



## Effective Health Care Clopidogrel After Drug Eluting Stents

### Results of Topic Selection Process & Next Steps

- *Clopidogrel After Drug Eluting Stents Disease* was found to be addressed by two 2015 systematic reviews evaluating short- versus long-term dual-antiplatelet therapy after drug-eluting stent implantation. Given that these recent systematic reviews cover this nomination, no further activity will be undertaken on this topic.
  1. Spencer FA, Prasad M, Vandvik PO, Chetan D, Zhou Q, Guyatt G. Longer- Versus Shorter-Duration Dual-Antiplatelet Therapy After Drug-Eluting Stent Placement: A Systematic Review and Meta-analysis. *Ann Intern Med.* 2015;163:118-126. doi: 10.7326/M15-0083. Available from: <http://www.sciencedirect.com/science/article/pii/S0735109715003459>
  2. Giustino G, Baber U, Sartori S, Mehran R, Mastoris I, Kini AS, Sharma SK, Pocock SJ, Dangas GD. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol.* 2015 Apr 7;65(13):1298-310. doi: 10.1016/j.jacc.2015.01.039. Available from: <http://annals.org/aim/article/2297227/longer-versus-shorter-duration-dual-antiplatelet-therapy-after-drug-eluting>

### Topic Description

**Nominator(s):** Duke University Evidence-based Practice Center

**Nomination Summary:** The nominator identified the duration of clopidogrel treatment as an area in which significant morbidity, mortality, and variation in utilization persists and therefore future systematic review development should be a priority. Answers to this question are expected to inform practice and guideline development, and ultimately improve the quality of care by reducing morbidity, mortality, and costs.

#### **Staff-Generated PICO**

**Population(s):** Patients who have received a drug eluting stent for coronary artery disease

Potential subgroups according to:

1. Anatomical location of implanted stent (major epicardial vessel [left anterior descending artery versus left circumflex artery versus right coronary artery] versus branch arteries)
2. Patients with comorbidities of interest (prior myocardial infarction, stroke, or concomitant peripheral arterial disease)
3. Patients with CYP2C19 polymorphisms who have lower levels of the active metabolite of clopidogrel

**Intervention(s):** Clopidogrel (with or without ASA therapy), 1 year post drug eluting stent implantation

**Comparator(s):** Clopidogrel (with or without ASA therapy), indefinite use post drug

eluting stent implantation

**Outcome(s):**

1. Benefits, including but not limited to:
  - 1.1. improvement in anginal symptoms
  - 1.2. improvement in quality of life
  - 1.3. reduction in in-stent thrombosis rates
  - 1.4. reduction in target vessel revascularization hospitalizations
  - 1.5. reduction in cardiovascular and all-cause mortality
2. Harms, including but not limited to:
  - 2.1. in-stent thrombosis
  - 2.2. repeat target vessel revascularization
  - 2.3. bleeding
  - 2.4. major adverse cardiovascular events
  - 2.5. adverse drug reactions
  - 2.6. increase cardiovascular hospitalizations
  - 2.7. increase in cardiovascular and all-cause mortality

**Key Questions from Nominator:** Should clopidogrel be prescribed indefinitely in patients who have received drug eluting stents for the treatment of CAD?

**Revised Key Questions:** Question not revised.

## Considerations

- Coronary artery disease (CAD) is the most common form of heart disease, and rates of CAD are increasing as the population ages. CAD and associated heart attacks are the number one killers of Americans each year.<sup>3</sup> Interventional cardiology has advanced the treatment of CAD, and percutaneous interventions (PCI), including angioplasty and stent placement, are increasingly frequent procedures. Within a year of being approved by the FDA, drug eluting stents (DES) were used in 80% of all intracoronary stents placements in the United States.<sup>4</sup>
- Clopidogrel, an antiplatelet medication approved by the FDA in 1997, is prescribed for many cardiovascular indications. Among these indications, clopidogrel is being used to prevent stent thrombosis in CAD patients who have had a DES placed.<sup>5</sup> In examining risk factors for DES thrombosis, there has been a relationship seen with discontinuation of antiplatelet therapy. When considering possible benefits of continuing therapy with clopidogrel beyond a year, the data available is not definitive. Although the risk of a stent thrombosis after a year is low, when a thrombosis does occur it is often life-threatening. Additional confounding variables in considering how long clopidogrel therapy should be used for DES patients are both the expense of clopidogrel therapy and increased bleeding risks with prolonged antiplatelet therapy.<sup>5</sup> Therefore, this is an area of clinical uncertainty with potential practice and policy impact.
- In addition to two 2015 systematic reviews,<sup>1,2</sup> we identified five meta-analyses that evaluate the optimal duration of dual-antiplatelet therapy after drug-eluting stents.<sup>6-10</sup>

- In 2016, the American College of Cardiology and the American Heart Association published a focused guideline update on “Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease.” This guideline recommends that patients with stable ischemic heart disease treated with dual-antiplatelet therapy after drug eluting stent, clopidogrel should be given for at least six months (strength of recommendation: strong; quality of evidence: moderate).<sup>11</sup>

## References

1. Spencer FA, Prasad M, Vandvik PO, Chetan D, Zhou Q, Guyatt G. Longer- Versus Shorter-Duration Dual-Antiplatelet Therapy After Drug-Eluting Stent Placement: A Systematic Review and Meta-analysis. *Ann Intern Med.* 2015;163:118-126. doi: 10.7326/M15-0083. Available from: <http://www.sciencedirect.com/science/article/pii/S0735109715003459>
2. Giustino G, Baber U, Sartori S, Mehran R, Mastoris I, Kini AS, Sharma SK, Pocock SJ, Dangas GD. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol.* 2015 Apr 7;65(13):1298-310. doi: 10.1016/j.jacc.2015.01.039. Available from: <http://annals.org/aim/article/2297227/longer-versus-shorter-duration-dual-antiplatelet-therapy-after-drug-eluting>
3. MedlinePlus. 2017. Coronary Artery Disease. United State National Library of Medicine. Accessed on March 29, 2017. Available from: <https://medlineplus.gov/coronaryarterydisease.html>
4. Spinler SA and Wilensky RL. Duration of clopidogrel therapy after placement of drug-eluting intracoronary stent. *Am J Health Syst Pharm.* 2007. 64:1432-4. PMID:17592011
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6. El-Hayek G, Messerli F, Bangalore S, et al. Meta-analysis of randomized clinical trials comparing short-term versus long-term dual antiplatelet therapy following drug-eluting stents. *The American journal of cardiology.* Jul 15 2014;114(2):236-242.
7. Liu C, Liu M, Chen D, et al. Effectiveness of prolonged clopidogrel-based dual antiplatelet therapy after drug-eluting stent implantation: Evidence-based meta-analysis. *Herz.* Aug 2015;40(5):795-802.
8. Navarese EP, Andreotti F, Schulze V, et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. *BMJ (Clinical research ed.).* Apr 16 2015;350:h1618.
9. Pandit A, Giri S, Hakim FA, Fortuin FD. Shorter (<=6 months) versus longer (>=12 months) duration dual antiplatelet therapy after drug eluting stents: a meta-analysis of randomized clinical trials. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* Jan 01 2015;85(1):34-40.
10. Yang J, Fan ZX, Yang CJ, Wang HB. A Meta-Analysis of Randomized Clinical Trials Comparing Shorter (Less or Equal Than 6 Months) and Longer (More or Equal Than 12 Months) Dual Anti-Platelet Therapy Following Drug-Eluting Coronary Stents. *Iranian Red Crescent medical journal.* Jul 2015;17(7):e26904.
11. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *The Journal of thoracic and cardiovascular surgery.* Nov 2016;152(5):1243-1275. Available from: [http://www.onlinejacc.org/content/68/10/1082?\\_ga=1.38856099.1045758913.1490893674](http://www.onlinejacc.org/content/68/10/1082?_ga=1.38856099.1045758913.1490893674)