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Is home monitoring of international normalised ratio safer than clinic-based monitoring?

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Abstract

A best evidence topic was written according to a structured protocol, to answer the question: 'In patients taking warfarin, is home self-monitoring of international normalized ratio (INR) safer than clinic-based testing in reducing bleeding, thrombotic events and death?' Altogether, 268 papers were found using the reported search. Five papers represented the highest level of evidence to answer the clinical question (four systematic reviews with meta-analysis and one meta-analysis). The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. The principal outcomes of interest were death, major haemorrhage, major thromboembolism, and time (or percentage time) spent within the therapeutic range, compared between self-monitoring/self-management and conventional management. Self-monitoring/self-management was associated with a significantly reduced risk of all-cause mortality of 26–42%. All meta-analyses reported on major thromboembolism, finding significant reductions in risk of ~50%. One meta-analysis found a 35% reduction in the risk of major haemorrhage, with the other four studies finding no significant difference. Only one study found self-monitoring/self-management to be associated with a significantly greater proportion of time within range, with another finding no significant difference in either the percentage of therapeutic results or in the time within range. The remaining two could not combine data for meta-analysis owing to methodological heterogeneity. We conclude that self-monitoring/self-management appears to be safer than conventional management. It is associated with consistently lower rates of thromboembolism and may also be associated with reduced risk of bleeding and death. This supports the updated guidance from the American College of Chest Physicians, recommending self-management of INR for patients who are both competent and motivated.

Keywords: Anticoagulation • INR • Warfarin • Home testing • Telemedicine • Self-monitoring • Point of care • Review

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS [1].

THREE-PART QUESTION

In [patients taking warfarin], is [home self-monitoring of international normalized ratio (INR)] safer than [clinic-based testing] in reducing [bleeding, thrombotic events and death]?

CLINICAL SCENARIO

A 62-year old woman with a mechanical heart valve is seen in clinic. She is taking warfarin and reports that she finds it inconvenient to regularly come for INR monitoring. She asks if she would be able to manage her INR at home to avoid the inconvenience of frequent clinic attendance. She has read online that home self-management is a safer technique than clinic-based testing and dose adjustment. You explain that you will check the literature to establish whether this is indeed the case.

SEARCH STRATEGY

MEDLINE 1950 to July 2012 using MEDLINE interface 'INR' OR 'international normali* ratio' OR 'prothrombin time' OR 'anticoagulation').ti,ab] AND 'self-monitor*' OR [('self monitor*' OR 'self-test*' OR 'self test*' OR 'home monitor*' OR 'home-monitor*' OR 'home test*' OR 'home-test*' OR 'self-manage*' OR 'self manage*' OR 'home manage*' OR 'home-manage').ti,ab], restricted to the English language. Reference lists were searched for additional articles.

SEARCH OUTCOME

268 papers were retrieved using the above search, of which 45 were identified as potentially relevant. Trials not using warfarin, restricted to children, not reporting on outcome measures of interest (i.e. haemorrhage, thrombosis and death), not using randomization, or not comparing self-monitoring or self-management to standard management were excluded. One systematic review was excluded that did not meta-analyse data on the outcome measures of interest, and one meta-analysis that included self-monitoring in its

Table 1: Best evidence papers

Author, date, journal and country, study type (level of evidence)	Patient group	Outcomes	Key results	Comment
Heneghan *et al.* (2006), Lancet, United Kingdom Systematic review with meta-analysis (level 1a)	14 RCTs *n* = 3049 (adults and children)	Effect of self-monitoring or self-management vs standard monitoring on: Thromboembolic events Major bleeding All-cause mortality Proportion of measurements within therapeutic range	Pooled OR estimates: 0.45 (95% CI 0.30–0.68) 0.65 (0.42–0.99) 0.61 (0.38–0.98) Data could not be pooled	This large systematic review with meta-analysis demonstrates a 55% reduction in thrombo-embolic events, a 35% reduction in major bleeding and a 39% reduction in all-cause mortality when patients self-monitor INR Data not presented here comparing self-management (self-monitoring plus dose adjustment) to standard management found greater reductions in the risk of thrombo-embolic events and all-cause mortality, but not for major bleeding. Most trials found improvements in the proportion of INR measurements within therapeutic range but owing to methodological differences these were not pooled
Wells *et al.* (2007), Open Med, Canada Systematic review with meta-analysis (level 1a)	16 RCTs 2144.6 person-years of follow-up for treatment group, 2316.1 person-years of follow-up for control group (total 4460.7 person-years)	Effect of self-monitoring or self-management vs conventional management on: Major haemorrhage Major thromboembolism All thromboembolism Death Percentage time within therapeutic range	Pooled OR estimates: 0.78 (0.53–1.14) Not significant 0.51 (0.35–0.74) 0.49 (0.32–0.74) 0.58 (0.38–0.89) 69 vs 61%, *P* <0.05	Meta-analysis found that self-monitoring or self-management were associated with a 49% reduction in major thromboembolism, a 51% reduction in all thromboembolism and a 42% reduction in death. In addition, there was a significant difference between the two groups for percentage time within therapeutic range. There was no significant benefit found for major haemorrhage. The authors state that the studies included were of variable quality and that although self-testing appears to be safer, it is unclear if this is the product of increased testing or improved patient education
Garcia-Alamino *et al.* (2010), Cochrane Database Syst Rev, United Kingdom Systematic review with meta-analysis (level 1a)	18 RCTs *n* = 4723 (adults and children)	Effect of self-monitoring or self-management vs standard management on: Thromboembolic events All-cause mortality Major bleeding Time and proportion of measurements within therapeutic range	Pooled RR estimates: 0.50 (0.36–0.69) 0.64 (0.46–0.89) 0.87 (0.66–1.16) Not significant Data could not be pooled	Meta-analysis found a 50% reduction in thromboembolic events, a 36% reduction in all-cause mortality but no significant improvement in major bleeding. Improvements in percentage of tests in range were reported in 17 studies, with six achieving statistical significance. However, owing to methodological differences these data could not be pooled
Bloomfield *et al.* (2011), Ann Intern Med, USA Meta-analysis (level 1a) (-)	22 RCTs *n* = 8413 (adults only)	Effect of self-monitoring or self-management vs standard management on: Thromboembolic events All-cause mortality Major bleeding Percentage of therapeutic results or percentage of time within therapeutic range	Pooled OR estimates: 0.58 (0.45–0.75) 0.74 (0.63–0.87) 0.87 (0.75–1.05) No significant difference	Meta-analysis found a 42% reduction in thromboembolic events and a 26% reduction in all-cause mortality. However, it was unclear if there was a beneficial effect on major bleeding. In addition, no significant difference was found between self-monitoring/self-management and standard management for either the percentage of therapeutic results, or percentage of time spent in therapeutic range. This makes it difficult to ascertain the mechanism by which thromboembolic events and mortality appear to be reduced Studies included in the meta-analysis were of variable quality and size. One study in particular represented over 25% of total patients studied

Continued

Table 1: (*Continued*)

Author, date, journal and country, study type (level of evidence)	Patient group	Outcomes	Key results	Comment
Heneghan *et al.* (2012), Lancet, United Kingdom	11 RCTs $n = 6417$ (adults only)	Effect of self-monitoring or self-management vs standard management on:	Pooled HR estimates:	Meta-analysis demonstrated a 49% reduced risk of thromboembolism but no significant reduction in risk of death or major bleeding. Subgroup analysis not presented here found the reduction in thromboembolism greatest in those aged <55
Systematic review with meta-analysis (level 1a)		Time to death	0.82 (0.62–1.09) Not significant	
		First major haemorrhage	0.88 (0.74–1.06) Not significant	
		Thromboembolism	0.51 (0.31–0.85)	

RCT: randomized controlled trial; OR: odds ratio; INR: international normalized ratio; CI: confidence interval; RR: relative risk; HR: hazard ratio.

definition of standard management was also excluded. Ultimately, four systematic reviews with meta-analysis (including one Cochrane review) and one meta-analysis were deemed the best evidence to answer the clinical question. Four of the five articles were level 1a on the Oxford Levels of Evidence scale, with one ranked as 1a(-).

RESULTS

The results of the five included articles are summarized in Table 1.

All five papers report data for major haemorrhage. Most of these classed major haemorrhage as that resulting in death, critical organ bleeding, surgical intervention, a fall in haemoglobin concentration of >2 g/dl, or needing a transfusion of two units or more. Data from 14 randomized controlled trials (RCTs), analysed by Heneghan *et al.*, found that self-monitoring/self-management was associated with a 35% reduced risk of major haemorrhage (odds ratio (OR) 0.65 (95% CI 0.42–0.99) [2]. However, the four other meta-analyses reporting specifically on major haemorrhage reported no significant difference compared with standard management [3–6].

All five meta-analyses reported specifically on major thromboembolic events. Major thromboembolism was generally classified as that resulting in death, stroke, arterial thrombosis or venous thromboembolism. All found self-monitoring/self-management to be associated with a significantly reduced risk of thromboembolism. Importantly, patients were included irrespective of the original indication for anticoagulant therapy. One meta-analysis excluded studies of <2 months [4], while two excluded studies of <3 months [3, 5]. The remaining two, both by Heneghan *et al.* and published six years apart, did not specify restrictions on duration of anticoagulant therapy [2, 6]. However, the shortest trial included in either study lasted 2 months. It is reasonable to infer that short-term (e.g. patients receiving treatment for DVT) courses of anticoagulation should be equally amenable to self-monitoring/self-management as longer-term courses, but none of the meta-analyses provide adequate data on the safety of self-monitoring/self-management for the high-risk initiation period of anticoagulant therapy.

The first meta-analysis by Heneghan *et al.*, published in 2006, found a 55% reduced risk of thromboembolism with self-monitoring/self-management (0.45 (0.30–0.68)) [2], while the more recent study reported a 49% reduced risk (0.51 (0.31–0.85)) [6]. Wells *et al.* and Garcia-Alamino *et al.* found similar reductions in risk [3, 4]. Bloomfield *et al.* reported a slightly more modest reduction of 42% (0.58 (0.45–0.75)) [5].

Mortality data were reported by all five meta-analyses. Four studies reported on all-cause mortality, which was reduced by 26–42% [2–5], but Heneghan *et al.* found no significant difference in time to death [6].

Only one of the reported studies found improvements in measures of percentage time within therapeutic range: Wells *et al.* found an improvement of 8% for self-monitoring/self-management against standard management ($P < 0.05$) [4]. The remaining three papers that analysed time within range provide inconclusive results: the 2006 paper by Heneghan *et al.* reported that methodological differences in time measurements between studies rendered data pooling impossible, and were therefore unable to report on their stated comparison measure of proportion of measurements within therapeutic range [2]. Similarly, the Cochrane review could not pool data for meta-analysis, again citing methodological differences [4]. Lastly, Bloomfield *et al.* found no significant difference in either the percentage of therapeutic results or the percentage of time within therapeutic range [5]. This may have arisen from the unequal sizes of the 22 RCTs they included, with one study in particular making up 25% of the total patients and thus having considerable potential to influence their overall conclusions. While Bloomfield *et al.* found no significant difference in measurements of time within therapeutic range or percentage of therapeutic results, they did report a significantly reduced risk of both thromboembolism and all-cause mortality; it is unclear how these benefits could be explained other than through an improvement in the time within therapeutic range and so it is possible that inter-study methodological differences may account for this.

CLINICAL BOTTOM LINE

The best available evidence suggests that self-monitoring/self-management appears to be safer than conventional management. It is associated with consistently lower rates of

thromboembolism and, from review of the evidence, may also be associated with reduced risk of bleeding and death. This supports the updated guidance from the American College of Chest Physicians, recommending self-management of INR for patients who are both competent and motivated [7].

Conflict of interest: none declared.

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