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# Optimal Aspirin Dose in Acute Coronary Syndromes

## An Emerging Consensus

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## Abstract

Numerous clinical trials testing the efficacy of aspirin for the secondary prevention of cardiovascular disease have been published. We reviewed the literature pertaining to aspirin dose in acute coronary syndrome patients. Clinical trials assessing the comparative efficacy of different doses of aspirin are scarce. This complex antiplatelet therapy landscape makes it difficult to identify the best aspirin dose for optimizing efficacy and minimizing risk of adverse events, while complying with the various guidelines and recommendations. Despite this fact, current evidence suggests that aspirin doses of 75–100 mg/day may offer the optimal benefit:risk ratio in acute coronary syndrome patients.

## Aspirin for Acute Coronary Syndrome Prior to the Percutaneous Coronary Intervention Era

The quest for the most favorable aspirin dose in acute coronary syndromes (ACS) has perplexed investigators and clinicians for many years. This discussion dates back to the early 1980s after the first positive randomized studies in patients with ACS were published. These small studies showed that aspirin, at doses from 75 mg/day up to 1300 mg/day, significantly reduced the incidence of cardiovascular (CV) death and myocardial infarction (MI) compared with placebo.[1–5]

The first official guideline recommendation for aspirin use in the ACS patient population resulted from the ISIS-2 study, which was the first to demonstrate a significant reduction in mortality with aspirin following MI.[6] This was a prospective, placebo-controlled, randomized trial of 17,187 post-MI patients that demonstrated aspirin, at a dose of 162 mg/day, resulted in a 23% reduction in the odds of death within 5 weeks and a 42% reduction when combined with streptokinase when compared with placebo. Major bleeding with aspirin was not significantly different from the placebo group. The ISIS-2 trial studied aspirin with or without thrombolytic therapy. It did not include patients treated with percutaneous coronary intervention (PCI), which is currently standard of care for ST elevation MI (STEMI). In addition, the above studies were not designed to test the efficacy and safety of various doses of aspirin. As such, the recommended dose of aspirin was the doses used in these trials.

## Aspirin for ACS in the PCI Era

Very few placebo-controlled studies have investigated aspirin use in PCI. Aspirin has been used empirically as a component of adjunctive medical therapy since the inception of PCI,[7–10] becoming standard of therapy following PCI owing to one randomized trial (the M-Heart II), which showed that 6 months of aspirin at 325 mg in patients undergoing planned percutaneous transluminal coronary angioplasty reduced the incidence of the primary clinical outcome (i.e., death, MI or clinically important restenosis), driven by a reduction in MI, when compared with placebo.[9]

The justification for the use of aspirin for long-term secondary prevention of ischemic events originates from the analyses by the Antithrombotic Trialists' (ATT) Collaboration. Their analysis showed that any use of aspirin (vs control) reduces the risk of nonfatal stroke, nonfatal MI and vascular death by 25–32% in patients at high risk of arterial thrombosis.[11,12] The effect in patients treated in the acute phase of MI and after a MI was similar.

There have been very few studies comparing the effectiveness of different doses of aspirin in the ACS patient population. The Antithrombotic Trialists' Collaboration analysis found no significant difference between doses >75 mg/day and doses <75 mg/day.[11,12] Re-examination of the data using random effects models demonstrated a lesser effect with increasing aspirin dose,[13] yet, these analyses do not offer true head-to-head dose comparisons.

The Cottbus Reinfarction Trial was a head-to-head study of 701 post-MI patients, which showed that, after 2 years, aspirin 30 mg/day was safer and more efficacious than 1000 mg of aspirin daily.[14] The small DUCCS-II trial randomized 162 acute MI patients receiving thrombolysis to aspirin 81 or 325 mg/day and found no significant difference in clinical outcomes or bleeding complications between the two doses.[15] Husted and colleagues showed a significant 55% reduction in the incidence of reinfarction with aspirin 100 mg/day compared with aspirin 1000 mg/day.[16] In addition, in this study, platelet aggregation and thromboxane formation were similar between doses, suggesting that the worse clinical outcome with the higher aspirin dose cannot be explained by different levels of platelet function inhibition.

## Rationale for Various Aspirin Doses

It has been speculated that the efficacy of aspirin may be limited by the concurrent inhibition of prostacyclin synthesis. Prostacyclin, like thromboxane, is a metabolite of prostaglandin H2 via COX-1, but has actions that counteract thromboxane's effect. Prostacyclin inhibits platelet activation, is an effective vasodilator and augments the antithrombotic activity of the endothelium. Inhibition of prostacyclin synthesis may increase thrombotic tendencies, which is the proposed mechanism responsible for the prothrombotic properties of the selective COX-2 inhibitors. Aspirin has a dose-related effect on prostacyclin synthesis, with substantial inhibition becoming apparent starting at doses in excess of 80 mg/day.[17] On the other hand, thromboxane synthesis has been shown to be fully inhibited with repeated doses of aspirin as low as 30 mg/day in normal subjects.[18] However, persistent thromboxane synthesis has been seen in up to 20% of ACS patients administered aspirin therapy and is associated with an increased risk of atherothrombotic events.[19]

Disease states with enhanced platelet turnover and/or endothelial damage (e.g., atherosclerosis) might decrease the effectiveness of low doses of aspirin and require higher or more frequent doses to suppress the production of thromboxane.[20] Aspirin binds irreversibly to circulating platelets, however, unbound drug remains in circulation for only a short time. Following the elimination of an aspirin dose, new uninhibited platelets are released into circulation. An accelerated platelet turnover does not allow newly generated platelets entering the circulation to be sufficiently exposed to aspirin and leads to a considerable proportion of circulating platelets uninhibited by aspirin. Only 20% of circulating platelets need to be uninhibited to produce normal hemostasis. Providing aspirin in divided doses has been shown to elicit better platelet inhibition in patients with an increased platelet turnover.[21–24]

From a pharmacologic standpoint, the most favorable aspirin dose is one that is safe and provides sufficient inhibition of platelet-dependent thromboxane formation, compensates for the daily influx of new platelets into the circulation and spares the inhibition of prostacyclin formation. Creating even more complexity is that fact that aspirin may exert antiplatelet properties through non-COX-1 pathways.[25,26] Since this 'ideal' dose is purely theoretical and not demonstrable by any biological assay, one should rest on the findings of major clinical trials to estimate the best dose. From trial data, the ISIS-2 trial effectively made the 162 mg/day aspirin dose the gold standard in ACS, but took place prior to the PCI era. The basis for dosing in PCI (325 mg/day) resulted from one small placebo-controlled study of non-ACS patients, which took place prior to the drug-eluting stent era.[11,12,14,16] Several studies have shown that low doses of aspirin appear to be the most favorable for long-term secondary prevention.

Doses ranging from 75 to 325 mg have become standard of care for ACS, however, there are differences of opinion on whether doses from 75 to 100 mg or 300 to 325 mg are more appropriate for routine use in patients following ACS and/or PCI.

## What the Guidelines for ACS Recommend

Prior ACS guidelines recommended moderate-to-high dose aspirin (162–325 mg) for at least 1 month after ACS and stent implantation ().[27,28] However, current ACS guidelines advocate for lower aspirin doses (75–162 mg) and base this recommendation on observational findings, to quote them, "An analysis from the CURE trial suggests a dose-dependent increase in bleeding in patients receiving aspirin plus placebo. The major bleeding event rate was 2.0% in patients taking less than 100 mg of aspirin, 2.3% with 100–200 mg, and 4.0% with greater than 200 mg per day. Therefore, lower aspirin doses of 75–162 mg per day are preferred for long-term treatment" ().[29–31] The very recently updated American College of Chest Physicians guidelines and 2013 American College of Cardiology/American Heart Association guidelines for the management of STEMI even recommend 75–100 mg and 81 mg of aspirin, respectively.[32,33] While the 2013 STEMI guidelines recommend a maintenance aspirin dose of 81–325 mg indefinitely (class I evidence), the guidelines go on to state that "81 mg daily is the preferred maintenance dose" (class IIa evidence).[33] These recommendations are predominantly based on the CURRENT-OASIS 7 trial, where low-dose aspirin (75–100 mg) was found to be similar to high-dose aspirin (300–325 mg) at reducing CV events, but with less minor bleeding.[34]

**Box 1. Aspirin dosing recommendations.**

**Prior ACS guidelines (2005 and 2007 updates)** [27,28]

**Class I**

- For UA/NSTEMI patients treated medically without stenting, aspirin (75–162 mg/day) should be prescribed indefinitely (level of evidence: A) [26]
- For UA/NSTEMI patients treated with bare-metal stents, aspirin 162–325 mg/day should be prescribed for at least 1 month (level of evidence: B), then continued indefinitely at a dose of 75–162 mg/day (level of evidence: A) [26]
- For UA/NSTEMI patients treated with DES, aspirin 162–325 mg/day should be prescribed for at least 3 months after sirolimus-eluting stent implantation and 6 months after paclitaxel-eluting stent implantation then continued indefinitely at a dose of 75–162 mg/day (level of evidence: B) [26]
- "After the PCI procedure, aspirin 325 mg daily should be given for at least 1 month after bare-metal stent implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which daily chronic aspirin use should be continued indefinitely at a dose of 75–162 mg (level of evidence: B)" [27]

**Current ACS guidelines (2004, 2011 and 2012 updates)** [29–31]

**Class I**

- Patients already taking daily aspirin therapy should take 81–325 mg before PCI (level of evidence: B) [23]. However, Class IIa: After PCI, it is reasonable to use aspirin 81 mg/day in preference to higher maintenance doses (level of evidence: B) [28]
- Patients with suspected STEMI should be given promptly aspirin 162 and 325 mg and continued indefinitely at a daily dose of 75–162 mg (level of evidence: A) [29]

**Class IIa**

- "After PCI, it is reasonable to use 81 mg/day of aspirin in preference to higher maintenance doses (level of evidence: B)" [30]

DES: Drug-eluting stent; NSTEMI: Non-ST elevation myocardial infarction; UA: Unstable angina.

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## Efficacy Comparisons of 75–100 Versus 300–325 mg

There is an abundance of data comparing the clinical efficacy of aspirin 81 mg versus aspirin 325 mg.[12,35–43] Most of these data come from indirect comparisons and observational data (). These retrospective analyses consistently show the lack of any increase in efficacy with a higher aspirin dosage.

**Table 1. Observational data comparing aspirin dose in cornerstone clinical trials.**

| Study population | Dose (mg/day) | n | Study findings | Ref. |
|---|---|---|---|---|
| Recent MI, stroke, TIA or double vascular bed disease | 75–162 | 2410 | No difference in death, MI, stroke, recurrent ischemia requiring hospitalization and urgent revascularization | [36] |
| | >162– | | | |

| | | | | |
|---|---|---|---|---|
| | 325 | 2179 | | |
| ACS | <150 | 6128 | No difference in death, MI or stroke | [13] |
| | >150 | 14,341 | | |
| Non-ST elevation ACS | 75–100 | 2695 | No difference in CV death, MI, stroke | [35] |
| | 101–199 | 1525 | | |
| | 200–325 | 2071 | | |
| PCI patients | <100 | 1056 | No difference in CV death, MI, stroke | [43] |
| | 101–199 | 538 | | |
| | >200 | 1064 | | |

ACS: Acute coronary syndrome; CV: Cardiovascular; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; TIA: Transient ischemic attack.

The use of higher aspirin doses in the first 3–6 months following PCI are based on trials that led to the approval of drug-eluting stents.[44,45] However, there was no dose comparison to establish if the higher dose was in fact needed over lower doses. That comparison took place in the only randomized study that directly compared the two aspirin doses in ACS patients.

## Bleeding Comparisons of 75–100 Versus 300–325 mg

As an antiplatelet agent, the most worrisome adverse effect of aspirin is bleeding. Observational data has shown that as aspirin dose increases so does the risk for bleeding, as demonstrated in the BRAVO and CURE trials.[35,36] A meta-regression analysis by Berger *et al.* found a significant association between aspirin dose and major bleeding and that the proportion of patients who experienced major bleeding was higher among patients who received aspirin 325 mg/day in comparison with those who received aspirin 81 mg/day.[39] However, randomized controlled trials, nonrandomized controlled trials and observational studies were included in this meta-analysis, and thus, these interpretations should be interpreted with caution. While the dose-related bleeding effect was reinforced by an additional meta-analysis that included 192,036 patients enrolled in 31 randomized controlled trials, doses of <100 mg/day were associated with a significantly lower rate of major bleeding events.[38] Another meta-analysis of almost 66,000 in 24 randomized controlled trials found no relationship between aspirin dose and gastrointestinal (GI) bleeding.[42]

In addition, the CURRENT-OASIS 7 study found no significant difference in major bleeding between the two doses (2.3% with 75–100 mg vs 2.3% with 300–325 mg; hazard ratio [HR]: 0.99; 95% CI: 0.84–1.17; p = 0.90); however, there were significantly more minor bleeds with the higher dose (5.0 vs 4.4%; p = 0.04).[46] GI bleeds were a rare occurrence, nevertheless, there was a small but statistically significant increase in major GI bleeding (47 [0.4%] vs 29 [0.2%]; p = 0.04) with high-dose versus low-dose aspirin.

While the majority of the *post-hoc* analyses of randomized trials support an increased risk of major bleeding with higher doses of aspirin compared with lower doses, it is not clear if this is seen in routine clinical practice. If the data are accurate, increasing the aspirin dose from 81 to 325 mg in the millions of people who take it could translate into hundreds of thousands of extra major bleeding events per year. However, when scrutinizing these data, one must keep in mind that retrospective analyses and observational data are often plagued by hidden confounders and associations, which may not be causally related. Furthermore, aspirin dose was not randomly assigned in these *post-hoc* analyses and is therefore prone to confounding bias (confounding by indication; i.e., higher risk patients [diabetics, larger infarcts and so on] given higher doses of aspirin) and how they are treated (e.g., patients receiving PCI generally receiving higher dose aspirin). Only one large randomized double-blind ACS study has directly compared

two doses of aspirin within the recommended dose range (75–325 mg), which showed no significant difference in major bleeding between high-dose and lower-dose aspirin.[34]

## Efficacy Comparisons of 75–100 Versus 300–325 mg

The CURRENT-OASIS 7 study was a two-by-two factorial design trial randomizing 25,086 patients with ACS to either double-dose clopidogrel (a 600-mg loading dose on day 1, followed by 150 mg daily for 7 days, and 75 mg daily thereafter) or standard-dose clopidogrel (a 300-mg loading dose and 75 mg daily thereafter) and either high-dose aspirin (300–325 mg daily) or low-dose aspirin (75–100 mg daily).[34]

In the head-to-head aspirin dose comparison of the CURRENT-OASIS 7 study, there was no significant difference between the high- and low-dose aspirin with respect to the primary end point (4.2 vs 4.4%; HR: 0.97; 95% CI: 0.86–1.09; p = 0.61). Nonetheless, patients assigned to the high-dose aspirin regimen had a significant reduction in recurrent ischemia (24 fewer events; 41 [0.3%] vs 65 [0.5%]; HR: 0.63; 95% CI: 0.43–0.94; p = 0.02) and numerically lower all-cause mortality (41 fewer deaths; 273 [2.2%] vs 314 [2.5%]; HR: 0.87; 95% CI: 0.74–1.03; p = 0.10).[34] However, this is confounded by the fact that these patients also received 7 days of 150 mg of clopidogrel versus 75 mg of clopidogrel ( ).[46,47]

**Box 2. Advantages and disadvantages of high- versus low-dose aspirin in acute coronary syndrome in the CURRENT-OASIS 7 study overall population.**

**High-dose aspirin (300–325 mg)**

**Efficacy**

- Less cases of recurrent ischemia 24 less events: 41 (0.3%) vs 65 (0.5%); HR: 0.63; 95% CI: 0.43–0.94; p = 0.02

**Safety**

- No increased risk for major bleeds. Study criteria: 282 (2.3%) vs 286 (2.3%); HR: 0.99; 95% CI: 0.84–1.17; p = 0.90. TIMI criteria: 197 (1.6%) vs 181 (1.4%); HR: 1.09; 95% CI: 0.89–1.34; p = 0.39
- No increased risk of fatal bleeds: 16 (0.1%) vs 15 (0.1%); HR: 1.07; 95% CI: 0.53–2.17; p = 0.85
- Significant reduction in the primary end point (e.g., CV death, MI and stroke) vs in-patients receiving double- vs standard-dose clopidogrel if on high- vs low-dose aspirin: 3.8 vs 4.6%; HR: 0.82; 95% CI: 0.69–0.98; p = 0.03
- Significant reduction in MI/stent thrombosis in PCI patients receiving double- vs standard-dose clopidogrel if on high- vs low-dose aspirin: 2.7 vs 3.8%; HR: 0.71; 95% CI: 0.56–0.90; p = 0.005

**Low-dose aspirin (75–100 mg)**

**Safety**

- Less minor bleeds: 5.0 vs 4.4%; p = 0.04
- Less GI bleeds: 47 (0.4%) vs 29 (0.2%); p = 0.04

CV: Cardiovascular; GI: Gastrointestinal; HR: Hazard ratio; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; TIMI: Thrombolysis in myocardial infarction. Data taken from [34–37,44,45].

A little more than two-thirds of patients underwent PCI in the CURRENT-OASIS 7 study. The PCI subgroup data mirrored the overall study results. High-dose aspirin did not significantly differ from low-dose aspirin, with respect to the primary efficacy and safety end points, but had a significant reduction in recurrent ischemia (31 [0.4%] vs 56 [0.7%]; relative risk: 0.56; 95% CI: 0.36–0.88; p = 0.011) and a significant increase in minor bleeds (5.0 vs 4.3%; relative risk: 1.18; 95% CI: 1.03–1.36; p = 0.019).[46]

## Newer $P2Y_{12}$ Receptor Antagonists (Prasugrel & Ticagrelor)

There was a statistical interaction between clopidogrel and aspirin dose (p= 0.04 for interaction) with the lowest event rates occurring in the group administered high-dose aspirin and high-dose clopidogrel.[46] However, overinterpretation of this interaction is not warranted as the opposite effect was found with tigacrelor. Ticagrelor was found superior to clopidogrel but only when used with aspirin at doses <100 mg.[48] Patients who received aspirin doses >100 mg seemed to have no benefit with ticagrelor (with a strong trend actually favoring clopidogrel) and more bleeding. However, the US FDA complete response review seems to contradict that a significant interaction between ticagrelor and aspirin dose exists.[49–51] Indeed, the FDA complete response review indicates that patients on ticagrelor and aspirin doses ≥300 mg did not have a significant increase in all-cause mortality (HR: 1.27; 95% CI: 0.84–1.93; p = 0.262) or CV mortality (HR: 1.39; 95% CI: 0.87–2.2; p = 0.170).[49,51] Moreover, patients with diabetes (regardless if they were on ticagrelor or clopidogrel) had a significant reduction in major adverse CV events (HR: 0.49; 95% CI: 0.34–0.63; p < 0.0001), 30-day all-cause mortality (HR: 0.33; 95% CI: 0.20–0.56; p < 0.0001) and 30-day CV mortality (HR: 0.35; 95% CI: 0.22–0.55; p < 0.0001) if they received high-dose (≥300 mg) aspirin.[48,50] Thus, more data are clearly needed to determine the optimal dose of aspirin, especially in diabetic patients receiving ticagrelor or clopidogrel. In addition, no statistical interaction has been observed with aspirin and prasugrel.[52,53] Indeed, prasugrel maintained increased efficacy and increased bleeding risk compared with clopidogrel independent of the aspirin dose used at the time of discharge.

It is well known that prasugrel and ticagrelor are very potent inhibitors of ADP-induced platelet aggregation. These agents have also been shown to block thromboxane-mediated pathways, which calls into question whether aspirin is even needed in conjunction with these antiplatelets.[54] Several pharmacodynamics studies have shown that aspirin provides little additional antiplatelet effect when used with potent $P2Y_{12}$ inhibitors.[55–57] At this time, no clinical trial has tested the impact of aspirin in the presence of strong $P2Y_{12}$ receptor blockade.

## Conclusion

Aspirin dosing has changed dramatically over the years, yet despite numerous clinical trials, the appropriate aspirin dose for ACS patients remains uncertain. Pharmacologic and observational data when considered in light of the results of the CURRENT-OASIS 7 study are in agreement that aspirin doses of 75–100 mg/day offer equal efficacy as higher doses, and that these lower aspirin doses may be safer with a reduced risk of bleeding. Still, uncertainty remains whether the uniform use of low-dose aspirin can be applied to all patients or if a tailored dosing approach could be used to target populations that are at risk of experiencing high residual platelet activity. Nevertheless, the weight of evidence and current guidelines support lower doses of aspirin (i.e., 81 mg in the USA and 75–100 mg in Europe) for most ACS patients.

## Future Perspective

An area of uncertainty is whether higher-dose regimens targeting high-risk populations is more effective than treating all patients uniformly. There are a proportion of patients at risk of high residual platelet activity with aspirin, a phenomenon that increases the risk for future thrombotic events.[58] Increasing the dose of aspirin to ≥300 mg has been shown to improve the laboratory response to aspirin.[17,19,59,60] In that regard, it has been proposed that certain high-risk patient populations, such as those with obesity, diabetes, post-ACS and a history of stent thrombosis, might benefit from diagnostic platelet function testing and dose adjustments based on the results.[61] Algorithms have been

developed to tailor aspirin therapy based on platelet function testing.[62] The prognostic value of high platelet reactivity during treatment has been shown repeatedly, but studies investigating the tailored approach have failed to show a reduction in clinical outcomes and, at this point, routine use of such treatment strategies is not recommended.[63]

## Sidebar

**Executive Summary**

**Aspirin for acute coronary syndrome prior to the percutaneous coronary intervention era**

- Aspirin significantly reduces the incidence of cardiovascular (CV) death and myocardial infarction (MI) compared with placebo in acute coronary syndrome (ACS) patients.

**Aspirin for ACS in the percutaneous coronary intervention era**

- The M-Heart II study showed that 6 months of aspirin 325 mg in patients undergoing percutaneous transluminal coronary angioplasty reduced the incidence of death, MI or clinically important restenosis when compared with placebo.

**Rationale for various aspirin doses**

- Aspirin has a dose-related effect on prostacyclin synthesis with substantial inhibition becoming apparent starting at doses in excess of 80 mg/day. On the other hand, thromboxane synthesis has shown to be fully inhibited with repeated doses of aspirin as low as 30 mg/day in normal subjects.
- Disease states with enhanced platelet turnover and/or endothelial damage (e.g., atherosclerosis) might decrease the effectiveness of low doses of aspirin and require higher doses to suppress the production of thromboxane.
- Persistent thromboxane synthesis has been seen in up to 20% of ACS patients administered aspirin therapy and is associated with an increased risk of atherothrombotic events.

**What the guidelines for ACS recommend**

- Prior ACS guidelines recommended moderate-to-high dose aspirin (162–325 mg) for at least 1 month after ACS and stent implantation.
- Current ACS guidelines advocate for lower aspirin doses (75–162 mg) and base this recommendation on observational findings.

**Efficacy comparisons of 75–100 versus 300–325 mg**

- Retrospective analyses consistently show a lack of any increase in efficacy with higher aspirin doses.
- The use of higher aspirin doses in the first 3–6 months following percutaneous coronary intervention are based on the trials that led to the approval of the drug-eluting stents.

**Bleeding comparisons of 75–100 versus 300–325 mg**

- A meta-regression analysis by Berger *et al.* found a significant association between aspirin dose and major bleeding.
- A dose-related bleeding effect with aspirin was also shown in a meta-analysis that included 192,036 patients enrolled in 31 randomized controlled trials in which doses of <100 mg/day were associated with a significantly

lower rate of major bleeding events.

- The CURRENT-OASIS 7 study found no significant difference in major bleeding between low- and high-dose aspirin.

**Efficacy comparisons of 75–100 versus 300–325 mg**

- In the CURRENT-OASIS 7 study, there was no significant difference between the high- and low-dose aspirin with respect to the primary end point.

**Newer P2Y $_{12}$ receptor antagonists (prasugrel & ticagrelor)**

- Ticagrelor was found superior to clopidogrel, but only when used with aspirin at doses <100 mg. Patients who received aspirin doses >100 mg seemed to have no benefit with ticagrelor (with a strong trend actually favoring clopidogrel) and more bleeding. However, more data are needed to determine the optimal dose of aspirin, especially in diabetic patients receiving ticagrelor or clopidogrel.

- No statistical interaction has been observed with aspirin and prasugrel.

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Papers of special note have been highlighted as:

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