

Long term Anticoagulation at Crossroads

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Since decenies, the main place in chronic anticoagulation (AC) is occupied by antivitamin K drugs (AVK), mainly warfarin. The development of low weight molecular heparins or new antiplatelet drugs did not change the situation.

In the last few years a new group of oral anticoagulants emerged in clinical practice. Their efficacy and safety seems to be so good, that they entered very quickly in guidelines (1,2), situation not often encountered in clinical medicine.

AVK have a very important limit: lack of adherence to long term therapy. It is considered

that only about 20% of patients with nonvalvular atrial fibrillation (AF) who started anticoagulation with AVK and have good indication to do so chronically remain on this therapy. The remaining 80% are in consequence in great danger. If the titration is not well performed or it is not performed at all, the main consequent risk is either of hemorrhage or of thrombo-embolic events. Other important limit is the large interference of AVK efficacy with concomitant administration of a large group of other drugs, as well as a strong influence of diet in the same respect.

Of course, AVK therapy has also good qualities. If well monitored, this therapy may adapt very well to difficult clinical conditions, like renal insufficiency or in aged persons. It may be used in some conditions, such as chronic therapy for valvular prostheses, where new anticoagulants have not yet an indication. They may be associated in well defined clinical conditions with antiplatelet therapy, which is not allowed to date for the new AC drugs. They have a good antidot, vitamin K. Last, but not least their cost is small at first glance.

The new drugs aproved to be used in some clinical conditions are: Dabigatran, which is a direct antithrombinic agent and Rivaroxaban

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and Apixaban, as inhibitors of the Xa factor. Other drugs were tested on humans, but to date are not used for different reasons: Ximelagatran, withdrawn in 2006 because of hepatic toxicity, Edoxaban, Betrixaban or Darexaban, which do not have yet a final destiny in clinical medicine (3).

To date, the clinical trials dedicated to different conditions include several tens of thousands of patients, being one of the largest category of clinical trials (3-6). The first indications approved were the prevention of the venous thromboembolism, followed soon by the therapy of the deep venous thrombosis and pulmonary embolism (1,3,5). A large field of interest was the anticoagulant therapy in atrial fibrillation (2,4,6). All the three drugs are approved or ready to be approved either in the USA and Europe to be used in this domain.

Another field of interest is the use of the new drugs in acute coronary syndromes (7). The exact place of this therapy in this field is not yet defined. We have to mention that their concomitant use with antiplatelet therapy is not defined as well (7).

The great advantage of the new oral AC drugs is their huge potential to have best adherence for a long term therapy, because they do not have to be monitored. Most of the studies showed that they are efficient and secure in their effect, being at least non-inferior to warfarin and sometimes, even superior in terms of less number of severe side effects. They seem to be little influenced by other concomitant therapy or diet, but some authors still suggest concern in this respect (6). In a word, they are efficient, secure, stable and easy to be administered.

These advantages may generate by themselves some potential weak points. We base our trust on their efficacy and security on a statistical base (the mean good result in clinical trials). However, would we be more secure to have the possibility to monitor their efficacy in the individual patient in front of us, how we use to do with AVK drugs? To date, such a test similar to the INR (International Normalized Ratio) to monitor the instant anticoagulant power is not available. It seems to be on research, as it is the search for an efficient and low cost antidote (6).

Another problem is the cost, high as usual for new and good drugs. Of course, in time the cost of these drugs could decrease. But even now, if for AVK drugs we consider the cost of the infrastructure to monitor the therapy, as well as the cost of the time dedicated to that medical visit, the total costs of AVK therapy or the cost of a new oral AC therapy could be comparable.

It is to be mentioned that the knowledge in the field of new AC is still changing, as it would be expected. Some recent review of the literature consider, for instance, that the bleeding risk of such therapy is greater than initially considered (8).

In conclusion, we face a moment of clear progress in cardiovascular therapy, comparable with the great moments of the last half a century, the introduction of ACE inhibitors, statins, sartans, fibrinolytics, new antiplatelet drugs and others. Let us hope that the final impact of the new anticoagulants will be even greater than presumed today.

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