# WORKSHOP ON PREVENTION OF ARTERIAL THROMBOEMBOLIC EVENTS IN ATRIAL FIBRILLATION
# 28 September 2010 - Paris

## Conclusions (Prepared by Nicolas DANCHIN, MD)

With the participation of Felicita ANDREOTTI, MD, Maria BORENTAIN, MD, Gerasimos FILIPPATOS, MD, Anselm GITT, MD, Kurt HUBER, MD, Jean-Yves LE HEUZEY, MD, Alain LEIZOROVICZ, MD, Maddalena LETTINO, MD, Gregory LIP, MD, Aldo MAGGIONI, MD, Giuseppe ROSANO, MD, Emmanuel TOUZE, MD, Freek VERHEUGT, MD,

The purpose of this workshop was to confront views on the usefulness of developing new anticoagulants for patients in atrial fibrillation, on the challenges regarding clinical development plans, and on safety issues.

**Atrial fibrillation is a growing concern:**
Because there is a strong link between age and the development of atrial fibrillation, it is expected that the number of patients with atrial fibrillation will grow considerably in the coming decades: compared with the 1990s, a 2.5 fold increase in the prevalence of atrial fibrillation is projected by 2050 in the USA. Briefly, the risk of atrial fibrillation is two-fold: an increased risk of developing heart failure, and an increased risk of stroke. In particular, there is a five-fold increase in the risk of ischemic stroke in atrial fibrillation patients. The proportion of stroke associated with atrial fibrillation increases with age, ranging from 7% in individuals aged 50-59 to 36% in those aged 80-89 years; in addition, atrial fibrillation is associated with an increased risk of recurrent stroke. Preventing stroke is therefore a major issue in patients with atrial fibrillation.

**Definition of target populations for clinical trials**
In observational cohorts, the annual risk of stroke in non anticoagulated patients ranges between 5% and 9%, reaching 23% in secondary prevention patients. In contrast, the risk of stroke in anticoagulated patients is in the order of 1% to 2% (ximelagatran and dabigatran trials). With antiplatelet agents alone, the risk of stroke is intermediary (from 2% to 3%).
The aim of antithrombotic treatment is therefore to prevent or limit the risk of ischemic stroke in these patients. This must be balanced, however, with a possible increase in the risk of hemorrhagic stroke and an increase in the overall risk of bleeding. In recent trials of patients on older or newer anticoagulants, the overall risk of bleeding ranges from 14% to 18%, the risk of major bleeding being about 3% and the risk of life-threatening major bleeding around 1-2%.

In patients on chronic vitamin K antagonists (VKA), the risk of bleeding is directly related to the target INR value, to the actual INR achieved (and the % time within the target INR interval), which goes along with the organization of care in terms of anticoagulation monitoring. The risk of bleeding is also dependent on many patient-related characteristics, beginning with age and past history of bleeding. Major bleeding rates are about twice as high in patients ≥ 75 years of age compared with patients <70 years of age, and a 3- to 5-fold increase in intracranial bleeding is observed in elderly patients, compared with younger ones.

Both the risk of ischemic stroke and the risk of bleeding have led to the development of prediction scores applicable to populations with atrial fibrillation. The $CHA_2DS_2$-VASC score is superior to the widely used $CHADS_2$ score for determining which populations are at very low risk of thromboembolic events with antiplatelet agents alone. Using this score, however, results in considering that virtually all atrial fibrillation patients except men under the age of 65 years should receive anticoagulant therapy rather than aspirin (patients with a $CHA_2DS_2$-VASC score of 1 are considered possible candidates for either aspirin or anticoagulant therapy, but with a marked preference for the latter treatment). Using the $CHA_2DS_2$-VASC score might help define target populations for clinical trials.
In addition, among specific population subsets, those with chronic heart failure are at increased risk of both thrombo-embolic arterial and venous events. The question of anticoagulation in these patients is particularly crucial. Likewise, patients with coronary artery disease and atrial fibrillation may pose the problem of triple antithrombotic therapy (dual antiplatelet therapy + anticoagulation); to date, there have been no specific randomized trials comparing different antithrombotic strategies in such populations. Finally, the question of patients with an ischemic stroke while adequately anticoagulated remains unresolved: should antiplatelet agents be added or should the level of anticoagulation be increased?

**Rationale for developing new oral anticoagulants**

The rationale for developing new anticoagulant agents is based upon the limitations of conventional Vitamin K antagonists. The newer agents, which act directly on factor Xa or thrombin, have linear PK, meaning that their effect is predictable and that fixed doses can be used; the onset and offset of action is rapid. In addition, no routine laboratory testing is required and there is no food interaction, a true clinical issue with vitamin K antagonists. The downside of these new agents, however, is that there is no antidote to promptly reverse their action, and, obviously, that we still lack long-term safety data. Monitoring the efficacy of these new drugs (which may be helpful in certain clinical situations) also remains an unresolved issue. Finally, impaired renal function and other medications may interfere with the effect of some of these agents. In particular, an interaction may exist between new drugs such as dronedarone and dabigatran, which warrants specific studies.
Regarding the long-term safety of new anticoagulants, the question of an increased risk of AMI has been raised following the results of both ximelagatran and dabigatran trials. Currently, the slight increase in AMI rate observed with thrombin inhibitors has not been found with anti-Xa agents. Also, it is difficult to determine whether antithrombin agents might have a true "pro-MI" effect, or whether warfarin, which was used as the comparator in the trials, might have a potent "anti-MI" effect.

**Methodology of clinical trials:**

Most trials accord on the choice of end-points, most usually occurrence of stroke or embolic arterial events for efficacy, and bleeding events for safety. However, the definition of these end-points might merit clarification (e.g. disabling strokes vs non-disabling strokes). Intriguingly, all-cause death or cardiovascular death usually are not part of the primary end-points of the trials.

Most of the trials use non-inferiority assumptions, using yearly event rates for defining the boundaries of non-inferiority. As the drugs are likely to be prescribed for a very long period of time, however, what may seem a marginal increase in the event rates (i.e. within the non-inferiority boundaries) may in fact result in a large increase in events after several years. This point should be taken into consideration when trials are designed, but also by regulatory authorities.

The optimal design for clinical trials with anticoagulants is debatable. To date, both open-label PROBE designs and double-blind trials have been used in phase 3 trials. Although the PROBE design guarantees that the clinical events committee members who allocate outcome events are blinded to the randomisation arm, these trials may have biases:

- Investigators may guess the nature of the next treatment allocation (e.g. blocks within sites), even in the case of central allocation: special measures should be taken, such as random block size
- Patients in one group may be followed more carefully and/or more frequently than the other group. This may be crucial in trials with anticoagulants: patients on VKA may come more often for INR measurements, and events might therefore be detected more easily.
- Compliance may be different because the medications may be perceived differently by the patients (suspected new adverse events…) or by the physicians (who may think one drug is more effective than another). Likewise, reporting of adverse events may differ according to the trial design: there was more dyspepsia reported in the dabigatran arms in RE-LY (allocated treatment known), whereas no such increase in dyspepsia was observed in the dabigatran venous thromboembolism trials, which were double-blind; this might have been due to the fact that either patients or physicians aware of a possible occurrence of dyspepsia with dabigatran more carefully sought this type of events in the dabigatran arms. Also, exploration of end-points may be different depending on the expected side effects: prevention of such a bias may be based upon systematic questionnaires on signs or symptoms.
- Grading of event severity may be reported differently depending on treatment arm; for the blinded clinical events committee to grade event severity, it is essential that investigators report all bleeding events (minor and major), and not only what they may consider major bleedings
- Lesley Wood et al. used ratios of Odds Ratios, for comparing open vs double blind studies: open studies were more frequently positive; however, there was no difference for mortality, and no difference for objective endpoints (e.g. ISIS 3 and GISSI 2 gave similar results in spite of different designs).

Conversely, a double-blind design with VKA in one arm will impose unnecessary blood sampling in the non-VKA arm. As compliance with the treatment may be influenced by the necessity to have frequent blood samplings (which might result in decreased drug compliance), drug compliance for the new anticoagulant in a double-blind trial may not truly reflect what it would be in the real life, and actually favor the VKA.

Overall, however, double-blind studies seem preferable, even if that requires using double-dummy techniques.

**Need for additional clinical trials in patients with atrial fibrillation**

Several populations at particular risk of bleeding and/or embolic events should be studied in specific clinical trials: these include very elderly patients and patients with renal failure. Likewise, anticoagulation regimens in atrial fibrillation patients undergoing stent implantation or with a recent acute coronary syndrome (i.e. patients with an indication for dual antiplatelet therapy) should be studied. The usefulness and efficacy of new anticoagulants for patients undergoing cardioversion should also be assessed.

Finally, direct head to head comparisons of new oral anticoagulants will be needed.

Beyond atrial fibrillation, the role of new anticoagulants will merit investigation in different clinical settings which may comprise: stable coronary artery disease, valvular heart disease, heart failure, non cardiogenic stroke, or pediatric populations.