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THE CHANGING FACE OF ATRIAL FIBRILLATION MANAGEMENT

Only three years ago, our clinical trials center began participating in anti-thrombotic trials that would have a significant impact for the future treatment for prevention of thromboembolic events in patients with non-valvular atrial fibrillation.

The first agent to be approved by the FDA as an alternative to warfarin was dabigatran, a direct thrombin inhibitor. Dabigatran (Pradaxa), approved in Oct. 2010, is taken twice daily but somewhat limited because of gastrointestinal symptoms (GIS). CANH will be starting a trial in

Jan. 2012 addressing patients that develop these GI symptoms. They will be randomized into two treatment arms either taking drug with food or adding propranolol to their medication regimen. Enrollment is for three months. It is possible that the early treatment of GIS might remedy this side effect associated with dabigatran.

The second drug to be FDA approved last month is the factor Xa inhibitor rivaroxaban (Xarelto). Although the drug has effects that last between 8 to 12 hours, factor Xa inhibition is not restored

for 24 hours, making once daily dosing possible.

Trials have now been completed for the Xa inhibitor, apixaban (Eliquis). The results of this trial are promising. The drug will be submitted for FDA approval. Finally edoxaban, a fourth agent, is in Phase III studies with patients being followed and completion expected in 2012. These Xa inhibitor drugs are both twice daily dosing and do not appear to have significant GI upset side effects.

Antiplatelet alternatives for warfarin have arrived.

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	EDOXYBAN	RIVAROXABAN	DABIGATRAN	APIXABAN
Route	Oral	Oral	Oral	Oral
Dosing	QD 60mg	QD 20mg	BID 150mg	BID 5mg
	CLcr30-50 30mg	CLcr30-49 15mg	CL <30 75mg	cr>1.5 2.5mg
Bioavailability	62%	80%	7%	66%
Clotting Factors	Xa	Xa	thrombin	Xa
Elimination	Renal 50%	Renal 66%	Renal 80%	Renal 27%
CYP metabolism	<4%	32%	None	15%
Monitoring	Xa if needed	Xa if needed		Xa if needed
Half Life	8-10hours	9-13hours	12-14hours	8-15hours
Reversibility	FFP	FFP	No antidote	FFP
Contraindicated	CLcr <30	CLcr <30	CLcr <30	CLcr<25

CETP INHIBITION REVISITED

A new generation of CETP inhibitors are being explored to raise HDL. As opposed to the older CETP inhibitor torcetrapib, new generation CETP inhibitors (dalcetrapib and anacetrapib) have not shown an increase in aldosterone or SBP, or direct toxic vascular effects such as impaired endothelial function and increased inflammation.

The Dal-Outcomes (dalcetrapib) trial is further along in research with

an ongoing Phase III outcomes study that has recruited 15,600 ACS patients worldwide. An article published in the *Journal of Research in Medicine* in 2010 provided data that suggests that modulation of CETP activity by dalcetrapib induces pre- β -HDL formation, important for reverse cholesterol transport.

Further assuring data was presented at the European Society of Cardiology Congress in 2011, in

Paris. Dal-PLAQUE recruited 130 patients with carotid disease that were randomized to dalcetrapib or placebo. At 24 months MRI imaging showed a lower increase in total vessel area on dalcetrapib compared to placebo.

The DEFINE trial with anacetrapib was also presented with an acceptable safety profile and promising HDL and LDL results. REVEAL, a Phase III outcome study, has begun.

REDUCE-IT TRIAL (Reduction of Cardiovascular Events with EPA—Intervention Trial)

The CANH Clinical Trials Center will initiate a new outcomes trial in the first quarter of 2012 assessing the EPA drug AMR101 for the reduction of cardiovascular events in patients with clinical cardiovascular disease or with multiple risk factors for cardiovascular disease.

The study is designed for patients with LDL-C at goal while on statin therapy, with established CVD or at high risk for CVD, and hypertriglyceridemia (TG >150-<500), to evalu-

ate the effect of 4 g/day AMR101 for preventing the occurrence of a first major cardiovascular event of the composite endpoint that includes:

- Cardiovascular death
- Non-fatal MI
- Non-fatal stroke
- Coronary revascularization
- Unstable angina

6900 patients will be recruited into this multi-center outcomes trial and followed up to 5 years. PI Sandip K. Mukherjee and Sub-I Nathan Kruger will lead the Investigative team at CANH

SOLID TRIAL CLOSES ENROLLMENT

Enrollment closed as 11,500 ACS patients were randomized to either darapladib 160mg or placebo in addition to standard of care. The TIMI 52 investigators postulate that direct inhibition of Lp-PLA2, a pro-inflammatory enzyme will reduce cardiovascular events in subjects

taking darapladib.

CANH enrolled ten patients into the trial and will continue to follow them until the trial finishes with the necessary endpoints. The primary endpoint is defined as major adverse cardiovascular events (MACE) that includes CV death, non-fatal myo-

cardial infarction and non-fatal stroke. Secondary endpoints will include major coronary events, total coronary events, individual components of MACE, and all-cause mortality.

Dr. Daniel Price heads the investigative team at CANH.

CANH AND YALE AORTIC INSTITUTE COLLABORATE ON ECHO STUDY FOR THORACIC ANEURYSM

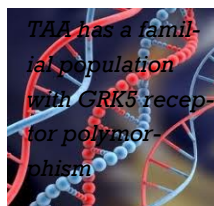
CANH and the Aortic Institute at Yale New Haven Hospital are looking to initiate a ground breaking trial for patients with thoracic aortic aneurysm. The study population will include 300 subjects diagnosed with TAA .

Primary Aim: Inhibition of TGF B signaling with an ARB in addition to standard of care (beta blocker therapy) may reduce the progression of TAA in both normotensive and hypertensive patients compared to beta blocker

therapy alone. It is unknown whether beta blocker therapy will be effective in the familial

population with GRK5 receptor polymorphism. The role of aortic strain will also be assessed in detecting risk of aortic dissection in this population.

Echocardiograms in the study have been performed at CANH and familial pediatric patients at YNH. Baseline



echo will determine aortic diameter, ejection fraction, and pulse wave velocity to measure aortic strain. Measurements will be done yearly and final assessment at three years.

A genetic sub-study will identify the patients that carry genetic predisposition for increased TGF B signaling. Primary clinical trial endpoint includes reduced aortic aneurysm growth rate. Secondary endpoints include aortic rupture, surgery, and death.

PAD Trial at CANH

CANH is considering a collaboration in a trial for peripheral arterial disease (PAD). EUCLID (Examining Use of ticagrelor In paD). Duke is selecting sites for this global trial that will enroll 11,500 patients and follow them for major cardiovascular events for 3-4 years.

Recently, data from PLATO, a phase III study comparing ticagrelor

to clopiogrel in ACS patients treated with aspirin demonstrated superiority of ticagrelor over clopiogrel in the prevention of fatal and non-fatal cardiovascular events leading to the approval of ticagrelor in patients with ACS.

The purpose of this trial is to test the hypothesis that ticagrelor monotherapy when compared to clopidogrel ther-

apy, will reduce the incidence of major cardiovascular outcomes in patients with established CAD. Note: the protocol prohibits the use of aspirin during the trial.

An Investigator Meeting will be held in North America near the end of the second quarter 2012. PI Jaime Gerber, will head the Investigative team at CANH

RESEARCH 2012 NEWSLETTER

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NEW FDA REGULATION TO IMPROVE SAFETY REPORTING

The FDA has published a new safety-reporting paradigm for drugs being studied under new drug applications (INDS). The new regulation that was effective as of March 28th, 2011, provides guidance on the causality assessment needed to determine that an adverse event may be caused by the drug.

Previously, investigators were directed to make a judgement and report only events that were considered drug related. In isolated incidences this was a difficult assessment to make. All serious adverse events must now be reported to the sponsor, regardless whether they are consid-

ered drug related. This change ensures that the IND sponsor maintains a complete view of a drug's safety profile.

The sponsor will be expected to review, monitor, and analyze, in real time, all accumulating safety data from all clinical trials and sites. To further enhance patient safety, the new regulation states that the sponsor must analyze in the aggregate events that are not interpretable as single cases and report them only if there is an observed imbalance between drug-treated group and the control group, suggesting that there is a relationship to the study drug. The regulation also stipulates that IND sponsors

should not report events that are study end points. Independent data safety monitoring boards review these events.

The FDA expects that the new regulation will reduce insignificant reporting and access to complete data critical in establishing the likelihood of a causal relationship between an adverse event and study drug. Therefore, causality of adverse events is best evaluated in the aggregate by the sponsor.