Update on Aspirin Resistance

September 1, 2008: A moderated poster, "Incomplete inhibition of thromboxane biosynthesis by ASA: determinants and effect on cardiovascular risk" presented by John Eikelboom at the 2008 Congress of the European Society of Cardiology confirmed that elevated urinary 11-dehydro thromboxane B2 (11dhTxB2) concentrations in ASA-treated patients were associated with an increased risk of stroke, myocardial infarction (MI) or cardiovascular (CV) death.

In a prospective multi-center study, baseline urinary 11dhTxB2 levels were measured in a population of 3261 high vascular risk patients from the CHARISMA trial who were on ASA therapy. The patients were followed for the occurrence of stroke, myocardial infarction or cardiovascular death. The results showed that urinary 11dhTxB2 concentrations in the highest quartile were associated with an increased risk of stroke, MI or CV death compared with the lowest quartile (Adjusted Hazard Ratio [HR] 1.66 to 2.61, p=0.03). Factors independently associated with higher urinary 11dhTxB2 levels included increasing age, female gender, history of peripheral artery disease, current smoking, and oral hypoglycemic or angiotensin converting enzyme (ACE) inhibitor therapy. ASA dose ≥ 150 mg.d, history of treatment with NSAIDS, history of hypercholesterolemia, and statin treatment were associated with lower 11dhTxB2 levels.

Based on the study results, the authors concluded that, "urinary concentrations of 11dhTxB2 are an externally valid and potentially modifiable determinant of stroke, MI or CV death in patients at risk of atherothrombotic events. The potential for higher doses of ASA and statins to reduce urinary 11dhTxB2 concentrations and CV risk should prompt randomized evaluation of the clinical efficacy of titrating doses according to 11dhTxB2 concentrations, and the clinical efficacy of other treatments that reduce thromboxane production."

Reference: Incomplete inhibition of thromboxane biosynthesis by ASA: determinants and effect on cardiovascular risk. J. Eikelboom, GJ Hankey,DL Bhatt, et al. European Heart Journal (2008) 29(Abstract Supplement), 404.

VWD Guidelines

(continued from page 2)

VWF:Ag is calculated to see if the decrease in activity and antigen levels is proportional. A ratio of <0.6 or <0.7 indicates dysfunctional VWF (i.e. possible type 2 VWD).

A VWF multimer test may be performed to determine the variable concentrations of the different sized VWF multimers, preferably using a frozen aliquot of the same plasma sample used for the initial round of VWD tests. The VWF Collagen Binding assay (CBA) may also be used to differentiate type 1 VWD from types 2A, 2B, or 2M. This test measure the binding of VWF to collagen, which is dependent on multimeric size. The largest multimers bind more avidly than smaller forms. Other specialized VWD tests used to classify VWD patients include low dose ristocetin platelet aggregation (RIPA), and the VWF-platelet binding assay (VWF:PB assay), used to diagnose type 2B VWD. The VWF:FVIII binding assay is useful for diagnosing type 2N VWD. It measures the ability of VWF to bind added exogenous FVIII. Additional studies for selected patients may include Gene sequencing, assays for antibodies to VWF, and platelet-binding studies.

In summary, the laboratory diagnosis of VWD is challenging, and in some cases, the testing may need to be tailored to individual patients. An accurate diagnosis and classification is critical as treatment depends on the specific subtype of the disease. For more information and VWD Management recommendations, see the full report, "The Diagnosis, Evaluation, and Management of von Willebrand Disease" which is available on the NHLBI Website (www.nhlbi.nih.gov) and from the NHLBI Health Information Center.

Table 2: Recommended Cut-off Values for Definitive Diagnosis of VWD

Condition	VWF:Ag (IU/dL)	VWF:RCo (IU/dL)	FVIII	Ratio of VWF:RCo/VWF:Ag
Type 1	30*	<30*	↓ or Normal	>0.5 - 0.7
Type 2A	<30 - 200*†	<30*	↓ or Normal	<0.5 - 0.7
Type 2B	<30 - 200*†	<30*	↓ or Normal	Usually <0.5 - 0.7
Type 2M	<30 - 200*†	<30*	↓ or Normal	<0.5 - 0.7
Type 2N	30 - 200	30 - 200	↓↓	>0.5 - 0.7
Type 3	<3	<3	↓↓↓ (< 10 IU/dL)	Not applicable
Normal	50 - 200	50 - 200	Normal	>0.5 - 0.7

*<30 IU/dL is designated as the level for a definitive diagnosis of VWD; there are some patients with type 1 or type 2 VWD who have levels of VWF:Ag and/or VWF:Rco of 30-50 IU/dL

†The VWF:Ag level in the majority of individuals with type 2A, 2B, or 2M VWD is <50 IU/dL