1. The AA-induced aggregation measured by light transmission aggregometry (LTA) is the most widely reported ex vivo technique to assess aspirin effect in platelets (1–3). With respect to our study potentially underestimating aspirin resistance in patients with unstable coronary syndromes, it should be noted that 23% (n = 47) of our percutaneous coronary intervention (PCI) patients were in that category. All of these patients were sensitive to aspirin (4). To the best of our knowledge, our prospective study is the largest reported in PCI patients and is concordant with Schwartz et al (5), who reported 1 of 190 patients resistant to aspirin using 1 μmol/l arachidonic acid (AA)-induced aggregation in platelet-rich plasma. The latter investigators also reported that 9% of patients exhibiting "resistance" were proven to be responders after strict adherence to aspirin treatment. These data are strikingly consistent with the results of our study (4).

2. Controversy remains regarding dose-dependent effects of aspirin on ex vivo platelet function. The latter effects may be COX-1 independent. We are currently conducting a double crossover study in outpatients that addresses these important issues.

3. With respect to the relation of ex vivo AA-induced aggregation to clinical outcomes, the single patient who was aspirin-resistant in our study had suffered a stent thrombosis. We agree that large-scale studies are necessary to firmly link ex vivo platelet function measurements to the occurrence of adverse ischemic events.

4. With respect to the assertion that the thrombelastograph (TEG) assay has not undergone extensive evaluation, it should be noted that the TEG platelet mapping assay has been cleared by the Food and Drug Administration as an automated platelet aggregation system. As reported in our study, a statistically significant correlation existed between measurements by LTA and TEG (r = 0.85; p < 0.001). We are currently studying the relation of TEG measurements to the occurrence of recurrent ischemic events (6). The TEG has been used for many years to guide therapy in patients with postsurgical bleeding.

5. We referred to a previous study of the VerifyNow assay using propyl gallate (PG) as the agonist (7). There are no published data correlating PG as an agonist to AA in the measurement of aspirin resistance. At the time we submitted our findings to JACC, PG was the only reported agonist used in the VerifyNow assay to assess platelet responsiveness to aspirin. Moreover, no major studies describing the new AA cartridge in the VerifyNow assay had occurred prior to, and none have occurred since, our submission to JACC.

6. The relation of aspirin dose to bleeding remains controversial. We believe that this subject would be best addressed by prospective studies and not by meta-analyses.

7. We agree that there is much confusion regarding aspirin "resistance," and this was indeed the stimulus to conduct our investigation. Stimulation by multiple pathways will affect measurements of ex vivo platelet function and the interpretation of drug "resistance." A technique that isolates the specific pathway targeted by the drug should be used to assess drug response. Therefore, we believe that failure to inhibit the primary target of aspirin (i.e., COX-1) should be the criterion for aspirin resistance. The primary message of our study was that the prevalence of aspirin resistance using this definition is rare after treatment with a 325-mg daily dose.

Finally, we emphasize that aspirin resistance may be an important phenomenon related to the occurrence of adverse clinical events. A standardized definition that will employ validated point-of-care methods to facilitate investigations in large-scale clinical trials is needed. A critical assessment of pathways affected by aspirin will also determine whether clinical events are only related to incomplete platelet COX-1 inhibition or to other anti-inflammatory or antioxidant properties of aspirin that may be dose-dependent.

Udaya S. Tantry, PhD
Kevin P. Bliden, BS
*Paul A. Gurbel, MD, FACC
*Sinai Center for Thrombosis Research
Hoffberger Building
Suite 56
2401 W. Belvedere Avenue
Baltimore, Maryland 21215
E-mail: pgurbel@lifebridgehealth.org

doi:10.1016/j.jacc.2006.03.020

REFERENCES

Bifurcation Coronary Lesions and the “Crush” Technique

We read with interest the study by Costa et al. (1) clarifying a number of important aspects of the treatment of bifurcation lesions by the crush technique. The investigators reported that “the majority of SB (side branch) lesions showed stent underexpansion with the smallest MSA (mean sent area) found at the SB ostium,” and that this underexpansion was not reliably detected by angiography. Given the potential implications of these findings on the development of both stent thrombosis and restenosis at the ostium of the SB, it would be interesting to know additional details on how the crush technique was performed in this study. Bench-testing has demonstrated procedural issues that maximize the likelihood of adequate dilation of the SB ostium, including
ensuring that the SB postdilation balloon is the same diameter or larger than the deploying balloon (2).

In addition, Colombo (3) has described the importance of performing “before kissing” a high-pressure balloon inflation in the side-branch so as to be sure to expand the stent fully at the ostium. Costa et al. (1) also found that “incomplete stent apposition in the crush area was common.” Some operators deliberately undersize the main vessel (MV) balloon during kissing inflation to avoid “oversizing” by the double balloons at the proximal end of the MV stent. We have previously shown that this leads to MV stent distortion (2,4) and incomplete crushing (2) and that these outcomes can be prevented or repaired by kissing with appropriately sized balloons in the MV and SB.

Finally, it is not clear whether Costa et al. (1): 1) performed a separate high-pressure inflation in the SB before kissing; 2) whether the MV and SB balloons were smaller, the same size, or larger than the deploying balloons (the reported stent and final balloon diameters are a mean of the study population); and 3) what pressures were achieved in the SB and MV balloons during kissing inflations. This information is particularly pertinent for those cases in which the MSA of the SB ostium was <4 mm² and when incomplete crushing was observed.

*Duncan C. McNab, MB, BS, MPhil
John Ormiston, MB, ChB
Mark W. I. Webster, MB, ChB

*Auckland City Hospital
Cardiology
Park Road
Grafton
Auckland, 1005
New Zealand
E-mail: duncanmcn@adhb.govt.nz

doi:10.1016/j.jacc.2006.03.028

REFERENCES


REPLY

The investigators of the referenced study (1) thank McNab and colleagues for their comments. Regarding questions about the procedural “steps” and final kissing balloon (KB) inflation among non-left main lesions (n = 20) treated with sirolimus-eluting stent (SES) crush stenting and final intravascular ultrasound (IVUS) in both branches, the responses are as follows:

1. Only 40% (8 of 20 patients) had a separate high-pressure inflation (>12 atm) in the side branch (SB) before KB;
2. final KB inflation (90%) was performed in the main vessel (MV) with a balloon of the same size as the “deployment” balloon in 89% (16 of 18 patients), with a smaller balloon in 5.6% (1 of 18 patients), and with a larger balloon in 5.6% (1 of 18 patients);
3. final KB inflation was performed in the SB using a same-size balloon (same as “deployment” balloon) in all but one case, 94.4% (17 of 18 patients); in one case a smaller balloon was used;
4. the pressure of the KB inflation was 10.4 ± 4.1 atm in the MV and 14.3 ± 3.8 atm in the SB.

When we consider these analyses in lesions with minimum stent area (MSA) at the SB ostium <4 mm² versus MSA >4 mm², we found:

1. similar rates of high-pressure balloon inflation in the SB prior to KB (42% vs. 38%, p = 0.8);
2. balloon pressure at the SB during KB was 14.6 ± 3.8 atm (<4 mm²) versus 15.6 ± 2.8 atm (>4 mm²), p = 0.6.

In addition, a comparison of lesions with incomplete crush (IC) versus “complete” crush (CC) showed that:

1. 33% of lesions with IC had SB high-pressure inflation before KB versus 25% of lesions with CC, p = 0.6;
2. IC had lower balloon pressure during KB in the SB (12.3 ± 3.7 atm for IC vs. 17 ± 3.8 atm for CC; p = 0.04).

Finally, we could not demonstrate any impact of high-pressure balloon inflation in the SB before KB on final luminal dimensions in the SB and on the incidence of IC; this may be due to the small sample size. However, these results showed that higher balloon pressures in the SB during KB inflation are associated with complete “crush” stent apposition, indicating that IC is associated with SB stent underexpansion (1).

Ricardo A. Costa, MD
Gary S. Mintz, MD

*Stephane G. Carlier, MD, PhD

*Columbia University Medical Center
Intravascular Imaging and Physiology
Cardiovascular Research Foundation
55 East 59th Street
6th Floor
New York, New York 10022
E-mail: scarlier@crf.org

doi:10.1016/j.jacc.2006.03.027

REFERENCE


Secondary Stroke Prevention and Antiplatelet Therapy

A truth that’s told with bad intent beats all the lies you can invent
—William Blake (1757–1827, Auguries of Innocence)

I was very disappointed to see JACC publish an opinion piece by Dr. Gebel that is basically a cleverly disguised advertisement for Aggrenox (1). Extended-release dipyridamole (ER-DP) and aspirin is sold as Aggrenox, which is made by Boehringer Ingelheim,