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

asymptomatic patients. Data was collected from 2,500 patients from 188 medical centers who were at high risk for surgery. The study found that 94.3% of asymptomatic patients were free from major complications (death, stroke or MI) after 30 days, which is higher than numbers reported previously from surgical trials. Octogenarians had the highest event rates at 8.9%, whereas younger patient event rates were almost halved at 4.8%. Low volume operators appeared to have similar results to high volume operators and safety was more dependent on the appropriate case selection.

To increase the odds of a successful procedure, Dr. Gray recommends the following strategies:

- Pre-procedure: acetylsalicylic acid and thieneopyridine
- Intra-procedure: anticoagulation therapy
- Post-procedure: discontinue anticoagulant therapy, continue antiplatelet therapy
- For the management of carotid body stimulation, early ambulation appears to be important

For stroke prevention in carotid stenting procedures, Dr. Gray emphasizes the following;

- Appropriate patient/lesion selection (type III arches, and retroflexed LCCAs are probably not good candidates for stenting due to decreased anatomical access)
- Use of appropriate anticoagulant
- Careful access technique
- Adequate embolic protection (when patients were predilated without embolic protection, the risk of experiencing an event increased)

Given the right patient and the right operator, this minimally invasive procedure could improve outcomes in patients with CAS.

Preventing Vascular Events with New Endovascular Therapies

Carotid Stenting and Stroke Prevention

To determine if carotid stenting reduces the risk of stroke, surgical and medical therapy trials must be compared to stenting trials, since no data directly comparing the procedures are available. Although this strategy is "a little imperfect," says William Gray, MD, Associate Professor of Clinical Medicine at Columbia University, "it's all we have."

	% Recurrent stroke per year	Trial
Natural history-symptomatic patient	13	NASCET
Natural history-asymptomatic patient	2.5/7.5	ACST/ACSRS
Medical therapy-symptomatic patient	2.5	SPARCL
Medical therapy-asymptomatic patient	N/A	N/A
Endarterectomy-symptomatic patient	4	NASCET
Endarterectomy-asymptomatic patient	1-3	ACST/ACAS
Carotid stenting-symptomatic + asymptomatic patient	1-2	SPARCL/ ARCHER/ SECURITY *Note: High-risk patients

These data show that surgery is able to prevent stroke better than medical therapy. Additionally, comments Dr. Gray, "carotid artery stenting has demonstrated equivalent stroke prevention efficacy compared to endarterectomy." Recently published EVA-3S trial in Europe, however, found higher incidence of stroke in symptomatic patients treated with stenting than with endarterectomy