Controversies in cardiovascular medicine

Systematic review of thienopyridine discontinuation and its impact upon clinical outcomes

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The optimal length of clopidogrel therapy in patients with acute coronary syndromes or in those who have undergone percutaneous coronary intervention (PCI) remains controversial. We therefore sought to determine the risk of both perioperative and premature discontinuation of clopidogrel. PubMed and EMBASE databases were searched January 2000 through March 2010 for articles written in English and reporting adverse clinical events following discontinuation of clopidogrel. Studies of perioperative clopidogrel cessation are mostly observational, but do suggest a hazard for adverse cardiac events. This appears to be especially high in the first month after PCI, but it is unclear whether there is a ‘safe’ window. Studies of ‘premature’ clopidogrel discontinuation, although mostly retrospective and statistically flawed, suggest that the first 6 months after stenting are highest risk; discontinuation with drug-eluting stents (DESs) is probably higher risk than with bare metal stents, but most studies are of DESs alone. There are no randomized trials sufficient to determine the optimal length of clopidogrel therapy; future randomized clinical trials may provide more clarity.

Keywords
Angioplasty • Clopidogrel • Stents • Surgery

Introduction

Dual antiplatelet therapy with aspirin and clopidogrel improves outcomes in patients with an acute coronary syndrome (ACS) or who are undergoing percutaneous coronary intervention (PCI).1–3 As such, current guidelines recommend dual antiplatelet therapy for ≥1 month (but optimally 12 months) in ACS patients who are medically managed, for ≥1 month (but optimally 12 months) in patients receiving a bare metal stent (BMS), and for 6 to ≥12 months in patients receiving a drug-eluting stent (DES).4–7 Still, premature discontinuation of thienopyridine therapy (by both patients and providers) is fairly common and is marked by higher rates of mortality and stent thrombosis.8–10 Although mechanisms for increased events following thienopyridine discontinuation have been postulated (Figure 1), including the ‘rebound’ phenomenon,11 the optimal length of therapy remains obscure. This is in part because cessation of clopidogrel therapy at any time point may be associated with adverse events.12

Given the uncertainty surrounding the optimal length of thienopyridine therapy in patients who have suffered an ACS or who have undergone PCI, we conducted a systematic review of available evidence regarding adverse cardiac events following discontinuation of clopidogrel. This review focuses on events associated with both perioperative cessation of clopidogrel and those associated with planned or unplanned clopidogrel cessation.

Methods

PubMed and EMBASE databases were searched for articles written in English and reporting adverse clinical events following discontinuation of clopidogrel. The time frame for the articles searched was January 2000 through March 2010. The following search terms were utilized: clopidogrel, acute coronary syndrome, discontinuation, adverse events, adherence, compliance, thrombosis, stent, and percutaneous coronary intervention. References of the articles identified in this manner were also reviewed for articles not identified by the search strategy. After this initial search, it was determined that two distinct

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groups of studies regarding clopidogrel cessation were present in the literature: perioperative clopidogrel discontinuation and clopidogrel discontinuation without a surgical context. Clinical trials, which included randomized studies, prospective cohort studies, and retrospective analyses, were included; abstracts and case reports were excluded. In addition, because of the limited number of articles regarding perioperative cessation of clopidogrel, articles regarding perioperative cessation of ticlopidine were included as well.

Abstracts retrieved by this search strategy were then reviewed for relevance to the present study. If relevant, the full text articles were retrieved and evaluated for inclusion in the present study by both authors independently. Discordance regarding inclusion was resolved by discussion. A total of 13 articles regarding non-randomized studies of perioperative cessation of clopidogrel or ticlopidine, two articles regarding randomized trials comparing different durations of clopidogrel therapy, and 16 articles of non-randomized studies of clopidogrel discontinuation without reference to surgery were ultimately chosen for inclusion in this review.

**Results**

**Perioperative cessation of clopidogrel**

The first reports of adverse events in patients undergoing non-cardiac surgery (NCS) up to 3 months after PCI were in the setting of ticlopidine therapy, with overall in-hospital mortality as high as 20%; mortality approached 90% in patients not taking ticlopidine perioperatively (Table 1). This NCS hazard soon after PCI was also apparent in patients on clopidogrel. Reddy et al. studied 56 patients undergoing NCS up to 15 days after PCI with a BMS, reporting two of five patients with perioperative stent thrombosis after discontinuing clopidogrel. Similarly, Schouten et al. examined 192 patients undergoing NCS up to 2 years after BMS or DES implantation, showing a 30.7% incidence of major adverse cardiac events (MACE) in patients who had discontinued clopidogrel and undergone NCS <30 days after PCI.

Figure 1 Potential mechanisms for increased thrombotic events following thienopyridine discontinuation.

More recent studies have included patients on clopidogrel with longer intervals between PCI and NCS and focused more upon patients with DESs and stent thrombosis as an endpoint. A modest case series from Compton et al. described 38 patients undergoing NCS a median of 260 days after PCI with DESs. They remarkably showed no perioperative adverse cardiac events, with 41% of patients continued on clopidogrel perioperatively. A similar case series of 96 patients undergoing NCS up to 3 years after PCI with a BMS or a DES, from Godet et al. reported a 2% incidence of stent thrombosis; 37% of patients continued clopidogrel perioperatively. And Vicenzi et al. in a case series of 103 patients undergoing NCS <1 year after PCI (stent type not given), showed a perioperative mortality of 4.9%. These authors state, ‘antiplatelet drug therapy was not, or only briefly, interrupted,’ but further details are not given. Rhee et al. however, reported a higher incidence of stent thrombosis (5%) in 141 patients undergoing NCS a mean of 7.6 months after PCI with DESs; although all patients had clopidogrel discontinued, patients with stent thrombosis were not taking clopidogrel for a longer time period. Lastly, Assali et al. described a case series of 78 patients undergoing NCS at least 6 months after DESs. Although 42% continued clopidogrel perioperatively, 2.6% suffered stent thrombosis and 7.7% death or MI.

A larger study by Rabbits et al. of 520 patients undergoing NCS up to 2 years after PCI with DESs showed MACE were actually increased, however, in patients who continued clopidogrel. Leibowitz et al. also reported on 216 patients undergoing NCS after either stenting or balloon angioplasty alone, showing a perioperative mortality of 12% overall; presence or absence of perioperative clopidogrel was not referenced.

Only one study included a (properly powered) multivariable analysis, a cohort of 481 patients/606 cardiac and non-cardiac surgeries a mean of 1.1 years after PCI with a BMS or a DES reported by Anwaruddin et al. Although the risk of MACE was increased in the first 30 days after surgery, neither aspirin nor clopidogrel interrupted, but further details are not given. Rhee et al. however, reported a higher incidence of stent thrombosis (5%) in 141 patients undergoing NCS a mean of 7.6 months after PCI with DESs; although all patients had clopidogrel discontinued, patients with stent thrombosis were not taking clopidogrel for a longer time period. Lastly, Assali et al. described a case series of 78 patients undergoing NCS at least 6 months after DESs. Although 42% continued clopidogrel perioperatively, 2.6% suffered stent thrombosis and 7.7% death or MI.

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It is readily apparent from the above discussion that there is surprisingly little data to guide perioperative management of patients on clopidogrel, with only small non-randomized case series available that are almost invariably without adequate multivariable adjustment. Furthermore, reporting of details regarding clopidogrel (aspirin, for that matter) cessation is inconsistent and often incomplete. In addition, many of the studies do not comment on stent thrombosis specifically or were performed before the standard definition was in force. There is also very little data regarding strategies for restarting clopidogrel in patients that have undergone NCS, although expert opinion and logic would dictate a loading dose of 600 mg as soon as feasible.

Despite this lack of data, the European Society of Cardiology issued recent guidelines regarding the timing of NCS in patients who have undergone PCI: a minimum of 6 weeks, but optimally 3 months, for BMSs; and a minimum of 12 months for DESs. The American College of Cardiology and American Heart Association have not issued formal guidelines regarding perioperative discontinuation of clopidogrel, although a science advisory was issued cautioning against premature discontinuation of clopidogrel in general. One can conclude from these perioperative studies that the risk of adverse cardiac events with NCS in patients who discontinue clopidogrel is probably higher within 6 months of PCI. Nevertheless, the data do not allow for discrimination.
between BMSs and DESs, and there is no clarity regarding a ‘safe’ time period for surgery and/or discontinuation of clopidogrel.

**Randomized trials of duration of clopidogrel therapy**

Two landmark trials, CURE and CREDO, first established the role of clopidogrel (with concurrent aspirin therapy) in patients with an ACS or undergoing PCI. In CURE, 12,562 patients with non-ST elevation MI or unstable angina were randomized to a clopidogrel 300 mg loading dose followed by 3–12 months of maintenance therapy, vs. placebo. In regard to the primary endpoint of cardiovascular death, MI, or stroke, the clopidogrel group had fewer events at a mean follow-up of 9 months (8.5 vs. 11.5%, relative risk 0.74, \( P = 0.02 \)). It should be noted, however, that both trials utilized dual hypotheses, and are thus susceptible to confounding; specifically, they tested the combination of clopidogrel loading and long-term therapy vs. no loading and short-term therapy after PCI.

Only two studies, however, have used a randomized design to compare different durations of clopidogrel. A recent study by Park et al. combined two separate trials that enrolled patients with DESs who were event-free at 12 months, with both randomizing between continued dual antiplatelet therapy vs. aspirin monotherapy. There was no benefit from continued clopidogrel in regard to MI or cardiac death (1.8 vs. 1.2%, \( P = 0.17 \) at a mean 1.1 years retospective cohort with multivariable adjustment

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Time from PCI to NCS</th>
<th>Design</th>
<th>In-hospital results</th>
<th>Thienopyridine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaluza et al.</td>
<td>40 patients with NCS after BMS</td>
<td>&lt;6 weeks/mean 13 days</td>
<td>Case series</td>
<td>20% mortality</td>
<td>7/8 not on ticlopidine died</td>
</tr>
<tr>
<td>Wilson et al.</td>
<td>207 patients with NCS after BMS</td>
<td>&lt;-2 months</td>
<td>Case series</td>
<td>4% MI or stent thrombosis</td>
<td>14% received thienopyridine less than 10 days before NCS</td>
</tr>
<tr>
<td>Sharma et al.</td>
<td>47 patients with NCS after BMS</td>
<td>&lt;-90 days</td>
<td>Case series</td>
<td>18.4% mortality</td>
<td>6/7 not on ticlopidine died</td>
</tr>
<tr>
<td>Reddy et al.</td>
<td>56 patients with NCS after BMS</td>
<td>&lt;-15 days</td>
<td>Case series</td>
<td>14% MACE</td>
<td>2/5 stent thromboses not taking clopidogrel</td>
</tr>
<tr>
<td>Compton et al.</td>
<td>38 patients with NCS after DES</td>
<td>Median 260 days</td>
<td>Case series</td>
<td>0% MACE</td>
<td>41% taking clopidogrel</td>
</tr>
<tr>
<td>Vicenzi et al.</td>
<td>103 patients with NCS after stenting</td>
<td>&lt;1 year</td>
<td>Case series</td>
<td>4.9% mortality</td>
<td>Clopidogrel only ‘briefly’ interrupted</td>
</tr>
<tr>
<td>Leibowitz et al.</td>
<td>216 patients with NCS after POBA (56%) or BMS (44%)</td>
<td>&lt;6 months/mean 33 days</td>
<td>Case series</td>
<td>12% mortality</td>
<td>Not reported</td>
</tr>
<tr>
<td>Schouten et al.</td>
<td>192 patients with NCS after BMS (48%) or DES (52%)</td>
<td>&lt;2 years</td>
<td>Case series</td>
<td>2.6% MACE</td>
<td>5/5 patients with MACE not on clopidogrel</td>
</tr>
<tr>
<td>Godet et al.</td>
<td>96 patients with NCS after DES</td>
<td>&lt;3 years/mean 14 months</td>
<td>Case series</td>
<td>2.0% stent thrombosis</td>
<td>37% continued clopidogrel</td>
</tr>
<tr>
<td>Rabbitts et al.</td>
<td>520 patients with NCS after DES</td>
<td>&lt;2 years/median 203.5 days</td>
<td>Case series</td>
<td>5.4% MACE</td>
<td>9.1% MACE if continued clopidogrel</td>
</tr>
<tr>
<td>Rhee et al.</td>
<td>141 patients with NCS after DES</td>
<td>&lt;12 months/mean 7.6 months</td>
<td>Case series</td>
<td>5.0% stent thrombosis</td>
<td>Patients with stent thrombosis off clopidogrel longer (12 vs. 51 days)</td>
</tr>
<tr>
<td>Assali et al.</td>
<td>78 patients with NCS after DES</td>
<td>&gt;6 months/mean 468 days</td>
<td>Case series</td>
<td>2.6% stent thrombosis, 7.7% death or MI</td>
<td>42% continued clopidogrel</td>
</tr>
<tr>
<td>Anwaruddin et al.</td>
<td>481 patients with surgery after DES</td>
<td>Mean 1.1 years</td>
<td>Retrospective cohort with multivariable adjustment</td>
<td>2.0% stent thrombosis, 9.0% MACE</td>
<td>37% on clopidogrel, but no effect of discontinuation upon MACE</td>
</tr>
</tbody>
</table>

NCS, non-cardiac surgery; BMS, bare metal stent; DES, drug-eluting stent; MI, myocardial infarction; MACE, major adverse cardiac events (definitions vary by trial).  
1 Ticlopidine.  
2 Ticlopidine and clopidogrel.
median follow-up of 19 months. Importantly, however, this event rate was lower than anticipated; the study was thus underpowered to detect a difference. Also worth mentioning is the RACS trial, which compared 30 vs. 180 days of clopidogrel after PCI with BMSs in 1004 patients. Unlike CURE and CREDO, all patients received the same 300 mg loading dose of clopidogrel. Although this study found that the 180-day group had less death, MI, or stroke at 6 months (5.0 vs. 1.7%, \( P = 0.01 \)), the study was greatly underpowered. Furthermore, although randomized, both of these trials were unblinded.

## Timing of clopidogrel discontinuation and adverse events

Numerous non-randomized studies have attempted to examine the hazard associated with ‘premature’ discontinuation of therapy (Table 2). What qualifies as premature, however, is of course variable and debatable. In addition, these studies focus upon patients who have undergone PCI and vary in their proportion of BMSs vs. DESs.

Again, some case series are suggestive of a hazard associated with clopidogrel discontinuation. One of the earliest reports of patients discontinuing clopidogrel after PCI is from Jeremias et al., who described outcomes of 652 patients with sirolimus-eluting stents (SESs). Although the incidence of stent thrombosis was only 1.1%, four of seven (57%) stent thromboses were in patients who had discontinued clopidogrel. In addition, all stent thromboses were within 13 days of PCI. This study, however, was descriptive and without multivariable adjustment. This potential hazard with early discontinuation of clopidogrel with DESs was revisited by Spertus et al., in an analysis of the PREMIER registry. Among 500 patients receiving DESs for acute MI, 13.6% stopped clopidogrel within 30 days. These patients were much more likely to die within 1 year (7.5 vs. 0.7%, \( P < 0.001 \)), and this difference was still significant after adjustment for the propensity to receive clopidogrel (hazard ratio 9.0, 95% confidence interval 1.3–60.6). A small series of patients reported by Jimenez-Quevedo et al., however, showed that of 80 patients in a clinical trial, 3.8% developed stent thrombosis after clopidogrel was discontinued at 1 year after SES implantation. This concern for late DES thrombosis after clopidogrel discontinuation was also described by Pfisterer et al., in a series of 746 patients in the BASKET-LATE trial. These patients all were without adverse cardiac events and stopped clopidogrel at 6 months after PCI with either a BMS or a DES; they were then followed for 1 year thereafter. Stent thrombosis was more frequent in the DES group, 2.6 vs. 1.6%, although there were only 16 events. Case series have thus suggested that both early and late clopidogrel discontinuation in patients with DESs might increase the risk of stent thrombosis.

Larger series of patients have also been published, but they still suffer from the problem of rare events that makes multivariable analysis tenuous. For example, a relatively large patient population of 2229 patients with DESs from Iakovou et al. yielded only 29 stent thromboses. In this study, premature discontinuation of clopidogrel or ticlopidine was defined as <3 months for SESs and <6 months for paclitaxel-eluting stents (PESs). They reported that five of 17 patients with premature discontinuation had stent thrombosis, with a univariable hazard ratio of 152 (52–442, \( P < 0.001 \)); they also reported a multivariable analysis, although this model was over-fitted due to the small number of stent thromboses. Similarly, Kuchulakanti et al. reported on 2974 registry patients with DESs. Among the 1.3% with stent thrombosis, 37% had discontinued clopidogrel, in comparison to 11% in the group without stent thrombosis. A multivariable logistic regression identified clopidogrel cessation as an independent risk factor for stent thrombosis, but this model was also over-fitted. A similar cohort of 1911 patients with DESs from Park et al. found a stent thrombosis rate of 0.8%, or 15 events. Premature clopidogrel discontinuation was defined as <6 months of clopidogrel; this was associated with a univariable hazard ratio of 15.3 (95% CI 5.2–44.8, \( P < 0.001 \)) and grossly over-fitted. Lastly, Banerjee et al. described outcomes in 530 patients who underwent PCI, of whom 85% received DESs, and were free of cardiovascular events at 6 months. Premature clopidogrel discontinuation in this case was defined as <1 year; mortality in such patients appeared to be higher at a mean of 2.4 years (14.8 vs. 3.5%, \( P < 0.001 \)). Again, multivariable analysis was performed but was over-fitted.

There are fortunately studies of clopidogrel discontinuation that are marked by more valid, although often more complex, methods of multivariable adjustment. The first group of such studies utilized stent thrombosis as the primary outcome. Airoldi et al. performed an analysis of 3021 patients with DESs, with stent thrombosis as the outcome (58 events). Utilizing multivariable Cox regression, they found that discontinuation of clopidogrel within 6 months of PCI was associated with stent thrombosis (HR 13.7, 95% CI 4.0–46.7, \( P < 0.001 \)); discontinuation between 6 and 18 months, however, was not associated with stent thrombosis. van Werkum et al. examined the effect of clopidogrel cessation upon a relatively large cohort of 437 patients with definite stent thrombosis, matching them to 866 controls without stent thrombosis. Using multivariable Cox regression, they found that clopidogrel discontinuation at any time point up to 1 year was associated with an increased risk of stent thrombosis. This effect was particularly pronounced for cessation <30 days after PCI, with a hazard ratio of 36.5 (95% CI 8.0–167.8, \( P < 0.0001 \)), but was also present for 30–180 days (HR 4.6, 95% CI 1.4–15.4, \( P < 0.01 \)) and 180–365 days (HR 5.9, 95% CI 1.7–19.8, \( P < 0.0004 \)). Lastly, Schulz et al. studied 6816 patients receiving DESs (both first-generation and ISAR stents). Utilizing numerous multivariable methods that included competing risk regression, they found that clopidogrel discontinuation was associated with stent thrombosis only in the first 6 months after PCI.

Given the difficulty of rare events inherent to studies of stent thrombosis, a second group of studies utilized combined endpoints. Briguori et al. reported results of a retrospective case–control study comparing SESs with BMSs in diabetics, but also analysed predictors of MACE in the SES group of 100 patients. Although this model was arguably over-fitted (four variables for 25 events), they constructed a Cox regression model with clopidogrel cessation as a time-dependent covariable. This yielded an adjusted hazard ratio for MACE of 20.6 (95% CI 1.6–265, \( P = 0.02 \)) associated with clopidogrel discontinuation, presumably at any
### Table 2  Studies of clopidogrel discontinuation and adverse cardiac events

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Design</th>
<th>Clopidogrel cessation time point</th>
<th>Events: clopidogrel vs. no clopidogrel</th>
<th>Adjusted hazard ratio for clopidogrel cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeremias et al.</td>
<td>652 patients with SES</td>
<td>Cohort</td>
<td>Not given</td>
<td>Stent thrombosis: 1.7 vs. 57%</td>
<td>n/a</td>
</tr>
<tr>
<td>Iakovou et al.</td>
<td>2229 patients with DES</td>
<td>Cohort</td>
<td>3 months for SES, 6 months for PES</td>
<td>HR for stent thrombosis off clopidogrel: 90 (30–270, P &lt; 0.001)</td>
<td>Over-fitted</td>
</tr>
<tr>
<td>Briguori et al.</td>
<td>100 patients with DM and SES</td>
<td>Cohort</td>
<td>Patient-dependent</td>
<td>MACE: 26 vs. 100%</td>
<td>HR 20.6 (1.6–265, P = 0.02)</td>
</tr>
<tr>
<td>Spertus et al.</td>
<td>500 patients with DES after MI</td>
<td>Cohort (PREMIER registry)</td>
<td>1 month</td>
<td>Mortality at 1 year: 0.7 vs. 7.5%, P &lt; 0.0001</td>
<td>HR 9.0 (1.3–60.6, P = 0.02)</td>
</tr>
<tr>
<td>Pfisterer et al.</td>
<td>746 patients with BMS (33%) or DES (67%)</td>
<td>Ad hoc analysis of BASKET-LATE</td>
<td>6 months</td>
<td>Stent thrombosis DES vs. BMS: 2.6 vs. 1.3%</td>
<td>n/a</td>
</tr>
<tr>
<td>Kuchulakanti et al.</td>
<td>2974 patients with DES</td>
<td>Cohort (REWARDS registry)</td>
<td>Not given</td>
<td>HR for stent thrombosis off clopidogrel: 0.21 (0.10–0.41, P &lt; 0.0001)</td>
<td>Over-fitted</td>
</tr>
<tr>
<td>Park et al.</td>
<td>1911 patients with DES</td>
<td>Cohort</td>
<td>6 months</td>
<td>HR for stent thrombosis off clopidogrel: 15.3 (5.2–44.8, P &lt; 0.001)</td>
<td>Over-fitted</td>
</tr>
<tr>
<td>Urban et al.</td>
<td>15157 patients with SES</td>
<td>Ad hoc analysis (e-Cypher)</td>
<td>Patient-dependent</td>
<td>n/a</td>
<td>No effect seen</td>
</tr>
<tr>
<td>Airoldi et al.</td>
<td>3021 patients with DES</td>
<td>Cohort</td>
<td>6 months</td>
<td>Stent thrombosis: 0.9 vs. 4.2% at 30 days</td>
<td>HR 13.7 (4.0–46.7, P &lt; 0.001)</td>
</tr>
<tr>
<td>Eisenstein et al.</td>
<td>1241 patients with BMS (60%) or DES (40%), event-free at 6 months</td>
<td>Cohort/landmark</td>
<td>6 months</td>
<td>Death and MI for DES at 2 years: 2.1 vs. 8.4%</td>
<td>3.1 vs. 7.2%, P = 0.02</td>
</tr>
<tr>
<td>Ho et al.</td>
<td>1455 patients with ACS and DES</td>
<td>Cohort</td>
<td>Patient-dependent</td>
<td>Mortality: 19.9 vs. 6.9%, P &lt; 0.001</td>
<td>HR 2.4 (1.6–3.6, P &lt; 0.001)</td>
</tr>
<tr>
<td>Jimenez-Quevedo et al.</td>
<td>80 diabetic patients with SES</td>
<td>Ad hoc analysis of the DIABETES trial</td>
<td>1 year</td>
<td>Stent thrombosis: 3 vs. 0%</td>
<td>n/a</td>
</tr>
<tr>
<td>Daemen et al.</td>
<td>8146 patients with DES</td>
<td>Ad hoc analysis of registry</td>
<td>Patient-dependent</td>
<td>n/a</td>
<td>No effect seen</td>
</tr>
<tr>
<td>Ho et al.</td>
<td>3137 patients with ACS, 50% with PCI</td>
<td>Cohort</td>
<td>Patient-dependent</td>
<td>n/a</td>
<td>IRR for first 90 days off clopidogrel: 1.82 (1.17–2.83)</td>
</tr>
<tr>
<td>Banerjee et al.</td>
<td>530 patients with BMS (15%) or DES (85%), free of events at 6 months</td>
<td>Landmark</td>
<td>1 year</td>
<td>Mortality: 3.5 vs. 14.8%, P &lt; 0.001</td>
<td>Over-fitted</td>
</tr>
<tr>
<td>van Werkum et al.</td>
<td>437 patients with stent thrombosis/866 without, after BMS (68%) or DES (32%)</td>
<td>Case-control</td>
<td>30 days, 6 months, and 1 year</td>
<td>n/a</td>
<td>30 days: HR 36.5 (8.0–167.8, P &lt; 0.0001)</td>
</tr>
</tbody>
</table>
| Schulz et al. | 6816 patients with DES | Cohort | 6 months | Hazard (sten thrombosis) with discontinuation first 6 months only)

DES, drug-eluting stent; SES, sirolimus-eluting stent; DM, diabetes mellitus; HR, hazard ratio; MACE, major adverse cardiac events (definition varies by trial).

*a No multivariable analysis performed.

*b Clopidogrel and ticlopidine.
Effects of thienopyridine discontinuation

This is somewhat in contrast to the findings by Ho et al., who studied a cohort of 1455 veterans after discharge, following PCI for an ACS with a DES or a BMS. Utilizing Veterans Administration pharmacy data, and multivariable Cox regression with clopidogrel use as a time-varying covariate, the adjusted hazard ratio for clopidogrel cessation in regard to all-cause mortality was 2.4 (95% CI 1.6–3.6). Furthermore, this effect was consistent for both BMSs and DESs and was seen at up to 18 months after discharge. Similarly, Ho et al. studied a similar cohort of 3137 veterans discharged on clopidogrel after an ACS, 50% of whom had undergone PCI. Using a multitude of adjustment methods, including Cox regression, Poisson regression, and propensity matching, they specifically examined the hazard of the first 90 days after clopidogrel cessation. Interestingly, this specific time interval, after multivariable adjustment, had an incidence rate ratio of 1.82 (95% CI 1.17–2.83).12

One study by Eisenstein et al. sought to compare the effect of clopidogrel discontinuation in BMSs vs. DESs. Among 1216 patients who were event-free at 6 months after PCI with BMSs or DESs, they compared the effect of clopidogrel therapy at that time point upon death and MI at 24 months. Using multivariable Cox regression and propensity score adjustment, they showed an adjusted incidence of 3.1% for patients with DESs on clopidogrel, vs. 7.2% without clopidogrel (P = 0.02); among patients with BMSs, however, there was no difference. A similar effect was found for patients event-free at 1 year: clopidogrel use continued to be associated with better outcomes in patients with DESs, but not BMSs.41

There are retrospective studies that have not found an effect of clopidogrel cessation upon stent thrombosis, although their number is relatively small. An analysis by Urban et al. of 15 157 patients with SESs and 126 stent thromboses did not show an effect of clopidogrel ‘compliance’ upon the risk of stent thrombosis. Similarly, Daemen et al. in a study of 8146 patients with DESs did not show the absence of clopidogrel therapy to be a risk factor for stent thrombosis. And a study of 10 778 patients with SESs from Kimura et al. showed that discontinuation of thienopyridine and aspirin therapy, but not the thienopyridine alone, was a risk factor for stent thrombosis. Furthermore, landmark analysis of patients event-free at 6 months did not show a benefit from thienopyridine therapy beyond this time point.

The absence of adequate randomized studies comparing different durations of clopidogrel therapy following PCI, and especially DESs, should now be conspicuous. Only the study by Park et al. had a reasonable number of patients; and although it did not suggest a hazard to clopidogrel discontinuation after 1 year, it was underpowered. Non-randomized case series and descriptive studies certainly suggest a hazard to clopidogrel discontinuation, especially within the first 30 days after PCI. Although later cohort studies with adequate multivariable adjustment better quantify this hazard, definitions of ‘premature’ discontinuation are highly variable. Indeed, some studies suggest that, although the highest risk is within the first 30 days, the hazard of discontinuation never disappears. Details regarding the hazard of aspirin discontinuation are also lacking in many reports, and continued therapy with aspirin is often assumed but rarely verified. It is also evident that many of these studies were exclusively in patients with DESs, although one study (Eisenstein et al.) suggested greater hazard from discontinuation of clopidogrel after 6 months or even 12 months for DESs compared with BMSs. A further complicating factor is the type of DESs, as the trials referenced in this review are almost exclusively SESs or PESs. One would expect lower rates of stent thrombosis in general with second-generation DESs, as suggested by studies like SPIRIT IV and COMPARE. Still, the risk of clopidogrel cessation at various time points with second-generation DESs is obscure, and probably requires a patient-level meta-analysis. It also bears mentioning that premature clopidogrel cessation is but one risk factor for stent thrombosis; factors such as diabetes mellitus, low ejection fraction, and lesion-based factors also influence this risk. Major professional societies have nonetheless issued guidelines regarding the optimal duration of clopidogrel therapy (Table 3) in order to bridge the considerable gap between evidence and clinical practice.

### Table 3  Recommendations for length of clopidogrel therapy

<table>
<thead>
<tr>
<th></th>
<th>ESC</th>
<th>ACC/AHA</th>
<th>ACCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bare metal stent</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Minimum</td>
<td>1 month</td>
<td>2–4 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Optimal</td>
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<td>12 months</td>
</tr>
<tr>
<td>Drug-eluting stent</td>
<td>6–12 months</td>
<td>12 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>12 months</td>
<td>12 months</td>
<td>12 months</td>
</tr>
</tbody>
</table>

ESC, European Society of Cardiology; ACC, American College of Cardiology; AHA, American Heart Association; ACCP, American College of Chest Physicians.

### Ongoing and future clinical trials

It is quite obvious from the above discussion that the ideal length of clopidogrel therapy and the hazard associated with discontinuation of clopidogrel are controversial. Especially because of concerns regarding DESs and late stent thrombosis, and because indefinite thienopyridine therapy exposes patients to an undue risk of bleeding, a number of randomized clinical trials have been proposed or are ongoing. One example is the ISAR-SAFE trial, which will randomize 6000 patients receiving DESs between 6 vs. 12 months of clopidogrel. Longer durations will be examined by the DAPT study, which will randomize 20 645 patients with BMSs or DESs to thienopyridine therapy for 12 vs. 30 months, and the ARCTIC trial, which will examine the same duration (as well as clopidogrel therapy ‘tailored’ by VerifyNow results) in 2500 patients. Second-generation DESs are being examined specifically in the OPTIMIZE trial in South America, comparing 3 vs. 12 months of DAPT, and the SECURITY trial in Europe, comparing 6 vs. 12 months of DAPT.

The recent emergence of prasugrel complicates the issue of thienopyridine discontinuation even further. Although this more potent alternative was given for up to 15 months in an exclusively ACS population undergoing PCI in the TRITON-TIMI 38 trial, there are no further data regarding the optimal length of PR.
Conflict of interest: none declared.

References

Effects of thienopyridine discontinuation


