1.02-6.88; p=0.046) (Bernard SA, et al. *NEJM* 2002; 346(8):557-563). Unlike in the studies of traumatic brain injury, no adverse outcomes were observed in cooled patients.

"Therapeutic hypothermia is one of the most exciting new therapies for cardiac arrest patients in the last decade," Raina M. Merchant, MD, from the University of Chicago, comments. "It has already begun to have a major impact on outcomes from cardiac arrest. It is only a matter of time before we see patients not only survive cardiac arrest, but survive it well."

Dr. Merchant says that American physicians are beginning to move forward with using this new therapy, especially in emergency rooms and intensive care units. In the next few years she predicts acceptance will improve and therapeutic hypothermia will be used frequently.

For more information on the therapy being practiced at the University of Chicago, please visit http://hypothermia.uchicago.edu.

Challenges and Issues in Developing Antithrombotic Therapies for ACS/PCI Use

"The glass is mostly full," stated assistant professor Robert P. Guigliano, MD, Harvard Medical School, in his presentation summary. The topic was "Challenges and Issues in Developing Antithrombotic Therapies for ACS/PCI Use," and he left little doubt that the difficulties are many. They are caused by the very complex physiological systems being addressed, by an array of pitfalls in drug testing and other practical issues. However, Dr. Giugliano affirmed that the future holds many promising new agents, and well-established testing methods can assess their value.

Robert P. Guigliano, MD

The path toward these new therapies is a challenging one. "We've skimmed off most of the cream. The bar for any new therapy is high," he said, "because we've been fairly successful in the past."

The history of physiologic complexity emerging to confound what seemed to be sound medical judgment is extensive. It was well represented by the case of the substantial success of intravenous GPIIb/IIIa inhibitors failing to persist in Phase III clinical trials of oral GPIIb/IIIa inhibitors. Mortality was higher versus aspirin across a range of major trials. "Our simplified view of platelet activation and anticoagulation isn't accurate enough and can sometimes mislead us," he said in an interview. "Also, drugs act in complex ways in more than one organ system and through more than one pathway."

On the novel antiplatelet horizon are more potent oral thienopyridines, intravenous PGY12 inhibitors, oral-reversible PGY12 inhibitors and thrombin receptor antagonists. Anticoagulants in development include oral direct thrombin inhibitors, oral factor Xa inhibitors and inhibitors of factors Va, VIIa, IXa. Noting that the possible combinations with already available agents (e.g., aspirin, dipyridamole, unfractionated and low-molecular-weight heparin, warfarin, thienopyridines, GPIIb/IIIa inhibitors, cilostazol, bivalirudin, fondaparinux, drug-eluting and bare metal stents) amount to 282 followed by 75 zeroes, Giugliano said that identifying optimal uses for future agents may seem to be dauntingly

complicated. Another layer of complexity is added by variable responses in different patient subsets.

The only way to get answers, though, is through clinical trials. Observational and "real world" studies, Dr. Giugliano warned, can lead to unclear and ambiguous answers. Among examples, he cited the dramatic -28% coronary artery disease (CAD) risk-protective effect of hormone replacement therapy in a meta-analysis of 13 observational trials with 74,269 women. But when tested in the more exacting setting of a randomized controlled trial (RCT) among 16,608 women, the finding reversed to a 29% *increase* in CAD. "The problem is that the real world is very messy and complex. Simpler designs asking a focused question are more likely to give unambiguous answers. If we are trying to answer a very narrow and specific question, then we have to control as much as possible," he said.

He cautioned also about mistakes in use of non-inferiority trials, agreeing with Sanjay Kaul, MD (Cedars Sinai Medical Center, Los Angeles), in his criticism of the ACUITY trial. ACUITY investigators found bivalirudin monotherapy to be non-inferior to therapy with enoxaparin or UFH with added GPIIb/IIIa inhibitor in ACS patients headed to the cath lab. Dr. Kaul objected to the trial's combined efficacy and safety outcome, which gave bivalirudin an edge despite slightly worse efficacy for ischemic events. The advantage appeared as a consequence of a large reduction in bleeding. The unconventional combining of safety and efficacy, Dr. Kaul said, inserted a bias favoring bivalirudin. Also, efficacy for the trial's active controls was insufficiently proven, and lastly, the allowable non-inferiority margin of 25%, as compared with 10-11% in other major non-inferiority trials in ACS, was too large.

Dr. Giugliano also reviewed practical concerns around the conduct of clinical trials such as the $100 million dollar price tag for large trials, the $1 billion dollar overall drug development cost, the legal/regulatory issues, the risks that results may go awry with concomitant speedy dissemination of "bad news," and the lack of incentives for trial investigators and coordinators.

As antidotes, he recommended centralizing laws and regulations concerning clinical trials, greater hospital support for recruiting patients and for rewarding physicians, financially or otherwise, who participate in clinical trials. "We need to work harder on the practical issues," he concluded.

Carotid Stent Placement: State-of-the-Art

When the carotid artery becomes occluded by atherosclerotic plaques such that a narrowing, or stenosis, is observed, a patient is diagnosed with carotid artery disease. Carotid artery stenosis (CAS) can lead to many neurological conditions including dizziness, numbness, confusion and ultimately stroke. Whether to remove the stenoic plaque surgically, or use a carotid stent has been widely debated; a symposium at the AHA's Scientific Sessions discussed the safety of carotid stents and when they should be used.

"It is important to note," says William Gray, MD, Associate Professor of Clinical Medicine at Columbia University, "that there are no data comparing the natural history or medical therapies to carotid stenting…period." Therefore, in order to compare carotid stenting to other procedures, some extrapolations must be made.

The CAPTURE (Carotid RX ACCULINK/RX ACCUNET Post-Approval Trial to Uncover Unanticipated or Rare Events) trial, a post-market study that had 100% neurological event follow-up led by Dr. Gray, was designed to determine if carotid stenting is a safe alternative to surgery in