

Innovative Medicine Shaping the Cardiology Market

Reviewing AHA and Looking Ahead

Companies

Amgen (AMGN)
Bayer
Boehringer Ingelheim
Bristol-Myers Squibb (BMY)
Daiichi Sankyo
Johnson & Johnson (JNJ)
Lilly (LLY)
Merck (MRK)
Pfizer (PFE)
Portola (privately held)
Regeneron (REGN)
Roche (RHHBY)
Sanofi (SNY)

Oral Anticoagulants

Pradaxa (dabigatran; Boehringer Ingelheim)
Xarelto (rivaroxaban; Bayer and Johnson & Johnson)
Eliquis (apixaban; Bristol-Myers Squibb and Pfizer)
Edoxaban (Daiichi Sankyo)
Betrixaban (Portola)

CETP Inhibitors

Anacetrapib (Merck)
Dalcetrapib (Roche)
Evacetrapib (Lilly)

PCSK9 Inhibitors

REGN 727 (Regeneron and Sanofi)
AMG145 (Amgen)

Other Agents

Vorapaxar (Merck)

- 2011 saw **novel oral anticoagulants** emerge as significant improvements to warfarin in a variety of clinical scenarios, the return of **CETP inhibitors** as a potential blockbuster drug class, and the emergence of **PCSK9** as a hot new target.
- At the American Heart Association (AHA) Scientific Sessions last month, cardiologists struggled with which new oral anticoagulant to use in which situation, and were impressed by the **positive results for Bayer and Johnson & Johnson's (JNJ) Xarelto (rivaroxaban) in ACS**. *inThought* predicts unique clinical roles for each of the lead oral anticoagulants.
- Although definitive results are still at least 18 months away, **CETP inhibitors from Roche, Merck (MRK), and Eli Lilly (LLY) appear to raise HDL to a large degree with acceptable safety**. Experts are cautiously optimistic.
- Anti-PCSK9 programs, led by those from Regeneron (REGN) / Sanofi (SNY) and Amgen (AMGN), are gaining significant momentum.
- 2012 promises to be another year of significant data in cardiovascular disease. **This report presents the state of the art**, reviewing relevant data and charting the future of each of the promising agents in these categories.

THROMBOTIC DISEASE

At the American Heart Association 2011 Scientific Sessions (AHA) last month, new data supported our thesis that use of the various novel oral anticoagulants is unlikely uniform amongst the subindications (Table 1). For stroke prevention in atrial fibrillation (SPAF), clinical data indicate Pfizer and Bristol-Myers Squibb's Eliquis (apixaban) may be most often preferred. However, for ischemic stroke risk reduction in those least likely to bleed, Boehringer Ingelheim's Pradaxa (dabigatran) will be an option for many. For acute coronary syndromes (ACS) including heart attack, Eliquis has not fared nearly as well as has Johnson & Johnson's Xarelto (rivaroxaban). Coming down the pike is edoxaban, now in phase III trials, with Daiichi surveying the various markets for its best point of entry. Eliquis, Xarelto, edoxaban, and Portola's betrixaban are factor Xa inhibitors. Pradaxa is a direct thrombin inhibitor. Ultimately, market performance will be a dynamic function of the interplay between clinical choices made in SPAF, venous thromboembolism prophylaxis and treatment, and ACS.

A significant proportion of individuals started on Pradaxa are likely to switch to Eliquis when it becomes available.

Anticoagulants for SPAF

It is generally accepted that for adequately-financed SPAF patients starting anticoagulant therapy, the new oral agents will be chosen over standard warfarin, as these new medicines overcome the need for monitoring and have generated encouraging results over an array of different subgroups. Those well-controlled on warfarin, however, are less likely to switch to a novel anticoagulant. A significant proportion of individuals having begun on Pradaxa, the first to be approved in the U.S., will switch to Eliquis when it becomes available.

Eliquis (apixaban; IAI 98%(A))

Original Eliquis for SPAF research was not featured at AHA. But at multiple review sessions, the drug was clearly discussed as the SPAF frontrunner.

Discussion focused on how to determine those low bleeding risk patients at high risk for ischemic stroke who may fare better with high dose Pradaxa than with Eliquis.

Table 1: Lead Oral Anticoagulants

Drug	Sponsor	Phase of Development	Comments
Pradaxa (dabigatran)	Boehringer Ingelheim	Approved globally for SPAF, approved for VTEp in the EU	First mover advantage in SPAF threatened; use preservation depends on net benefit seen for patients at low bleeding risk
Xarelto (rivaroxaban)	Bayer and Johnson & Johnson	Approved globally for SPAF and VTE. One ACS phase III trial complete	New data rejuvenates upcoming regulatory review and market prospects for ACS.
Eliquis (apixaban)	Bristol-Myers Squibb and Pfizer	Approved in EU for VTEp, regulatory review for SPAF	Market leadership depends on upcoming real-world performance in SPAF
Edoxaban	Daiichi Sankyo	Approved in Japan for VTEp, phase III for other indications elsewhere	Strong contender in SPAF given once daily dosing and potential for benefit:risk superior to that of Xarelto
Betrixaban	Portola	Approaching phase III in VTEp, phase II complete in SPAF	Lost partnership with Merck, but still has potential.

SPAF: stroke prevention in patients with atrial fibrillation

VTEp: venous thromboembolism prevention

VTEt: venous thromboembolism treatment

ACS: acute coronary syndrome

IAI: *inThought* Approvability Index (probability of FDA approval)

Most of the discussion centered around the results of the ARISTOTLE trial, originally presented at the European Society of Cardiology (ESC) 2011 Congress this past August, in which Eliquis outperformed warfarin at survival and bleeding endpoints but not at an ischemic stroke endpoint. ARISTOTLE randomized 18,201 AF patients to Eliquis 5mg twice daily or standardly dosed warfarin. After a median follow-up of 1.8 years, Eliquis was shown to provide a 21% reduction in the risk of all stroke or systemic embolism, a 31% reduction in bleeding, and an 11% reduction in all-cause mortality. Thus, Eliquis became the first of the new oral anticoagulants to demonstrate significant all-cause mortality reduction compared with warfarin. In all-comers, Pradaxa approached significance in this respect, and a strong trend was observed with Xarelto.

Additionally, the stroke data indicated that for every 1000 patients treated for 1.8 years Eliquis, prevents 6 strokes - 4 hemorrhagic and 2 ischemic - 15 major bleeds, and 8 deaths.

The results of the phase III AVERROES trial (n=5,599; mean CHADS2 risk of 2.0) showed that the same dose of Eliquis was statistically superior to daily low or high dose aspirin for reducing both stroke and systemic embolism. Not seen were significant increases in major bleeding, fatal bleeding, or intracranial bleeding. Notably, enrollees were those unsuitable for vitamin K antagonist therapy such as warfarin. Furthermore, there were no significant differences in the risk of hemorrhagic stroke between recipients of Eliquis and aspirin.

In AVERROES, event rates of the secondary efficacy endpoint (a composite of stroke, systemic embolism, myocardial infarction, or vascular death)

were 4.2% for Eliquis and 6.4% for aspirin, a relative risk reduction of 34%. Cardiovascular hospitalization rates were lower for Eliquis recipients than for aspirin recipients - 12.6% versus 15.9%, $p<0.001$.

Discontinuation rates in AVERROES were significantly lower in the Eliquis group than in the aspirin group ($p=0.03$), and the annual event rates for major bleeding were non-significantly lower with Eliquis ($p=0.57$). There was no evidence of hepatotoxicity associated with Eliquis.

Pradaxa (dabigatran)

Original Pradaxa for SPAF research was not featured at AHA, but at multiple review sessions, the drug was viewed as, at least, a viable option for SPAF and, at most, the oral anticoagulant of choice for ischemic stroke risk reduction in those with a low risk of adverse bleeding. Most of the discussion centered around the results of the RE-LY trial (n= 18,113), originally presented at ESC Congress 2009 in which Pradaxa's low dose proved non-inferior, and its high dose superior, to warfarin in terms of reducing the risk of stroke and non-central nervous system (CNS) embolism.

In RE-LY, Pradaxa 150mg twice daily reduced the annualized risk of the stroke/peripheral embolic event primary endpoint by 34% ($p<0.001$) and the risk of hemorrhagic stroke by 74% ($p<0.001$) compared with warfarin. This dose was associated with a slightly but significantly ($p=0.048$) increased risk of heart attack, a secondary endpoint, a point that has been inconsistently interpreted by physicians.

Over a median two-year follow-up, the annualized rates of the primary endpoint were 1.53% for low

SPAF Experts:

"I would put (apixaban's) ARISTOTLE (result) somewhere in between the two doses of dabigatran in RE-LY."

"The three (phase III) trial designs make it difficult to compare the three agents directly. ROCKET (rivaroxaban) and ARISTOTLE (apixaban) were blinded, whereas RE-LY (dabigatran) was open label, and ROCKET enrolled higher-risk patients than the other two."

"Rivaroxaban once daily was at a distinct disadvantage as the primary endpoint was set at a point after the drug was stopped in ROCKET, and a lot of events occurred when enrollees were crossed back onto warfarin. This is in contradistinction to what happened in ARISTOTLE (with apixaban) where endpoint data were collected when three-quarters of the enrollees were still on study drug. That's one reason I think that what we see in the real world will absolutely differ from what we've seen even in these rather robust trial circumstances."

(110mg)-dose Pradaxa, 1.11% for high-dose Pradaxa, and 1.69% for warfarin. The relative risks of the primary endpoint were 0.91 (95% CI 0.74-1.11) for the low-dose ($p < 0.001$ for noninferiority) and 0.66 (95% CI 0.53-0.82) for the high-dose ($p < 0.001$ for superiority). Annualized mortality rates were 3.75%, 3.64%, and 4.13%, respectively with relative risk of 0.91 (95% CI 0.80-1.03, $p = 0.13$) for low dose Pradaxa and 0.88 (95% CI 0.77-1.00, $p = 0.051$) for high dose Pradaxa. Hemorrhagic stroke rates were 0.12%/year ($p < 0.001$), 0.10%/year ($p < 0.001$), and 0.38%, respectively, and rates for major bleeding were 2.71 ($p = 0.003$), 3.11 (not significant), and 3.36, respectively. Significantly greater discontinuation rates were seen with Pradaxa, and were attributable to excess dyspepsia, the drug's primary adverse effect.

Successive RE-LY subgroup analyses demonstrated Pradaxa's utility compared to warfarin across a broad range of parameters, including at various levels of stroke risk stratification score (based on CHADS2 as well as CHADS2-VASc systems) irrespective of the use of antiplatelet or other concomitant therapies; independent from individual trial centers' times in therapeutic range; and irrespective of whether recipients had permanent, paroxysmal, or persistent non-valvular atrial fibrillation. Overall, bleeding-related, and liver-related adversity, tolerability, and discontinuation profiles were all consistent with both clinical relevance and results from the overall RE-LY program.

Xarelto (rivaroxaban)

Original Xarelto for SPAF research was not featured at AHA, but at multiple review sessions, the drug was discussed as a convenient, once daily option in SPAF despite its relatively poor label. Most of the discussion centered around the results of the ROCKET-AF trial, originally presented at last year's AHA, in which Xarelto proved non-inferior to warfarin in terms of reducing the risk of stroke and non-CNS embolism.

The Xarelto package insert has a boxed warning indicating that users should not discontinue it before talking with their prescribing healthcare professional as "discontinuing...can increase the risk of stroke."

In ROCKET-AF, warfarin recipients spent only 57.8% of the time in therapeutic range. Not only did this

introduce a degree of benefit:risk uncertainty, it also raised concerns about both the Xarelto and warfarin doses tested, and the risk of adversity upon Xarelto cessation. There proved to be a significantly increased risk of stroke in the Xarelto arm in the 28-day period its cessation whilst enrollees transitioned to another anticoagulant. Some investigators have attributed this phenomenon to rivaroxaban's short half-life and/or the lack of dual anticoagulation during the transition. Some investigators, though, believe that an underestimation of benefit magnitude may have resulted from the agent's relatively early discontinuation.

At AHA, Xarelto was viewed as a convenient, once daily option in SPAF despite its relatively poor label.

ROCKET-AF (NCT00403767, $n = 14,264$) on-treatment analysis showed that once-daily Xarelto was superior to warfarin for reducing the risk of stroke and systemic embolism with a 21% relative risk reduction demonstrated (1.2%, 2.2%, $p = 0.015$). In the more rigorous intent to treat (ITT) analysis, non-inferiority was demonstrated (2.1%, 2.4%, $p < 0.001$). Additionally, those receiving Xarelto experienced fewer myocardial infarctions (0.9%, 1.1%, $p = 0.121$) and had a reduced all-cause mortality rate compared with warfarin (1.9%, 2.2%, $p = 0.073$).

Importantly, results from a secondary prevention ROCKET-AF subgroup showed that Xarelto numerically outperformed warfarin over two key parameters: on treatment recurrent strokes or non-CNS embolism in the safety population (13% relative risk reduction; 2.26 events per 100 patient-years, 2.60 events per 100 patient-years, HR 0.87, 95% CI [0.87, 1.07]); and on intracranial hemorrhage rate (0.59 events per 100 patient-years, 0.8 events per 100 patient-years, HR 0.74, 95% CI [0.47, 1.51]). This subpopulation consisted of patients with a prior history of stroke or transient ischemic attack (TIA).

Comparable (major plus non-major clinically relevant bleeding events, major bleeding events, intracranial hemorrhages) and at least numerically advantageous / clinically significant (critical organ bleeds, bleeding-related deaths) rates of adversities were observed. However, Xarelto recipients had increased rates of hemoglobin/hematocrit drops (2.8, 2.3 per 100 patient-years) and transfusion requirements (1.6, 1.3 per 100 patient-years) compared with warfarin recipients. Abnormal laboratory liver function parameters were similar between the groups as

well as were rates of discontinuation due to adverse events. Rivaroxaban was well tolerated in this trial

In the phase III Japanese J-ROCKET-AF study, 1,280 study subjects with atrial fibrillation and a prior history of stroke, transient ischemic attack, or systemic embolization were randomized to once daily Xarelto or adjusted-dose warfarin. Rates of major and non-major clinically-relevant stroke or systemic embolism were similar in the Xarelto and warfarin groups (18.0%, 16.4% per year, HR 1.11, 95% CI [0.87-1.42]). Xarelto's relative risk reduction for stroke or non-CNS systemic embolism was 51% (1.3%, 2.6% per year; HR 0.49, not significant). Oddly, the trial was powered for tolerability rather than efficacy.

Edoxaban (branded as Lixiana in Japan; IAI 83%(A), increased from 58%(B))

Original edoxaban for SPAF research was not featured at AHA. However, the drug was included as a viable competitor to the other oral anticoagulants at multiple sessions. The drug has generated a significant amount of supportive data and an important real-world performance profile in Japan for VTE management in the setting of once daily dosing. Most of the discussion centered around anticipation for phase III results from ENGAGE-AF TIMI 48.

The 24-month, ENGAGE-AF TIMI 48 trial (NCT00781391) was initiated in December 2008. It pits two dosing regimens of edoxaban (30mg and 60mg, both once daily) versus dose-adjusted warfarin for the composite primary endpoint of stroke and systemic embolic events. Sites in North and South America, Africa, Asia (including Japan), Europe, Australia, and New Zealand have completed enrolment of 21,107 study subjects as of December, 2010. We expect results in early 2013.

Data from two phase II trials showed that both dosing regimens of edoxaban are efficacious in a total of 56 warfarin-naive Japanese patients with atrial fibrillation. No thromboembolic events were reported in either trial. In a phase IIb trial for the prevention of stroke/systemic embolic events (SEE) among 1,146 patients with non-valvular atrial fibrillation, the incidence of major and clinically relevant non-major bleeding events was significantly higher in the 30 and 60mg twice daily edoxaban groups (7.8% and 10.6%, respectively) than it was in the dose-adjusted warfarin group (3.2%). In contrast, and underlying the choice of

dosing regimens advancing, the incidence of major and clinically relevant non-major bleeding events in the 30 and 60mg once daily edoxaban groups was comparable to that achieved in the warfarin group. Although this investigation was not powered to detect efficacy, there were no significant differences in the rates of secondary efficacy endpoints across treatment groups, with respect to major cardiac adverse events, and pharmacokinetic and pharmacodynamic properties.

A phase I trial in healthy volunteers demonstrated that edoxaban significantly reduced thrombus formation (venous and arterial) and thrombin generation up to five hours post-dose. A total of 12 healthy men received a single 60mg dose of the agent. The reductions in both venous and arterial thrombosis at 1.5 hours post-dose (28% and 26%, respectively) and five hours post-dose (21% and 17%, respectively) were significant versus pre-dose values; at 12 hours post-dose, a 3% reduction in both venous and arterial thrombosis was observed. The percentage reductions in thrombin generation (ETP) were significant at 1.5 hours post-dose (28%) and five hours post-dose (10%), but not at 12 hours post-dose (-3%). Anti-factor Xa activity was 3.6, 1.6 and 0.3 IU/mL at 1.5, 5 and 12 hours post-dose, respectively.

Once daily edoxaban's tolerability, discontinuation, bleeding-related adversity, and non-bleeding-related adversity profiles have been otherwise reassuring.

Betrixaban (IAI 45%(B))

Portola's betrixaban has completed phase IIb investigation and is poised to advance to phase III in the appropriate commercial environment. In the first half of 2011, Merck returned all rights to betrixaban, and since then Portola has been "exploring its developmental options." From a clinical trial support perspective, the agent is appropriate for advancement.

In the phase IIb, randomized, double-blind EXPLORE Xa trial (NCT00742859, n=508), betrixaban 40mg once daily for at least three months significantly reduced the incidence of major and clinically relevant non-major bleeds compared with dose-adjusted warfarin (0.8%, 5.5%), whereas such risk with the 60mg and 80mg doses was similar to warfarin (3.9%, 3.9%, 5.5%). The incidence of any bleeding was significantly lower in betrixaban 40mg and 80mg recipients compared with warfarin recipients (17.3%, 18.9%, 31.5%). The number of

events in the secondary composite endpoint of death, stroke, myocardial infarction, or other systemic embolism ranged from 0-1 in each of the four dosing groups, and this was the expected stroke/embolic event rate for the warfarin control group. One stroke each occurred in the betrixaban 60mg and 80mg groups, and there was one death each in the betrixaban 40mg and warfarin groups

The most frequently reported excess adverse events in the betrixaban groups combined in EXPLORE Xa were diarrhea (6%, 0.8%), nausea (5.5%, 1.6%), constipation (5.2%, 2.4%), headache (5.2%, 2.4%), and peripheral edema (6.8%, 7.9%). A greater number of patients in each of the three betrixaban groups discontinued treatment compared with the open-label warfarin group (8.7-9.4%, 6.3%).

Anticoagulants for ACS

In cardiology, aside from SPAF, the other area of primary exploration for novel anticoagulants is acute coronary syndrome (ACS). ACS is currently the purview of antiplatelet therapy, often dual antiplatelet therapy (with Plavix or Effient or Brilinta plus aspirin). The development of anticoagulation for ACS has been fraught with failures. Recently, Eliquis failed in ACS. But at AHA, Xarelto began to make a comeback for oral anticoagulants in ACS with strong initial data. Anticipation is high for triple antithrombotic combinations with clinically acceptable benefit to risk ratios.

At AHA, Xarelto began to make a comeback for oral anti-coagulants in ACS.

Eliquis (apixaban)

Eliquis's APPRAISE-2 trial (NCT00831441, projected n=10,848) was designed to evaluate the agent for the prevention of cardiovascular death, non-fatal myocardial infarction, or ischemic stroke in subjects with a recent ACS. The randomized, double-blind, placebo-controlled trial effort was discontinued in November, 2010 per recommendation of an independent Data Monitoring Committee that saw evidence of a clinically important increase in bleeding among Eliquis recipients that was not offset by meaningful reductions in ischemic events.

Xarelto (rivaroxaban; IAI 60%(B))

The lower of two doses of Xarelto evaluated in the ATLAS ACS 2 TIMI 51 trial (n=15,526; mean duration of therapy 13 months, maximum 31 months) yielded encouraging results,

reducing overall and cardiovascular mortality compared with placebo despite an increased risk of bleeding and intracranial hemorrhage (ICH). Although sorting through this benefit:risk scenario offers ample conundra, triple antithrombotic therapy for ACS is back on the table.

This investigation compared two doses of Xarelto with placebo in ACS patients, all of whom were on low-dose (75-100mg) aspirin and 93% of whom were also on Plavix (clopidogrel). The high risk cohort featured about 50% of patients having had a prior STEMI. Study drug was initiated, on average, 4.6 days after an ACS event. Potential enrollees with a previous stroke or TIA were excluded, given their propensity to bleed, especially intracranially.

ACS Experts:

"Low dose Xarelto's 32% relative reduction in all-cause mortality and a 36% reduction for those on dual antiplatelet therapy translates into one death prevented for every 56 patients treated for two years. This is big! The mortality benefit outweighs the bleeding concerns. There was no increase in fatal bleeding. When you look at folks who had an intracerebral hemorrhage, 80% of those on placebo died but only 30% on rivaroxaban died and in patients who had strokes during ATLAS, those on rivaroxaban had less disability than those on placebo."

"This (rivaroxaban for ACS) is a significant advance. It is the first time that an antithrombotic has shown a reduction in mortality when added to dual antiplatelet therapy. But to what extent that mortality reduction is precise and how it occurs is a bit of a mystery - stroke was not improved and there was no reduction in MI with the low dose.... It may be by a reduction in sudden death and there was a small reduction in stent thrombosis."

"Three issues contributed to rivaroxaban's trial success: selecting a lower dose than the equivalent of apixaban used in its failed study, excluding patients with previous stroke or TIA, and high-risk study subject enrichment - these are the patients with the most to gain."

Both Xarelto doses reduced a composite cardiovascular death/MI/stroke primary endpoint with an increased bleed risk, the 2.5mg (ultralow dose) twice-daily cohort with a more acceptable benefit:risk than the 5mg twice daily group. Overall, there was a significant 16% relative risk reduction for the primary efficacy endpoint with the two doses in aggregate, with a threefold increase in major bleeding and intracranial hemorrhage but no significant increase in fatal bleeding. No evidence of drug-induced hepatotoxicity was seen in the study.

The ATLAS ACS TIMI 46 trial looked at escalating doses of Xarelto in 3,500 patients following standard antiplatelet therapy of low-dose aspirin with or without a thienopyridine antiplatelet agent. Its primary efficacy endpoint was death, myocardial infarction (MI; heart attack), stroke, or severe recurrent ischemia requiring revascularization. Xarelto provided a 21% relative risk reduction of this primary efficacy endpoint ($p=0.1$) and a statistically significant 31% relative risk reduction of a secondary endpoint of death, MI, or stroke ($p=0.028$). 2.5mg and 5mg twice daily had emerged with the most acceptable benefit to risk ratios, combined associated with a 46% relative risk reduction of the composite secondary endpoint when dosed in addition to aspirin, and a 45% relative risk reduction of the same when dosed in combination with aspirin and a thienopyridine.

In ATLAS ACS TIMI 46 there was a significant dose trend ($p<0.001$) with regard to overall bleeding-related adversity, but no study arm was halted due to increased bleeding. Rates of clinically significant bleeding were placebo: 3.3%, rivaroxaban 5mg: 6.1%, 10mg: 10.9%, 15mg: 12.7%, 20mg: 15.3%. Most bleeding (82%) was classified as bleeding requiring medical attention, rather than TIMI major or TIMI minor bleeding. No evidence of drug-induced hepatotoxicity was seen in the study.

Venous Thromboembolism at AHA

Although most often the purview of non-cardiology specialists, several AHA presentations featured review data from trials of the novel oral anticoagulants for the prevention or treatment of venous thromboembolism (VTE) in various clinical settings. One key presentation featured original data suggesting that Eliquis, as had been seen with Xarelto before it, is not ready for the prime time management of VTE in medically ill patients.

Although the various novel, oral, warfarin-replacing anticoagulants clearly possess clinical utility for both the prevention and therapy of VTE in multiple perioperative and recurrent disease settings, it remains unclear the agents' utility in the primary, VTE-susceptible medically ill.

At AHA, Dr. Samuel Z. Goldhaber presented findings from the ADOPT trial ($n=6,528$, only 4,495 evaluable) in which was found that 30 days of Eliquis was not superior to a 6 to 14 day course of subcutaneous enoxaparin (Lovenox, Sanofi) for VTE prevention in a medically ill cohort. Although Xarelto's failed MAGELLAN trial, Lovenox's EXCLAIM trial, and this program all show that VTE risk extends beyond the time of hospital discharge in this patient population, risk reduction strategies beyond the standard Lovenox course evaluated in ADOPT remain elusive.

ADOPT's primary efficacy outcome was a 30-day composite of VTE-related death, pulmonary embolism (PE), symptomatic deep vein thrombosis (DVT), or asymptomatic proximal-leg DVT, as detected by ultrasound on day 30. 2.71% of evaluable Eliquis recipients and 3.06% of evaluable Lovenox recipients met primary endpoint criteria (relative risk with Eliquis 0.87; $p=0.44$, highly NS). Moreover, major bleeding was two and a half times more likely with Eliquis receipt (0.47%, 0.19%; relative risk 2.58; $p=0.04$) by day 30. The absolute bleeding risk attributable to Eliquis, though, was said by many to approximate that of aspirin.

Various means of study re-design related to timing of dosing and study subject retention appears in order for future investigations of VTE risk reduction by anticoagulation in medically ill cohorts.

Novel Antithrombotics for ACS

A novel mechanism of action being explored for acute coronary syndromes (ACS) is thrombin receptor antagonism, a hybrid antiplatelet/anticoagulant molecular activity. Developmental drugs of this class have not fared well, and the major AHA presentation of relevant original clinical research reveals no further promise. Their designated nomenclature suffix is "-paxar."

Vorapaxar

Merck's vorapaxar, a protease-activated receptor 1 (PAR-1) antagonist that blocks thrombin-induced platelet activation, had its TRACER registration trial ($n=12,944$) halted earlier this year after an

interim safety analysis revealed an excess of intracranial hemorrhage in vorapaxar recipients with a history of stroke. At AHA, data confirmed that this agent is unlikely to have a benefit to risk ratio appropriate for clinical use. Adding it to standard therapy significantly raised the risk of major bleeding complications, including intracranial hemorrhage, over two years without evidence of a clinically meaningful effect magnitude.

Vorapaxar (40mg loading, 2.5mg/day) did not deliver a significant advantage to placebo-controlled standard ACS therapy for the primary endpoint of cardiovascular death, MI, stroke, hospitalization for ischemia, or urgent revascularization. There was a nonsignificant trend toward benefit, with a reduction in a secondary endpoint of CV death/MI/stroke garnering $p=0.072$. Failure at the primary endpoint trumps such Pyrrhic victory, however, as well as an absolute 1.4% reduction in myocardial infarction ($p=0.021$) and a trend toward reduction in ischemic strokes. Over two years, vorapaxar was associated with significantly increased GUSTO moderate or severe bleeding (GUSTO severe bleeding went up by 35%; $p<0.001$), as well as bleeding that was TIMI criteria-significant (TIMI major bleeding risk increased 53%; $p<0.001$).

A second phase III investigation is ongoing - the Thrombin-Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2°P TIMI-50) trial which evaluates vorapaxar as chronic therapy in the setting of both cardiovascular and peripheral artery disease. This study is thought to be less enriched with patients on background dual antithrombotic therapy thus with a better chance to show a decreased bleeding propensity across a full sample. Results are expected in 2012.

Vorapaxar's IAI score stands at 19%(F). Eisai's atopaxar, not rated, is stalled in phase II investigation.

DYSLIPIDEMIA: CETP Inhibitors

Five years ago, the high profile failure of Pfizer's cholesteryl ester transfer protein (CETP) inhibitor torcetrapib was thought by many to represent a drug class effect, but given recent results with product candidates from Merck, Roche, and Lilly, hope has returned that CETP inhibitors (Table 2) may become a blockbuster drug class. But despite supportive imaging and subclinical marker profiles, still we have observed a cardiovascular mortality signal in the anacetrapib program despite its having neither the hypertension nor the cortisol profiles as its ill-fated predecessor.

Table 2: Lead CETP Inhibitors

Developer, Drug	IAI Score; Phase	Phase III Cardiovascular Outcomes Trials			Early Results			Comments
		Initiation	Completion (est.)	Study Design	HDL Rise	LDL Fall	Caveats	
Merck's anacetrapib	55%(C); III	June, 2011	2Q17; REVEAL HPS-3 TIMI-55 recently began enrolling patients	n~30,000; LDL>100 excluded, all HDL included; primary MACE endpoint	138%	36%	Numerical excess in CV deaths in DEFINE gives many experts pause.	Phase III DEFINE trial has already met primary and secondary efficacy and safety endpoints.
Roche and Japan Tobacco's dalcetrapib	50%(C); III	April, 2008	2Q13; dal-OUTCOMES enrollment complete	n=15,872; LDL>100 excluded, all HDL included; primary MACE endpoint	31%	no change	Paradoxical molecular associations may foreshadow less benefit in diabetics.	dal-PLAQUE 2 phase III imaging study also ongoing.
Lilly's evacetrapib	50%(A); II	To be determined		Opportunity exists to evaluate LDL-lowering capacity in those less well controlled than have entered competitors' phase III trials.	54%-129%	14%-36%	Phase II data still maturing.	Extent of further investigation to be determined.

Original evacetrapib data were featured at AHA, while anacetrapib and dalcetrapib data were merely reviewed.

Evacetrapib

Data support evacetrapib's advancement to phase III clinical outcomes investigation alongside anacetrapib and dalcetrapib. The agent, like anacetrapib, raises HDL and lowers LDL when used with statins. The nearly 400 patient investigation divided dyslipidemics into one of 10 treatment groups for 12 weeks: placebo; evacetrapib monotherapy 30mg/day, 100mg/day, or 500mg per day; or a statin (simvastatin 40mg/day, atorvastatin 20mg/day, or rosuvastatin 10mg/day) plus or minus evacetrapib 100mg/day. Two primary efficacy endpoints were sought: percentage change in both HDL and LDL. Evacetrapib was associated with both a dose-dependent increase of HDL (53.6%-128.8%) and a dose-dependent reduction of LDL (13.6%-35.9%); the evacetrapib + statin combinations yielded an impressive LDL-lowering magnitude (46.1%-52.3%).

Evacetrapib did not show any of the adversity issues that contributed to the demise of torcetrapib, such as effects on aldosterone or salivary cortisol. Moreover, not observed were excesses of hypertension and liver-, muscle-, or kidney-associated biochemical abnormalities.

Dalcetrapib

Post-hoc analysis of data from four phase II trials enrolling an array of dyslipidemic, cardiometabolic phenotypes (n=488) showed that dalcetrapib 600mg outperformed placebo over a broad range of subclinical markers of disease regression and lowered event risks, including HDL, apolipoprotein A-I, and apolipoprotein B. Paradoxical molecular marker associations were more so seen in patients with type II diabetes or metabolic syndrome.

The randomized, placebo-controlled, phase IIb dal-PLAQUE (n=130, time horizon of 24 months) trial relieved some of the concerns left behind from the torcetrapib experience. In this trial, plaque burden parameters improved with dalcetrapib 600mg daily versus placebo. The trial assessed dalcetrapib's effect on atherosclerotic plaque in study subjects with coronary heart disease and other coronary risk factors. PET/CT imaging did not reveal evidence of a pro-inflammatory effect of dalcetrapib at 6 months. MRI showed a significant dalcetrapib advantage in terms of a reduction in total vessel area as well as a trend towards reduction in average wall area both at 24 months (-4.01 mm² [-7.23, -0.80]; p=0.041 and -2.20 mm² [-4.54, 0.13]; p=0.120 respectively). No plaque progression on MRI during the 24 months thus could be concluded. Several other imaging parameter outputs validated this conclusion. HDL increased by 31% with dalcetrapib after 24 months, with no significant increases in inflammatory biomarkers.

CETP Inhibitor Experts:

"We still don't know what the relationship between CETP inhibition, HDL raising, and cardiovascular outcomes will be. CETP is complicated; there is not necessarily a linear relationship between the magnitude of CETP inhibition and cardiovascular risk reduction. The maximal CETP inhibition may not prove to be the best, clinically."

"CETP inhibitors that not only raise HDL but also lower LDL – anacetrapib and evacetrapib – might prove most effective for folks whose LDLs are higher than desired, so maybe we'll have the opportunity to study evacetrapib in folks whose LDLs are higher and not already optimally controlled (as opposed to the LDL ceiling limitation placed on anacetrapib and dalcetrapib study entrants)."

"As far as I have seen, neither the dose of evacetrapib to be tested in phase III nor its design parameters such as breadth of LDL and HDL levels are set. Those decisions are up to the sponsor."

"(Anacetrapib's first phase III study) DEFINE is too small to show definitive benefit, but at least major adverse cardiovascular events trended in the right direction."

The randomized, placebo-controlled, phase IIb dal-VESSEL trial (n=476, time horizon of 36 weeks) lent initial support for the agent's advancement. HDL levels increased by 31% in this study as well, and coronary endothelial function (as measured by flow mediated dilatation), inflammatory marker (CRP, ICAM, VCAM, IL-6), oxidative stress marker (MPO), and coagulation marker coagulation (tPA, PAI-1) parameters proved reassuring. LDL levels did not change throughout the time horizon of this program.

The tolerability, adverse event, serious adverse event, and discontinuation profiles in both dal-PLAQUE trial and dal-VESSEL were reassuring. In dal-VESSEL, a primary safety outcome measure of the effect of dalcetrapib on blood pressure as measured by 24-hour ambulatory blood pressure monitoring at week 4 was likewise reassuring, not even changing significantly out to 36 weeks.

Anacetrapib

In the randomized, double-blind, placebo-controlled DEFINE trial (n=1,623, 76-week treatment period), anacetrapib 100mg daily or placebo was added to ongoing statin therapy (+/- other lipid-modifying medications). Anacetrapib was associated with decreasing LDL (p<0.001) and increasing HDL (p<0.001) at 24 weeks in patients with coronary heart disease (CHD) or CHD risk-equivalent disease (primary endpoint). Positive effects were also seen at the levels of mean apo A-1, apo B (-21%), non-HDL cholesterol, and median LDL-like particle.

In a 589-subject study, randomized, double-blind, phase IIb, investigation as monotherapy and in combination with atorvastatin 20mg, dose escalating anacetrapib (10, 40, 150 and 300mg) showed multiple positive effects on lipids in dyslipidemias with either primary hypercholesterolemia or mixed hyperlipidemia. Part one of this program evaluated lipid levels for an 8-week period during therapy; part two, a reversal phase, assessed lipid levels 8 weeks after stopping therapy as subjects continued to receive either placebo or atorvastatin.

In part one, anacetrapib monotherapy reduced LDL by 16%, 27%, 40%, and 39%, respectively, compared with placebo. HDL levels were increased by 44%, 86%, 139%, and 133%, respectively. Combination therapy proved additive for both LDL and HDL. In part two, 8 weeks post-cessation results with anacetrapib monotherapy included LDL changes

from baseline of 0%, -1.2%, -9.3%, and -15.3%, respectively, and HDL changes from baseline of 3.7%, 18.6%, 40.5%, and 43.4%, respectively. Eight weeks after cessation from combination therapy revealed respective LDL percentage changes from baseline of 1.7%, -3.9%, -11.2%, and -11.9% and HDL percentage changes from baseline of 2.6%, 13.1%, 40.7%, and 41.8%.

In a placebo-controlled, 48-subject phase II effort, anacetrapib lowered LDL and raised HDL in a dyslipidemic cohort when the agent was administered at meal times for 28 days. In the placebo group (n=9), HDL increased from baseline by an average 0.37% and LDL increased by 3.11%. Mean HDL increases of 41.02%, 80.06%, 104.20%, and 129.38% were observed in the anacetrapib 10mg (n=10), 40mg (n=9), 150mg (n=10), and 300mg (n=10) groups, respectively. The corresponding LDL decreases were -4.99%, -31.38%, -33.66%, and -37.75% (SE 6.39), respectively.

In DEFINE, there was no significant difference between its two groups with regard to blood pressure, serum electrolytes, or aldosterone levels. The pre-specified adjudicated cardiovascular endpoint (defined as cardiovascular death, myocardial infarction, unstable angina, or stroke) was similar between groups during the 76-week treatment phase (2.0%, 2.6%). Nevertheless, within the cardiovascular endpoint data, it must be noted that for cardiovascular death alone, a numerical excess of cardiovascular deaths (4 to 1) disfavored anacetrapib. The incidence of drug-related adverse events (11.4%, 10.7%), serious adverse events (15.2%, 14.8%), and drug-related serious adverse events (0.2%, 0.5%), and discontinuations (8.1%, 7.9%) was also similar between the two groups.

In phase I and the dose-ranging phase IIb experience, anacetrapib's blood pressure, liver toxicity, muscle toxicity, tolerability, and discontinuation profiles were reassuring.

Anti-PCSK9 Drug Candidates

According to numerous experts, proprotein convertase subtilisin/kexin type 9 (PCSK9) is the most important new drug target for LDL lowering.

Amgen's AMG145

At AHA, Dias, et al's *A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Ascending Single Dose Study to Evaluate the Safety, Tolerability and Pharmacodynamics of AMG145* showed that the Amgen program is closing some of the lag time to

the lead PCSK9 program from Sanofi and Regeneron. AMG145 is a fully human monoclonal antibody against PCSK9 now with solid support for its ambitious, ongoing phase II investigation. The data at AHA were the first mature data from its first-in-human, phase I, randomized, double-blind, placebo-controlled, ascending-single-dose study (n=56) in healthy volunteers. At least 5 phase II investigations are planned or underway. The agent met its single dose, subcutaneous and intravenous, safety and tolerability primary endpoint with great reassurance.

Single SC and IV administrations of AMG145 decreased mean LDL by as much as 64% versus placebo subjects. Dose-dependent effects at the levels of LDL lowering, time to nadir, and duration of LDL lowering were observed. Dynamics and kinetics were predictable and reproducible. No serious adverse events were reported and no subjects discontinued due to adversity.

The supportive data, supportive expert commentary, and initiation of an ambitious mid-phase trial program elevate AMG145's IAI score to 34%(B) from 21%(C).

REGN 727

REGN 727 leads the PCSK9 pack with an IAI score of 48%(A) given an impressive benefit to risk ratio generated in two phase II trials to date. REGN 727, also a fully human monoclonal antibody, reduced LDL by 30% to 65% over 12 weeks, depending on dose/regimen, significantly greater than the 10% reduction seen for the placebo group in a heterozygous familial hypercholesterolemia sample (n=77) in a randomized phase II trial.

In a 90-subject study, phase II, polygenic hypercholesterolemia cohort, it was shown that switching from a stable dose of anti-

hyperlipidemics to REGN 727 in combination with high-dose atorvastatin reduced LDL levels to a significantly greater extent than high-dose atorvastatin alone. In the program, patients were randomized to switch to REGN 727 in combination with atorvastatin 80mg/day, REGN 727 in combination with atorvastatin 10mg/day, or atorvastatin 80mg/day alone. Over 8 weeks, mean LDL levels were reduced by 65% in both REGN 727 groups versus 17% in the high-dose atorvastatin group.

In phase I investigation (NCT01026597), REGN 727 dose-dependently reduced LDL and apolipoprotein-B levels in volunteers. At the highest dose tested, the mean LDL reduction from baseline exceeded 60% and lasted for at least 30 days. REGN 727 did not change HDL levels.

In the phase II heterozygous familial hypercholesterolemia program, REGN 727's addition generated acceptable 12-week tolerability, no serious adverse events, and no clinically significant liver abnormalities. Injection-site reactions were the most common adversities.

The high- or low-dose atorvastatin combination trial was significant for one patient discontinuing due to an allergic reaction (rash) and one patient with mildly elevated liver enzymes at baseline who had an elevation in liver enzymes of >3 but ≤5 times the upper limit of normal during receipt of REGN 727 and high-dose atorvastatin. One serious event was not considered to be related to treatment.

In the phase I program, the agent was well tolerated in volunteers. No dose-limiting toxicities were observed. Clinically meaningful elevations of liver transaminases were not observed.

Anti-PCSK9 Drug Candidate IAI Scores

Sanofi and Regeneron's REGN 727: 48%(A)
Amgen's AMG145: 34%(B)
Anylam and Tekmira's ALN-PCS: 16%(B)
Santaris's SPC5001: 14%(C)
Novartis's LGT209: pending

Research programs at Bristol-Myers Squibb / Isis and Santaris are likely to contribute additional candidates.