On money and

Any pharmaceutical company wishing to see a new drug covered by health insurance must not only demonstrate its effectiveness but also its cost-effectiveness. That the – usually complex – pharmacoeconomic analyses are not decisive becomes apparent yet again for new anticoagulation drugs. Not even if the issue is tackled by the Health Council.

ARNO VAN 'T HOOG

In the Netherlands some 400,000 people use vitamin K antagonists (coumarin derivatives) for a variety of reasons to maintain their coagulation balance. It may be temporary, after a hip operation for instance, or permanent, to prevent thrombosis in patients with atrial fibrillation, a common cardiac arrhythmia. This condition can lead to blood clots forming in the patient's heart; these clots can then block the blood vessels in the brain.

Tens of thousands of people have to visit a Thrombosis Service every other week to have their blood coagulation checked. This is because the vitamin K antagonists (VKAs) they take can interact with food and medicines and thus influence the effect of these VKAs. It's therefore essential to check the patient's blood on a regular basis and if necessary adjust the dosage with a whole or half coumarin tablet.

ENORMOUS MARKET

It has been quite obvious for many years that alternatives were on the horizon, the so-called new oral anticoagulants (NOACs). Whereas VKAs slow down the formation of coagulation factors, NOACs block the factors. This route is less susceptible to interaction with drugs, food and alcohol for instance. Monitoring the patient's blood is no longer necessary.

Two new drugs – dabigatran (Pradaxa) and rivaroxaban (Xarelto) – are already covered by insurance in the Netherlands to prevent thrombosis after knee or hip replacement surgery. This is a relatively limited field of application but both drugs have meanwhile been registered in Europe to prevent embolism (blood vessel blockages) in patients with atrial fibrillation; a much wider indication.

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Health Council usually avoids involvement with individual drugs

Manufacturers Boehringer Ingelheim and Bayer consequently submitted a request to the Dutch Ministry of Health, Welfare and Sport to have their drugs included in the drug reimbursement system, i.e. reimbursement through the basic health insurance.

The Health Care Insurance Board (CvZ) normally advises the minister on this subject. However, in this case of new anticoagulants the minister also asked advice from the National Health Council. This was because of the large number of patients, the high costs involved and potential problems facing the Thrombosis Services. These centres would then need to monitor fewer patients.

The Health Council is normally concerned with aspects of public health and not with individual drugs. "However, the market for anticoagulants is so extensive that it has now become a public health issue", says Maarten Postma, professor in pharmacoeconomics at the University of Groningen and consultant for the Health Council Committee that advised the minister. The committee has examined the complete dossier, says Postma: the medical section on clinical studies, the current situation in the Netherlands, and the economic section that provides a cost-effectiveness analysis: the pharmacoeconomic calculation of all the effects of the new pharmaceutical drugs in comparison with the current treatment.

SEVERAL SOURCES

A computer model was developed for a pharmacoeconomic study; all clinical and economic data were entered, as well as data on the savings in costs that would be achieved by the new treatment. When drug manufacturers submit a request for reimbursement they include their own analysis, and the CvZ then checks the hypotheses and the underpinnings of the model.

The analyses using computer models can be extremely complex, says Postma. It can take years to build up and fine-tune it. "For instance: it's complex for NOACs

blood flows

because you have to maintain a balance between coagulation and decoagulation. Too much decoagulation increases the risk of bleeding. Consequently you have to find out how big that risk is, and how much the treatment will cost and the lingering effects. You have to know the average age of the patients, whether they are still able to work, and what the consequences are in terms of life quality. On the other hand, too little decoagulation increases the risk of blood clots. This means that you have to enter the data for a series of individual disorders into the model. The process is generally easier for a new painkiller for instance, but can be even more complex for a new vaccine."

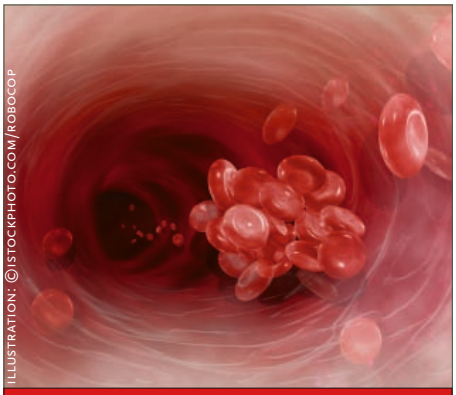
It's impossible to retrieve such medical and economic data from a single source. Some studies date back 10 years and therefore need correcting. And given that each country follows a different treatment strategy, studies conducted in other countries are virtually never suitable for use in the Netherlands. Postma: "Effect and cost are always spedific to the country where the study is carried out."

Ultimately the Quality Adjusted Life Years (QALYs) that patients will gain from treatment is determined; this is a measure of the health benefits gained in the form of extra years of life plus the quality of that life. The value of QALY is between 1 (one year in good health) and 0 (death).

IFS AND BUTS

In spite of the complexity of these models, at the end of the day a pharmacoeconomic analysis is a simple sum involving three variables, explains Postma. The cost of a new drug, minus the resulting savings, divided by the QALYs. This sum gives us an incremental cost-effectiveness ratio: the number of Euros spent per QALY. According to the Health Council this is approximately 12,000 Euros per QALY in the case of NOACs. This is below the 20,000 taken as the approximate limit (not established officially) for an acceptable level of cost-effectiveness.

According to the Health Council, given that repeated monitoring is either no longer needed or the monitoring frequency is very much reduced, the new anticoagulants are cost-effective and can substantially simplify anticoagulation treatment . As far as their effect is concerned, it is at least that of VKAs – and possibly slightly more effective and safer – and should therefore be available to physicians and patients, writes the council.



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'Thrombosis Services envisage their future going downhill'

Despite this unambiguous statement, the advice still involves several 'ifs' and 'buts'; relating mainly to the costs and benefits of the Thrombosis Services. The care these centres provide with the current drugs should bring the anticoagulation check-ups carried out in the Netherlands up to a higher level compared to neighbouring countries and therefore there is less room for improvement by administering NOACs. A smaller health improvement gives rise to doubts regarding cost-effectiveness. The Health Council therefore recommends that the introduction should be supervised with caution and extra research should be carried out.

LOBBYING

Bregt Kappelhoff, clinical pharmacologist and market access manager at Boehringer Ingelheim (dabigatran manufacturer) wonders what results that research will yield. "For dabigatran registration the EMA has imposed the condition that real-life post-marketing research must be carried out worldwide; a condition met by Dutch centres. Similar research is also being conducted for rivaroxaban. I am well able to understand the wishes of the Health Council for specific Dutch research but what is the precise research question, and what is the added value on top of the other two studies?"

The conclusion that much better results are being achieved by the Dutch system of thrombosis centres is very brash, says Kappelhoff. There are virtually no clinical data on hand to support that claim. "We've put a great deal of research into this." Politics, the economy and third-party interests also play a role alongside all the clinical studies and cost-effectiveness analyses, is his conclusion. "The Thrombosis Services have existed for 50 years and they now feel that the emergence of NOACs will affect their future. They too are lobbying to promote their own interests."

It's still uncertain when the ministry will come up with a definitive decision on reimbursement. The CvZ has meanwhile submitted a positive advice, says Kappelhoff. The Health Council has also given its positive advice, even though it wants to see additional research and measures. |

On Monday October 1st there will be a session on pharmacoeconomics at the FIGON Dutch Medicines Days

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13_Kadertekst