interstage myocardial infarction observed with staged CAS-OHS (in most cases, PCI can be safely performed first) and perioperative stroke observed with combined CEA-OHS (1). In this regard, because the majority of stroke during OHS are related to aortic cross-clamping, an off-pump surgical approach would be advisable, as recently suggested (4). Finally, patients not suitable for PCI may take advantage of another option; that is, a simultaneous hybrid revascularization by CAS immediately followed by coronary artery bypass graft, which displayed a cumulative 30-day and 12-month event rate of 4% and 7%, respectively, after a tailored antithrombotic strategy (5).

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REFERENCES

1. Shishehbor MH, Venkatachalam S, Sun Z, et al. A direct comparison of early and late outcomes with three approaches to carotid revascularization and open heart surgery. J Am Coll Cardiol 2013;62:1948–56.
2. Ribichini F, Tomai F, Reimers B, et al. Clinical outcome after endovascular, surgical or hybrid revascularisation in patients with combined carotid and coronary artery disease: the Finalised Research In ENDovascular Strategies Study Group (FRIENDS). EuroIntervention 2010;6:328–35.
3. Tomai F, Pesarini G, Castriota F, et al. Early and long-term outcomes after combined percutaneous revascularization in patients with carotid and coronary artery stenoses. J Am Coll Cardiol Intv 2011;4:560–8.
4. Borioni R, Weltert L, De Paulis R, et al. Early results of synchronous carotid endarterectomy and off-pump coronary revascularization. J Cardiovasc Surg 2012;53:363–7.
5. Versaci F, Reimers B, Del Giudice C, et al. Simultaneous hybrid revascularization by carotid stenting and coronary artery bypass grafting: the SHARP study. J Am Coll Cardiol Intv 2009;2:393–401.

Learning More From the Dabigatran Concentrations in the RE-LY Study

We read with great interest the paper by Reilly et al. (1), which demonstrated that higher trough plasma dabigatran concentrations were associated with: 1) decreasing risk of stroke/systemic embolic event (SEE); and 2) increasing major bleeding risk in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial (2). The paper provides useful insights into the relationship between dabigatran exposure and clinical events but raises several questions.

1. Time lag from blood samples to events.

The dabigatran concentrations reported by Reilly et al. (1) were from blood samples that were mostly collected 1 month after enrollment. In contrast, the majority of the strokes/SEE in the RE-LY study occurred >12 months after enrollment (2). This difference limits the inferences that can be drawn from the observed relationship between dabigatran concentrations and adverse events, because of intraindividual changes during the time lag (e.g., altered renal function [3]) or addition/withdrawal of interacting medicines (4–7).

Could the temporal relationship between events and blood samples be described more specifically? Furthermore, was the correlation between trough concentrations and events stronger for those with a shorter time lag?

2. Variability in trough concentrations.

In the RE-LY study, a subgroup of those on dabigatran etexilate contributed additional blood samples at 3, 6, and 12 months after enrollment (1). These data could provide insights into intraindividual variability in trough plasma dabigatran concentrations over time.

3. Therapeutic index.

According to Reilly et al. (1), their data demonstrated that dabigatran has a wide therapeutic index. This is a strong claim, which we question. Data in their Table 1 and Figure 2 show that for a 72-year-old male with atrial fibrillation, diabetes mellitus, and previous stroke, there was a 3-fold increase in risk of major bleeding events between the 10th and 90th percentiles of trough concentrations. Furthermore, they found that the ischemic stroke/SEE risk declined steeply at low concentrations, with little additional benefit from higher concentrations. These data actually allow a

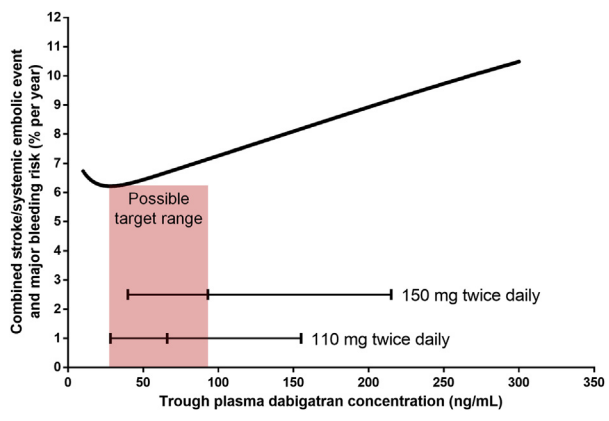

Figure 1 Combined Event Risk Versus Trough Concentrations

Combined event risk compared with trough concentrations for a 72-year-old male with atrial fibrillation, diabetes mellitus, and previous stroke. The **shaded** zone indicates a possible target concentration range. The lower limit is higher than indicated by the curve because of the greater uncertainty in the event risk–concentration relationship at the lower concentrations. The **horizontal bars** indicate the 10th, 50th, and 90th percentiles of trough concentrations in the RE-LY study according to dabigatran etexilate dose rate (1).

more formal development of a possible target trough concentration range.

An example of a range for this individual may be derived by adjusting the lines of best fit of the event risk–concentration curves by using event weighting according to the hazard ratios of death described by Eikelboom et al. (8) and then combining the lines of best fit (Fig. 1). Note that for the patient described here, the therapeutic range is relatively narrow compared with the 10th to 90th percentiles of trough concentrations and would certainly not be considered a wide therapeutic range.

4. Trough concentrations outside the 10th and 90th percentiles.

By definition, 20% of individuals treated with dabigatran etexilate in the RE-LY study had concentrations outside the 10th to 90th percentiles of trough plasma dabigatran concentrations. Did the outcomes for these individuals differ from the rest of the cohort? Dose adjustment to "improve" the drug exposure for these 20% of patients may be beneficial. Could the authors describe the characteristics of the individuals with trough plasma dabigatran concentrations that were below the 10th percentile and above the 90th percentile?

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REFERENCES

1. Reilly PA, Lehr T, Haertter S, et al., RE-LY Investigators. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients in the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol 2014;63:321–8.
2. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.
3. Stangier J, Rathgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. Clin Pharmacokinet 2010;49:259–68.
4. Hartter S, Sennewald R, Nehmiz G, Reilly P. Oral bioavailability of dabigatran etexilate (Pradaxa(®)) after co-medication with verapamil in healthy subjects. Br J Clin Pharmacol 2013;75:1053–62.
5. Hartter S, Koenen-Bergmann M, Sharma A, et al. Decrease in the oral bioavailability of dabigatran etexilate after co-medication with rifampicin. Br J Clin Pharmacol 2012;74:490–500.
6. Stangier J, Stahle H, Rathgen K, Fuhr R. Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. Clin Pharmacokinet 2008;47:47–59.
7. Huisman MV, Lip GY, Diener HC, Brueckmann M, van Ryn J, Clemens A. Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: resolving uncertainties in routine practice. Thromb Haemost 2012;107:838–47.
8. Eikelboom JW, Connolly SJ, Hart RG, et al. Balancing the benefits and risks of 2 doses of dabigatran compared with warfarin in atrial fibrillation. J Am Coll Cardiol 2013;62:900–8.

The Missing Link Between High-Density Lipoprotein Cholesterol and Inflammatory Response in Cardiovascular Disease

In the recently published post-hoc analysis from the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, low high-density lipoprotein cholesterol (HDL-C) levels remained a powerful and independent predictor of cardiovascular (CV) risk in 2,193 patients with stable ischemic heart disease (1). This finding was also confirmed in patients with low-density lipoprotein cholesterol (LDL-C) levels <70 mg/dl. However, both in primary prevention, as in the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial (2), as in secondary prevention (3), potent statin therapy may lead to no relation between HDL-C and residual CV risk. Furthermore, the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) Investigators have shown that there was no incremental clinical benefit from the addition of niacin to statin therapy despite a significant and sustained increase in HDL-C (4).

We feel that the missing link to understanding this unclear relation of HDL-C and residual CV risk in patients using intensive lipid-lowering medication relies on the degree of systemic inflammation. In fact, although HDL-C modulates cholesterol availability in the cell membrane, which promotes reverse cholesterol transport (HDL-C's main antiatherogenic effect), it also influences the immune response, the hematopoietic stem cells maturation, and ultimately the leukocyte number (5–7). HDL-C also plays a key role in the humoral innate immune response, as HDL-C induces the long pentraxin 3 (PTX3), and PTX3 levels are increased in animal models with genetically increased HDL levels. PTX3 deficiency then results in increased inflammation and bone marrow monocytosis (8). Again, in a prospective multiethnic trial that enrolled patients with ST-segment elevation myocardial infarction (9), high levels of systemic inflammation, defined by increased levels of interleukin-6 and C-reactive protein (CRP) within 6 h of the onset of symptoms, were associated with a significant reduction in HDL-C compared with patients with ST-segment elevation myocardial infarction and low levels of systemic inflammatory markers (10). Furthermore, inflammation induces major changes in HDL-C composition. Mediators of inflammation such as tumor necrosis factor–alpha and interleukin-6 induce expression of serum amyloid A and group IIA secretory phospholipase A_2, which dramatically alter HDL apolipoprotein content and levels, respectively (7). All this evidence suggests a profound link between inflammatory response in patients with atherosclerosis and the levels and composition of HDL-C. In our opinion, this link is underexplored in the subanalyses of large clinical trials aimed at increasing HDL-C levels and in studies on the predictive value of HDL-C levels on residual CV risk.