Strategies to Optimize Antiplatelet Effects and Minimize Bleeding in NSTE-ACS

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Patients with non-ST-elevation (NSTE) acute coronary syndrome (ACS) are treated with antiplatelet and anticoagulation to reduce ischemic complications [Hamm CW et al. *Eur Heart J* 2011; Wright RS et al. *J Am Coll Cardiol* 2011]. The presentations in this session focused on selecting the appropriate therapies and improving short- and long-term outcomes in patients with NSTE-ACS.

CHOOSING THE BEST ANTITHROMBIN THERAPY

Marco Valgimigli, MD, PhD, Erasmus Medical Center, Rotterdam, The Netherlands, reviewed the evidence on anticoagulants for patients with NSTE-ACS. The anticoagulants, unfractionated heparin (UFH), enoxaparin, and fondaparinux are recommended for patients with NSTE-ACS regardless of whether an early invasive or conservative strategy is chosen. In constrast, bivalirudin is only indicated for patients who are being considered for revascularization with an early invasive strategy [Hamm CW et al. *Eur Heart J* 2011; Wright RS et al. *J Am Coll Cardiol* 2011].

A meta-analysis of six trials reported an initial 50% relative risk reduction (RRR) in myocardial infarction (MI) or death and a 2-fold increase in major bleeding in patients treated with UFH plus acetylsalicylic acid (ASA) versus ASA alone. After 12 weeks the RRR decreased to 33% [Oler A et al. *JAMA* 1996]. Results of other UFH studies are shown in Table 1.

Table 1. Studies of Unfractionated Heparin

Study	Design	Results
FUTURA/OASIS 8 [Steg PG et al. *Am Heart J* 2010]	▪ UFH 50 U/kg vs 85 or 60 U/kg with GpIIb-IIIa inhibitor after fondaparinux ▪ Death/MI/TVR at 30 days ▪ Major bleeding at 30 days	▪ Death/MI/TVR: LD 4.5% vs SD 2.9% (HR, 1.56; 95% CI, 0.98–2.48; p=0.06) ▪ Major bleed: LD 2.2% vs SD 1.8% (HR, 1.20; 95% CI, 0.64–2.23; p=0.57) ▪ Heterogeneity: p=0.02
Enoxaparin vs UFH in NSTE-ACS [Petersen JL et al. *JAMA* 2004]	▪ Systematic review of ESSENCE, TIMI 11B, ACUTE II, INTERACT, A to Z, and SYNERGY trials ▪ Death/MI at 30 days ▪ Major bleeding at 30 days	▪ Death/MI: enoxaparin 10.1% vs UFH 11.0% (OR, 0.91; 95% CI, 0.83–0.99) ▪ Major bleed: enoxaparin 4.7% vs 4.5% (HR, 1.04; 95% CI, 0.89–1.30)
SYNERGY [Ferguson JJ et al. *JAMA* 2004]	▪ Enoxaparin vs UFH ▪ Death/MI at 30 days ▪ TIMI major bleeding at 30 days	▪ Death/MI: enoxaparin 14.0% vs UFH 14.5% (HR, 0.96; 95% CI, 0.86–1.06; p=0.40) ▪ Major bleed: enoxaparin 9.1% vs UFH 7.6% (p=0.008)

GpIIb-IIIa=glycoprotein IIb/IIIa; LD=low dose; MI=myocardial infarction; SD=standard dose; TVR=target vessel revascularization; UFH=unfractionated heparin.

In OASIS-5 [Yusuf S et al. *N Engl J Med* 2006], fondaparinux was noninferior to enoxaparin for reducing ischemic events at 9 days but significantly reduced mortality by 17% (HR, 0.83; 95% CI, 0.71 to 0.97; p=0.02) and bleeding by 50% (HR, 0.52; 95% CI, 0.44 to 0.61; p<0.001).

The ACUITY trial [Stone GW et al. *N Engl J Med* 2006] reported that for patients receiving percutaneous coronary intervention (PCI), bivalirudin plus provisional glycoprotein IIb/IIIa inhibitor (GPI) was noninferior to UFH or enoxaparin ± provisional GPI for the ischemic events while major bleeding significantly lower (3.0% vs 5.7%; RR, 0.53; 95% CI, 0.43 to 0.65; p<0.001). In ISAR-REACT 4, [Kastrati A et al. *N Engl J Med* 2011] patients with NSTE-ACS treated with PCI were randomized to bivalirudin or UFH plus abciximab. Bivalirudin was noninferior for the endpoint of death, recurrent MI or urgent target vessel revascularization (13.4% vs 12.8%; RR, 0.96; 95% CI, 0.74 to 1.25; p=0.76) and had lower rates of major bleeding (2.6% vs 4.6%; RR, 1.84; 95% CI, 1.10 to 3.07; p=0.02).

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Prof. Valgimigli concluded that fondaparinux in medically treated patients and bivalirudin in PCI patients appears to be efficacious while having a favorable safety profile in terms of bleeding.

CHOOSING THE RIGHT ANTIPLATELET AGENT

The current antiplatelet agents available for $P2Y_{12}$ inhibition in patients with NSTE-ACS are clopidogrel, prasugrel, and ticagrelor. Strategies to select the optimal agent were discussed by Matthew J. Price, MD, Scripps Clinic, La Jolla, California, USA.

Table 2 summarizes major trials evaluating antiplatelet agents in patients with ACS. These studies demonstrate the efficacy of prasugrel and ticagrelor compared with clopidogrel, although these agents also were associated with higher bleeding rates.

Table 2. Antiplatelet Studies in NSTE-ACS

Study	Design	Results
TRITON-TIMI 38 [Wiviott SD et al. *N Engl J Med* 2007]	▪ Prasugrel vs clopidogrel ▪ Thienopyridine-naïve ACS with/without STE undergoing PCI ▪ 450 days post randomization	▪ CV death/MI/stroke: prasugrel 9.9% vs clopidogrel 12.1% (HR, 0.81; 95% CI, 0.73–0.90; p<0.001) ▪ Major bleeding: prasugrel 2.4% vs clopidogrel 1.8% (HR, 1.32; 95% CI, 1.03–1.68; p=0.03)
TRILOGY ACS [Roe MT et al. *N Engl J Med* 2012]	▪ Prasugrel vs clopidogrel ▪ Medically managed UA/NSTEMI patients <75 years ▪ Median follow-up 17 months	▪ CV death/MI/stroke: prasugrel 13.9% vs clopidogrel 16.0% (HR, 0.91; 95% CI, 0.79–1.05; p=0.21) ▪ Similar rates of major bleeding between groups
PLATO [Wallentin L et al. *N Engl J Med* 2009]	▪ Ticagrelor vs clopidogrel ▪ ACS patients with/without STE ▪ Medically managed and PCI-treated patients ▪ 360 days post randomization	▪ CV death/MI/stroke: ticagrelor 9.8% vs clopidogrel 11.7% (HR, 0.84; 95% CI, 0.77–0.92; p<0.001) ▪ Major bleeding: ticagrelor, 4.5% vs clopidogrel, 3.8%; p=0.03

ACS=acute coronary syndrome; CV=cardiovascular; DM=diabetes mellitus; GPI=glycoprotein inhibitor; MI=myocardial infarction; NSTEMI=non-ST elevation myocardial infarction; PCI=percutaneous coronary intervention; STE=ST elevation; UA=unstable angina; UR=urgent revascularization.

Dr. Price concluded that treatment for NSTE-ACS should be individualized according to ischemic and bleeding risk. Prasugrel or ticagrelor are preferred when markers of ischemic risk are present, including positive troponin or elevated biomarkers correlated with higher absolute event rates. For noninvasively managed patients, ticagrelor is superior to clopidogrel. Clopidogrel should be used when bleeding risk is high, particularly when concomitant oral anticoagulation is indicated or contraindications are present.

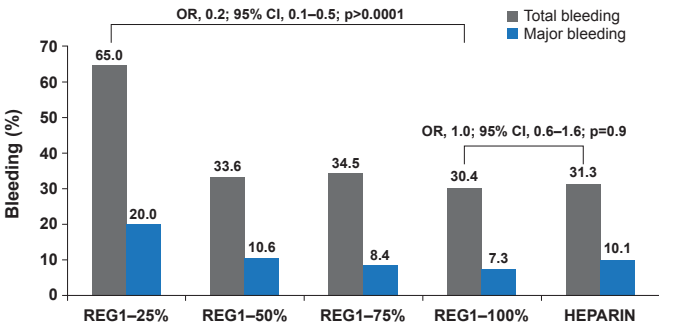
NOVEL ANTICOAGULATION TARGETS AND AGENTS

According to John H. Alexander, MD, MHS, Duke Clinical Research Institute, Durham, North Carolina, USA, available anticoagulants are effective for NSTE-ACS, but there is room for improvement both for control of ischemic events and for bleeding complications.

Otamixaban is a specific, direct Factor Xa inhibitor that was studied in moderate- to high-risk NSTE-ACS with planned early invasive management [Steg PG et al. *JAMA* 2013]. Compared to UFH plus eptifibatide, otamixaban did not improve rates of death or MI (5.5% vs 5.7%; RR, 0.99; 95% CI, 0.85 to 1.16; p=0.93) and increased major bleeding (3.1% vs 1.5%; RR, 2.13; 95% CI, 1.63 to 2.78; p<0.001).

REG1 is a two-component, actively controllable anticoagulant system consisting of the Factor IX inhibitor, pegnivacogin and the control agent, anivamerson, which has a specific affinity for pegnivacogin. The RADAR trial [Povsic TJ et al. *Eur Heart J* 2013] evaluated REG1 versus heparin in NSTE-ACS patients undergoing femoral catheterization. At 30 days, ACUITY bleeding had occurred in 65.0%, 33.6%, 34.5%, 30.4%, and 31.3% of patients with 25%, 50%, 75%, and 100% reversal and heparin, respectively (Figure 1). At least 50% pegnivacogin reversal was needed to prevent bleeding. There were numerically but not statistically fewer ischemic events with REG1 versus heparin (3.0% vs. 5.7%, p=0.1). A Phase 3 trial comparing REG1 with bivalirudin, REGULATE-PCI, is ongoing [NCT01848106].

Figure 1. RADAR: ACUITY Bleeding Through 30 Days



REG1=pegnivacogin plus control agent, anivamerson.

Reproduced from Povsic TJ et al. A Phase 2, randomized, partially blinded, active-controlled study assessing the efficacy and safety of variable anticoagulation reversal using the REG1 system in patients with acute coronary syndromes: results of the RADAR trial. *Eur Heart J* 2013;34(31)248-2489. With permission from Oxford University Press.

Post-ACS, a number of new oral anticoagulants (NOACs) have been studied. A meta-analysis of the NOACs, ximeligatran, apixaban, rivaroxaban, dabigatran, and darexaban added to single or dual antiplatelet therapy (DAPT) for post-ACS therapy, reported only modest reductions in cardiovascular events and substantial increases in bleeding [Oldgren J et al. *Eur Heart J* 2013]. Included studies included a variety of agents as well as intensities of anticoagulation.

Dr. Alexander concluded that available anticoagulants are effective for acute management of NSTE-ACS but

challenges remain with ischemic events and bleeding. For post-acute management of NSTE-ACS, adding an anticoagulant at therapeutic doses to current antiplatelet may reduce ischemic events and but increases bleeding. Future studies exploring different doses and new combinations of antiplatelet and anticoagulant agents will define the role of anticoagulation in post-ACS treatment.

LONG-TERM ANTICOAGULATION THERAPY

Freek W.A. Verheugt, MD, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands, explored the use of novel anticoagulants for long-term therapy and described the potential for eliminating aspirin or warfarin. Results of a nationwide cohort study in Denmark are shown in Table 3 [Lamberts M et al. *Circulation* 2012].

Table 3. Bleeding and Ischemic Events

	Bleeding (events/100 person years)	Post-MI or PCI Ischemic Events (events/100 person years)
Triple therapy	14.2	20.1
Vitamin K + single antiplatelet therapy	9.7	19.4
DAPT	7.0	26.3
Vitamin K monotherapy	7.0	26.9
Single antiplatelet therapy	6.9	38.0

The ASPECT-2 [van Es RF et al. *Lancet* 2002] and WARIS-II [Hurlen M et al. *N Engl J Med* 2002] studies reported that warfarin alone or combined with aspirin was more effective for preventing ischemic events after MI than aspirin alone but was associated with increased bleeding. In the WOEST trial [Dewilde WJM et al. *Lancet* 2013], patients treated with OAC plus clopidogrel and ASA versus OAC plus clopidogrel had significantly increased bleeding (44.4% vs 19.4%; HR, 0.36; 95% CI, 0.26 to 0.50; p<0.0001) and all-cause mortality (6.3% vs 2.5%; HR, 0.39; 95% CI, 0.16 to 0.93; p=0.027). Ischemic events were not increased by dropping ASA. Another recent study found that OAC plus clopidogrel was equal to or better than triple therapy with respect to ischemic events and bleeding rates [Lamberts M et al. *J Am Coll Cardiol* 2013].

In the RE-LY study [Dans AL et al. *Circulation* 2013], patients receiving DAPT plus warfarin or dabigatran (110 or 150 mg) had the highest major bleeding rates compared with those receiving single or no antiplatelet therapy, with the lowest absolute risk among patients on dabigatran 110 mg.

The evidence shows that in patients requiring oral anticoagulation, DAPT reduces recurrent ischemic events after stenting for ACS but increases bleeding significantly. The use of safer OACs may reduce bleeding in this situation. Omitting ASA and treating with an anticoagulant and clopidogrel after stenting in atrial fibrillation patients seems promising but needs to be confirmed in future trials.