned to aspirin 300 to 325 mg daily versus 75 to 100 mg daily combined with clopidogrel 75 mg daily had no increase in mortality (143 deaths with high-dose aspirin, 156 deaths with low-dose aspirin; HR, 0.93; 95% CI, 0.74–1.16).

Limitations of this meta-analysis include that it is based on published data and not on pooling of individual patient data, and therefore it was not possible to perform subgroup analyses according to history of coronary heart disease or to explore consistency of the treatment effects on mortality in key subgroups.

We hypothesize that in cohorts with a sufficiently high frequency of coronary artery disease, addition of clopidogrel to aspirin results in a neutral effect on mortality, explained by a reduction in myocardial infarction being offset by increases in fatal hemorrhage and moderate hemorrhage that are associated with death. Cohorts with overall low mortality rates and low frequencies of coronary artery disease, such as the SPS3 cohort and asymptomatic subgroup of the CHARISMA trial, may have increased mortality with dual antiplatelet therapy because the absolute reduction in coronary events does not offset death related directly or indirectly to bleeding complications.

However, we cannot exclude that the results of SPS3 could be caused by extreme play of chance. Nevertheless, we hypothesize that the chronic use of dual antiplatelet therapy with clopidogrel and aspirin may adversely affect mortality compared with aspirin monotherapy in cohorts with low rates of coronary artery ischemia, such as those participating in the SPS3 trial.

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Disclosures

None.

References


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SUPPLEMENTAL MATERIAL:

Appendix I: Trials and studies that were excluded and reasons why (online data).

(Alphabetically)


Kennedy J, Hill MD, Ryckhorst K et al for the FASTER Investigators. Fast assessment of stroke and transient ischemic attack to prevent early recurrence (FASTER): a randomized controlled pilot trial. Lancet Neurol 2007; 6: 961-9. Deaths not clearly reported. One fatal CNS bleed among clopidogrel assigned, but uncertain if other deaths during the 90 days follow-up interval. Given the number of recurrent strokes, there would predictably been some fatal ischemic strokes. About 28% were deemed lacunar, but requirement for entry within 24 hours and short follow-up, as well as vague criteria for lacunar makes comparability to SPS3 dubious.


Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; 352: 1179-89. 30-day mortality data are included, but randomly-assigned clopidogrel vs. aspirin given for only the initial 2-4 days before coronary intervention was undertaken.


Wang Y and Johnston C. Rationale and design of a randomized, double blind trial comparing the effects of a 3 month clopidogrel-aspirin regimen versus aspirin alone for the treatment of high-risk patients with acute nondisabling cerebrovascular event. *Am Heart J* 2010; 160: 380-386. e1. Results not published yet.

Duration of treatment was 7 days in 100 patients to assess microembolic signals.
**Effect of Addition of Clopidogrel to Aspirin on Mortality**

*Abstract*

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| 背景および目的：Secondary Prevention of Small Subcortical Strokes (SPS3) 試験において，アスピリンへのクロピドグレルの追加はラクナ梗塞患者における死亡率の予防に乏しい上昇を観察した。我々は，既往の無作為化試験のメタ解析からアスピリンへのクロピドグレルの追加が死亡率に及ぼす影響を評価した。 | **表4** 長期追跡試験におけるアスピリンへのクロピドグレルの追加の致死的出血に対する影響 |
|---|---|---|---|
| 試験 | 併用 | アスピリン単独 | OR (95 % CI) |
| SPS31 | NR | NR | ... |
| CHARISMA10 | 26 | 17 | 1.53 (0.83 ~ 2.82) |
| CURE11 | 11 | 15 | 0.74 (0.34 ~ 1.61) |
| ACTIVE A12 | 42 | 27 | 1.57 (0.96 ~ 2.55) |
| CASCADE13 | 0 | 0 | 1.02* (0.02 ~ 52) |
| CREDO14 | NR | NR | ... |
| REAL-LATE ZEST LATE15 | NR | NR | ... |
| CASPAR16 | 2 | 1 | 2.01 (0.18 ~ 22) |
| 全期試験 | 81 | 60 | 1.35 (0.97 ~ 1.90) |
| NR: 報告なし。 | * 各セルに 0.5 を加えて推定。 |

**表5** 長期追跡試験におけるアスピリンへのクロピドグレルの追加の心筋梗塞に対する影響

<table>
<thead>
<tr>
<th>試験</th>
<th>併用</th>
<th>アスピリン単独</th>
<th>OR (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPS31</td>
<td>30</td>
<td>38</td>
<td>0.78 (0.48 ~ 1.26)</td>
</tr>
<tr>
<td>CHARISMA10</td>
<td>185</td>
<td>197</td>
<td>0.94 (0.77 ~ 1.15)</td>
</tr>
<tr>
<td>CURE11</td>
<td>324</td>
<td>419</td>
<td>0.77 (0.66 ~ 0.89)</td>
</tr>
<tr>
<td>ACTIVE A12</td>
<td>90</td>
<td>115</td>
<td>0.78 (0.59 ~ 1.03)</td>
</tr>
<tr>
<td>CASCADE13</td>
<td>4</td>
<td>1</td>
<td>4.31 (0.47 ~ 40)</td>
</tr>
<tr>
<td>CREDO14</td>
<td>70</td>
<td>90</td>
<td>0.77 (0.56 ~ 1.07)</td>
</tr>
<tr>
<td>REAL-LATE-ZEST LATE15</td>
<td>10</td>
<td>7</td>
<td>1.42 (0.54 ~ 3.74)</td>
</tr>
<tr>
<td>CASPAR16</td>
<td>NR</td>
<td>NR</td>
<td>...</td>
</tr>
</tbody>
</table>
| MI: 心筋梗塞。NR: 報告なし。
* 前値の各セルに 0.5 を加えて推定。 |

主要結果の論文では非致死的 MI のみが報告されている。Berger PB, et al. (6) の Table 3から全 MI を推定。