Dr. Ezekowitz pointed out a few important characteristics of betrixaban, including its effective half-life of approximately 20 hours and the fact that it is being codeveloped with an antidote. No dose adjustments for renal impairment or major drug interactions were anticipated during this trial, because betrixaban is excreted mostly unchanged through bile, with minimal renal excretion, and it is not a substrate for the CYP450 system.

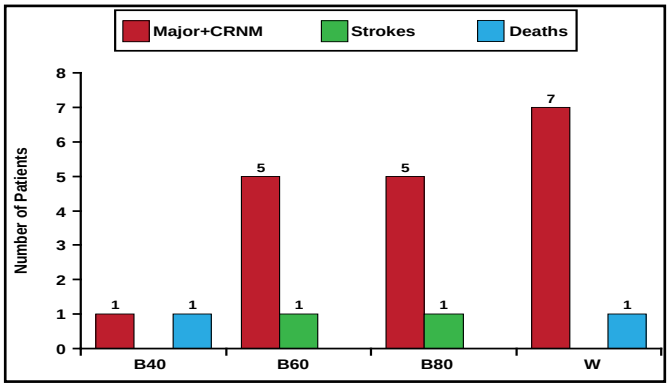
In EXPLORE-Xa, 508 patients with nonvalvular AF and at least one risk factor for stroke were randomized to receive betrixaban 40 mg (n=127), 60 mg (n=127), or 80 mg (n=127) or open-label warfarin (n=127) with an international normalized ratio goal of 2 to 3. The mean age was 74 years, and the median follow-up was 4.9 months (minimum follow-up 3 months; maximum follow-up 12 months). Patients were excluded from participation in the study if they had active endocarditis, AF due to reversible cases or mechanical heart valve, scheduled major surgery or pulmonary vein ablation, or repeated systolic blood pressure >160 mmHg; had received hemodialysis within one year; or experienced a recent ischemic stroke, systemic embolic event, or acute coronary syndrome within 30 days. The primary endpoint was occurrence of major or clinically relevant nonmajor bleeding. The secondary endpoints were time to occurrence of any bleeding (major, clinically relevant nonmajor, and minimal) and time to occurrence of death, stroke, myocardial infarction (MI), or other systemic embolism.

At 3 months, the rate of major or clinically relevant nonmajor bleeding in the betrixaban 40-mg group (n=1) was significantly less than in the warfarin group (n=4). Bleeding rates in the groups that received betrixaban 60 mg (n=4) and 80 mg (n=5) were comparable with rates that were observed in the warfarin group. The number of strokes and deaths was low in all treatment groups (Figure 1). Patients who received the 40-mg betrixaban dose demonstrated a slight increase in d-dimer from baseline, and there was a trend toward a dose response with d-dimer activity across the dose spectrum.

Adverse events were equally distributed among the groups, with the exception of gastrointestinal adverse events. The incidence of vomiting, nausea, and diarrhea was more common in patients who received betrixaban. There was no difference in the incidence of alanine aminotransferase >2x the upper limit of normal in any of the groups (2.4% for betrixaban and warfarin groups).

Betrixaban 40 mg, 60 mg, and 80 mg appear to be well tolerated in patients with AF or atrial flutter. There was a dose-dependent effect on the primary endpoint of major or clinically relevant nonmajor bleeding that was associated with betrixaban therapy. More comprehensive evaluation in a larger study population is needed to determine the safety and efficacy of betrixaban therapy.

Figure 1. Bleeds, Strokes, and Deaths.



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Pooled Analysis of the REAL-LATE and ZEST-LATE Trials

Dual antiplatelet therapy (aspirin plus clopidogrel) did not appear to be more effective than aspirin alone in reducing the rate of cardiac death or myocardial infarction (MI), according to pooled data from the Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation and Late Coronary Artery Thrombotic Events (REAL-LATE; NCT00484926) and Evaluation of the Long-Term Safety After Zotarolimus-Eluting Stent, Sirolimous-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions Late Coronary Arterial Events (ZEST-LATE; NCT00590174) Trials. The two trials were merged due to their design similarity and slow enrollment, and merged results were presented by Seung-Jung Park, MD, PhD, Asan Medical Center, Seoul, Korea.

Current guidelines recommend the use of clopidogrel 75 mg daily for at least 12 months post-drug-eluting stent (DES) implantation, provided that the patient is not at high risk of bleeding. While early discontinuation of dual antiplatelet therapy is associated with a higher risk of late stent thrombosis in patients with DES, there is no consistent data regarding the appropriate treatment duration and the long-term outcomes that are associated with dual antiplatelet therapy in these patients. The merged data analysis by Dr. Park and colleagues sought to compare antiplatelet strategies in patients on dual antiplatelet therapy who were free of major adverse cardiovascular events (MACEs) and major bleeding for at least 12 months post-DES implantation.

Patients in these two open-label trials were randomized to receive either clopidogrel 75 mg daily plus low-dose aspirin (100 to 200 mg daily; n=1357) or low-dose aspirin alone (n=1344). Patients were well matched at baseline. However,

the REAL-LATE participants included a broader population that did not limit clinical or lesion characteristics. Exclusion criteria across the studies included contraindications to antiplatelet drugs, concomitant vascular disease or other indications that required the long-term use of clopidogrel, noncardiac comorbidities that limited life expectancy to <1 year, and participation in another drug or coronary device study. Follow-up evaluations were performed every 6 months, and the median duration of follow-up was 19.2 months. The primary endpoint was the first occurrence of MI or death from cardiac causes postrandomization. The secondary endpoints included major bleeding, as defined by Thrombolysis in Myocardial infarction (MI) criteria; a composite of death or MI; a composite of death, MI, or stroke; a composite of cardiac death, MI, or stroke; or individual components, including death, MI, stroke of any cause, definite stent thrombosis, or repeat revascularization.

The risk of cardiac death or MI was similar for both groups (1.8% for dual therapy vs 1.2% for monotherapy; p=0.17). The composite risk of MI, stroke, or death from any cause was slightly higher in the dual therapy group (HR, 1.73; 95% CI, 0.99 to 3.00; p=0.051), as was the composite risk of MI, stroke, or death from cardiac causes (HR, 1.84; 95% CI, 0.99 to 3.45; p=0.06). However, neither of these increases reached statistical significance. The risks that were associated with the individual components of the secondary endpoint were similar in both groups. Overall, the use of dual antiplatelet therapy beyond 12 months post-DES implantation did not significantly reduce the risk of MI or death from cardiac causes compared with aspirin monotherapy.

Dr. Park concluded that this study had insufficient statistical power to determine the safety of clopidogrel discontinuation after 12 months. Therefore, larger clinical trials with a longer-term follow-up are needed to evaluate the risk of clopidogrel discontinuation.

Further Reading: Park S-J et al. Duration of Dual Antiplatelet Therapy after Implantation of Drug-Eluting Stents. *N Eng J Med* 15 Apr 2010;362(15):1374-1382.

Diuretic Optimization Strategies Evaluation in Acute Heart Failure

There is no evidence of benefit for various initial administration or dosing strategies of furosemide therapy in patients with acute decompensated heart failure (ADHF). However, the high-intensification (2.5 x chronic daily oral dose) dosing strategy was associated with improvements or trends toward improvement in multiple areas. Findings from the Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE-AHF; NCT00577135) Study were presented by G. Michael Felker, MD, Duke Clinical Research Institute, Durham, NC.

Intravenous (IV) loop diuretics are commonly prescribed for patients with ADHF. However, there is some debate concerning the risk, benefit, and appropriate use of higher-dose diuretics. There is also an absence of prospective studies and trial evidence to provide clinicians with consistent guidelines for diuretic management. In light of current uncertainty pertaining to the appropriate administration and dosing of diuretics, DOSE-AHF investigators set out to evaluate the safety and efficacy of two administration (bolus Q 12 hours vs continuous infusion) and two dosing (low intensification of 1 x chronic daily oral dose furosemide vs high intensification of 2.5 x chronic daily oral dose furosemide) strategies.

DOSE-AHF was a double-blind, randomized trial with a 2x2 factorial design that included 308 patients with prior clinical diagnosis of acute heart failure (AHF; defined by at least one symptom and one sign) who were identified within 24 hours of hospital admission. All patients were taking oral furosemide 80 mg to 240 mg daily with an anticipated need for IV loop diuretics for at least 48 hours. Patients were excluded from participation if they received or planned to receive IV vasoactive therapy or ultrafiltration therapy for HF; had acute coronary syndrome within 4 weeks; and had systolic blood pressure <90 mmHg, serum creatinine>3.0 mg/dL at baseline, B-type natriuretic peptide (BNP) <250 pg/mL, or N-terminal pro-BNP (NT-proBNP) <1000 pg/mL.

The coprimary endpoints were the efficacy endpoint of patient global assessment by visual analog scale (VAS) over 72 hours using area under the curve (AUC) and the safety endpoint of renal function assessment, defined as change in creatinine from baseline to 72 hours. The study was 88% powered for detecting a creatinine difference of 0.2 mg/dL and a 600-point difference in VAS. Statistical significance for the two primary endpoints was p≤0.25. VAS was assessed at 6, 12, 24, 48, and 72 hours. The secondary endpoints are contained in Table 1.

The difference in global symptom relief and renal function was not statistically significant at 72 hours with regard to administration method (bolus vs continuous infusion) or dose (low vs high intensification). Additionally, results for all secondary endpoints were similar, regardless of the method of furosemide administration. Though transient changes in renal function occurred in patients who received high-intensification therapy prior to 60 days, the difference between the two groups dissipated by Day 60. High-intensification therapy was associated with improvements or trends toward improvement in multiple