Questions to the Panel

Circulatory System Devices Panel
December 7 and 8, 2006

On-Label Use of DES

1. When used in accordance with their labeled indications, are DES associated with an increased rate of stent thrombosis, death, or myocardial infarction compared to bare metal stents? If a DES safety concern exists:

    a. What is the relationship, if any, between stent thrombosis and clinical endpoints such as myocardial infarction or cardiac death?

    b. Compared to BMS, are DES associated with an increased rate of all-cause mortality?

    c. Do the safety concerns apply equally to both of the currently approved DES?

    d. Do the safety concerns outweigh the benefits for DES compared to BMS (i.e., reduction in repeat revascularization procedures)?

    e. Should the current labeling (indications, contraindications, warnings or precautions) be modified? If so, please provide your recommendations for modifications.

2. Current data indicate that termination of dual antiplatelet therapy prior to the duration as recommended in the DES label is associated with a higher risk of stent thrombosis. Current ACC/AHA/SCAI PCI Practice Guidelines recommend clopidogrel therapy for at least 3 months after CYPHER stent implantation, at least 6 months after TAXUS stent implantation (reflecting the recommendations in the present label for the CYPHER and TAXUS stents, respectively), and ideally up to 12 months in patients who are not at high risk of bleeding (Class IB recommendation). The European Society of Cardiology recommends clopidogrel administration for 6 to 12 months after DES implantation (Class IC recommendation).

    Given the currently available data please consider the following questions:

    a. Do the current data support a recommendation for an extended duration of dual antiplatelet therapy?

        i. If extended dual antiplatelet therapy is recommended, what duration of administration would you recommend, and what data support this recommendation?

ii. If an extended dual antiplatelet therapy is recommended, would you further recommend restarting dual antiplatelet therapy in stable patients who have already stopped clopidogrel?

b. If anti-platelet therapy needs to be stopped due to a concurrent compelling medical condition, what strategies do you recommend to reduce the risk of DES thrombosis until antiplatelet therapy can be reinstituted?

i. If the patient were to remain on only one of the two antiplatelet agents (aspirin or clopidogrel), which agent should be continued?

Real-World Clinical Use of DES

3. The pivotal randomized trials of CYPHER and TAXUS submitted for FDA approval primarily involved use of DES in non-complex patients and lesions. Following these approvals, it is estimated that a majority of DES are implanted in lesions outside of their current indications for use, such as in-stent restenosis lesions, bifurcation lesions, coronary artery bypass grafts, acute myocardial infarction, chronic total occlusions, overlapping and multiple stents per vessel and in patients with multivessel disease and chronic renal insufficiency. Given currently available data, are there safety concerns regarding stent thrombosis, death, and myocardial infarction rates for DES use in these complex patients and lesions?

    a. If so, can lesion subsets or patient populations at a particularly higher risk of DES thrombosis within the "off-label" patient population be identified?

    b. Among the "off-label" population, would the antiplatelet therapy modifications discussed previously for on-label use apply differently to this population or include other patient subgroups?

    c. If DES thrombosis concerns regarding more complex lesions or patient subsets have been identified, do they apply equally to both of the currently approved DES?

    d. Although diabetic patients were included in the randomized control trials submitted for DES approval, neither of the approved DES have a specific labeled indication for use in diabetics (either insulin-requiring or non-insulin requiring). Is there a DES thrombosis safety concern for this important high risk cardiovascular subgroup?

4. Given the currently available data and remaining areas of uncertainty, do the risks of stent thrombosis in the broad population of patients currently treated with DES in US clinical practice potentially outweigh the benefits (i.e., reduced repeat revascularization procedures) compared to the previous standard of care (e.g., medical therapy, BMS, CABG) such that the current DES labeling (indications, contraindications, warnings, precautions) should be modified?

5. In addition to current FDA efforts, what patient and/or physician education or other outreach measures (i.e., Public Health Notification) could potentially reduce the risk of stent thrombosis?

6. What long-term data need to be collected to help further define the risk of thrombosis in DES?

    a. Should future premarket studies conducted to support approval of new DES be modified to better assess thrombosis risk?

    b. Should the long-term follow-up of the pivotal trial cohorts and post-approval studies currently mandated by FDA be modified?

7. The optimal duration of dual-antiplatelet therapy in DES patients is undefined. Indefinite clopidogrel use may not prevent very late stent thrombosis, may expose patients to an unacceptable increased risk of bleeding, and has important economic considerations. Please comment specifically on the clinical study designs that would be most informative and yet feasible to evaluate this risk given current patterns of DES use and uncertainty regarding the optimal duration of dual antiplatelet therapy.

8. Please provide any other recommendations that you believe would assist FDA and the clinical and patient communities in their goal to minimize the risk of DES thrombotic events and maximize the risk-benefit ratio associated with use of these devices.