Meeting Report


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The 71st Scientific Sessions of the American Heart Association were held on November 8–11, 1998 at the Dallas Convention Center in Dallas, TX. There were over 4,500 abstracts presented, covering virtually all aspects cardiovascular medicine. It is well beyond the scope of this meeting report to attempt to cover all the presentations that would be of interest to the readership of this journal. This report covers selected new developments in anticoagulant, antithrombotic, antiplatelet, and thrombolytic therapeutics that were presented at this AHA meeting.

ANTICOAGULANTS

M. Cohen et al. (Allegheny General Hospital, Pittsburgh, PA and Hahnemann Univ., Philadelphia, PA) grouped the patient population enrolled in the ESSENCE clinical trial to evaluate the relative efficacy of a low molecular weight heparin, enoxaparin (Lovenox®), and unfractionated heparin in patients presenting with different symptoms. ESSENCE was an international, randomized, double-blind, parallel-group clinical trial that directly compared enoxaparin with heparin in patients with unstable coronary artery disease or non-Q-wave myocardial infarction. ESSENCE demonstrated a >16% reduction in the relative risk of death, myocardial infarction, or recurrent ischemia after 30 d in patients treated for 2.6 d with subcutaneous enoxaparin compared with patients treated with adjusted-dose intravenous unfractionated heparin. Enoxaparin was significantly more effective than heparin in patients with (1) baseline ST segment depression, (2) older patients (>65 years of age), (3) women, (4) patients who did not smoke, (5) patients who presented with ECG changes or (6) had a prior myocardial infarction, and (7) patients who had used aspirin. Enoxaparin tended toward superiority over heparin in patients who had (1) a prior percutaneous transluminal coronary angioplasty (PTCA), (2) a prior coronary artery bypass graft (CABG), (3) diabetes, or (4) T-wave inversions on their ECG, and (5)
men. Enoxaparin and heparin were apparently equivalent in efficacy in patients who were (1) current smokers, (2) had no baseline ECG changes, and (3) who had not taken aspirin regularly.

P. Baum et al. (Washington Univ., St. Louis, MO) described the antithrombotic effects of a novel factor Xa inhibitor, BX-807834, and compared it with rTAP (recombinant tick anticoagulant peptide), another factor Xa inhibitor (DX-9065a), and a low molecular weight heparin (ardeparin). The drugs, administered by intravenous bolus, were evaluated for their ability to inhibit thrombus formation in a rabbit model of arterial and venous thrombosis. In the arterial thrombosis model thrombus formation was induced by electrical injury to the carotid artery. On a molar basis, BX-807834 appeared to be the most potent inhibitor in this model (ED$_{50}$s were 0.2, 1, and 5 $\mu$mol/kg for BX-807834, rTAP, and DX-9065a, respectively). In the venous thrombosis model, thrombus formation was induced by a cotton thread placed in the superior vena cava. On a molar basis, BX-807834 was a more potent inhibitor of venous thrombosis than was ardeparin (ED$_{50}$s were <0.008 and 0.3 to 0.6 $\mu$mol/kg for BX-807834 and ardeparin, respectively). In this model, the prothrombin time and activated partial thromboplastin time were unchanged from baseline values with BX-807834. This factor Xa inhibitor may be a promising new drug for the treatment of arterial and venous thrombosis.

A. A. K. Hasan et al. (Univ. Michigan, Ann Arbor, MI) described the mechanism of action of a class of naturally occurring peptidic thrombin inhibitors that include bradykinin and its metabolites. Hasan had previously shown that plasma kininogens are selective inhibitors of $\alpha$-thrombin activation of platelets and endothelial cells. Bradykinin, a bradykinin analog (MKRPPGFSPFRSSRIG), and a pentapeptide derived from the analog (RPPGF) were shown to inhibit thrombin-induced Ca$^{2+}$ mobilization in platelets, platelet aggregation, and secretion. In these experiments, thrombin was unable to cleave the N-terminal extracellular domain of the thrombin receptor (PAR1, protease-activated receptor-1) in the presence of bradykinin or its analogs. ADP-, collagen-, U46619-, or thrombin-receptor-activating peptide (SFLLRN)-induced platelet activation was not inhibited by bradykinin or its analogs. RPPGF has been called thrombostatin and it is an angiotensin-converting enzyme breakdown product of bradykinin. New data have demonstrated that RPPGF also inhibited activation of protein C on thrombomodulin and inactivation of protein S, suggesting that RPPGF may interact with thrombin substrates. Binding studies showed that thrombin binds to peptides mimicking the thrombin cleavage site on PAR1, bovine and human protein C, and protein S. RPPGF also bound to the protease cleavage sites on PAR2 and PAR3. The data confirm that RPPGF binds to certain substrates of thrombin, thereby preventing proteolysis. Moreover, RPPGF was also shown to bind to the active site of thrombin crystals in a retro-manner (in the opposite direction from its binding to thrombin’s substrates), suggesting that RPPGF is a bivalent thrombin inhibitor.

**PLATELET INHIBITORS**

M. Ochiai et al. (Teikyo Univ., Tokyo, Japan) compared cilostazol with ticlopidine (both with aspirin) as adjunctive agents in primary stenting for acute myocardial infarction (AMI). Cilostazol is an inhibitor of cyclic AMP phosphodiesterase (it is more specific for
type III) that inhibits platelet aggregation and acts as a vasodilator. Ticlopidine (Ticlid®) is an inhibitor of ADP-induced platelet aggregation. Forty-four patients undergoing elective primary stenting using a Palmaz-Schatz stent were treated with aspirin and cilostazol (200 mg/d) or ticlopidine (200 mg/d) for 6 m. Subacute stent thrombosis did not occur in either treatment group. Restenosis was evident in 5 patients (24%) administered ticlopidine and target vessel revascularization (TLR) was performed in 4 patients (21%). In the cilostazol group, restenosis was not evident in any patients (0%) and TLR was not necessary for any patients (0%). Six months after the procedure mean lumen diameter (MLD; measured by angiography) was significantly greater in the cilostazol group than in the ticlopidine group and the late loss of lumen diameter (difference in MLD immediately after stenting and six months later) was also significantly greater in the ticlopidine group. The authors concluded that cilostazol is more effective than ticlopidine after primary stenting since it results in a better clinical and angiographic outcome.

D. Fischman et al. (Jefferson Medical College, Philadelphia, PA) reported the results of the STRESS III clinical trial that compared the efficacy of high-pressure stent deployment and reduced anticoagulation using ticlopidine plus aspirin with ordinary stent deployment using aspirin plus warfarin. This latter regimen was used in the STRESS I clinical trial that compared stenting with PTCA. This earlier trial showed that stenting produced fewer acute complications than PTCA but that this benefit was lost 6 m later due to significantly greater late loss of lumen diameter in the stent group. In STRESS III, 250 patients were enrolled and the clinical outcome one year after the procedure was compared to the PTCA and stenting groups in STRESS I. The incidence of any myocardial infarction, CABG, TLR, and combination of any adverse cardiac event were significantly lower in the group undergoing high pressure stent deployment with aspirin and ticlopidine than in the PTCA group. The incidence of any major adverse cardiac event was also 37% lower with the newer stenting procedure with aspirin and ticlopidine than the previous stent procedure with aspirin and warfarin. High pressure stent deployment with reduced anticoagulation appears to confer significant improvement in clinical outcomes compared to the previously used method and drug regimen.

V. Patel et al. (Cleveland Clinic, Cleveland, OH) studied a subgroup of patients in the EPISTENT clinical trial that had abnormal coronary blood flow, defined as TIMI grade 2 or less, before elective stenting or PTCA. EPISTENT randomized 2,285 patients to a GPIIb/IIIa antagonist, abciximab (ReoPro®), plus PTCA, abciximab plus stent, or stent alone. Abciximab is a monoclonal antibody targeting the platelet fibrinogen receptor, also known as GPIIb/IIIa. Preprocedural abnormal blood flow was observed in 441 (19.3%) patients, while preprocedural TIMI grade-3 flow was seen in the remaining 1,844 patients (80.7%). Moreover, the former group of patients had more complex lesions (24% vs. 11%) and intracoronary thrombus (44% vs. 9%). Clinical outcomes (death, myocardial infarction, and urgent revascularization) were assessed after 30 d in the two groups of patients. Abciximab reduced the incidence of the composite clinical endpoints in both groups of patients. In patients with abnormal blood flow, the event rate was decreased from 9.8% in the stent group to 6.5% in the abciximab plus stent or PTCA group. In patients with normal blood flow, the event rate was decreased from 10.9% in the stent group to 6.1% in the abciximab plus stent or PTCA group. Abciximab administration (with stent or PTCA) was also associated with a greater frequency of TIMI grade-3 flow in patients with
abnormal preprocedural blood flow (85% vs. 77%). Adjunctive therapy of abciximab appears to confer additional benefit to patients with abnormal coronary blood flow who are undergoing elective stenting or PTCA.

C. Bode et al. (Univ. Heidelberg, Germany) measured the binding of abciximab to platelets in a small group of patients (n = 21) with AMI that were treated with abciximab alone or abciximab with a thrombolytic agent (reteplase (Retavase®), a genetically engineered t-PA). Fourteen of these patients required additional therapy in the form of PTCA or stenting and all patients also received aspirin. Abciximab binding was measured using a fluorescent goat anti-mouse Fab fragment and flow cytometry and fibrinogen occupancy of its receptor (GPIIb/IIIa) was measured using a fluorescent chicken anti-human fibrinogen antibody. The results showed that 80% of platelet GPIIb/IIIa was occupied after bolus injection of abciximab. Receptor occupancy remained constant for as long as abciximab infusion was continued (12 h). Receptor binding decreased slowly after termination of infusion. About 60% of platelet GPIIb/IIIa were occupied after 3 d and 27% after 6 d. Fibrinogen binding to ADP-stimulated platelets was markedly affected in patients also administered ticlopidine. Recovery of fibrinogen binding was greatly delayed by ticlopidine (fibrinogen bound to only 36% of platelet GPIIb/IIIa 6 d after termination of abciximab infusion in the presence of ticlopidine compared to 82% in its absence). The results show that ticlopidine maintains inhibition of platelet function after abciximab infusion has stopped. Reteplase had no affect on any of these parameters.

M. Gibson et al. (Allegheny General Hospital, Pittsburgh, PA) presented some results from the TIMI 14 dose-ranging clinical trial of abciximab as an adjunctive agent in thrombolysis. It is believed that administration of abciximab together with a thrombolytic agent may accelerate thrombolysis and help achieve better blood flow. Patients with an AMI within 12 h of treatment and ST-segment elevation were enrolled in the study. Several dosing regimens were evaluated: (1) accelerated t-PA, (2) abciximab alone (bolus plus 12-h infusion), (3) abciximab plus reduced doses of streptokinase, or (4) abciximab plus various reduced dosage regimens of t-PA. All patients also received aspirin and heparin. The endpoint was restoration of blood flow assessed by angiography using the corrected TIMI frame count (CTFC). Abciximab alone was not effective in restoring blood flow and most other drug regimens were not superior to accelerated t-PA. However, abciximab plus a 15-mg bolus t-PA followed by 35 or 50 mg infused over a 60-min period provided significantly faster restoration of blood flow (CTFC = 31.2 vs. 37.1, p = 0.02). Dose confirmation studies are ongoing.

R. P. Giugliano et al. (Brigham & Women’s Hospital, Boston, MA) presented more data from the TIMI 14 dose-ranging trial of abciximab as an adjunctive agent in thrombolysis. Giugliano divided the patients into subgroups based on symptoms and other characteristics to determine whether any enhancing effects of abciximab were common to all patients. In the entire patient cohort, TIMI 3 flow after 90 min was achieved in 57% of patients treated with accelerated t-PA, 32% with abciximab alone, 42% with abciximab plus streptokinase, 47% with abciximab plus bolus t-PA only, 63% with abciximab plus bolus t-PA and a 30-min infusion, and 76% with abciximab plus bolus t-PA and a 60-min infusion. Odds ratios for patient subgroups were calculated for the most efficacious regimen, abciximab plus bolus t-PA with a 60-min infusion, versus accelerated t-PA. Abciximab plus t-PA showed superiority over t-PA alone in a wide range of patient subgroups, but particularly in older patients (≥65 y), patients with a non-anterior myo-
cardial infarction, patients presenting with symptoms of 3 h duration or less, non-smokers, men, and patients without diabetes.

R. F. Storey et al. (Univ. Hospital, Nottingham, England) described the effects of a new platelet ADP receptor (type P$_{2Y}$) antagonist, AR-C69931MX, on platelets in the presence or absence of aspirin. AR-C69931MX is being evaluated as adjunctive therapy with aspirin in the prevention of recurrent ischemic events. When platelets were stimulated to aggregate (in whole blood) with ADP, streptokinase, adrenaline, serotonin, U46619, platelet-activating factor, thrombin receptor–activating peptide, or collagen, AR-C69931MX proved superior to aspirin in inhibiting platelet aggregation to all these agonists except collagen. The combination of aspirin and AR-C69931MX was no more potent than AR-C69931MX alone, except for collagen. The greatest inhibition of collagen-stimulated platelets was with the combination of the two drugs. Aspirin alone was not as effective and AR-C69931MX alone was the least effective.

M. J. Quinn et al. (Royal College of Surgeons, Dublin, Ireland) evaluated the effects of chronic administration of an orally available GPIIb/IIIa antagonist, xemilofiban (SC-54684A), on platelet GPIIb/IIIa number and occupancy. Xemilofiban was administered for 60 d in patients undergoing PTCA. Baseline blood samples were taken and then again immediately before PTCA and 6 h and 60 d later. Total receptor number and free unoccupied receptor (GPIIb/IIIa that had not bound xemilofiban) were determined. The results show that chronic treatment with xemilofiban had no effect on total receptor number (~50,000 receptors per platelet) at all time points. In addition, constant and prolonged occupancy of GPIIb/IIIa by xemilofiban was maintained throughout the study period. Inhibition of platelet aggregation was also observed as long as xemilofiban was administered.

R. A. Harrington et al. (Duke Univ., Durham, NC) presented the results of the APLAUD clinical trial, a dose-finding and tolerability study of lotrafiban (SB 214857), a new oral platelet GPIIb/IIIa antagonist. Patients with a variety of vascular disorders, including recent myocardial infarction (31% of patients), unstable angina (31%), stroke (24%), or transient ischemic attacks (TIA) (14%) were randomized to placebo or four different doses of lotrafiban (5, 20, 50, or 100 mg b.i.d.) for 12 w. All patients also received aspirin. Major bleeding events occurred in 0.9%, 3.1%, 2.9%, and 12.1% of patients administered 5, 20, 50, or 100 mg lotrafiban. The high frequency of major bleeding events in the 100-mg group prompted discontinuation of treatment at that dose level before the trial was completed. Inhibition of platelet aggregation was dose dependent (measured 2 w after the start of therapy): 33% inhibition with placebo or 5-mg dose, 47% with 20 mg, 87% with 50 mg, and 100% with 100 mg. APLAUD was not powered to determine efficacy.

F. Catella-Lawson et al. (Univ. Pennsylvania, Philadelphia, PA) described the results of a dose-ranging clinical trial of another oral GPIIb/IIIa antagonist, Klerval™, in 320 patients with a recent acute coronary syndrome. Klerval™ or placebo was administered for 8 w. There were no major bleeding episodes in any patients, but a downward dose adjustment was required in 7.9% of patients on Klerval™ due to episodes of minor bleeding. Thrombocytopenia, defined as a fall in platelet count of 40% or more from baseline, occurred in 13.7% of patients administered Klerval™. Inhibition of platelet aggregation in this group of patients with unstable coronary artery disease (CAD) was dose dependent (all patients were also administered aspirin): 5% inhibition with placebo,
21% with 75 mg, 24% with 100 mg, and 34% with 125 mg. Interestingly, Klerval™ was not as potent in inhibiting platelet aggregation in this group of patients as it was in a previous study of patients with stable CAD: 13% inhibition with placebo, 59% with 75 mg, 63% with 100 mg, and 74% with 125 mg. The investigators concluded that the risk of major bleeding events was low with Klerval™ and that Klerval™ may induce delayed thrombocytopenia and be more efficacious in patients with stable CAD than with unstable CAD.

K. Eto et al. (Teikyo Univ., Tokyo, Japan) described the effects of a novel antiplatelet agent in inhibiting platelet aggregation in patients with unstable angina. The investigators asked the question of whether von Willebrand factor (vWF) may play a more important role in inducing platelet aggregation during high shear stress, such as is believed to occur in patients with unstable angina. A cone-plate viscometer was used to measure vWF-dependent shear-induced platelet aggregation in platelets obtained from patients with documented unstable angina both during and between attacks. The contribution of vWF to platelet aggregation was determined with AJvW-2, an anti-human vWF monoclonal antibody. Interestingly, vWF-dependent platelet aggregation under high shear conditions was 2.4-fold greater when platelets were obtained from patients experiencing angina than from patients in between attacks. AJvW-2 completely inhibited high shear stress induced platelet aggregation from all patients (as well as from healthy controls). Enhanced vWF-dependent platelet aggregation during high shear may be explained by increased vWF antigen levels measured in patients experiencing angina. Larger vWF multimers were also detected during angina, and this may also contribute to enhanced platelet aggregation. The data suggest that targeting vWF-dependent platelet aggregation with a drug may be an effective therapy in the treatment of unstable angina. Eto and his colleagues extended their observations with AJvW-2 to include platelets obtained from patients undergoing stent implantation. Shear-induced platelet aggregation was once again measured in a viscometer. Plasma levels of vWF antigen increased significantly (nearly 2-fold) after stent implantation and vWF-dependent high shear induced platelet aggregation was almost 2-fold greater using platelets obtained after stent implantation than in platelets obtained from the same patients before stent implantation. AJvW-2 completely inhibited shear-induced platelet aggregation from these patients. The data suggest that AJvW-2 may be effective in inhibiting stent thrombosis following deployment.

THROMBOLYTIC AGENTS

F. Wang-Chow et al. (Genentech, San Francisco, CA) evaluated various dosing regimens for TNK-tPA, a genetically engineered variant of native tissue plasminogen activator (t-PA). The data from two different clinical trials were analyzed and grouped according to outcome and patient weight. The trials were the TIMI 10B trial, which was an angiographic trial comparing TNK-tPA with accelerated t-PA, and ASSENT I, a dose-ranging safety trial of TNK-tPA. Patients were grouped into quartiles based on weight-adjusted dose (≤0.37, >0.37 to 0.44, >0.44 to 0.55, and >0.55 mg/kg TNK-tPA). In the two lower weight-adjusted groups TIMI grade-3 flow was observed in <56% of patients and the CTFC was ~53. In the two higher weight-adjusted groups, TIMI grade-3 flow was observed in >62% of patients and the CTFC was ~43. In addition, in ASSENT I and TIMI 10B a decrease in mortality and an increase in the frequency of TIMI grade-3 flow was observed.
observed with an increase in weight-adjusted dose, respectively. TIMI 10B also showed an improvement in CTFC with an increase in the weight-adjusted dose. These results were used to devise a simple five-increment weight-adjusted dosing regimen for TNK-tPA that is being used in the Phase III ASSENT II clinical trial comparing TNK-tPA with accelerated t-PA. The target weight-adjusted dose is 0.53 mg/kg. ASSENT III, enrolling about 16,500 patients, is designed to show that these two thrombolytic agents are equivalent in efficacy. The data are expected to be presented sometime in 1999.

F. W. Bar et al. (Univ. Hospital, Maastricht, Netherlands) evaluated dosing regimens of a novel thrombolytic agent, Rescuepase (saruplase) in 2,410 patients with an AMI. Saruplase is a recombinant unglycosylated single-chain urokinase-type plasminogen activator. In this clinical trial, called BIRD (Bolus versus Infusion of Rescuepase Development), saruplase was administered as a single bolus injection of 80 mg or as a bolus injection of 20 mg followed by a 60-min infusion of 60 mg. The clinical outcome 1 m after treatment was similar in the two groups of patients. Mortality was about 6%, reinfarction occurred in 5% to 6.5% of patients, and severe bleeding complications (excluding access site hematomas) was observed in 2.1% to 2.5% of patients. The results indicate that the more convenient single-bolus dosing of saruplase is equivalent in efficacy to the previously used bolus-plus-infusion dosing.