New Oral Anticoagulants and Antiplatelet Drugs

Written by ***Toni Rizzo***

Oral Anticoagulants

The benefit of oral anticoagulation following acute coronary syndrome (ACS) has been demonstrated in warfarin trials, showing significant reductions in myocardial infarction (MI) and stroke at the expense of an increased risk of bleeding. The impact of oral direct thrombin inhibitors and direct factor Xa inhibitors in ACS patients has been the subject of several clinical trials that were presented by Christopher B. Granger, MD, Duke University Medical Center, Durham, North Carolina, USA.

In the Phase III Acute Coronary Syndrome [APPRAISE-2; Alexander JH et al. *N Engl Med* 2011] study of apixaban combined with antiplatelet therapy in high-risk ACS patients, apixaban was not more effective than placebo (HR, 0.95; 95% CI, 0.80 to 1.11; p=0.51). The study was stopped early because of significantly increased risk of major bleeding with apixaban (1.3%) versus placebo (0.5%; HR, 2.59; 95% CI, 1.50 to 4.46; p=0.001).

The Efficacy and Safety Study for Rivaroxaban in Patients with Acute Coronary Syndrome [ATLAS ACS 2-TIMI 51] trial randomized patients with recent ACS to rivaroxaban 2.5 mg BID (n=5174), rivaroxaban 5.0 mg BID (n=5176), or placebo (n=5176) [Mega JL et al. *N Engl J Med* 2012]. The incidence of the primary endpoint of cardiovascular (CV) death, MI, and stroke was 8.9% with rivaroxaban (both doses) versus placebo (10.7%; HR, 0.84; 95% CI, 0.74 to 0.96; modified intention-to-treat [mITT] p=0.008). Patients treated with low-dose rivaroxaban versus placebo had significantly reduced rates of the primary endpoint (9.1% vs 10.7%; HR, 0.84; mITT p=0.02), CV death (2.7% vs 4.1%; HR, 0.66; mITT p=0.002), and all-cause death (2.9% vs 4.5%; HR, 0.68; mITT p=0.002). This survival benefit was not observed with rivaroxaban 5.0 mg. TIMI major bleeding rates were significantly increased with rivaroxaban 2.5 mg (1.8%; HR, 3.46; p<0.001) and rivaroxaban 5.0 mg (2.4%; HR, 4.47; p<0.001) versus placebo (0.6%).

The What Is the Optimal Antiplatelet & Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting [WOEST; NCT00769938; De Wilde W. ESC 2012] trial is the first study to compare an oral anticoagulant regimen (warfarin and clopidogrel) with and without aspirin in patients undergoing coronary stenting. Although the trial had some limitations, the double- versus triple-therapy group had significantly lower TIMI bleeding (19.5% vs 44.9%; HR, 0.36; 95% CI, 0.26 to 0.50; p<0.001). Double therapy also appeared to be associated with reduced rates of major adverse cardiac events (MACE; 11.3% vs 17.1%; HR, 0.60; 95% CI, 0.38 to 0.94; p=0.025).

The APPRAISE-2 and ATLAS-2 trials of novel factor Xa inhibitors in patients also taking aspirin and clopidogrel both demonstrated a 3- to 4-fold increased risk of major bleeding, including intracranial hemorrhage (ICH). Factors such as the dose, patient population, and chance may account for the benefit observed with rivaroxaban but not with apixaban. The WOEST trial has demonstrated the potential for a more favorable benefit/risk balance by discontinuing aspirin in some patients on oral anticoagulants.

Antiplatelet Agents

Robert A. Harrington, MD, Stanford University Medical Center, Stanford, California, USA, discussed the current state of adenosine diphosphate (ADP) blockers and emerging approaches to antiplatelet therapy. Antiplatelet therapy is the cornerstone of acute coronary syndrome care, supported by a large body of evidence. Studies have shown that more intense ADP blockade is better than less intense blockade. Although most of the effect is on reduction of MI, the Efficacy and Safety of Adding Clopidogrel to Aspirin or Use of Metoprolol in Myocardial Infarction [COMMIT; COMMIT Collaborative Group. *Lancet* 2005] and PLATO trials showed that mortality reductions are possible. However, balancing efficacy and safety is a challenge, especially with combination therapy.

Patients with ACS, especially those without ST-segment elevation (STEMI) are an increasingly complex group with many variables that must be considered when making treatment decisions, including renal and hepatic function, advanced age, comorbidities, and prior cardiac procedures. Antiplatelet trials have concentrated on early therapy but the risk in patients with non-STEMI accrues over time, with 35% to 40% mortality at 6 to 8 years after the index event.

The benefits and risks of clopidogrel have been carefully quantified in large randomized trials and through extensive clinical experience. It is an excellent drug but has limitations, including relatively slow onset of action, modest platelet inhibition, and considerable variability in effect based in part on genetic polymorphisms and drug interactions. Prasugrel and ticagrelor have demonstrated efficacy in trials and can be used as alternatives to clopidogrel in some settings. Features of prasugrel and ticagrelor are shown in Table 1.

Table 1. Features of New ADP Blockers.

Prasugrel	Ticagrelor
Commercially available	Commercially available
Thienopyridine; prodrug	Non-thienopyridine; not a prodrug
More rapid onset and more potent than clopidogrel	More rapid onset and more potent than clopidogrel
No CYP genetic issue	No CYP genetic issue
Validated in large RCTs in NSTE and STE PCI as better than clopidogrel 300 mg dosed before procedure	Validated in large RCTs in NSTE and STE ACS (upstream) vs clopidogrel 300 and 600mg, with benefits on MI and mortality
Early and late effects	Early and late effects
Increased bleeding risk, including fatal bleeding	Increased bleeding risk; increased dyspnea
TRILOGY trial showed no benefit in medically managed ACS	Issues in United States with aspirin dose
	Ongoing RCTs in secondary prevention

ACS=acute coronary syndrome; MI=myocardial infarction; NSTE=non-ST-segment elevation; RCT=randomized controlled trial; STE=ST-segment elevation; PCI=percutaneous coronary intervention.

The European and US guidelines have incorporated the following into the latest ACS guidelines:

- Treat all patients with aspirin
- Treat medium- to high-risk percutaneous coronary intervention (PCI) patients with dual antiplatelet therapy before PCI (clopidogrel, ticagrelor, glycoprotein IIb/IIIa inhibitors) and at PCI (clopidogrel, ticagrelor, prasugrel, glycoprotein IIb/IIIa inhibitors)
- Treat with dual therapy with aspirin and an ADP blocker when a conservative strategy is used
- Use loading doses of ADP blockers.
- Treat for at least 12 months
- Glycoprotein IIb/IIIa inhibitors have no benefit in low-risk patients on aspirin/ADP
- Prasugrel is potentially harmful in patients with history of stroke or transient ischemic attack.

New agents in development include cangrelor, a rapid acting IV ADP blocker studied in two randomized trials in patients undergoing PCI. Although cangrelor did not reduce MACE in this setting [Harrington RA et al. *N Engl J Med* 2009; Bhatt DL et al. *N Engl J Med* 2009], secondary analyses suggested that cangrelor has benefits in certain contexts. The Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention [CHAMPION PHOENIX; NCT01156571] trial is underway to test cangrelor versus clopidogrel in PCI patients. Vorapaxar and other thrombin receptor blockers have been extensively studied. In the Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients with Acute Coronary Syndrome [TRA•CER], vorapaxar added to dual therapy did not reduce MACE and was associated with significantly increased GUSTO moderate/severe bleeding versus placebo ($p<0.001$), including increased ICH ($p<0.001$) [Tricoci P et al. *N Engl J Med* 2012]. For secondary prevention in subjects with established atherosclerotic vascular disease, the Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients with Atherosclerosis [TRA 2°P-TIMI 50] demonstrated that the addition of vorapaxar versus placebo reduced the incidence of CV death, MI, or stroke (9.3% vs 10.5%; HR, 0.87; 95% CI, 0.80 to 0.94; $p<0.001$) but was associated with increased ICH and major bleeding (Table 2) [Morrow DA. *N Engl J Med* 2012.]

Table 2. TRA 2°P-TIMI 50: Bleeding Endpoints (Overall Population).

3-Year KM Rate (%)	Placebo (n=13,166)	Vorapaxar (n=13,186)	HR (95% CI)	p Value
GUSTO moderate or severe	2.5	4.2	1.66 (1.43–1.93)	<0.001
TIMI clinically significant	11.1	15.8	1.46 (1.36–1.57)	<0.001
TIMI non-CABG major	1.8	2.8	1.46 (1.22–1.75)	<0.001
Intracranial	0.5	1.0	1.94 (1.39–2.70)	<0.001
Fatal	0.2	0.3	1.46 (0.82–2.58)	0.190

CABG=coronary artery bypass graft; KM=Kaplan-Meier.