need for ongoing monitoring of the impact of new guidelines.

Regarding the preliminary data presented at the American College of Cardiology 2014 meeting, our data on VGS were not entirely captured (only ICD9-CM codes 421.0 and 041.00 were used). Furthermore, the VGS IE diagnosis established by DeSimone et al. (2) raises serious concern because the VGS does not carry a unique ICD-9 CM code (unlike staphylococcus, enterococcus, and so forth). This etiology was assumed by including ICD-9 CM code 041.09 or ICD-9 CM code 041.00 ("Streptococcus infection in conditions classified elsewhere and of unspecified site, other Streptococcus") among patients carrying the diagnosis of IE (2). The accuracy of VGS diagnosis and drawing major conclusions based on nonspecific coding can be erroneous. Feedback from many experts attending the American College of Cardiology 2014 meeting helped us overcome this limitation in our study, resulting in elimination of VGS group. Hence, our conclusion "there has been a significant rise in the incidence of streptococcus IE following 2007 guideline" is statistically sound and the study design valid. Whether the temporal association noted in our study reflects a causal relationship cannot be deduced from our study design. We acknowledged this in the limitation section.

We appreciate the suggestion of DeSimone and colleagues to look at VGS as a specific subgroup. However, as pointed out by Dayer and Thornhill (5), this has to be done in a randomized controlled design to eliminate the inherent limitations of a retrospective database.

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REFERENCES

1. Bor DH, Woolhandler S, Nardin R, et al. Infective endocarditis in the U.S., 1998–2009: a nationwide study. PLoS One 2013;8:e60033.

2. DeSimone DC, Tleyjeh IM, Correa de Sa DD, et al. Incidence of infective endocarditis caused by viridans group streptococci before and after publication of the 2007 American Heart Association's endocarditis prevention guidelines. Circulation 2012;126:60–4.

3. Thornhill MH, Dayer MJ, Forde JM, et al. Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. BMJ 2011;342:d2392.

4. Dayer MJ, Jones S, Prendergast B, et al. Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series analysis. Lancet 2015;385:1219–28.

5. Dayer M, Thornhill M. Antibiotic prophylaxis guidelines and infective endocarditis: cause for concern? J Am Coll Cardiol 2015;65:2077–8.

Impact of Clinical Presentation on Dual Antiplatelet Therapy Duration

Let's Re-Evaluate Our Priorities

We read with interest the paper by Yeh et al. (1) published in the *Journal*, reporting on a subgroup analysis from the DAPT (Dual Antiplatelet Therapy) trial in which the effect of an extended treatment with DAPT beyond 1 year was investigated in patients presenting with or without myocardial infarction at the time of stent implantation. The authors concluded that the benefit of an extended treatment persisted irrespective of the clinical presentation.

We believe the results of this analysis only poorly support this conclusion for the following motivations. Reducing mortality is the ultimate goal of cardiovascular medicine. However, the use of combined endpoints, encompassing fatal and nonfatal events, such as myocardial infarction or cerebrovascular accident, is necessary to increase study power and limit the number of patients needed in clinical trials. Death traditionally comprises a small fraction of such composite outcomes after percutaneous coronary intervention. Therefore, the underlying foundation for combining fatal and nonfatal outcomes as a reliable measure of a given treatment effect requires that nonfatal endpoints are independently associated with fatal events and that the strength of this association is somewhat comparable across nonfatal endpoints. The rationale for extending DAPT beyond the recommended period is to prevent myocardial infarction, both stent- and nonstent-related, and by that improving survival.

In contrast, the DAPT study showed an increase in mortality by an extended course of treatment, and the subgroup analysis by Yeh et al. (1) strongly suggests that the excess of fatality originates from patients presenting without myocardial infarction. In this patient subset, prolonged DAPT duration was associated to a 43% mortality increase. However, the interaction testing for mortality did not reach the formal level of significance (P_{int}: 0.13). Importantly, interaction testing is known to be underpowered, and

it greatly increases the risk of incorrectly concluding that no interaction effect exists when in reality it does (2). When we calculated the power of detecting such interaction in the DAPT study as suggested by Brookes et al. (3) this was roughly as low as 29%.

Misinterpreting such a finding, which has indeed a plausible biological explanation (i.e., patients without prior myocardial infarction are at lower risk for ischemic recurrences, show lower platelet reactivity, and have potentially higher rate of bleeding when treated with prolonged antithrombotic therapy) (4), may expose a large number of patients to unnecessary bleeding events, which do carry prognostic implications and may ultimately worsen outcomes.

Defining which subgroups of patients derive a benefit and which harm from an extended DAPT regimen is urgent, given the level of uncertainty clearly voiced by the medical community (5).

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REFERENCES

1. Yeh RW, Kereiakes DJ, Steg PG, et al. Benefits and risks of extended duration dual antiplatelet therapy after PCI in patients with and without acute myocardial infarction. J Am Coll Cardiol 2015;65:2211–21.

2. Pocock SJ, Hughes MD, Lee RJ. Statistical problems in the reporting of clinical trials. A survey of three medical journals. N Engl J Med 1987;317:426–32.

3. Brookes ST, Whitely E, Egger M, Smith GD, Mulheran PA, Peters TJ. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol 2004;57:229–36.

4. Costa F, Vranckx P, Leonardi S, et al. Impact of clinical presentation on ischaemic and bleeding outcomes in patients receiving 6- or 24-month duration of dual-antiplatelet therapy after stent implantation: a pre-specified analysis from the PRODIGY (Prolonging Dual-Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) trial. Eur Heart J 2015;36:1242–51.

5. Valgimigli M, Costa F, Byrne R, Haude M, Baumbach A, Windecker S. Dual antiplatelet therapy duration after coronary stenting in clinical practice: results of an EAPCI survey. EuroIntervention 2015;11:68–74.

REPLY: Impact of Clinical Presentation on Dual Antiplatelet Therapy Duration

Let's Re-Evaluate Our Priorities

The DAPT (Dual Antiplatelet Therapy) study showed reduction in stent thrombosis and myocardial infarction (MI) and an increase in bleeding with continued thienopyridine therapy beyond 12 months after coronary stent treatment (1). In subgroup analysis (2), continued thienopyridine therapy provided consistent reductions in ischemic endpoints irrespective of clinical presentation (MI Group, hazard ratio: 0.27 for stent thrombosis and 0.42 for MI; No MI Group, hazard ratio: 0.30 for stent thrombosis and 0.60 for MI). Global Utilization of Streptokinase moderate or severe bleeding was increased with continued thienopyridine in both groups (hazard ratio: 2.38 and 1.53, respectively). The conclusions, that extended dual antiplatelet therapy reduced stent thrombosis and MI but increased bleeding irrespective of clinical presentation, are objectively supported by the results of this substudy.

The DAPT study was not powered to evaluate the effect of continued thienopyridine on mortality. We nevertheless published the MI subgroup data for mortality to fully acknowledge the importance of this outcome. However, emphasis on a nonsignificant, albeit underpowered, interaction for an individual component endpoint in a non-pre-specified analysis could lead to an erroneous conclusion because of either type I or type II error. Thus, the finding, although notable, should be considered hypothesis-generating, not conclusive.

Although bleeding is certainly a risk of continued dual antiplatelet therapy, the difference in mortality seen in the DAPT study was not, in fact, accounted for by a difference in antecedent bleeding (1). In addition, a secondary blinded adjudication using a sensitive definition for bleeding-related death did not support bleeding as the primary reason for the difference in mortality. Finally, a large comprehensive meta-analysis found no relationship between extended duration dual antiplatelet therapy and mortality (3). Subsequent meta-analyses focused only on drug-eluting stent populations have been driven by the DAPT study results, and have selectively excluded studies with populations for whom the relationship between antiplatelet therapy and mortality, as mediated by bleeding, are applicable (4).

Mortality is undoubtedly a critically important endpoint in the evaluation of the risks and benefits of any therapy. We believe that the mortality differences observed in the DAPT study require careful attention because of the potential for harm to the many individuals exposed to this treatment. However, the expedient explanation that bleeding explains the observed mortality differences is not currently supported by trial data. A disciplined interpretation