Clinical Presentation 1: A 68-year-old man with a history of treated dyslipidemia was admitted with non–ST-segment–elevation myocardial infarction (MI). Coronary angiography showed a thrombotic subtotal occlusion of the proximal dominant right coronary artery and 50% stenosis in the mid left anterior descending and first obtuse marginal arteries. He underwent percutaneous coronary intervention (PCI) to the proximal right coronary artery with a second-generation drug-eluting stent (DES). How do you decide on the duration of dual antiplatelet therapy (DAPT) in this individual?

Clinical Presentation 2: An 81-year-old woman weighing 52 kg with a history of hypertension and gastroesophageal reflux disease presented with Canadian Cardiovascular Society class III stable angina. Myocardial perfusion imaging showed a moderate area of anterior ischemia. At coronary angiography, she had an eccentric 95% calcified lesion in the mid left anterior descending artery. She also had mild disease (≈30% stenosis) in the proximal right coronary and mid left circumflex coronary arteries. The left anterior descending artery was stented with a second-generation DES. How do you apply the evidence for DAPT in this patient?

Background

DAPT with aspirin and a P2Y$_{12}$ receptor inhibitor is an essential component of the treatment of patients with acute coronary syndromes (ACS) and those undergoing PCI. DAPT after ACS reduces death and MI compared with aspirin alone, both in patients treated with PCI and in those who are managed conservatively. After elective PCI for stable coronary disease, DAPT reduces ischemic events and stent thrombosis (ST). However, these benefits come at the cost of increased risk of bleeding, raising the question about how to best balance efficacy and safety in determining the duration of DAPT.

Duration of DAPT After ACS

What Is the Evidence?

Current treatment guidelines recommend 1 year of DAPT after ACS. This recommendation is based largely on the duration of treatment in the pivotal P2Y$_{12}$ receptor inhibitor.
inhibitor studies.13,10 Accumulating data support extending DAPT beyond 1 year after MI. In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial,11 among patients with prior MI, adding clopidogrel to aspirin was associated with a reduction in cardiovascular death, MI, or stroke compared with treatment with aspirin alone.12 The DAPT trial demonstrated that in patients treated with PCI, compared with 12 months of treatment, extending DAPT for 30 months with clopidogrel or prasugrel reduced ST by two thirds and the composite of death, MI, or stroke by about one third, with ≈2.5-fold greater major bleeding.13 The ischemic benefit with extended DAPT was larger when PCI was performed in the setting of MI rather than stable angina.5 A second trial, Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54), showed a reduction in ischemic events with ticagrelor in high-risk patients with a prior MI 1 to 3 years before enrollment.14 Treatment up to 3 years with ticagrelor at a dose of 90 or 60 mg twice daily resulted in a 1.2% absolute or 15% relative risk reduction in the composite of cardiovascular death, MI, or stroke compared with placebo. This benefit also came at the cost of more major bleeding (but not fatal or intracranial bleeding), which was ≈2.5-fold greater with ticagrelor. The overall tolerability of ticagrelor seemed more favorable at the lower dose of 60 mg twice daily compared with the higher dose of 90 mg twice daily.

In a meta-analysis of >33,000 patients stabilized after ACS, extended DAPT beyond 1 year resulted in an absolute risk reduction of 1.1% in the composite of cardiovascular death, MI, or stroke (number needed to treat, 91) over a mean follow-up of 31 months at a cost of a 0.8% absolute increase in major bleeding (number needed to harm, 132; Figure 1).15 Importantly, significant reductions in each component of the composite were observed, including cardiovascular death, and intracranial hemorrhage and fatal bleeding events were infrequent and not significantly increased. The studies typically consisted of predominantly biomarker-positive patients with ACS and excluded patients at high risk of bleeding. Therefore, the results may not be generalizable to all patients with ACS. Patients with ACS who have tolerated DAPT without bleeding and are not at high risk of bleeding appear to be most suitable for extended therapy beyond 1 year.

**Recommendations for Individualizing Duration of DAPT After ACS**

A pragmatic approach that individualizes the duration of DAPT after ACS on the basis of the balance of bleeding and ischemic risk within the context of the available evidence is suggested.

1. Except for patients at very high bleeding risk (eg, prior intracranial hemorrhage, recent gastrointestinal bleeding, or concomitant anticoagulation use), at least 1 year of treatment with DAPT should remain the standard.

2. Among those at very high bleeding risk or among those who experience significant bleeding while on DAPT, a shorter duration of <1 year is advisable. A minimum duration of 1 month is recommended if PCI is performed with a bare metal stent or current-generation DES.

3. In patients at increased risk of bleeding (eg, age >75 years, prior stroke/transient ischemic attack, low body weight <60 kg, renal dysfunction on dialysis, liver synthetic dysfunction), 1 year of DAPT is sufficient.

4. In all others, extended DAPT beyond 1 year is advised, particularly among those with clinical (eg, diabetes mellitus, peripheral artery disease, additional prior cardiovascular event, prior coronary revascularization) or angiographic (eg, left main stenting, bifurcation stenting) features associated with high ischemic risk. A dose of ticagrelor 60 mg twice daily or clopidogrel 75 mg daily is recommended beyond 1 year.

5. An ongoing assessment of bleeding and ischemic risk should be performed at least annually to determine whether DAPT should be continued.

<table>
<thead>
<tr>
<th>Major adverse cardiovascular events</th>
<th>Risk Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death</td>
<td>0.76 (0.67 - 0.90)</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.85 (0.74 - 0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.70 (0.55 - 0.88)</td>
<td>0.003</td>
</tr>
<tr>
<td>Stent Thrombosis (Definite/Probable)</td>
<td>0.81 (0.68 - 0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>1.73 (1.19 - 2.50)</td>
<td>0.004</td>
</tr>
<tr>
<td>Non-cardiovascular death</td>
<td>1.03 (0.86 - 1.23)</td>
<td>0.76</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.92 (0.83 - 1.03)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Figure 1. Risk of individual cardiovascular and bleeding end points in a comparison of extended dual antiplatelet therapy (DAPT) with aspirin alone in patients with myocardial infarction. CI indicates confidence interval. Reproduced with permission from Udell et al.15 Copyright © 2016 European Society of Cardiology.
Duration of DAPT After Second-Generation DES Implantation for Stable Coronary Disease

What Is the Evidence?
The recommended duration for DAPT after implantation of a DES was extended to 1 year after recognition of late ST with the first-generation devices. Lower risk of late ST with the current second-generation DES has been the basis for the reconsideration of abbreviating the duration of DAPT after PCI. Recently, several randomized, controlled studies have shown reduced bleeding rates with no increase in ischemic events, including ST, with a shortened duration of DAPT <12 months, challenging the notion that 1 year of DAPT is routinely necessary with current-generation DES in a non-ACS setting. However, these studies should be interpreted in the context of their small sample size and reduced statistical power, open-label design with potential for observer bias, lower-than-expected event rates, and follow-up limited in many cases to 1 year. Combined analyses of these trials of standard versus abbreviated duration of DAPT demonstrate in both groups similar rates of mortality, MI, and ST with lower rates of bleeding with 3 to 6 months compared with ≥12 months of DAPT (Figure 2). Therefore, the 2014 European and 2016 US guidelines recommend DAPT for 6 months after implantation of a second-generation DES for a non-ACS indication.

Extended DAPT beyond 1 year was associated with a reduction in ST and the composite of death, MI, or stroke in the large DAPT trial. However, noncardiovascular mortality was unexpectedly greater with extended DAPT. A meta-analysis of 10 studies including >31 000 patients also found an increase in noncardiovascular mortality with extended DAPT, which was not offset by benefit in cardiac mortality. Although the definitive mechanisms of the greater risk of noncardiovascular mortality remain unclear, greater propensity to bleeding on DAPT might increase mortality in patients who have trauma or in whom cancer develops. These results do not favor routinely extending DAPT beyond 12 months in non-ACS patients treated with current second-generation DES. Although clopidogrel remains the currently recommended P2Y12 receptor inhibitor in DAPT after PCI in non-ACS patients, a number of studies are examining the effectiveness of alternate P2Y12 receptor inhibitors with varying durations of DAPT.

Recommendations for Individualizing Duration of DAPT After Coronary Stenting in a Non-ACS Stable Setting

1. Except for those at high bleeding risk, at least 6 months of DAPT is recommended.
2. Among those at high bleeding risk, a shorter duration of DAPT (eg, 3 months) is recommended, with a minimum treatment duration of 1 month.
3. Extending DAPT beyond 12 months might be considered for patients not at high risk of bleeding with high-risk clinical or angiographic features.
Resolution
The first patient with non–ST-segment-elevation MI treated with a single contemporary second-generation DES is not at increased risk for bleeding. Therefore, we recommended treatment with aspirin and ticagrelor 90 mg twice for the first year. If there is no evidence of significant bleeding, DAPT should be continued after the first year with ticagrelor at a reduced dose of 60 mg twice daily. Clopidogrel 75 mg daily is a reasonable alternative to ticagrelor if there are side effects or barriers to long-term adherence such as cost. Bleeding and ischemic risk should be assessed at least annually.

The second patient with stable ischemic heart disease with a single-vessel focal discrete lesion who was treated with a contemporary second-generation DES is at higher-than-average bleeding risk because of her older age and low body weight. Because her ischemic risk is not higher than average and her bleeding risk is relatively high, we recommended treating her with aspirin and clopidogrel for 3 to 6 months.

Disclosures
Dr Bagai has received speaker’s honoraria from AstraZeneca. Dr Bhattacharjee discloses the following relationships: Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; Board of Directors: Boston VA Research Institute and Society of Cardiovascular Patient Care; chair: American Heart Association Quality Oversight Committee; Data Monitoring Committee: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute; honoraria: American College of Cardiology (senior associate editor, Clinical Trials and News, ACC.org), Belvoir Publications (editor in chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (editor in chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (guest editor; associate editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, Cardiology Today’s Intervention), Society of Cardiovascular Patient Care (secretary/treasurer), and WebMD (CME steering committees); other: Clinical Cardiology (deputy editor); research funding: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi Aventis, and The Medicines Company; royalties: Elsevier (editor, Cardiovascular Intervention: A Companion to Braunwald’s Heart Disease); site coinvestigator: Biotronik, Boston Scientific, and St. Jude Medical; trustee: American College of Cardiology; and unfunded research: FlowCo, Plx Pharma, and Takeda. Dr Eikelboom has received honoraria and research support from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly Inc, Janssen, Pfizer, and Sanofi Aventis. Dr Mancini has received honoraria from AstraZeneca. Dr Cohen discloses consulting relationships with AstraZeneca, Eli Lilly Inc, Amgen, Medtronic, and Abbott Vascular; research support from AstraZeneca, Medtronic, and Boston Scientific; and speaking honoraria from AstraZeneca and Abbott Vascular. Dr Vijayaraghavan has received honoraria from AstraZeneca and educational support from Pfizer, Bristol-Myers Squibb, and St. Jude Medical. Dr Tanguay has received research support from Abbott Vascular, AstraZeneca, Eli Lilly Inc, GlaxoSmithKline, Ikaria, and Roche, as well as speaking or consulting honorarium from Abbott Vascular, Actelion, AstraZeneca, Bayer, and Eli Lilly Inc. Dr Verma has received honoraria or grant support from Abbott Vascular, AstraZeneca, Bayer, BI, Lilly, Pfizer, Merck, Novartis, Amgen, Sorin, Abbott, and Janssen. Dr Mehta has received research grants from AstraZeneca and Boston Scientific. Drs Cheema and Udell report no conflicts.

References


Individualizing Duration of Dual Antiplatelet Therapy After Acute Coronary Syndrome or Percutaneous Coronary Intervention


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