**Cochrane Corner: Self-monitoring and self-management of oral anticoagulation.**

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**Word count 1110**
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## Background

Use of oral anticoagulants such as warfarin is increasing. Part of the reason for this is the rising prevalence of atrial fibrillation, an ageing population, and the widening indications for treatment based on evidence of benefit in reducing risk of stroke. A meta-analysis of 29 randomized trials including 28,044 participants with atrial fibrillation found warfarin decreased the absolute risk of stroke by 2.7% per year (number needed to treat [NNT] 37) compared to placebo or no treatment, and by 0.7% per year (NNT = 143) when compared to aspirin. [1]

Management of warfarin, however, is challenging because of the considerable variability in warfarin's action and the narrow 'therapeutic range,' which requires frequent testing of international normalized ratio (INR) values and appropriate adjustment to prevent major complications. Often, poor control means that much of the potential benefit is not realised. Point-of-care devices, which allow self-testing of INR, with a drop of whole blood, are one of the options to optimise management by potentially reducing the need to attend anticoagulation clinics and offering the possibility for more continuous measurement. [2] The first randomized trial of patient self-testing, published in 1989, included 50 patients on warfarin but with poorly controlled INRs, found that self-testing in the home setting provided accurate measurements, was feasible and achieved superior control when compared with standard anticoagulation clinic care. [3] Over time there have been a number of further randomized controlled trials (RCTs) done to establish the effectiveness of self-monitoring. In parallel, self-testing devices have generally proved to be reliable and analytically accurate. [4]

Trials that have evaluated self-monitoring usually adopt two types of self-monitoring models. In some, a (trained participant tests their INR test and informs their healthcare provider of the result. In others, there is a greater degree of self-management where a trained participant tests their INR, interprets the result, and adjusts the drug dosage accordingly. [5] Given the growing evidence base, we updated our systematic review of the impact of patient self-monitoring or self-management on treatment with oral anticoagulation therapy. [5]

## Review Methods

We included RCTs of self-monitoring or self-management of oral anticoagulation compared with standard monitoring, and meta-analysed thrombotic events, major haemorrhage (e.g. haemorrhage requiring hospital admission or transfusion), all-cause mortality and time in therapeutic range (TTR), and proportion of measurements within the therapeutic range as the primary outcomes of interest. The intervention was compared to control of and dosage by clinician; anticoagulation managed services or anticoagulation clinics. The review was performed using standard Cochrane systematic review techniques including comprehensive searches (updated on the 1 July 2015); quality assessment using the Cochrane risk of bias tool and GRADE; a test for publication bias; pooling of data using a fixed-effect model and assessment of heterogeneity (where heterogeneity existed a random-effects model was used). A

sensitivity analysis was undertaken by excluding studies at high risk of bias and pre-specified subgroup analyses were done examining the effect according to clinical indication (mechanical valve replacement or atrial fibrillation) and monitoring strategy. A post-hoc subgroup analysis according to type of care (specialist anticoagulation clinic, or family physician) was also undertaken, since this seemed informative to practice.

**Main Results**

A total of 28 studies (published between 1989 and 2015) provided data on 8,950 participants. Six trials included only participants on lifelong anticoagulation therapy following mechanical valve insertion; two included participants on long-term anticoagulation for atrial fibrillation and 19 included participants on long-term anticoagulation for any indication. According to GRADE the available evidence was judged to be only moderate, due to flaws in study design; most commonly there was an absence of information about the allocation concealment procedure or blinding.

There was a reduction in thromboembolic events for those who self-monitored or self-managed (RR 0.58, 95% CI 0.45 to 0.74), with no significant effects on major haemorrhage (or secondary outcome of minor haemorrhage) or all-cause mortality. (Table 1 summary of findings). In the three studies (n = 1,295) of participants with mechanical valves, self-monitoring or self-management did reduce mortality (RR 0.50, 95% CI 0.29 to 0.86), and in eight studies (n=3,058) self-management alone significantly reduced all-cause mortality (RR 0.55, 95% CI 0.36 to 0.84); the subgroup interaction was significant when compared with self-monitoring alone (p=0.02)

The average proportion of people that were initially sampled but subsequently excluded or did not agree to randomisation was 68% (range 31% to 88%). Of participants assigned to the intervention 25% (range 0% to 57%) were unable to complete self-monitoring or self-management. Main reasons for the drop-outs were: problems with the device, physical limitations preventing self-testing and problems with attending the training assessments or failing the assessment.

**Limitations of the evidence**

The overall quality of the evidence was moderate; sometimes because of risk of bias across the studies, but in some cases due to the imprecision of some effect estimates due to low numbers of events for outcomes such as thromboembolic events (total events 230) and all-cause mortality (total events 448). For minor haemorrhage the evidence was low quality due to serious risk of bias, but also due to substantial heterogeneity in the pooled effect ($I^2$ = 82%).

**Implication for practice**

The review provides evidence that patients on oral anticoagulation can successfully self-monitor, and even self-manage their INR with reductions in thromboembolic

events and no increase in harms. These results are particularly relevant for younger patients and those with mechanical valves: In an individual patient data meta-analysis by our group, [6] a significant reduction in thromboembolic events was reported, hazard ratio (HR) 0.51 (95% CI 0.31 to 0.85); in patients under 55 years of age, marked reductions in thrombotic events were observed (HR 0.33, 95% CI 0.17 to 0.66), and in patients with mechanical heart valve (HR 0.52, 95% CI, 0.35 to 0.77). In addition, available evidence suggests that older patients also benefit if they are willing and able: in a real world cohort study of 296 participants at 12 months, 267 (90%) were still self-monitoring and the TTR improved with age. [7]

Several guidelines currently recommend self-monitoring as one strategy to improve the management of OAT. [8] [9] However, uptake is variable. For example, self-monitoring has become an established practice in some countries, such as Germany. In contrast, several barriers to increased uptake of self-monitoring have been identified in the UK, [10] despite being advocated by the National Institute for Health and Care Excellence (NICE). [2] In some instances point of care devices have proven to be inaccurate, [11] and therefore it is essential that patients are regularly reviewed with external quality assurance undertaken. [12] Furthermore, for widespread uptake there is a need to further evaluate the training packages on offer as, many patients seemingly start testing with minimal input from health services. [13]

**Competing Interests**

CH has received expenses from the WHO and holds grant funding from the NIHR, the NIHR School of Primary Care Research and the WHO. ES And KM have no competing interests.

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Table 1

Patients on long-term anticoagulant therapy (treatment duration longer than two months) irrespective of the indication for treatment
Settings: Primary care, specialist clinics (Europe, America, Canada)
Intervention: Self-monitoring or self-management
Comparison: Standard care

| Outcomes | Illustrative comparative risks* (95% CI) | Relative effect | No of Participants | Quality of the evidence |
|---|---|---|---|---|

| | **Assumed risk** | **Corresponding risk** | (95%CI) | (studies) | (GRADE) |
|---|---|---|---|---|---|
| | Standard care | Self-monitoring or self-management | | | |
| Thromboembolic events<br>Follow-up: 3 to 57 months | Study population | | RR 0.58 (0.45 to 0.74) | 7594 (18 studies) | ⊕⊕⊕⊖<br>Moderate 1 |
| | 35 per 1000 | 21 per 1000 (16 to 26) | | | |
| | Moderate risk population | | | | |
| | 22 per 1000 | 12 per 1000 (10 to 16) | | | |
| All-cause mortality<br>Follow-up: 6 to 57 months | Study population | | RR 0.85 (0.71 to 1.01) | 6358 (11 studies) | ⊕⊕⊕⊖<br>Moderate 1 |
| | 64 per 1000 | 54 per 1000 (45 to 64) | | | |
| | Moderate risk population | | | | |
| | 0 per 1000 | 0 per 1000 (0 to 0) | | | |
| Major haemorrhage<br>Follow-up: 4 to 57 months | Study population | | RR 0.95 (0.80 to 1.12) | 8018 (20 studies) | ⊕⊕⊕⊖<br>Moderate 1 |
| | 62 per 1000 | 59 per 1000 (50 to 69) | | | |
| | Moderate risk population | | | | |
| | 18 per 1000 | 17 per 1000 (14 to 20) | | | |
| Minor haemorrhage<br>Follow-up: 4 to 57 months | Study population | | RR 0.97 (0.67 to 1.41) | 5365 (13 studies) | ⊕⊕⊖⊖<br>Low2 |
| | 217 per 1000 | 210 per 1000 (145 to 306) | | | |
| | Moderate risk population | | | | |
| | 45 per 1000 | 44 per 1000 (30 to 63) | | | |