Predictors of Early Discontinuation of Dual-Antiplatelet Therapy: Room for Improvement

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Drug-eluting stents (DES) have revolutionized the approach to percutaneous coronary interventions and have substantially reduced restenosis compared with bare metal stents.1,2 Despite their advantages, DES are not without disadvantages. In particular, patients who receive DES remain at risk of a 1% to 2% incidence of stent thrombosis, which is often fatal.3,4 Dual-antiplatelet therapy (DAT) in the form of a thienopyridine and aspirin improves outcomes in patients who receive DES,3,5 and early termination of DAT is associated with worse outcomes.6 Consequently, recommendations for the sirolimus-eluting stent and the paclitaxel-eluting stent include a minimum of 12 months of uninterrupted thienopyridine therapy, while maintaining long-term aspirin therapy for the patients’ underlying coronary disease.7 As such, early discontinuation of a thienopyridine should only be considered if bleeding risk substantially outweighs thrombotic risk or considered temporarily if a major invasive procedure is necessary.7

While a strong body of evidence and evidence-based guidelines support the importance of continuing DAT for a full year with a DES to improve outcomes and reduce stent thrombosis and the negative consequences of early discontinuation, adherence rates are suboptimal. Ho et al (2007)8 found that 20% of patients had discontinued clopidogrel therapy within 6 months of receiving a bare-metal stent or DES. Results from the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery Registry showed that 14% of acute coronary syndrome patients had discontinued DAT within the first 30 days following placement of a DES—a period with a high risk of stent thrombosis.10 Results from the current article by Ferreira-González et al11 are similar, suggesting that over 14% of patients had permanently or temporarily interrupted at least one antiplatelet therapy (AT) following DES.

Medication nonadherence in general and discontinuation of DAT specifically are associated with poor outcomes in high-risk coronary artery disease patients.12 In fact, the single greatest predictor of stent thrombosis is premature discontinuation of DAT.6 Studies from Canada have demonstrated higher mortality among patients who delayed filling a clopidogrel prescription after hospital discharge due to formulary restrictions for clopidogrel.13,14 In a contemporary cohort receiving DES, Ho et al (2010)15 determined that 1 in 6 patients have a delay in filling clopidogrel after hospital discharge, and this delay was associated with adverse effects. This study noted an increased risk of death or myocardial infarction among patients with any delay in filling clopidogrel after hospital discharge. A large proportion of these adverse events occurred within the first 30 days of hospital discharge, particularly for patients with any delay in filling clopidogrel. These early adverse events coincide with the timing of early stent thrombosis seen in various observational data sets.16

While there are posited to be many potential reasons for nonadherence to DAT after DES, including cost of the medication, logistics of obtaining the medication at discharge, and lack of understanding of the intended medication regimen, few studies have explored this issue. Often, reasons for early discontinuation vary, and discordance exists between reasons provided by physicians and patients. A recent qualitative study found that physicians were more likely to cite cost and poor transitions in care from the inpatient setting to the outpatient setting as the reasons for early discontinuation of DAT, while patients were more likely to cite a lack of understanding about the purpose and duration of DAT as reasons for early discontinuation.17

The article by Ferreira-González et al in the current issue of Circulation adds to our understanding of early discontinuation of DAT.11 In this particular study, investigators followed a total of 1622 patients hospitalized between January and April 2008 in 29 participating hospitals across Spain for 1 year after receiving at least 1 DES. Patients were contacted by phone at 3, 6, 9, and 12 months to determine if at least one AT had been discontinued and, if so, the reasons for discontinuation. Over 14% (234) of patients had permanently or temporarily interrupted at least one AT, usually clopidogrel. A DAT discontinuation rate of 3% to 3.5% remained constant across all time intervals. The mortality rate was significantly higher in individuals who discontinued DAT within the first 3 months compared with patients who did not (12% vs 4.9%). Circumstances for DAT discontinuation were determined for 218 patients; of these, 109 (6.7%) patients discontinued at least 1 AT because of a bleeding event or invasive procedure, but only half (n=56, 3.5%) of these events or surgical procedures were major by the authors’ definition. The predictors of a bleeding event were history of major hemorrhage, the presence of renal impairment, or peripheral arterial

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disease. In 70 (4.3%) patients who discontinued, the reason for discontinuation was a medical decision not related to a bleeding event. This was most predicted by concurrent use of an oral anticoagulant, which may have increased concern for bleeding risk or reduced fears for a thrombotic event. Additional predictors of discontinuation were lack of patient instruction about the medications and having the procedure done in a private hospital (as opposed to a university). Finally, only 39 patients (2.4%) stopped at least one AT of their own volition. This was mostly predicted by immigration status and consumption of psychotropic agents.

The discontinuation rate of 14% in the Ferreira-González study is lower than some estimates and may reflect ongoing improvements in patient selection, education, and awareness about DAT. However, the reasons for early discontinuation in this study and a discontinuation rate of 1 in 7 demonstrate more opportunity for improvement. For example, the high rate of premature DAT discontinuation because of a perceived bleeding event was in contrast to the actual low rate of a major bleeding event. This shows the need to provide health care providers with further guidance about the true risks, benefits, and tradeoffs of DAT therapy. While increased risk of a bleeding event has been observed for the duration of DAT, the fear of a major bleed often outweighs the perceived benefits of DAT. Results from the Clopidogrel for the Reduction of Events During Observation (CREDO) study found an insignificant increase in the risk of a bleeding event when compared with placebo for up to 1 year of DAT, but also found a 27% reduction in the risk of death, myocardial infarction, or stroke.

Even when bleeding is not a concern, it appears that confusion may exist about optimal duration of DAT. In this study, almost a third of patients discontinued at least one AT following a medical decision not related to a bleeding event, again emphasizing the need for continued efforts to assist medical providers managing DAT. These decisions are often complicated by inconsistency in national and international DAT guidelines. Therefore ongoing efforts are essential to promote the practice of evidence-based guidelines, consistency of guidelines, and the application of these guidelines in clinical practice.

Several system-level barriers described in the current article are of interest. Patients who received a DES from a hospital with written information and/or predischarge counseling about DAT were less likely to stop an AT early, underscoring the importance of patient education on therapeutic treatments and goals. It is estimated that more than 30% of discharged patients do not understand their discharge instructions on returning home. A series of qualitative patient interviews in the United States demonstrated that many patients were unclear of their follow up plan, the duration of their therapies, and the transition from hospital to home. Quality improvement initiatives to support detailed written patient instructions on duration of thienopyridine therapy are essential. Careful and well-thought-out transitioning of care plans from the different patient settings are vital to optimizing treatment in both inpatient and, eventually, outpatient settings.

Finally, higher discontinuation and a higher bleeding rate among patients with a history of hemorrhage, peripheral arterial disease, or renal impairment hints at the ongoing need for more appropriate patient selection prior to DES placement, given that these patients have a high risk for complications at baseline. Additionally, patients consuming psychotropic drugs are often not compliant with therapeutic recommendations and would not be ideal for long-term DAT.

The importance of continuing DAT with minimal interruption cannot be understated. The Ferreira-González study emphasizes that discontinuation of DAT was rarely associated with major bleeding events, but more often associated with clinical and patient decisions unrelated to bleeding. Opportunities to improve adherence to DAT following implantation of DES include more education and resources for patients and physicians, such as ongoing initiatives like Hospital 2 Home, which provide support during the vulnerable transition period between providers and hospital systems with the goal of improving quality and reducing adverse events and readmissions. While Hospital 2 Home is not specifically focused on DAT, research demonstrating the importance of discharge planning and transitions of care for optimal DAT adherence suggest that these programs would likely improve outcomes in multiple ways. These efforts will ultimately provide hospitals, providers, and patients with the tools necessary to tackle the problems of nonadherence in general and the very specific issue of DAT discontinuation.

For now, health care providers should ensure that transitions from the inpatient to outpatient setting post-DES are seamless, that discharge instructions are clear about medication use, and that follow up is arranged.

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