COMMENT: For UA/NSTEMI patients the risk of a CV event within the first 10 days appears to increase continuously as the loading dose is delayed, accelerating after the start of the PCI. This pattern of events is similar if other classifications of CV events are used, e.g., investigator reported, and for shorter timeframes, e.g., events within 2 days, although the pattern is not as clear because of lower rates of events. While there are few UA/NSTEMI patients with loading dose given at hour 3 after PCI, the hour 3 results are consistent with the results at later hours. However, it is possible the high rates at later hours have nothing to do with delay in the loading dose but with the possibility that loading doses were delayed in these patients because the patients were experiencing problems during their PCIs.

For STEMI patients, the rates of CV events within the first 10 days show a U-shaped relationship to the timing of the loading dose similar to what the FDA pharmacometrics reviewer described for primary endpoint events throughout the study. Investigators were not supposed to delay thienopyridine administration until after angiography as for UA/NSTEMI patients and could enroll patients as long as 14 days after a STEMI. The STEMI data in TAAL may be too limited and too variable to assess effects of the timing of the loading dose. The UA/NSTEMI data appear to be more useful.

I disagree with the conclusions of the FDA primary clinical reviewer and the pharmacometrics reviewer that the lowest incidence of CV death, nonfatal MI, or nonfatal stroke was achieved when the loading dose was administered at the start or within 30 minutes of the start of PCI. For UA/NSTEMI patients the rates of early CV events appear to increase continuously as the loading dose is delayed. The TAAL data suggest that delaying the loading dose is bad for both clopidogrel and prasugrel and that administering either one after the start of PCI leads to higher short-term CV event rates. TAAL does not provide evidence regarding the optimal timing of the loading dose other than earlier is better.

Prasugrel is known to have a more rapid onset for platelet inhibition than clopidogrel; how much of the early benefit of prasugrel is related to the protocol-driven delay in loading dose can not be ascertained from TAAL. The Division discussed with the sponsor at several meetings that, if the timing of clopidogrel in TAAL was not identical to the timings in the clopidogrel trials, a superiority claim over clopidogrel would not be supported by TAAL. What was not discussed but should have been obvious is that the nonstandard timing should have been discussed in the informed consent. Because of the nonstandard timing of clopidogrel use, as well as the excess bleeding with prasugrel, TAAL does not support a superiority claim of prasugrel over clopidogrel.

Discussion

I interpret all of these results as follows: The preclinical studies suggest, but are not conclusive, that prasugrel is a tumor promoter in mice. The clinical results in TAAL are also suggestive of a promoter effect. While it is tempting to dismiss the clinical findings as due to ascertainment bias due to increased bleeding with prasugrel, the delay in the divergence of the incidence plots for four+ months, the continued divergence of most plots through 16 months, the lack of evidence for an ascertainment bias for solid tumors other than GU, the cancer deaths leaning in the wrong direction, and the lack of a similar ascertainment bias in CHARISMA do not support the ascertainment bias hypothesis.

Besides drug effect, one other possible explanation is a play of chance resulting in more cancer prone individuals ending up in the prasugrel group. While this remains possible, I think it is unlikely because of the size of TAAL, the excellent balance in cancers reported as on-going at baseline, and the significant p values for the most relevant comparisons (0.024 and 0.0013). While these p values do not have the same strength of evidence as that of a pre-specified primary efficacy endpoint, neither were they picked as unusual from data dredging the trial results. The p value of 0.024 is generated by the initial analysis I had envisioned based on my review of the pre-clinical data.

One limitation of TAAL is the quality of the data. TAAL was not pre-specified to examine cancer rates, although cancer events are routinely captured in most CV trials and were captured prospectively in TAAL. TAAL did not capture prospectively a complete history of all cancers. However, from a patient perspective, a cancer recurrence is as deadly as or usually more deadly than a new cancer—prasugrel looks as bad for treatment-emergent solid cancer AEs as it does for new solid cancers. So the data quality issue (the lack of cancer histories) that some reviewers have viewed as insurmountable does not make the TAAL cancer results uninterpretable. TAAL raises a serious safety concern. I don't think that safety concern can be put to rest by manipulating TAAL data; another study is needed.

I am not impressed at all by the counterargument that the finding lacks biologic plausibility because we have never seen a similar pattern before. We have no large randomized trials of documented tumor promoters in humans. We should not assume that we know exactly what to expect based on animal studies. The evidence for a problem is far stronger in TAAL than it was at NDA submission times for the recent withdrawals from market, such as Vioxx and Zelnorm.

The efficacy data from TAAL document a reasonable benefit on reduction in MIs. However, there is no overall mortality benefit and there is little evidence of a benefit beyond 15-30 days. The benefit is clearly not a superiority claim for prasugrel over clopidogrel both because of the study drug timing issues and because of the substantially worse bleeding with prasugrel. I can argue that the short term benefit justifies immediate approval, although only for short term use, but I can also argue that approval should be delayed until the planned trial in medically managed ACS addresses the cancer promotion issue.

One issue that I have not discussed is the relevance of pharmacogenomic variation to the use of clopidogrel and prasugrel. The active metabolites of both of these prodrugs are formed by the action of various CYP enzymes. The sponsor alleges that the active metabolite of clopidogrel is

generated poorly in individuals with some CYP2C19 variants, producing clopidogrel nonresponsiveness and lowered efficacy. Several published articles, including one based on TAAL data, document reduced efficacy in individuals with various CYP2C19 loss of function alleles. (Collet, Hulot et al. 2009; Mega, Close et al. 2009; Simon, Verstuyft et al. 2009) The sponsor also alleges that prasugrel is more robust regarding metabolic pathways producing the active metabolite and hence has less potential for nonresponsiveness. Individuals nonresponsive to clopidogrel due to genetic polymorphisms may be a target population for taking prasugrel regardless of the cancer and bleeding risks.

Another issue that I have not discussed is the formulation problem of conversion from salt to base form. Please see the FDA CMC and CDTL reviews for the details on this problem. Because I would project that cancer promotion should not have a steep dose-response relationship, the formulation problem is not important for the cancer issue. It could affect other safety and efficacy and hence is relevant to risk/benefit analyses. My overall judgment is that, because TAAL showed efficacy and acceptable non-cancer related safety despite a less than ideal formulation, the formulation problem should not be an absolute bar to approval. However, it is another factor that argues for delaying full approval until the sponsor addresses all outstanding issues with new data and a new formulation.

References

Arumugam, P. J., A. Joseph, et al. (2002). "Severe dysplastic lesions in the colon; how aggressive should we be?" Colorectal Disease **4**(5): 345-347.

Boorman, G., D. Dixon, et al. (2004). "Society of toxicologic pathology position on assessment of hyperplastic lesions in rodent carcinogenicity studies." Toxicol Pathol **32**(1): 124-5.

Carcinogenic_Potency_Project. (2008). "Carcinogenic Potency Database (CPDB)." from http://toxnet.nlm.nih.gov.

Collet, J. P., J. S. Hulot, et al. (2009). "Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study." Lancet **373**(9660): 309-17.

Karagas, M. R. (1994). "Occurrence of cutaneous basal cell and squamous cell malignancies among those with a prior history of skin cancer. The Skin Cancer Prevention Study Group." J Invest Dermatol **102**(6): 10S-13S.

Maronpot, R. R., T. Harada, et al. (1989). "Documenting foci of hepatocellular alteration in two-year carcinogenicity studies: current practices of the National Toxicology Program." Toxicol Pathol **17**(4 Pt 1): 675-83; discussion 683-4.

Mega, J. L., S. L. Close, et al. (2009). "Cytochrome p-450 polymorphisms and response to clopidogrel." N Engl J Med **360**(4): 354-62.

Peto, R., J. Emberson, et al. (2008). "Analyses of cancer data from three ezetimibe trials." N Engl J Med **359**(13): 1357-66.

Riddell, R. H. (1999). "East meets West: what is early cancer?" Can J Gastroenterol **13**(6): 495-7.

Sabatine, M. S., C. P. Cannon, et al. (2005). "Effect of Clopidogrel Pretreatment Before Percutaneous Coronary Intervention in Patients With ST-Elevation Myocardial Infarction Treated With Fibrinolytics: The PCI-CLARITY Study." JAMA **294**(10): 1224-1232.

Sabatine, M. S., H. N. Hamdalla, et al. (2008). "Efficacy and safety of clopidogrel pretreatment before percutaneous coronary intervention with and without glycoprotein IIb/IIIa inhibitor use." American Heart Journal **155**(5): 910-917.

Simon, T., C. Verstuyft, et al. (2009). "Genetic determinants of response to clopidogrel and cardiovascular events." N Engl J Med **360**(4): 363-75.

Steinhubl, S. R., P. B. Berger, et al. (2002). "Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial." Jama **288**(19): 2411-20.

Stolte, M. (2003). "The new Vienna classification of epithelial neoplasia of the gastrointestinal tract: advantages and disadvantages." Virchows Arch **442**(2): 99-106.

Terry, M. B., A. I. Neugut, et al. (2002). "Reliability in the classification of advanced colorectal adenomas." Cancer Epidemiol Biomarkers Prev **11**(7): 660-3.

Wiviott, S. D., E. Braunwald, et al. (2007). "Prasugrel versus clopidogrel in patients with acute coronary syndromes." N Engl J Med **357**(20): 2001-15.

Yusuf, S., F. Zhao, et al. (2001). "Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation." N Engl J Med **345**(7): 494-502.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Marciniak
5/6/2009 01:32:59 PM
MEDICAL OFFICER
This version replaces all prior versions.

NDA 22,307
Prasugrel
Bleeding and Outcomes II
February 2, 2009

Review
I asked Ququan Liu, M.D., M.S. to perform additional analyses looking at outcomes in patients who had survived a TIMI Major bleed or in patients who had survived a TIMI Major or Minor bleed. Dr. Liu's analyses are summarized below.

Had a Nonfatal TIMI Major Bleed				
Outcome	**Prasugrel (N=146)**	**Clopidogrel (N=111)**	**HR**	**95% CI HR**
Primary Endpoint	43 (29.5%)	36 (32.4%)	0.87	0.56, 1.36
CV Death	16 (11.0%)	9 (8.1%)	1.44	0.64, 3.27
Nonfatal MI	17 (11.6%)	21 (18.9%)	0.62	0.33, 1.18
Nonfatal Stroke	11 (7.5%)	11 (9.9%)	0.74	0.32, 1.72
CV Death and/or MI	33 (22.6)	26 (23.4%)	0.97	0.58, 1.63
ALL Death	28 (19.2)	13 (11.7)	1.73	0.90, 3.35
Did NOT Have a Nonfatal TIMI Major Bleed				
Outcome	**Prasugrel (N=6595)**	**Clopidogrel (N=6605)**	**HR**	**95% CI HR**
Primary Endpoint	588 (8.9%)	727 (11.0%)	0.80	0.72, 0.89
CV Death	110 (1.7%)	131 (2.0%)	0.84	0.65, 1.08
Nonfatal MI	454 (6.9%)	590 (8.9%)	0.76	0.68, 0.86
Nonfatal Stroke	49 (0.7%)	47 (0.7%)	1.05	0.7, 1.56
CV Death and/or MI	545 (8.3%)	686 (10.4%)	0.79	0.70, 0.88
ALL Death	153 (2.3)	173 (2.6)	0.89	0.71, 1.10
These analyses are descriptive only since the comparisons are not randomized. **Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.**				

Had a Nonfatal TIMI Major or Minor Bleed				
Outcome	**Prasugrel (N=303)**	**Clopidogrel (N=231)**	**HR**	**95% CI HR**
Primary Endpoint	73 (24.1%)	60 (26.0%)	0.92	0.65, 1.29
CV Death	24 (7.9%)	17 (7.4%)	1.13	0.61, 2.11
Nonfatal MI	42 (13.9%)	35 (15.2%)	0.91	0.58, 1.42
Nonfatal Stroke	13 (4.3%)	13 (5.6%)	0.74	0.34, 1.60
CV Death and/or MI	62 (20.5%)	48 (20.8%)	0.99	0.68, 1.44
ALL Death	40 (13.2)	23 (10.0)	1.37	0.82, 2.30
Did NOT Have a Nonfatal TIMI Major or Minor Bleed				
Outcome	**Prasugrel (N=6438)**	**Clopidogrel (N=6485)**	**HR**	**95% CI HR**
Primary Endpoint	558 (8.7%)	703 (10.8%)	0.79	0.71, 0.88
CV Death	102 (1.6%)	123 (1.9%)	0.84	0.64, 1.09
Nonfatal MI	429 (6.7%)	576 (8.9%)	0.74	0.66, 0.84
Nonfatal Stroke	47 (0.7%)	45 (0.7%)	1.05	0.70, 1.58
CV Death and/or MI	516 (8.0%)	664 (10.2%)	0.77	0.69, 0.87
ALL Death	141 (2.2)	163 (2.5)	0.87	0.70, 1.09
These analyses are descriptive only since the comparisons are not randomized. **Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.**				

Dr. Hicks's Analyses:

± TIMI Major Bleed and Risk of Death
Relative Risk of Death in Patients Having a Nonfatal TIMI Major Bleed (Prasugrel/Clopidogrel), 95% CI:
1.64 (0.89, 3.01)

Relative Risk of Death in Patients NOT having a Nonfatal TIMI Major Bleed (Prasugrel/Clopidogrel), 95% CI:
0.89 (0.71, 1.10)

Relative Risk of Death (Prasugrel Patients Having a Nonfatal TIMI Major Bleed/Prasugrel Patients NOT having a Nonfatal TIMI Major Bleed), 95% CI:
8.27 (5.72, 11.94)

Relative Risk of Death (Clopidogrel Patients Having a Nonfatal TIMI Major Bleed/Clopidogrel Patients NOT having a Nonfatal TIMI Major Bleed), 95% CI:
4.47 (2.63, 7.61)

± TIMI Major or Minor Bleed and the Risk of Death
Relative Risk of Death in Patients having a Nonfatal TIMI Major or Minor Bleed (Prasugrel/Clopidogrel), 95% CI:
1.33 (0.82, 2.15)

Relative Risk of Death in Patients NOT having a Nonfatal TIMI Major or Minor Bleed (Prasugrel/Clopidogrel), 95% CI:
0.087 (0.70, 1.09)

Relative Risk of Death (Prasugrel Patients having a Nonfatal TIMI Major or Minor Bleed/Prasugrel Patients NOT having a Nonfatal TIMI Major or Minor Bleed), 95% CI:
6.03 (4.32, 8.40)

Relative Risk of Death (Clopidogrel Patients having a Nonfatal TIMI Major or Minor Bleed/Clopidogrel Patients NOT having a Nonfatal TIMI Major or Minor Bleed), 95% CI:
3.96 (2.61, 6.01)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Hicks
2/4/2009 12:15:24 PM
MEDICAL OFFICER

NDA 22,307
Prasugrel
Stent Thrombosis Results in TRITON
Karen A. Hicks, Medical Officer

Review of Supplemental Stent Thrombosis Reports

Materials Reviewed:

- NDA 22,307, Prasugrel
  Sequence 0069
  Correspondence Date: 12/5/2008
  Date Received: 12/5/2008
  Date Review Completed: 1/5/2009

- NDA 22,307, Prasugrel
  Sequence 0081
  Correspondence Date: 1/15/2009
  Date Review Completed: 1/20/2009

- NDA 22,307, Prasugrel
  Sequence 0084
  Correspondence Date: 1/29/2009
  Date Received 1/29/2009
  Date Review Completed: 1/30/2009

*Please note: the sponsor was supposed to originally submit the stent thrombosis results in September 2008. However, the results were not submitted until December 5, 2008.

Conclusions:

1. I recommend granting the sponsor a claim for the reduction of stent thrombosis with prasugrel. I reviewed the catheterization and percutaneous coronary intervention (PCI) reports from a random sample of 57 out of 174 subjects in TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN, with Prasugrel) who were adjudicated by the TRITON CEC as having Academic Research Consortium (ARC) definite or probable stent thrombosis. Additionally, I reviewed the catheterization and PCI reports for 6 patients (2 prasugrel, 4 clopidogrel) who were thought by the investigator to have stent thrombosis but were inadvertently NOT sent to the TRITON CEC for adjudication of stent thrombosis. The sponsor never referred these 6 cases to the CEC for adjudication because they believed there was a significant reduction of stent thrombosis with prasugrel, and they did not think these events would impact the study conclusions. No angiograms were available for my review.

    - Out of the 57 cases which were adjudicated by the TRITON CEC as definite or probable stent thrombosis (ARC criteria), I agreed with 45 of the interpretations. However, I classified the remaining 12 cases as follows:

        - 6 cases: no stent thrombosis (although angiography would be needed in two of these cases for a final decision)
        - 1 case: definite stent thrombosis
        - 5 cases: likely definite stent thrombosis

    - Out of the 6 investigator reported cases of stent thrombosis which were never referred to the TRITON CEC for adjudication, I thought 3 of these cases were not consistent with stent thrombosis.

I asked the sponsor to have an angiographic core laboratory perform a blinded review of the angiograms for the 18 subjects described above. Additionally, the sponsor was asked to have the angiographic core laboratory review the angiograms for 18 case-matched control subjects.

Angiographic core laboratory review was performed by PERFUSE. Subsequently, all cases were reviewed by the Harvard Clinical Research Institute CEC for final adjudication. The results are summarized as follows:

a. **Six Cases of Investigator Reported Stent Thrombosis that were NOT Adjudicated by the TRITON CEC (and that the Reviewer thought were Suspicious):**

Following review by the angiographic core laboratory (PERFUSE) and the Harvard Clinical Research Institute (HCRI) CEC, these 6 cases of investigator reported stent thrombosis (2 prasugrel, 4 clopidogrel) were downgraded to 3 cases of definite stent thrombosis (3 clopidogrel). My review of these cases was consistent with the results from PERFUSE and HCRI.

b. **12 Cases that were TRITON CEC Adjudicated as Definite Stent Thrombosis (and that the Reviewer thought were Suspicious):**

From the review of the 12 cases initially adjudicated by the TRITON CEC as definite stent thrombosis, PERFUSE adjudicated 7 cases as having angiographic evidence of stent thrombosis and 5 cases as not having angiographic evidence of stent thrombosis. HCRI adjudicated 7 cases as definite (3 prasugrel, 4 clopidogrel), 1 case as probable (clopidogrel), and 4 cases as no stent thrombosis (3 clopidogrel, 1 prasugrel). In the case of Subject 01022421407, PERFUSE did not see angiographic evidence of thrombus or total occlusion involving the stent, but the clinical report documented the presence of thrombus likely involving the stent; therefore, HCRI adjudicated this case as probable stent thrombosis.

i. I concurred with the four cases of no stent thrombosis (Subjects 01000613703 (clopidogrel), 01010721034 (clopidogrel), 55084522273 (clopidogrel), and 61051219720 (prasugrel)).

ii. In the case of Subject 01003315389 (prasugrel) which I did not think was stent thrombosis because by the catheterization report, the vessel appeared to be totally occluded at the mid right coronary artery percutaneous transluminal coronary angioplasty (PTCA) site and not the proximal stent site, PERFUSE noted that "no revascularization [was] filmed after stent thrombosis. Thrombosis occurred at the edge of [the] stent. It is possible that it could be thrombosis of a distal PTCA site." However, HCRI adjudicated this case as definite stent thrombosis.

iii. In the case of Subject 54044022962 (prasugrel) which I did not think was stent thrombosis because the catheterization report stated the patient had "instent restenosis," PERFUSE saw angiographic evidence of thrombus and HCRI adjudicated the case as definite stent thrombosis.

iv. Lastly, I thought Subject 01022421407 was likely a stent thrombosis, but per HCRI, the case was adjudicated as "probable." Please see the detailed explanation above.

c. **18 Case-Matched Control Subjects:**

All cases were adjudicated by PERFUSE and HCRI as no stent thrombosis.

Given the results in this subset of patients, if we assume similar results for the 174 cases of definite or probable stent thrombosis adjudicated by the TRITON CEC, the stent thrombosis reduction seen with prasugrel is still robust. Therefore, I recommend granting the sponsor a claim for the reduction of stent thrombosis with prasugrel.

2. The TRITON Clinical Endpoints Committee (CEC) adjudicated a total of 335 investigator-identified events, which included 135 (2.10%) events in the prasugrel group and 200 (3.11%) events in the clopidogrel group. Of these events, 43% of the events in the prasugrel group (58/135) and 58% of the events in the clopidogrel group (116/200) were classified as ARC definite or probable stent thrombosis. The CEC downgraded 60% of the investigator reported events of stent thrombosis in the prasugrel group (81/135) and 44% of the investigator reported events of stent thrombosis in the clopidogrel group (88/200). Therefore, the CEC downgraded a greater percentage of prasugrel than clopidogrel cases of investigator reported stent thrombosis. The 16% absolute difference in the downgrades between treatment groups was a concern. This imbalance suggested there could have been a particular clinical presentation that occurred more commonly in the prasugrel group that tended to be downgraded by the CEC as not conclusive of stent thrombosis. However, in TRITON, investigators did not specify the criteria they used for reporting an event as stent thrombosis. However, the 195 downgrades by the TIMI Study Group appeared to be reasonable, as did the 65 upgrades, and TIMI Study Group worst case analyses with downgrades and upgrades still demonstrated a statistically significant reduction in stent thrombosis with prasugrel. Nevertheless, central adjudication from raw data was requested to evaluate the trial for potential bias.

3. At the time the TRITON protocol was developed, there were no uniform criteria for the diagnosis of stent thrombosis. However, concerns about late stent thrombosis with drug eluting stents arose at the European Congress of Cardiology in 2006, and on December 7-8, 2006, the FDA Circulatory System Devices Panel met to discuss the safety of drug eluting stents. On May 1, 2007, standardized definitions for stent thrombosis were published by the Academic Research Consortium (ARC),[1] and the TRITON-TIMI 38 Steering Committee decided to incorporate stent thrombosis as the seventh secondary endpoint in the clinical trial.

   The Division of Cardiovascular Devices at the Center for Devices and Radiological Health uses the ARC criteria and angiographic core laboratory review to evaluate stent thrombosis in device trials.

   An indication for the reduction of stent thrombosis is an important label claim. To support this claim and to attempt to eliminate bias, I recommend requiring angiographic core laboratory review for angiographic confirmation and/or autopsy/thombectomy evidence for pathological confirmation of stent thrombosis in clinical trials, as proposed by the Academic Research Consortium (ARC). Study protocols should prespecify these requirements so that these data can be gathered prospectively. TRITON did not prespecify these requirements.

4. Investigator reported stent thrombosis and clinical adjudication of stent thrombosis may not be consistent with angiographic confirmation as determined by core laboratory review or pathological confirmation as determined by autopsy or by examination of tissue retrieved following thrombectomy. Angiographic review can be critical in distinguishing whether there is abrupt closure of a vessel due to stent thrombosis, a dissection distal to the stent, or a dissection at a percutaneous transluminal coronary angioplasty site. Angiographic review can also be helpful in determining whether restenosis, and not stent thrombosis, is the cause for a myocardial infarction in the target vessel territory.

---

[1] **Cutlip DE, S Windecker, R Mehran, A Boam, DJ Cohen, G-A van Es, PG Steg, M-A Morel, L Mauri, P Vranckx, E McFadden, A Lansky, M Hamon, MW Krucoff, PW Serruys and on behalf of the Academic Research Consortium, 2007, Clinical End Points in Coronary Stent Trials: A Case for Standardized Definitions, Circulation 115:2344-2351.**

REVIEWER RECOMMENDATIONS:

1. I recommend approval of prasugrel for the reduction of cardiovascular events (including stent thrombosis) in acute coronary syndrome (ACS) patients with unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI) when managed with percutaneous coronary intervention (PCI) and in patients with STEMI when managed with primary or delayed PCI.

2. I do NOT recommend short-term use of prasugrel or a switching strategy at a particular time point from prasugrel to clopidogrel because such a strategy has not been studied to date. Based on the stent thrombosis results, most cases of stent thrombosis in the clopidogrel treatment group occurred within the first 30 days, while most cases of stent thrombosis in the prasugrel treatment group occurred > 24 hours to 30 days. I would be especially concerned about any switch that took place within the first 30 days, because any substantial change in inhibition of platelet aggregation could convey an increased risk of stent thrombosis. Patients should only be switched from prasugrel to clopidogrel if they cannot tolerate prasugrel.

3. Although prasugrel use in patients $\geq$ 75 years of age is not recommended due to the increased risk of fatal bleeding, if a patient was otherwise healthy and was at increased risk of stent thrombosis, I would consider placing such a patient on prasugrel. Patients falling into this category include those with severe coronary artery disease who have undergone extensive stent implantation. Other patients $\geq$ 75 years of age who may be candidates for prasugrel include those who are known to be "poor responders" to clopidogrel and have multiple stents in place or those experiencing recurrent ischemic events on clopidogrel. Physicians would need to carefully consider the risks and benefits in these patients on an individual basis prior to recommending prasugrel. Additionally, all of these patients would need to be counseled about the increased risk of fatal hemorrhage.