# European Society of Cardiology, 2009 Congress and A Comparison of Two Asthma Medications

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## European Society of Cardiology

The 2009 Annual Meeting of the European Society of Cardiology (ESC) offered a wealth of presentations to about 30,800 attendees from August 29 to September 2, in Barcelona, Spain. Among many varied offerings, one stood out in unquestionably sharper outline than the rest. The RELY Trial in patients with atrial fibrillation signaled the likely end of the decades-long search for a substitute for warfarin, that effective but problematic rat poison–derived anticoagulant. Other key trials reviewed here address the challenges of lowering cholesterol to guideline levels and of walking the narrow path between the Charybdis and Scylla of ischemia and bleeding risk in the setting of acute coronary syndrome (ACS). Finally, Professor Frans Van de Werf, MD, who received an ESC gold medal for his career-long work in ACS in anticoagulant/antiplatelet trials, provides a commentary on the previously discussed "hot sessions."

### *Potential Warfarin Replacement Takes Center Stage*

#### The RELY Trial (Warfarin and Dabigatran)

- Author S. J. Connolly, MD (Hamilton, Ontario), presented by Shamir Mehta, MD, McMaster University, Hamilton, Ontario, Canada
- John Camm, MD, St. George's University, London, U.K.

Atrial fibrillation (AF) is responsible for one-sixth of all strokes. Although warfarin (Coumadin, Bristol-Myers Squibb) reduces stroke by 64% in patients with AF, it causes significant increases in intracranial and other hemorrhages. Because of the need for constant monitoring of this agent, only 50% of eligible patients receive it, and prothrombin times within the therapeutic range—an International Normalized Ratio (INR) of 2 to 3—are controlled in only about half of those receiving it.

In the RELY study (*R*andomized *E*valuation of *L*ong-Term anticoagulation Therap*y*), investigators enrolled 18,113 patients with nonvalvular AF and at least one other risk factor for stroke. Patients were randomly assigned to three groups of about 6,000 each. They received open-label warfarin, adjusted to an INR of 2 to 3; dabigatran 110 mg twice daily; or dabigatran 150 mg twice daily. Median follow-up was two years. Dabigatran etexilate (Pradaxa, Boehringer Ingelheim) is an anticoagulant and a direct thrombin inhibitor (DTI).

In a non-inferiority analysis, both dabigatran doses were non-inferior to warfarin for the primary endpoint of reducing stroke ($P < 0.001$). At the 150-mg twice-daily dose, dabigatran was superior to warfarin in reducing the incidence of stroke and systemic embolism by 34%. The relative risk (RR) was 0.66, with a 95% confidence interval (CI) of 0.53 to 0.82 ($P < 0.001$).

Major bleeding rates with dabigatran 150 mg twice daily (3.11% of patients per year) were similar to those with warfarin (3.36% of patients per year) ($P = 0.31$). The rate of major bleeding associated with dabigatran 110 mg twice daily was 20% lower than that of warfarin (2.71% per year; $P = 0.003$).

For the 150-mg and 110-mg twice-daily dabigatran doses, compared with warfarin, significant RR reductions were found for hemorrhagic stroke (74% and 69%, respectively; $P < 0.001$ for both). The vascular mortality rate was also lower for dabigatran 150 mg twice daily (RR reduction, 15%; $P = 0.04$).

Importantly, abnormal liver function, defined as alanine transaminase or aspartate transaminase levels of more than three times the upper limit of normal (ULN) and concurrent bilirubin levels of more than two times the ULN, was not more frequent with dabigatran.

After noting that dabigatran reduced strokes and that patients needed less monitoring and no pharmacogenomic studies, ESC discussant Dr. Camm said, "Dabigatran is not just a superior therapy. It is also a stimulus to a paradigm change in anti-thrombotic management of atrial fibrillation."

Pointing to a wide variety of anticoagulant agents under development, he added, "Although dabigatran is superior to warfarin for patients with atrial fibrillation and cardiovascular risk, the results of RELY should not derail trials with other drugs."

#### The PLATO Trial (Brilinta)

- Dr. Lars C. Wallentin, Uppsala Clinical Research Center, University Hospital, Uppsala, Sweden
- Clyde Yancey, MD, Medical Director, Baylor Heart and Vascular Institute, and Chief, Cardiothoracic Transplantation, Baylor University Medical Center, Dallas, Texas

In patients with ACS, reduced rates of death from vascular causes, myocardial infarction (MI), or stroke, were found for

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ticagrelor (Brilinta, AstraZeneca) when compared with clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi-Aventis) in PLATO (A Study of Platelet Inhibition and Patient Outcomes). Overall major bleeding risks were not increased. Ticagrelor is an oral, reversible, direct-acting inhibitor of the adenosine diphosphate (ADP) receptor ($P_2Y_{12}$).

PLATO included 18,624 patients (9,333 receiving ticagrelor; 9,291 receiving clopidogrel) who were admitted to the hospital with ACS with or without ST-segment elevation. Although guidelines recommend dual antiplatelet therapy with aspirin and clopidogrel for ACS, clopidogrel responses can be variable, and bleeding risks are increased in ACS patients undergoing percutaneous coronary intervention (PCI).

In this multicenter, double-blind, randomized trial, patients received ticagrelor (180 mg as a loading dose and 90 mg twice daily as a maintenance dose) or clopidogrel (300 to 600 mg as a loading dose and 75 mg daily thereafter). The primary endpoint was a composite of death from vascular causes, MI, or stroke.

At 12 months, the primary composite endpoint was reported significantly less often with ticagrelor (9.8%) than with clopidogrel (11.7%) (hazard ratio [HR], 0.84; 95% CI, 0.77–0.92; $P < 0.001$). This treatment effect appeared within 30 days and was maintained throughout the study period.

Secondary endpoints favoring ticagrelor included:

- MI (5.8% for ticagrelor, 6.9% for clopidogrel; $P = 0.005$).
- death from vascular causes (4% for ticagrelor vs. 5.1% for clopidogrel; $P = 0.001$).
- death from any cause (4.5% for ticagrelor vs. 5% for clopidogrel; $P < 0.001$).

Major bleeding rates were similar between the treatment groups: 11.6% with ticagrelor and 11.2% with clopidogrel ($P = 0.43$). Major bleeding rates not related to coronary artery bypass grafting (CABG) were higher with ticagrelor (4.5%) than with clopidogrel (3.8%) ($P = 0.03$), with more fatal intracranial bleeding but less bleeding of other types. Dyspnea was more common with ticagrelor, leading to discontinuation of treatment in 0.9% of patients and in 0.1% of those receiving clopidogrel ($P < 0.001$).

American Heart Association president Dr. Clyde Yancey said in an interview that the rapid reversibility of ticagrelor, compared with the thienopyridines, would allow patients to proceed more readily to bypass surgery.

"The take-home [message] is that this drug, if approved, would mean a third option," he stated. (Clopidogrel and prasugrel [Effient, Daiichi Sankyo/Lilly] are the other two.)

## The SEPIA–ACS1 TIMI 42 Study (Otamixaban)

- Marc Sabatine, MD, Brigham and Women's Hospital, Boston, Mass.

In the search for better anticoagulants, the SEPIA–ACS1 trial revealed promising reductions in ischemic event risk in patients presenting with non–ST-segment elevation ACS for otamixaban (XRP0673A, Sanofi-Aventis), a novel synthetic, direct selective inhibitor of factor Xa.

Dr. Sabatine noted that even though unfractionated heparin (UFH) has been the cornerstone of anticoagulant therapy for non–ST-segment elevation ACS, its unpredictable pharmacodynamics necessitate frequent monitoring.

SEPIA–ACS1 compared five doses of otamixaban, in a 0.08-mg/kg bolus, followed by intravenous (IV) infusions ranging from 0.035 to 0.175 mg/kg per hour and UFH plus the glycoprotein IIb/IIIa inhibitor (GPI) eptifibatide (Integrilin, The Medicines Company). The randomized, double-blind, dose-ranging trial included 3,241 patients (mean age, 61 years; 31% female) within 24 hours of presentation with non–ST-segment elevation ACS.

The primary efficacy endpoint was the composite of all-cause death, new MI, severe recurrent ischemia leading to urgent revascularization, or the rescue use of a GPI (through day 7). Non-CABG TIMI major or minor bleeding was the primary safety endpoint. The arm receiving the lowest otamixaban dose was withdrawn from the study because of inadequate anticoagulation.

The primary endpoint rate was lower in all of the other otamixaban arms than in the UFH/GPI arm. At intermediate otamixaban doses of 0.105 and 0.140 mg/kg per hour, the primary endpoint was reported in 3.8% and 3.6% of patients, respectively, compared with 6.2% for UFH plus GPI.

Risk reductions were about 40% (RR, 0.61 and RR, 0.58, respectively, for 0.105 and 0.140 mg/kg per hour; $P = 0.02$). Death or MI reductions with otamixaban were about 45% (RR, 0.52 and RR 0.56) compared with UFH plus GPI. Bleeding rates did display a dose response with the otamixaban doses ($P = 0.0001$), with a 5.4% bleeding rate for the highest otamixaban dose. The bleeding rate in the intermediate arms (3.1–3.4%; RR = 1.15–1.26), however, was not significantly higher than in the UFH/GPI arm (2.7%).

The use of GPI as a rescue medication was similar for the otamixaban and UFH/GPI groups, but thrombotic complications were somewhat higher for the intermediate doses (3.35% vs. 2.4% for UFH plus GPI).

In identifying an optimal dose range for otamixaban in which risks of death and ischemic events were reduced and bleeding risks were the same as with UFH plus GPI, SEPIA–ACS1 "achieved our goal," Dr. Sabatine said. "Otamixaban 0.105 to 0.140 mg/kg per hour appears to be the best range for further study as a replacement for UFH plus GPI."

## Ezetimibe Plus Atorvastatin or Doubled Atorvastatin in High-Risk Patients With Coronary Heart Disease

- Lawrence A. Leiter, MD, University of Toronto, Toronto, Ontario, Canada

Treatment guidelines in the U.S., Europe, and Canada all identify low-density lipoprotein-cholesterol (LDL-C) as the major lipid target for patients' hypercholesterolemia. A prior multicenter, double-blind, parallel-group study showed greater reductions from baseline levels of LDL-C when ezetimibe (Zetia, Merck/Schering-Plough) was added to atorvastatin 40 mg (Lipitor, Pfizer) than when the atorvastatin dose was doubled. (Vytorin is the brand name of the combination of ezetimibe and atorvastatin). The current analysis aimed to determine the efficacy of these two dosing strategies in

attaining lipid and high-sensitivity C-reactive protein (hs-CRP) targets identified by European and Canadian guidelines.

In the study, patients at high risk for coronary heart disease (CHD) were first stabilized with atorvastatin 40 mg for four to five weeks. A high risk was defined, according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, as having CHD or an equivalent risk conferring a 10-year risk of CHD of more than 20%, according to the Framingham calculation. Patients whose LDL-C levels were not below 1.8 mmol/L (70 mg/dL) were randomly assigned to receive atorvastatin plus 10 mg of ezetimibe (n = 288) or to 80 mg of atorvastatin (n = 291).

After six weeks of treatment, LDL-C reductions from baseline were significantly greater for the atorvastatin/ezetimibe group as follows:

- in LDL-C (–16%, $P < 0.001$)
- in total cholesterol (–10%, $P < 0.001$)
- in apolipoprotein B (apo-B) (–10%, $P < 0.001$)
- in the ratio of total cholesterol to high-density lipoprotein-cholesterol (HDL-C) (–10%; $P < 0.001$)

A 7% greater reduction in hs-CRP did not reach statistical significance ($P = 0.174$).

About 75% of patients reached LDL-C targets of less than 2 mmol/L (77 mg/dL) and total cholesterol levels of below 4 mmol/L (155 mg/dL) with ezetimibe/atorvastatin, compared with 45% taking the doubled atorvastatin dose. All other dual target combinations (LDL-C with total cholesterol to HDL-C ratio, LDL-C with apo B, and LDL-C with hs-CRP) demonstrated advantages for ezetimibe/atorvastatin (Vytorin).

In both groups, drug-related adverse events were uncommon. Liver enzyme elevations were rare. Drug-related discontinuations of therapy were reported in fewer than 1% of patients in both groups.

Dr. Leiter concluded, "Adding ezetimibe 10 mg to atorvastatin 40 mg brought more patients with hypercholesterolemia at high risk for coronary heart disease to dual treatment targets than doubling the atorvastatin dose."

He said that adding ezetimibe to statin therapy provides a well-tolerated, effective lipid-altering therapeutic option for patients at high risk for CHD. He emphasized, however, that the ultimate clinical effect of ezetimibe in combination with statins is still unknown.

## Commentary on Hot Line I Sessions (PLATO, RELY, SEPIA–ACS1 TIMI 42)

• Frans Van de Werf, MD, Chairman, Cardiovascular Medicine, University of Leuven, Leuven, Belgium

"There is still a high incidence of recurrent ischemic events in patients treated in accordance with guidelines," stated Dr. Van de Werf in an interview after his presentation of results from a Harris Interactive Survey. Conducted among 500 cardiologists from the U.K. and Europe, the survey showed that 96% agreed that ACS patients receiving antiplatelet therapy are still at risk for subsequent events.

Commenting on the ESC's Hot Line results for PLATO, RELY, and SEPIA–ACS1, Dr. Van de Werf said that PLATO's ticagrelor is important as the first direct-acting, reversible inhibitor of the $P_2Y_{12}$ ADP receptor. Although there are known genetic variants that can make some patients resistant to clopidogrel, no variants are recognized so far with ticagrelor. Ticagrelor also offers superior efficacy, an acceptable risk of bleeding, with a slight increase in interventions.

"This is a step forward," he said. The slight disadvantage of twice daily dosing, he added, "is not a disaster."

Surgeons usually prefer to wait for about five days after the last clopidogrel dose to avoid bleeding, and transfusion rates for patients treated surgically after they receive prasugrel are also high, said Dr. Van de Werf. Stopping treatment with these agents then raises ischemic risks.

He added, "Therefore, ticagrelor's reversibility makes it attractive."

Moving from antiplatelet agents to the anticoagulation cascade and the RELY and SEPIA–ACS1 trials, he said:

> This was very impressive data for the direct thrombin inhibitor dabigatran. RELY was the most important study presented here, because it suggests for the first time that we can replace warfarin for atrial fibrillation with another oral agent. We knew already that this class of agents was beneficial for venous thromboembolism, but now this is a clear cardiac indication.

He added that while other oral agents are in the pipeline, especially direct oral factor Xa inhibitors such as rivaroxaban (BAY 59-7939, Xarelto, Bayer/Ortho) and otamixaban, "clearly, dabigatran is first, and it is going to be difficult to do better."

In principle, there are no theoretical advantages suggesting that anti–factor Xa antithrombotic agents are superior to DTIs, with the anti-Xa agents reducing the generation of new thrombin and the DTIs blocking thrombin's effects. Bleeding risks could be higher with the Xa inhibitors, he said, "but we will have to await the results of trials and compare outcomes."

Regarding the IV anti-Xa agent otamixaban, which was tested in the acute phase of the phase 2 SEPIA–ACS1 trial, Dr. Van de Werf echoed Drs. John W. Eikelboom and Jeffrey I. Weitz from McMaster University in Hamilton, Ontario, Canada, in their commentary accompanying *The Lancet* publication of RELY data. Those authors suggested that with other drugs such as bivalirudin (Angiomax, The Medicines Company/BenVenue) on the market, the need for new IV agents such as otamixaban might be minimal.

Dr. Van de Werf said, "Whether this is needed, I don't know."

However, he does see potential for Schering-Plough's TRA, the first agent in the new class of thrombin-receptor antagonists that block the protease-activated receptor ($PAR_1$) for thrombin.

He said, "The nice thing in the phase 2 trials seems to be that [otamixaban] does not increase bleeding times and still reduces ischemic risk. If the benefit persists in ongoing phase 3 trials, "that will again be a major step forward."

He suggested also that combinations of the new agents might turn out to be effective.

Finally, he reiterated the importance of RELY and the possibility of a replacement for warfarin.

"Before this, all our attempts have failed. If you cannot generate new myocardium yet, then this is it," he concluded.

# Beclomethasone-HFA (Qvar) and Fluticasone (Flovent) for Asthma

## *Fewer Emergencies and Lower Costs with Beclomethasone-HFA*

The second section of this article is based on an interview that Mr. Alexander conducted in September with Maureen J. Lage, PhD, Managing Member of HealthMetrics Outcomes Research in Groton, Connecticut.

A study comparing two inhaled medications in patients with persistent asthma—beclomethasone dipropionate hydrofluoroalkane (BDP-HFA; Qvar, Ivax/Teva) and fluticasone propionate (FP; Flovent, GlaxoSmithKline)—found advantages in both outcomes and costs for BDP-HFA.

Reviewing the impact of asthma treatment on the nation's health care system, study author Dr. Lage said that in 2004 there were nearly one-half million asthma hospitalizations, 1.8 million emergency department (ED) visits, and 14.7 million outpatient physician office visits. About one-third of the individuals with asthma require at least one asthma-related ED or urgent-care visit each year. Economic losses related to asthma are also substantial. Almost 10 million workdays were lost in 2003, and children's asthma-related school absences resulted in a $719.1 million loss of parents' productivity. The direct annual cost of asthma is approximately $5.1 billion.

Although current evidence and guidelines recommend inhaled corticosteroids (ICSs) as a class, she noted that interpreting data from available comparisons within this class are confounded by variances in potencies, delivery routes, and formulations.

Dr. Lage and her colleagues conducted a retrospective analysis from Medstat's Commercial Claims and Encounter Database (a large national health claims database) from July 2002 to July 2007. The analysis included 13,968 patients who initiated therapy with BDP-HFA (n = 3,332) or FP (n = 10,745) and who had not received the study medication in the prior year. Participants had persistent asthma without chronic obstructive pulmonary disease (COPD) in the pre-study year. Ages ranged from five to 64 years.

Persistent asthma was defined as meeting one of four criteria in the year before the index date:

- four or more asthma prescriptions dispensed
- one or more inpatient discharges with a primary diagnosis of asthma
- one or more ED visits with a diagnosis of asthma
- four or more outpatient diagnoses of asthma and two or more asthma prescriptions dispensed

The investigators calculated the probability of an ED visit and estimated patients' adherence to therapy through a medication possession ratio (MPR)—a measure of the percentage of days pharmacotherapy was prescribed over the one-year post-study period. Annual costs were then calculated. In adjusting the results, the team controlled for differences in patients' demographics, general health status, medical comorbidities, pre-study period use of health care resources, the year they began taking asthma medication, and severity of asthma.

The use of BDP-HFA, compared with FP, was associated with a 17% reduction in the odds of an ED visit (odds ratio [OR] = 0.834, 95%; confidence interval [CI], 0.751–0.925), and a 30% reduction in the odds of an asthma-related ED visit (OR = 0.697; 95% CI, 0.571–0.852).

The odds of a hospitalization were reduced minimally with BDP-HFA (OR = 0.984), and the odds of an asthma-related hospitalization were increased somewhat (OR = 1.095). With BDP-HFA, there was an increase in the odds of obtaining an MPR of at least 50% (OR = 1.324; 95% CI, 1.164–1.506) or at 75% (OR = 1.311; 95% CI, 1.072–1.604) but no differences for MPRs of 80% or 90%.

The researchers converted all costs to 2007 dollars using the medical component of the Consumer Price Index. Total medical costs were significantly lower among patients initiating therapy with BDP-HFA ($5,063) compared with those starting FP ($5,377) ($P = 0.0042$). The difference was driven by significantly lower total prescription drug costs ($2,336 for BDP-HFA vs. $2,581; $P < 0.0001$) and significantly lower ED costs in the BDP-HFA cohort ($185 vs. $249 for FP; $P < 0.0001$).

Asthma-related outpatient costs ($191 vs. $224, $P < 0.0001$) and ED costs ($28 vs. $45; $P < 0.001$) were significantly lower with BDP-HFA, whereas asthma-related inpatient costs ($101 vs. $59; $P < 0.0001$) and drug costs ($451 vs. $540; $P < 0.0001$) were significantly lower with FP. Dr. Lage speculated that the higher asthma-related inpatient costs might have been related to the longer hospital stay of the BDP-HFA cohort (5.80 days vs. 4.76 days for the FP cohort; $P = 0.0752$). Furthermore, the higher asthma-related drug costs of BDP-HFA might have been accounted for by the higher adherence rates in that population.

Total outpatient or inpatient costs did not vary significantly between groups, and there was no significant difference among patients who began BDP-HFA or FP therapy with respect to total asthma-related medical costs ($971 vs. $961; $P = 0.7422$).

Dr. Lage cited several baseline differences between the two cohorts. Although they were corrected for in the analysis, they are noteworthy. For instance, patients who initiated therapy with BDP-HFA were significantly older (mean age, 40 years vs. 31 years), more likely to be female (62% vs. 58%), tended to reside in the Western states (48% vs. 29%), and were more likely to be insured by a health maintenance organization (44% vs. 30%). Preferred provider organization insurance was more common among the FP patients (46% vs. 38% for BDP-HFA).

Patients receiving BDP-HFA were found to be in poorer general health, as measured by the Charlson score and total diagnoses in the pre-study period.

Comorbidities of otitis media or pneumonia in the pre-study period were more common in the FP patients, whereas sinusitis, gastroesophageal reflux disease (GERD), obesity,

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bronchitis, and depression were more common diagnoses in the pre-study period in the BDP-HFA group, possibly a result of the age differences in the groups.

Visits to allergists and pulmonologists, as well as the use of spirometry, bronchodilators and nebulizers, were more common for the BDP-HFA patients, but ED and hospital visits in the pre-study period were more common for the FP cohort. Dr. Lage emphasized that because the study was based on an administrative claims database, it included only patients with medical and outpatient prescription benefit coverage. Results cannot be extrapolated to other populations.

Summarizing the retrospective, multivariate analysis, she observed that in this population with persistent asthma, patients who started therapy with BDP-HFA had "significantly lower odds of requiring an ED visit or asthma-related ED visit and significantly higher odds of reaching a medication possession ratio threshold of 0.50 or 0.75, compared with those who initiated therapy with FP."

Dr. Lage also noted that total medical, prescription drug, ED, and asthma-related outpatient and asthma-related ED costs were significantly lower for BDP-HFA than for FP. In concluding, she cautioned that although this study demonstrated advantages for BDP-HFA over FP, "further research is required to compare more fully the medical outcomes and costs associated with the current variety of ICS medications." ■