Duration of Dual Antiplatelet Therapy after Coronary Stent Placement: How long is too long?


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Resident Rounds

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Learning objectives:

1. Define dual antiplatelet therapy and its’ role in therapy for patients after coronary artery stenting.
2. Understand the pathophysiology behind acute coronary syndromes, percutaneous coronary interventions and stent thrombosis.
4. Examine the benefits and risks of the medications used for dual antiplatelet therapy.
5. Formulate recommendations based on the current literature to find the best evidence-based recommendation for the duration of dual antiplatelet therapy in this population.
I. **Background: Acute coronary syndromes and the role of dual antiplatelet therapy**
   A. **Definitions**
      1. Dual antiplatelet therapy (DAPT) = Combination of aspirin and a P2Y$_{12}$ platelet receptor inhibitor to prevent stent thrombosis after a percutaneous coronary intervention
      2. Percutaneous coronary intervention (PCI) = reperfusion of a coronary artery based on placement of either a bare metal stent (BMS) or a drug-eluting stent (DES) in patients with acute coronary syndrome (ACS)
   B. **Epidemiology**
      1. 1.1 Million Americans will have an ACS event this year. The following are risk factors for coronary artery disease:
         a) Age: >45 years in men and >55 years in women
         b) Smoking
         c) Hypertension
         d) Hyperlipidemia
         e) Diabetes Mellitus
         f) Physical Inactivity
         g) Overweight or obese body mass index
         h) Family history of coronary heart disease or stroke
      2. Coronary heart disease is estimated to have direct and indirect costs on the healthcare system of $195 Billion
      3. 62% of patients with a ST-segment elevated myocardial infarction are treated with PCI

II. **Pathophysiology of ACS requiring PCI**
   A. ACS develops due to underlying coronary artery disease
      1. Development of atherosclerotic plaques that narrow the coronary lumen resulting in decreased oxygen supply to the myocardium
      2. Classified based on electrocardiogram changes: ST-segment elevation myocardial infarction (MI), non ST-segment elevation MI, or unstable angina
      3. Significant stenosis is defined as $\geq$ 70% narrowing of the coronary artery requiring intervention and revascularization through coronary stent placement
B. Post-intervention with stent placement alone is not optimal as coronary stents are susceptible to thrombosis themselves resulting in re-occlusion of the coronary artery
   1. Dual therapy with antiplatelet medications is recommended to reduce this risk for stent thrombosis\textsuperscript{5}
   2. Stent Thrombosis occurs primarily in the first 30 days after stent placement
      a) Overall prevalence ranges from 0.2\% - 0.6\% per year\textsuperscript{6}
      b) However mortality after stent thrombosis can be as high as 45\%\textsuperscript{7}

III. \textit{2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention}

A. Most current version published in 2011 as a joint effort from the American College of Cardiology Foundation, American Heart Association, and Society for Cardiovascular Angiography and Interventions

B. Classifications:
   1. Class I: the strongest recommendation and the intervention \textbf{should} be performed
   2. Class IIa: benefit still greater than the risk and the intervention is \textbf{reasonable}
   3. Class IIb: benefit may be equal to the risk and the intervention \textbf{may be considered}
4. Level A to C represents the certainty of treatment effect from strongest evidence to weakest
C. Recommendations:

1. CLASS I
   a) After PCI, use of aspirin should be continued indefinitely. (Level of Evidence: A)
   b) The duration of P2Y\textsubscript{12} inhibitor therapy after stent implantation should generally be as follows:
      (1) In patients receiving a stent (BMS or DES) during PCI for ACS, P2Y\textsubscript{12} inhibitor therapy should be given for at least 12 months. (Level of Evidence: B)
      (2) In patients receiving DES for a non-ACS indication, clopidogrel 75 mg daily should be given for at least 12 months if the patient is not at high risk of bleeding (Level of Evidence: B)
      (3) In patients receiving BMS for a non-ACS indication, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks). (Level of Evidence: B)
   c) Patients should be counseled on the importance of compliance with DAPT and that therapy should not be discontinued before discussion with their cardiologist. (Level of Evidence: C)

2. CLASS IIa
   a) After PCI, it is reasonable to use aspirin 81 mg per day in preference to higher maintenance doses. (Level of Evidence: B)
   b) If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by a recommended duration of P2Y\textsubscript{12} inhibitor therapy after stent implantation, earlier discontinuation (e.g., 12 months) of P2Y\textsubscript{12} inhibitor therapy is reasonable. (Level of Evidence: C)

3. CLASS IIb
   a) Continuation of clopidogrel, prasugrel, or ticagrelor beyond 12 months may be considered in patients undergoing placement of DES. (Level of Evidence: C)

IV. Pharmacotherapy of Dual Antiplatelet Therapy
   A. Aspirin
      1. Irreversibly inhibits formation of prostaglandin derivative, thromboxane A2 thereby inhibiting platelet aggregation
      2. Pharmacodynamics
         a) Absorption: rapid
         b) Distribution: into most body fluids and tissues
         c) Metabolism: hydrolysis to salicylate $\rightarrow$ hepatic conjugation $\rightarrow$ excretion
d) Excretion: urinary
e) Half-life: 3 hours for metabolites
f) Dosing: 81 mg - 325 mg

3. Adverse effects⁹
a) Low incidence of bleeding - 2%
b) Gastrointestinal ulcer - 6-30%

B. P2Y₁₂ Platelet inhibitors
1. Block the P2Y₁₂ component of the ADP receptors on the platelet surface which prevents activation of the GPIIb/IIIa receptor complex and preventing platelet aggregation.¹⁰

Figure 2

![Image](http://www.atmph.org/article.asp?issn=17556783;year=2013;volume=6;issue=1;spage=14;epage=19;aulast=Patel)

2. Clopidogrel¹⁰
a) Thienopyridine
b) Pharmacodynamics
   (1) Absorption: well absorbed and dose-dependent time to peak
   (2) Distribution: 98% protein binding
   (3) Metabolism: pro-drug that requires hepatic hydrolysis mediated by the CYP2C19 enzyme to active metabolite
   (4) Excretion: 50% urine, 46% feces
   (5) Half-life: 6 hours for pro-drug, 30 minutes for active metabolite
c) Adverse effects¹⁰
   (1) Gastrointestinal bleeding: 2%

3. Prasugrel¹¹
a) Thienopyridine
b) Pharmacodynamics
   (1) Absorption: rapid
   (2) Distribution: large volume of distribution for active metabolite
(3) Metabolism: intestinal and serum hydrolysis → oxidation via CYP450 enzymes to active metabolite

(4) Excretion: 68% urine, 27% feces

(5) Half-life: 7 hours for active metabolite

c) Adverse effects\textsuperscript{11}

(1) Hypertension: 8%
(2) Headache: 6%
(3) Gastrointestinal bleeding: 2%

4. Ticagrelor\textsuperscript{12}
   a) Non-thienopyridine
   b) Pharmacodynamics
      (1) Absorption: Rapid
      (2) Distribution: large volume of distribution
      (3) Metabolism: hepatic activation by CYP3A4/5 enzyme to active metabolite
      (4) Excretion: 26% urine, 58% feces
      (5) Half-life: 7 hours for parent drug, 9 hours for active metabolite

c) Adverse effects\textsuperscript{12}

(1) Major Bleeding: 12%
(2) Dyspnea: ≥ 14%

Table 1: Antiplatelet therapy table\textsuperscript{9-12}

<table>
<thead>
<tr>
<th>Medication</th>
<th>MOA</th>
<th>Reversible Platelet Inhibition</th>
<th>Pro-drug</th>
<th>Reversal strategy</th>
<th>Pearls</th>
<th>Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Inhibits cyclooxygenase-1 and 2</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No antidote Normal platelet function within 7-10 days Chronic NSAID use can compromise antiplatelet effects; Monitor for GI ulceration</td>
<td>Varies $0.77</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Clopidogrel (Plavix\textsuperscript{®})</td>
<td>Inhibits P2Y\textsubscript{12} component of ADP receptors</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No antidote Normal platelet function within 7-10 days CYP2C19 inhibitors or polymorphisms may affect concentration of active metabolite</td>
<td>75mg: $208.80</td>
</tr>
</tbody>
</table>
Prasugrel (Effient®) | Inhibits P2Y<sub>12</sub> component of ADP receptors | No | Yes | No antidote | Reduce maintenance dose to 5 mg in patients <60 kg | Contraindicated in patients with history of stroke, TIA | Normal platelet function within 5-9 days | $388.08

Ticagrelor (Brilinta®) | Inhibits P2Y<sub>12</sub> component of ADP receptors | Yes | No | No antidote | Maintenance aspirin dose should not exceed 81 mg | CYP3A4 drug interactions | Normal platelet function within 3-5 days | BID dosing | $342.54

V. The Controversy: Short-term Versus Long-term DAPT

A. Benefit from longer duration of DAPT

1. Decreased risk of late-stent thrombosis
   a) Risk factors for stent thrombosis include:\textsuperscript{13}:
   b) Older age
   c) Diabetes mellitus
   d) late-onset or early stopping of antiplatelet therapy
   e) insufficient response to antiplatelet therapy
   f) inappropriate stent placement or type
   g) suboptimal PCI
   h) renal insufficiency
   i) low left ventricular ejection fraction
2. Decreased risk of major adverse cardiovascular and cerebrovascular events

B. Risk of prolonged duration of DAPT
   1. Increased risk of minor and major bleeding, especially for at risk patients
      a) Bleeding definitions used in clinical trials:
         b) Thrombolysis in Myocardial Infarction: TIMI
            (1) Major: intracranial hemorrhage, overt hemorrhage resulting in hemoglobin decrease of ≥ 5 g/dL, fatal bleeding
            (2) Minor: clinically overt hemorrhage resulting in hemoglobin decrease of 3- <5 g/dL
      c) Global use of strategies to open occluded arteries: GUSTO
         (1) Severe or life-threatening: intracerebral hemorrhage, substantial hemodynamic compromise
         (2) Moderate: requiring blood transfusion in absence of hemodynamic compromise
         (3) Mild: bleeding that does not meet above criteria

2. Potential increased risk of death from all causes

VI. Literature Review

Table 2: Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials.\textsuperscript{15}

<table>
<thead>
<tr>
<th>Objective</th>
<th>To assess the benefits and risks of 2 separate DAPT strategies, short term (&lt;12 months) or extended (&gt;12 months) in comparison to standard 12 month therapy after PCI with drug-eluting coronary stents</th>
</tr>
</thead>
</table>
| Exclusion criteria | • Observational design  
 • Patients without documented coronary artery disease or those with peripheral artery/cerebrovascular disease  
 • PCI without stents or with BMS  
 • No reporting of duration of DAPT |
| Clinical endpoints | Primary = cardiovascular mortality, MI, STent thrombosis (ST), major bleeding and overall mortality  
 Secondary = repeat revascularization, cerebrovascular accident |
| Results | • 338 initial studies → 295 excluded based on title or abstract → 33 had some exclusion criteria: 10 randomised trials included overall  
 • Cardiovascular mortality and MI: 8 trials included data on cardiovascular mortality and all 10 included data on MI  
   ○ No significant difference between short-term or extended DAPT and standard 12 month DAPT for cardiovascular mortality  
   ○ Significant reduction in MI for extended DAPT in

Kernodle Duration of DAPT
comparison with 12 month therapy (Appendix A)

- Stent Thrombosis: all 10 studies included data on definite/probable stent thrombosis:
  - No significant difference in ST for short term and 12 month DAPT
  - Significant 67% odds reduction of definite/probable ST with extended DAPT compared to standard therapy; also significant reduction in definite and very late stent thrombosis for extended therapy (Appendix B)
  - Number needed to treat (NTT): 152

- Major Bleeding: all 10 studies included data according to TIMI criteria
  - Short-term therapy had a significant reduction in major bleeding; NNT = 385
  - Extended therapy had a significant 62% increase in major bleeding;
  - Number needed to harm = 135 (Appendix C)

- All cause mortality: all 10 trials had data for all cause death
  - No significant difference for short-term DAPT
  - Significantly higher risk of all cause death in extended DAPT
  - Number needed to harm: 238 (Appendix D)

Author's Conclusion

The two main findings were that short term DAPT resulted in no similar rates of ST and MI, but was associated with a decreased risk of major bleeding. Secondly, extended DAPT showed significant reductions in ST and MI but increased risk of major bleeding and increased all cause mortality. Current standard of 12-month therapy may be inappropriate and it may be better to customize and shorter duration or extended duration of therapy based on the patient.

Limitations/Strengths

- Limitations:
  - Meta-analysis design allows for only trial level data not specific patient data
  - Exclusion of lots of trials

- Strengths:
  - Included only randomised trials
  - Included broad set of patients including stable and unstable, low and high risk patients
  - Variety of antiplatelet agents used in the trials and variety of drug-eluting stents
  - Conducted sensitivity analyses using patients with with or without ACS, younger and older than 65 years, those treated with different P2Y₁₂ Platelet inhibitors which showed no significant differences

Application to practice

It is appropriate to examine patient characteristics when making a clinical decision on duration of DAPT. A broad recommendation for 12 month therapy may be less appropriate and could be replace with short-term or extended DAPT depending on the patient.
Table 3: **Twelve or 30 months of dual antiplatelet therapy after drug eluting stents**

Mauri L, Kereiakes DJ, Yeh RW, et al.

<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>To determine whether DAPT beyond the standard 12 months reduces the rate of either coronary-stent thrombosis or ischemic events. This trial examined the risk and benefits of continuing DAPT beyond 1 year.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>An international, multicenter randomized, placebo-controlled trial. Uniform randomized trial design across all sites. Patients were enrolled within 72 hours after stent placement. They were started on open label aspirin and thienopyridine therapy. Then at 12 months eligible patients were randomly assigned to continue thienopyridine or start placebo in a 1:1 method. All patients continued aspirin therapy. Patients continued taking medication or placebo until 30 months. Follow-up continue for an additional 3 months after therapy ceased.</td>
</tr>
</tbody>
</table>
| **Study population** |  ● Inclusion criteria  
  ○ 18+ years of age  
  ○ Eligible for DAPT after treatment with a DES  
  ○ Enrolled within 72 hours after stent placement  
  ○ Adherent to thienopyridine in first 12 months  
  ● Exclusion criteria  
  ○ Major cardiovascular or cerebrovascular event at 12 months  
  ○ Repeat revascularization in first 12 months  
  ○ Moderate or severe bleeding in first 12 months  |
| **Clinical endpoints** | Co-primary efficacy = definite or probable ST and major adverse cardiovascular and cerebrovascular events  
  Primary Safety = moderate or severe bleeding according to the GUSTO criteria  |
| **Results** |  ● 25, 682 Patients enrolled → 5020 randomized to aspirin +thienopyridine, 4941 randomized to aspirin +placebo (Appendix E)  
  ● Thienopyridine group had a significant lower incidence of stent thrombosis: 0.4% vs 1.4% and a significantly reduced incidence of MACCE: 4.3% vs 5.9% (Appendix F)  
  ● However in comparison to placebo the thienopyridine group had a significantly increased rate of death from all causes: 2.0 vs 1.5%  
    ○ Death from cardiac causes showed no significant differences  
    ○ Significant differences in cancer related deaths  
  ● The thienopyridine group had significantly increased rate of severe or moderate bleeding: 2.5% vs 1.6%  
    ○ Did not meet non-inferiority criteria compared to placebo  |
| **Author’s Conclusion** | In patients treated with drug-eluting stents, irrespective of which stent or thienopyridine, continuation of thienopyridine plus aspirin therapy extended beyond 1 year reduced the risk of ischemic events in comparison to aspirin alone.  |
| **Limitations/Strengths** |  ● Limitations  
    ○ Large number of patients excluded due to occurrence of cardiovascular event, major bleeding, stent thrombosis or non-adherence  
    ○ May not be generalizable to BMS patients or non-thienopyridine treatments  |
No comparison among the different thienopyridines
- Funded by stent and pharmaceutical manufacturers

- Strengths
  - Large, international randomized trial
  - Unblinded, independent data and safety monitoring committee
  - Broad inclusion of patients with a variety of DESs and thienopyridine treatments
  - Appropriately powered
  - Follow-up of discontinuation of study medication for additional 3 months
  - High retention rate for follow-up (94.3% across both treatment groups)

Application to practice
- There may be additional benefit to continue thienopyridine use beyond 12 months in patients with no major cardiovascular events, bleeding events, or stent thrombosis. This may be limited due to the increased risk of bleeding and increased risk of death from all causes.

VII. Conclusion
A. Increased duration of DAPT past 12 months is likely beneficial for most patients especially those most at risk for stent thrombosis
  1. Excluding patients at high risk for bleeding
B. In contrast, shortened DAPT therapy less than 12 months may be beneficial for some patients
  1. Especially those at high risk for bleeding
C. Application to practice:
  1. Evaluate patients currently receiving DAPT for bleeding risk, and if eligible for continued duration of therapy advise patient to have discussion with provider
  2. Make recommendation to prescribers to continue DAPT beyond 12 month recommendation if appropriate
D. Areas for further research
  1. Continue to study the desired duration of DAPT to maximize benefits and minimize bleeding risk
  2. Analysis between thienopyridines and other antiplatelet medications (i.e. ticagrelor) in regards to all cause mortality and bleeding outcomes17
Acknowledgements:

Nathan Pope, PharmD, BCACP, FACA; Residency Director; HEB Pharmacy/ The University of Texas College of Pharmacy PGY1 Residency Program

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References


8. Witzenbichler B. Dual antiplatelet therapy after drug eluting: is it time to slacken the reins?. J Am Coll Cardiol. 2012; 6(15)


Abbreviations

ACS – Acute Coronary Syndrome
ADP – Adenosine diphosphate
BMS – Bare metal stent
CAD – Coronary Artery Disease
DAPT – Dual antiplatelet therapy
DES – Drug-eluting stent
GI – Gastrointestinal
GUSTO - Global use of strategies to open occluded arteries
MACCE – Major adverse cardiovascular or cerebrovascular event
MI – Myocardial infarction
NNT – Number needed to treat
NSAID – Non-steroidal anti-inflammatory
PCI – Percutaneous coronary intervention
ST – Stent Thombosis
TIMI – Thrombolysis in Myocardial Infarction
Appendices

Appendix A \textsuperscript{14}:

<table>
<thead>
<tr>
<th>Study</th>
<th>No of events/total</th>
<th>Odds ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (95% CI)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Short term</td>
<td>12 month</td>
<td>M-H, fixed</td>
<td>M-H, fixed</td>
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<tr>
<td><strong>Cardiovascular mortality</strong></td>
<td></td>
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<tr>
<td>EXCELLENT\textsuperscript{12}</td>
<td>2/722</td>
<td>3/721</td>
<td>4.2</td>
<td>0.66 (0.31 to 3.99)</td>
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<tr>
<td>ITALIC\textsuperscript{18}</td>
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<td>3/924</td>
<td>4.2</td>
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<td>32/1606</td>
<td>44.5</td>
<td>0.91 (0.54 to 1.50)</td>
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<td>24/987</td>
<td>33.1</td>
<td>1.00 (0.57 to 1.78)</td>
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<td>4/1058</td>
<td>5.7</td>
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<td>6/717</td>
<td>8.2</td>
<td>1.05 (0.34 to 3.28)</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td>68/5977</td>
<td>72/6013</td>
<td>100.0</td>
<td>0.95 (0.68 to 1.33)</td>
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<tr>
<td><strong>Test for overall effect:</strong></td>
<td>z = 0.31, P = 0.76</td>
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<table>
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<th>Extended</th>
<th>12 month</th>
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<tr>
<td>DAPT\textsuperscript{10,19}</td>
<td>50/5020</td>
<td>52/4941</td>
<td>73.4</td>
<td>0.95 (0.64 to 1.40)</td>
</tr>
<tr>
<td>DES LATE\textsuperscript{20,21}</td>
<td>28/2531</td>
<td>19/2514</td>
<td>26.6</td>
<td>1.47 (0.92 to 2.64)</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td>78/7551</td>
<td>71/7455</td>
<td>100.0</td>
<td>1.09 (0.79 to 1.50)</td>
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<td><strong>Test for heterogeneity:</strong></td>
<td>$\chi^2 = 1.50$, df = 2, P = 0.22, I$^2$ = 34%</td>
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<td><strong>Test for overall effect:</strong></td>
<td>z = 0.50, P = 0.62</td>
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</table>

<p>| | | | | |</p>
<table>
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<th></th>
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<tbody>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>Short term</td>
<td>12 month</td>
<td>Odds ratio (95% CI)</td>
<td>Weight (%)</td>
</tr>
<tr>
<td>EXCELLENT\textsuperscript{7,7}</td>
<td>13/722</td>
<td>7/721</td>
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<td>11.9</td>
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<td>42/1606</td>
<td>34.9</td>
<td>1.17 (0.77 to 1.78)</td>
</tr>
<tr>
<td>PRODIGY\textsuperscript{2,16}</td>
<td>28/983</td>
<td>30/987</td>
<td>25.0</td>
<td>0.94 (0.55 to 1.58)</td>
</tr>
<tr>
<td>RESET\textsuperscript{17}</td>
<td>2/1059</td>
<td>4/1058</td>
<td>3.4</td>
<td>0.50 (0.09 to 2.73)</td>
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<tr>
<td>SECURITY\textsuperscript{6}</td>
<td>21/682</td>
<td>19/717</td>
<td>15.4</td>
<td>1.17 (0.62 to 2.19)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>132/7975</td>
<td>120/8020</td>
<td>100.0</td>
<td>1.11 (0.87 to 1.43)</td>
</tr>
<tr>
<td><strong>Test for heterogeneity:</strong></td>
<td>$\chi^2 = 3.00$, df = 6, P = 0.81, I$^2$ = 0%</td>
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<tr>
<td><strong>Test for overall effect:</strong></td>
<td>z = 0.64, P = 0.40</td>
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<table>
<thead>
<tr>
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<th>Extended</th>
<th>12 month</th>
<th>Odds ratio (95% CI)</th>
<th>Weight (%)</th>
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<tbody>
<tr>
<td>ARCTIC-Interruption\textsuperscript{17,18}</td>
<td>9/845</td>
<td>9/841</td>
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<tr>
<td>DAPT\textsuperscript{10,19}</td>
<td>99/5020</td>
<td>198/4941</td>
<td>84.5</td>
<td>0.48 (0.38 to 0.62)</td>
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<tr>
<td>DES LATE\textsuperscript{20,21}</td>
<td>19/2531</td>
<td>27/2514</td>
<td>11.6</td>
<td>0.70 (0.39 to 1.26)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>127/8196</td>
<td>234/8096</td>
<td>100.0</td>
<td>0.53 (0.42 to 0.66)</td>
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<td><strong>Test for overall effect:</strong></td>
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Kernodle \textsuperscript{14} Duration of DAPT
Appendix B:

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<th>Study</th>
<th>No. of events/total</th>
<th>Odds ratio (95% CI)</th>
<th>Weight</th>
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<tr>
<td></td>
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<td>M-H, fixed</td>
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<tr>
<td>Definite or probable stent thrombosis</td>
<td></td>
<td>M-H, fixed</td>
<td></td>
</tr>
<tr>
<td>EXCELLENT</td>
<td>6/722 1/721</td>
<td>3.1 6.03 (0.72 to 50.24)</td>
<td>100.0 1.32 (0.83 to 2.08)</td>
</tr>
<tr>
<td>ISAR-SAFE</td>
<td>5/1998 4/2007</td>
<td>12.4 1.26 (0.34 to 4.69)</td>
<td>100.0 1.32 (0.83 to 2.08)</td>
</tr>
<tr>
<td>ITALC</td>
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<td>1.6 7.01 (0.36 to 135.85)</td>
<td>100.0 1.32 (0.83 to 2.08)</td>
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<tr>
<td>OPTIMIZE</td>
<td>13/1605 12/1606</td>
<td>37.0 1.00 (0.49 to 2.38)</td>
<td>100.0 1.32 (0.83 to 2.08)</td>
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<td>PRODIGY</td>
<td>10/983 9/987</td>
<td>27.6 1.12 (0.45 to 2.76)</td>
<td>100.0 1.32 (0.83 to 2.08)</td>
</tr>
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<td>RESET</td>
<td>2/1059 3/1058</td>
<td>9.3 0.67 (0.11 to 3.99)</td>
<td>100.0 1.32 (0.83 to 2.08)</td>
</tr>
<tr>
<td>SECURITY</td>
<td>3/682 3/717</td>
<td>9.1 1.05 (0.21 to 5.23)</td>
<td>100.0 1.32 (0.83 to 2.08)</td>
</tr>
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<td>Total (95% CI)</td>
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<td></td>
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<tr>
<td>ARCTIC-interruption</td>
<td>0/665 3/641</td>
<td>4.4 0.14 (0.01 to 2.74)</td>
<td>100.0 1.00 (0.40 to 2.53)</td>
</tr>
<tr>
<td>DAPT</td>
<td>19/5020 65/4941</td>
<td>81.8 0.29 (0.17 to 0.48)</td>
<td>100.0 1.00 (0.40 to 2.53)</td>
</tr>
<tr>
<td>DES LATE</td>
<td>7/2531 11/2514</td>
<td>13.8 0.63 (0.24 to 1.63)</td>
<td>100.0 1.00 (0.40 to 2.53)</td>
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<td>Total (95% CI)</td>
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<td>Definite stent thrombosis Short term 12 month</td>
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<td>ISAR-SAFE</td>
<td>5/1998 3/2007</td>
<td>33.4 1.68 (0.40 to 7.02)</td>
<td>100.0 1.00 (0.40 to 2.53)</td>
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<tr>
<td>PRODIGY</td>
<td>4/983 6/987</td>
<td>66.6 0.67 (0.19 to 2.37)</td>
<td>100.0 1.00 (0.40 to 2.53)</td>
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<td>Total (95% CI)</td>
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<td>Extended 12 month</td>
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<tr>
<td>ARCTIC-interruption</td>
<td>0/665 3/641</td>
<td>4.8 0.14 (0.01 to 2.74)</td>
<td>100.0 1.00 (0.40 to 2.53)</td>
</tr>
<tr>
<td>DAPT</td>
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<td>80.1 0.25 (0.14 to 0.45)</td>
<td>100.0 1.00 (0.40 to 2.53)</td>
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<tr>
<td>DES LATE</td>
<td>7/2531 11/2514</td>
<td>15.1 0.63 (0.24 to 1.63)</td>
<td>100.0 1.00 (0.40 to 2.53)</td>
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<td>Total (95% CI)</td>
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<td></td>
<td>Late stent thrombosis Short term 12 month</td>
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</tr>
<tr>
<td>EXCELLENT</td>
<td>6/722 1/721</td>
<td>5.9 6.03 (0.72 to 50.24)</td>
<td>100.0 1.00 (0.40 to 2.53)</td>
</tr>
<tr>
<td>OPTIMIZE</td>
<td>4/1605 1/1606</td>
<td>5.9 4.01 (0.45 to 35.92)</td>
<td>100.0 1.00 (0.40 to 2.53)</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>10/983 9/987</td>
<td>52.9 1.12 (0.45 to 2.76)</td>
<td>100.0 1.00 (0.40 to 2.53)</td>
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<tr>
<td>RESET</td>
<td>10/1059 3/1058</td>
<td>20.8 0.14 (0.01 to 2.76)</td>
<td>100.0 1.00 (0.40 to 2.53)</td>
</tr>
<tr>
<td>SECURITY</td>
<td>3/682 2/717</td>
<td>14.5 0.21 (0.01 to 4.30)</td>
<td>100.0 1.00 (0.40 to 2.53)</td>
</tr>
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<td>Total (95% CI)</td>
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<tr>
<td></td>
<td>Very late stent thrombosis Extended 12 month</td>
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<tr>
<td>ARCTIC-interruption</td>
<td>0/665 3/641</td>
<td>4.4 0.14 (0.01 to 2.74)</td>
<td>100.0 1.00 (0.40 to 2.53)</td>
</tr>
<tr>
<td>DAPT</td>
<td>19/5020 65/4941</td>
<td>81.8 0.29 (0.17 to 0.48)</td>
<td>100.0 1.00 (0.40 to 2.53)</td>
</tr>
<tr>
<td>DES LATE</td>
<td>7/2531 11/2514</td>
<td>13.8 0.63 (0.24 to 1.63)</td>
<td>100.0 1.00 (0.40 to 2.53)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>26/8196 79/8096</td>
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Test for heterogeneity: χ²=4.20, df=6, P=0.65, I²=0%
Test for overall effect: z=1.18, P=0.24

Test for overall effect: z=1.18, P=0.24

Test for heterogeneity: χ²=2.43, df=2, P=0.30, I²=18%
Test for overall effect: z=4.98, P<0.001

Test for heterogeneity: χ²=0.89, df=1, P=0.33, I²=0%
Test for overall effect: z=0.01, P=0.99

Test for overall effect: z=0.01, P=0.99

Test for heterogeneity: χ²=2.94, df=2, P=0.23, I²=32%
Test for overall effect: z=4.92, P<0.001

Test for overall effect: z=4.92, P<0.001

Test for heterogeneity: χ²=6.66, df=4, P=0.16, I²=40%
Test for overall effect: z=0.67, P=0.50

Test for overall effect: z=0.67, P=0.50

Test for heterogeneity: χ²=2.43, df=2, P=0.30, I²=18%
Test for overall effect: z=4.98, P<0.001

Test for overall effect: z=4.98, P<0.001

Test for overall effect: z=4.98, P<0.001
Appendix C\textsuperscript{14}:

<table>
<thead>
<tr>
<th>Study</th>
<th>No of events/total</th>
<th>Odds ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>Short term</td>
<td>12 month</td>
<td>M-H, fixed</td>
<td>M-H, fixed</td>
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<tr>
<td>EXCELLENT\textsuperscript{22}</td>
<td>7/645</td>
<td>1/641</td>
<td>1.0</td>
<td>7.02 (0.86 to 57.24)</td>
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<tr>
<td>ISAR-SAFE\textsuperscript{23}</td>
<td>8/1998</td>
<td>12/2017</td>
<td>74.4</td>
<td>1.21 (1.01 to 1.27)</td>
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<tr>
<td>ITALIC\textsuperscript{24}</td>
<td>8/926</td>
<td>7/924</td>
<td>74.4</td>
<td>1.21 (1.01 to 1.27)</td>
</tr>
<tr>
<td>OPTIMIZE\textsuperscript{24}</td>
<td>43/1605</td>
<td>45/1606</td>
<td>24.6</td>
<td>1.41 (0.84 to 2.39)</td>
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<tr>
<td>PRODIGY\textsuperscript{2,26}</td>
<td>5/983</td>
<td>9/987</td>
<td>100.0</td>
<td>1.62 (1.26 to 2.09)</td>
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<tr>
<td>RESET\textsuperscript{27}</td>
<td>5/1059</td>
<td>8/1058</td>
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<tr>
<td>SECURITY\textsuperscript{28}</td>
<td>6/682</td>
<td>7/717</td>
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</tr>
<tr>
<td>Total (95% CI)</td>
<td>114/7975</td>
<td>125/8200</td>
<td>100.0</td>
<td>0.91 (0.71 to 1.18)</td>
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</table>

Test for heterogeneity: $\chi^2=1.90$, df=6, $P=0.93$, $I^2=0\%$
Test for overall effect: $z=2.21, P=0.02$

Appendix D\textsuperscript{14}:

<table>
<thead>
<tr>
<th>Study</th>
<th>No of events/total</th>
<th>Odds ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (95% CI)</th>
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<td>Short term</td>
<td>12 month</td>
<td>M-H, fixed</td>
<td>M-H, fixed</td>
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<td>EXCELLENT\textsuperscript{22}</td>
<td>7/645</td>
<td>1/641</td>
<td>7.9</td>
<td>0.77 (0.29 to 2.08)</td>
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<td>27.8</td>
<td>1.44 (0.91 to 2.26)</td>
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<tr>
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<td>43/1605</td>
<td>45/1606</td>
<td>100.0</td>
<td>1.30 (1.02 to 1.66)</td>
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<td>9/987</td>
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<tr>
<td>RESET\textsuperscript{27}</td>
<td>5/1059</td>
<td>8/1058</td>
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<tr>
<td>SECURITY\textsuperscript{28}</td>
<td>6/682</td>
<td>7/717</td>
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<tr>
<td>Total (95% CI)</td>
<td>114/7975</td>
<td>125/8200</td>
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</table>

Test for heterogeneity: $\chi^2=1.25$, df=3, $P=0.54$, $I^2=0\%$
Test for overall effect: $z=2.12, P=0.03$
Appendix E:

25682 Stent-Treated Subjects Enrolled

22866 DES-Treated Subjects Enrolled

5261 Not Eligible for Randomization:
- 14 Did Not Meet Enrollment Criteria
- 2638 Experienced Events
- 203 Died
- 575 Myocardial Infarction
- 186 Stroke
- 128 Stent Thrombosis
- 1620 Revascularization
- 616 Severe/Moderate GUSTO Bleeding
- 1465 Other Randomization Exclusion Criteria
- 1144 Noncompliance

7644 Eligible but Not Randomized:
- 5808 Withdraw Consent
- 1745 Randomization Out of Window/Lost to Follow-Up
- 36 Other
- 55 Unknown

9561 DES-Treated Subjects Randomized at 12 Months

5020 Randomized to Aspirin + Blinded Thienopyridine
- 332 Withdrew Consent
- 88 Lost to Follow-Up
- 17 Not Available for Follow-Up

4732 (94.3%) Clinical Follow-Up Available at 33 Months
- 9 Withdrew Consent
- 34 Lost to Follow-Up
- 8 Not Available for Follow-Up

4691 Randomized to Aspirin + Blinded Placebo
- 116 Withdrew Consent
- 91 Lost to Follow-Up
- 16 Not Available for Follow-Up

4714 (94.9%) Clinical Follow-Up Available at 33 Months
- 12 Withdrew Consent
- 43 Lost to Follow-Up
- 4 Not Available for Follow-Up
Appendix F:\n
<table>
<thead>
<tr>
<th>Months after Randomization</th>
<th>Thienopyridine</th>
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</table>

**Thienopyridine**
- 12-30 Months: HR 0.71 (0.59-0.85)
- 12-33 Months: HR 0.82 (0.70-0.97)
- 4.3% vs. 5.9%
- P<0.001

**Placebo**
- 12-33 Months: 5.6% vs. 8.5%
- P=0.02

**No. At Risk**

<table>
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<th>Time Period</th>
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