Balancing the risks of bleeding and stent thrombosis: A decision analytic model to compare durations of dual antiplatelet therapy after drug-eluting stents

Pallav Garg, MBBS, MSc, [a,f] **Benjamin Z. Galper, MD, MPH,** [b,f] **David J. Cohen, MD, MSc,** [c] **Robert W. Yeh, MD, MSc,** [d,e] **and Laura Mauri, MD, MSc** [b,e] ***Ontario, Canada; Boston, MA; and Kansas City, MO***

Background After coronary stent placement, whether dual antiplatelet therapy (DAPT) duration should be extended to prevent late stent thrombosis (ST) or adverse cardiovascular events is uncertain.

Methods To define the reduction in ischemic events required to outweigh increased bleeding with longer-duration DAPT, we developed a decision-analytic Markov model comparing DAPT durations of 6, 12, and 30 months after DES. Separate models were developed for patients presenting with and without an acute coronary syndrome (ACS). We used sensitivity analyses to identify the incremental benefit of longer-duration DAPT on either ST or the composite of cardiac death, myocardial infarction, and ischemic stroke (major adverse cardiovascular and cerebrovascular events [MACCEs]) required to outweigh the increased risk of bleeding associated with longer DAPT. The outcome from each strategy was quantified in terms of quality-adjusted life years.

Results In the non-ACS population, in order for 30 months of DAPT to be preferred over 12 months of therapy, DAPT would have to result in a 78% reduction in the risk of ST (relative risk [RR] 0.22, 3.1 fewer events per 1000) and only a 5% reduction in MACCE (RR 0.95, 2.2 fewer events per 1000) as compared with aspirin alone. For the ACS population, DAPT would have to result in a 44% reduction in the risk of ST (RR 0.56, 3.4 fewer events per 1000) but only a 2% reduction in MACCE (RR 0.98, 2.3 fewer events per 1000) as compared with aspirin alone, for 30 months of DAPT to be preferred for 12 months.

Conclusions Small absolute differences in the risk of ischemic events with longer DAPT would be sufficient to outweigh the known bleeding risks. (Am Heart J 2015;169:222-233.e5.)

Introduction

Although stent thrombosis (ST) is a rare event after percutaneous coronary intervention (PCI) with drug-eluting stents (DESs), the morbidity and mortality from ST remain high.[1,2] The use of dual antiplatelet therapy (DAPT) has been shown to reduce the rate of ST in the first few months after PCI with a DES, but the effect of DAPT on late and especially very late ST (VLST) is less certain.[3,4] The appropriate duration of DAPT after PCI with DES is therefore an area of ongoing investigation. Although the association between longer treatment with DAPT and an increased risk of bleeding is well recognized, decreased risks of ischemic events such as ST with longer duration DAPT are less evident,[5–7] and recent studies that have compared short-term and long-term DAPT have been underpowered to detect differences in ST risk.[8–13] Furthermore, adverse cardiovascular events, such as plaque rupture beyond the stented segment, are more frequent late events than ST, and it is therefore also important to consider the impact of potential risk reduction in cardiac death, myocardial infarction (MI), and stroke attributable to longer-duration DAPT.[14,15]

Decision analysis is a tool for combining data from multiple sources that can be useful in guiding complex medical decisions, especially when there is uncertainty regarding one or more key parameters. The optimal duration of DAPT post-PCI is a complex medical decision that must balance the risks of bleeding on DAPT with the expected benefit in ischemic event reduction from

From the [a]*Division of Cardiology, London Health Sciences Center, London, Ontario, Canada,* [b]*Division of Cardiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA,* [c]*Division of Cardiology, Saint Luke's Mid-America Heart Institute, University of Missouri-Kansas City, Kansas City, MO,* [d]*Division of Cardiology, Massachusetts General Medical Hospital, Harvard Medical School, Boston, MA, and* [e]*Division of Cardiology, Harvard Clinical Research Institute, Boston, MA.*

[f]*Co-first authors.*

Journal subject codes: [100] Health policy and outcome research, [24] Catheter-based coronary interventions: stents, [3] Acute coronary syndromes, [186] Platelet Function Inhibitors.

Submitted October 27, 2014; accepted November 5, 2014.

Reprint requests: Laura Mauri, MD, MSc, 75 Francis St, Boston, MA 02115.

E-mail: lmauri1@partners.org

0002-8703

http://dx.doi.org/10.1016/j.ahj.2014.11.002

DAPT. A decision analytic model that can simultaneously assess the risks of bleeding and ischemia on DAPT is ideally suited to determine the threshold risk reduction in ischemic events required to make longer-duration DAPT a preferred strategy. We, therefore, developed a decision analytic Markov model to compare DAPT durations of 6, 12, and 30 months post-PCI with DES in order to identify the magnitude of reduction in ischemic events that would outweigh the expected increased bleeding risk from longer-duration DAPT.

Methods

A Markov model simulates transitions between distinct health states that would occur over a lifetime in a cohort of patients undergoing a selected treatment strategy.[16,17] We derived treatment-related morbidity and mortality probabilities from published literature and assessed the outcome of treatment in terms of quality-adjusted life years (QALYs).

There is considerable uncertainty regarding whether there is an ischemic benefit with longer DAPT duration, via reduction in either stent-related events or ischemic events unrelated to the stent. Therefore, we did not seek to determine whether there is a benefit of longer-duration DAPT. Our base-case model did not assume any benefit of DAPT on ischemic end point of ST or the composite of cardiac death, MI, and ischemic stroke (major adverse cardiovascular and cerebrovascular events [MACCEs]). We used the decision analytic model to solve for the threshold of benefit of longer DAPT duration on either ST or MACCE that would be required to outweigh the increased risk of bleeding associated with longer-duration DAPT.

Patient population

Our model was designed to be applied to a patient undergoing PCI with DES. Because patients with and without acute coronary syndrome (ACS) have different risks of ischemic and bleeding events post-PCI, we constructed separate decision analytic models for these populations.[18] For the non-ACS population model, patients were treated with DAPT for 6, 12, or 30 months after PCI. Because guidelines recommend 12 months of DAPT for any patient presenting with ACS,[19] only DAPT durations of 12 and 30 months were evaluated in the ACS population model. Dual antiplatelet therapy was assumed to be treatment with clopidogrel 75 mg daily and low-dose aspirin. Where possible, the characteristics of the patient population were chosen to match those of contemporary population-based PCI registries.

Decision model structure

Fig. 1A depicts the outcomes of the chosen strategy in the form of a decision tree. During the initial 6-month follow-up period, patients could experience noncardiac death or cardiac death unrelated to ST. In the absence of these events, patients were at risk for ST or nonfatal MI (non–ST-related). All patients with ST were assumed to have a fatal or nonfatal MI and were at risk for sudden cardiac death.[3,4] All patients were at risk for bleeding events, including fatal bleed, hemorrhagic stroke, major bleed (noncerebrovascular), minor bleed, and ischemic stroke.

During the ensuing 6-month periods, survivors of the first 6 months after the index procedure were at risk for the same events, in addition to background risks of noncardiac and cardiac mortality. We assumed that patients could experience one ischemic and one bleeding event for every 6 months after the index PCI procedure.

The Markov model that describes potential health states and transitions after the index PCI on DAPT is depicted in Fig. 1B. The specific health states that we considered included the following: (1) survivors with ST, (2) survivors with nonfatal MI, (3) survivors with hemorrhagic stroke, (4) survivors without events, and (5) death. Each of these health states was further stratified according to the presence or absence of a prior major bleeding event, whether an individual was on DAPT, and the presence of a prior event requiring further DAPT (eg, ST or nonfatal MI). In each health state, during each 6-month cycle, we modeled ST, nonfatal MI, and ischemic stroke in addition to cardiac death and noncardiac death as well as bleeding events. Upon completing the assigned DAPT duration without further ischemic events, patients were assumed to continue aspirin monotherapy for the remainder of their life. Patients surviving an ischemic event such as ST or nonfatal MI were assumed to return back to the original DAPT treatment strategy (eg, further 12 months DAPT if in the 12-month DAPT strategy). Patients who had a hemorrhagic stroke were assumed to be treated with aspirin alone in the long term. Patients who had major or minor bleeding were continued on DAPT for the duration of the term. The model was run until all patients have died (lifetime horizon).

Ischemic events estimates

To determine the probability of ischemic events post-PCI, separate meta-analyses of the literature on ischemic outcomes after PCI were performed for patients initially presenting with or without ACS (Table I and online Appendix Supplementary material). Studies that did not distinguish patients with and without ACS were not included. We observed in our meta-analyses that ischemic event probabilities other than VLST were relatively constant beyond 6 months after PCI. Thus, except for VLST, all 6-month ischemic event probabilities beyond 12 months after PCI were assumed to be constant and identical to the 6- to 12-month event probabilities derived from meta-analyses (Table I). The ischemic event probabilities beyond 6 months after PCI were assumed to reflect the probabilities of ischemic events for patients off DAPT. The true effect of DAPT duration on the relative risk of ischemic events was not estimated from the literature and was the primary focus of our sensitivity analyses.