CHAPTER 8

GENERAL DISCUSSION AND SUMMARY
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Oral anticoagulant therapy has changed little since the development of the coumarin drugs after the Second World War. The basic nature of the therapy, i.e. the balancing between thrombosis and haemorrhage, makes it a therapy difficult to manage. Add to this the many influences from co-morbidity, co-medication, diet, metabolism, etc, and it becomes clear that there is little inherent stability to coumarin anti-vitamin K treatment.

Oral anticoagulant therapy will always be part of medicine. Where its use was initially confined to the treatment of venous thrombosis its area of application has increased widely with our progress in surgery and invasive procedures, and our knowledge of thrombophilia and cardiovascular disease.

Many attempts have been made in the past to improve this therapy in the absence of practical alternatives. The introduction by the World Health Organization (WHO) of the International Normalized Ratio (INR) has greatly benefited oral anticoagulation management in the sense that results from different laboratories could at last be compared. The institution of dedicated anticoagulation clinics in some parts of the world has certainly improved the management of oral anticoagulant care, not in the least in the Netherlands where there is a highly structured system of regional anticoagulation clinics ('trombosediensten') responsible for all aspects of this treatment. The definition of INR target ranges for the different indications for oral anticoagulant treatment has further standardized care. Regularly various international and national institutions and study groups publish guidelines on anticoagulant therapy\(^{1-9}\).

More interest has recently been shown in external influences on coumarin treatment, i.e. on the effects of co-morbidity, co-medication and diet, and guidelines have been adopted especially dealing with the influence of other drugs on the INR.
Choice of coumarin

Surprisingly, only a few anti-vitamin K coumarin drugs are used in oral anticoagulant therapy (OAT). They differ mostly in their plasma half-life. Acenocoumarol (Sintrom®) has a half-life of 11 hours, warfarin (Dicoumadin®, Marevan®) of 40 hours and phenprocoumon (Marcoumar®) of 140 hours. The geographical distribution of the use of the different coumarin has resulted in few studies comparing the different coumarins. From a first study comparing acenocoumarol (t 1/2 = 11 hours) with warfarin (t 1/2 = 40 hours) it became clear that looking at time spent within the predefined INR target range, anticoagulant therapy with the longer-acting warfarin proved superior. This led us to perform two studies comparing acenocoumarol (t 1/2 = 11 hours) and the longest-working coumarin, phenprocoumon (t 1/2 = 140 hours).

In chapter 2 we describe a retrospective study in which 288 patients on acenocoumarol were closely matched for the indication for oral anticoagulant therapy, age, sex, date of start of treatment, and duration of treatment with 288 patients on phenprocoumon. These 456 patients with 7245 INR checks yielded a follow-up of 230 patient-years. The quality of OAT calculated over the whole treatment period was higher in patients treated with phenprocoumon as expressed by number of INR checks in the therapeutic range (phenprocoumon: 42.7%, acenocoumarol: 36.5%, difference: 6.1%, CI95 of the difference: 3.0 - 9.3%) and by time in range (phenprocoumon: 46.6%, acenocoumarol: 41.6%, difference: 5.0%, CI95 of the difference: 1.5 – 8.6%). After the initial 6 weeks of OAT, when a more stable effect should have been reached, the differences became more pronounced (difference: 6.1%, CI95: 1.8 – 10.4%). To discount for possible bias based on more experience with one of the coumarin drugs the study was repeated on a smaller patient group (51 patient pairs) from another anticoagulation clinic with a reverse distribution in use of the two coumarins, but this confirmed the earlier results.

In chapter 3 we describe another study comparing the quality of anticoagulant therapy delivered with acenocoumarol and phenprocoumon. In this study we used the cross-section of the files method to look at more than 22,000 patients in 6 Dutch anticoagulation clinics. INR checks of patients who received phenprocoumon were within the therapeutic range 50% of the time compared with 43% for acenocoumarol (OR 1.32, 95% CI 1.24-1.41). Moreover, patients on phenprocoumon required 15% fewer monitoring visits and had more stable INR values. These observations were consistent for all six clinics.

From our own studies comparing acenocoumarol and phenprocoumon and the studies comparing acenocoumarol and warfarin, it seems that the use of the longer-acting coumarins results in a higher percentage of time within the predefined INR target range. Although the studies were not designed to analyse differences in clinical outcome, it is not unreasonable to propose that a higher percentage of time within the INR target range would be reflected in less thrombotic and hemorrhagic events. Most interesting would be a comparison between the two longer-acting coumarins, warfarin and phenprocoumon themselves.
Patient self-management

As in diabetes care patient self-management has started to make inroads in oral anticoagulant treatment. After the technology became available to make home testing by the patients possible, several countries have started trying out full patient self-management. It was first introduced in countries without a structured system of anticoagulation clinics, and consequently a disappointing low standard of oral anticoagulant care, and resulted in an important improvement in treatment quality. It was not clear whether the same improvement could be expected in places with high standards of care.

Chapter 4 describes the large randomized prospective two-centre (Leiden-Lichtenvoorde) study which was set up to analyze the effects of patient self-testing, full patient self-management and patient training on the quality of oral anticoagulant care versus the standard of care delivered by the Dutch system of regional anticoagulation clinics. Four patient groups were analyzed; under a Zeelen-design one group was unaware of its participation and reflected existing anticoagulant care. The three other groups were fully trained for patient self-management but were afterwards randomized for self-management, for self-testing with dosing by anticoagulation clinics, or for returning to the existing standard of care but having been fully trained. In the Dutch environment with a high standard of anticoagulant treatment delivered by a structured system of regional anticoagulation clinics the patients on self-management performed as well as the patients dosed by the anticoagulation clinics, removing any obstacles for the introduction of the system of patient self-management of oral anticoagulant care in the Netherlands. In this regard the Leiden-Lichtenvoorde study, together with the Academic Medical Center Amsterdam (AMC) study, has been pivotal and has also laid down the frame for the practical set up of the selection, training and management of these patients.

Chapter 5 describes the study on the effects of life of patient self-management, self-testing and training on the Quality of Life of patients under oral anticoagulation. This study was performed within the Leiden-Lichtenvoorde study described in chapter 4. It is evident from our results that patient self-management in the field of oral anticoagulant therapy also results in an improvement in patient quality of life as compared to management by specialized anticoagulation clinics. This is borne out by an increased sense of general treatment satisfaction and a diminished perception of treatment related distress or social strain. From the baseline assessment it was also clear that overall the general treatment satisfaction indicated by the patients in the Dutch system of specialized anticoagulation clinics was higher than in Germany where anticoagulation treatment is mostly done by family physicians, although this difference may also be attributable to cultural differences between patients in different countries.
Paracetamol

Oral anticoagulant therapy is heavily influenced by co-medication. Painkillers are especially important in this regard because acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAID) increase the bleeding tendency by interfering with platelet aggregation. Paracetamol is routinely advocated by the anticoagulation clinics as a safe painkiller and anti-fever drug. Some disquiet arose when there were indications in the literature that paracetamol could increase the INR\(^1\). The indications came from a retrospective analysis in which several confounding factors could have influenced the result, particularly the minor illness leading to the use of the drug.

Chapter 6 describes a double blind randomized controlled trial in which 31 outpatients on coumarin oral anticoagulant therapy with phenprocoumon were randomised for placebo, 1500mg paracetamol daily or 3000mg paracetamol daily for 14 days during the stable phase of coumarin therapy and INR values measured at day 1, 8, 15, 22 and 29. The study was set-up to look at the inherent effect of paracetamol on the INR without taking into account the effect of any condition necessitating the intake of the medication. There was a uniform but slight rise in the mean INR of 0.46 at day 8 in both paracetamol groups independent of the dose. On day 15 there was no difference between placebo and paracetamol at a dose of 1500mg daily, and this remained the case in the two weeks after the intake of the study drug. A small rise against placebo continued in the paracetamol 3000mg daily group at day 15 (+0.22) and in the two weeks after paracetamol intake. This led us to conclude that the sustained use of paracetamol (acetaminophen) during oral anticoagulant therapy in itself does not provoke clinically relevant INR changes, but that any important INR rises will predominantly be the result of the illness necessitating the intake of this medication in the first place.
Treatment quality and recurrence risk

The INR target ranges reflect a balance between an acceptable risk for thrombosis and an acceptable risk for bleeding complications. Even within the INR target range oral anticoagulant treatment has a risk for severe bleeding complications of around 1.8%/year. The definition of the INR target ranges has been the result from a large number of studies but in few cases has the real INR level been used in the analysis instead of the predefined target INR. We wanted to analyze to what extent low INR levels during the initial treatment of an acute venous thrombotic event contribute to the occurrence of recurrence of thrombosis in subsequent years.

Chapter 7 describes our analysis of the treatment quality in the Leiden Thrombophilia Study (LETS), a population-based case-control study on risk factors for venous thrombosis, which has been published previously\cite{14-16} and in which many genetic and acquired factors have been investigated. In our analysis 266 patients with a total follow up of 2495 patient-years were studied. During follow up 58 recurrences were diagnosed (cumulative recurrence risk of 21.8% over 9 years). Mean INR during initial therapy was 2.90, with 90% of the time spent above an INR of 2.0, and even almost 40% above an INR of 3.0. Owing to the high quality of oral anticoagulant care we were unable to identify a crucial lower limit of the INR level necessary to prevent recurrence, and we observed no relation between risk of recurrence and mean INR or duration of treatment. Patients considered at a higher risk by the treating physician, probably on the basis of the absence of provoking circumstances or the presence of thrombophilia, were on the whole treated for longer periods and at slightly higher INR levels, the latter probably because of a tendency by dosing physicians at the anticoagulation clinic to keep patients they considered as ‘high risk’ more at the higher end of the desired INR range in a belief that higher INRs are related to a lower risk of recurrent thrombosis.
Conclusions

The studies included in this thesis were set up to look at different ways in which the quality of oral anticoagulant treatment can be improved.

Should we restrict ourselves to only one coumarin drug when this delivers the highest percentage of time spent within the pre-defined INR target range? From our studies it is clear that the longer-acting coumarins are superior in this regard but the studies were too small to analyze whether this translated itself into a lower recurrence rate and less bleeding complications. Larger studies should look at this in the future.

Patient self-management seems a way to further improve treatment quality, certainly in countries without a highly structured system of regional anticoagulation clinics. The gain in quality as compared to the high standard of quality available in the Netherlands is small but it has also become clear that the system of self-management brings with it an important beneficial effect on the Quality of Life of the patients. Both studies from this thesis dealing with patient self-management have been pivotal in establishing this treatment modality in the Netherlands.

The disquiet over the routinely advocating of paracetamol as a safe painkiller and antipyretic for patients under oral anticoagulation has been partly assuaged by the randomized study in which patients were given various concentrations of paracetamol or placebo. More attention has to be given to the effects on the INR of the condition necessitating the intake of paracetamol, more than to the inherent effect of the medication itself on the INR.

We were unable to identify a crucial INR target which has to be sustained to prevent recurrent thrombosis because of the high quality of anticoagulant care in our studies. With good management of oral anticoagulant therapy for deep venous thrombosis according to the existing international guidelines, recurrent thrombosis can not be ascribed to primary treatment failure but rather to underlying or external circumstances. Further developments should go towards further improving the quality of the management itself, i.e. the fine-tuning of the INR within the target ranges for almost the whole of the time, as it is not unreasonable to argue that this would be reflected in less thrombotic and hemorrhagic complications. Keeping the INR above 2.0 for most of the advised treatment period will protect as much as possible against recurrences. If this can goal can be met further refinement of the management technique should aim at lowering the number of haemorrhagic complications through over-anticoagulation.
References


