Benchmark for time in therapeutic range in venous thromboembolism: a systematic review and meta-analysis

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CRD summary
This review concluded that the time within the International Normalised Ratio target range (TTR) varied from 56% to 75% depending on whether data for the first three months were included. Substantial variation in treatment regimen, method to calculate TTR, and the possibility for TTR to be higher in clinical practice, means the generalisability of the overall results is uncertain.

Authors' objectives
To assess the quality of anticoagulant control by providing a benchmark for the time within the target range (TTR) of the International Normalised Ratio for different treatment durations in patients with venous thromboembolism.

Searching
MEDLINE and EMBASE were searched for studies published in nine European languages between January 1990 and May 2012.

Study selection
Randomised controlled trials (RCTs) and cohort studies were eligible if they reported the TTR in patients treated with vitamin K antagonists for either a deep vein thrombosis (DVT) confirmed by a non-compressible venous segment on ultrasound, or a pulmonary embolism confirmed by Computed Tomographic Pulmonary Angiography and/or high probability ventilation/perfusion scan. Patients had to be adults, recruited consecutively, and treated with vitamin K antagonists for at least three months.

The treatment regimen varied considerably across studies. Most studies defined the therapeutic range as an International Normalised Ratio between 2.0 and 3.0. TTR was assessed between one and over 12 months after diagnosis of venous thromboembolism. Most studies reported TTR as the percentage in range over time. TTR was most commonly recorded between one and six months after diagnosis. Most studies had less than 25% of patients with cancer.

Three reviewers independently selected studies for the review; disagreements were resolved by discussion.

Assessment of study quality
Quality was assessed in terms of patient recruitment, reporting of exclusions from the study, handling of missing data, methods used to address potential sources of bias, duration of follow-up and losses to follow-up.

Two reviewers independently assessed study quality. Disagreements were resolved by discussion or referral to a third reviewer.

Data extraction
Two reviewers independently extracted data from each study in order to calculate the mean difference for the TTR since confirmation of venous thromboembolism; disagreements were resolved by discussion.

Methods of synthesis
Weighted means were calculated for the TTR for different time-periods since the diagnosis of venous thromboembolism; sample size was used to weight the studies.

Results of the review
Forty studies (26,064 patients; range 33 to 2,413) were included in the review; 32 were RCTs and eight were cohort studies. Of the 40 studies, seven did not report recruiting patients consecutively, three did not report reasons for excluding patients from the study, 10 did not report adequately dealing with missing data, and eight did not report...
efforts to minimise bias. Where reported, loss to follow-up ranged from zero to 8.1%.

The proportion of patients with therapeutic range varied between 35% and 83% across studies. The weighted mean for the TTR was 54.0% in the first month, 55.6% during the one to three month period, and 60.0% with at least six months of treatment when International Normalised Ratios for the first month were included. In studies that reported TTR without International Normalised Ratios in the first month, the TTR was 60.0% in the two to three month period, and 75.2% in the four to 12 or longer period.

**Authors' conclusions**

Reported quality of vitamin K antagonists treatment was highly dependent on the time-period since the start of treatment; TTR ranged from approximately 56% in studies including the first month to 75% in studies excluding the first three months.

**CRD commentary**

The authors addressed a clear research question supported by reproducible inclusion criteria. Relevant sources were searched, but the search was limited and publication and language bias could not be ruled out. The authors stated that the search strategy was available in an on-line appendix; this could not be found. Each stage of the review process was conducted in duplicate, which reduced the risk of error and bias.

Appropriate criteria were used to assess study quality, but criterion that assessed bias was not clearly defined. It was unclear whether patients were recruited consecutively in seven studies, despite this being a requisite for inclusion. The impact of including these studies was not assessed in sensitivity analyses, but results from these studies did not appear to differ substantially from the other studies that recorded TTR at similar time-points.

Substantial variation across studies in treatment regimen, method to calculate TTR, and the possibility for TTR to be higher in clinical practice, means the generalisability of the overall results is uncertain.

**Implications of the review for practice and research**

**Practice:** The authors stated that when calculating TTR, including time-periods with interruptions in vitamin K antagonists treatment were acceptable, but for the relationship with adverse events, bridging periods should be excluded. The authors qualified this by stating that as TTR was predictive of thromboembolic and bleeding complications for patients on vitamin K antagonists, a proper calculation of TTR in the vitamin K antagonists group was important to assess the adequacy and quality of novel anticoagulants.

**Research:** The authors suggested that drug trials and real life registries with a vitamin K antagonists control group should report the TTR in a uniform manner, to allow adequate comparison of data. The use of linear interpolation was also recommended due to its high validity and the frequency with which it is currently used in studies. The authors also stated that although the clinical consequences of the results were uncertain, the reported quality of vitamin K antagonists treatment should be taken into consideration while interpreting results from trials with new anticoagulants.

**Funding**

No funding.

**Bibliographic details**

Erkens PMG, ten Cate H, Buller HR, Prins MH. Benchmark for time in therapeutic range in venous thromboembolism: a systematic review and meta-analysis. PLOS ONE 2012; 7(9): e42269

**PubMedID**

23049730

**DOI**

10.1371/journal.pone.0042269

**Original Paper URL**

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0042269
Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Anticoagulants /economics /pharmacology /therapeutic use; Benchmarking; Cost-Benefit Analysis; Databases, Bibliographic; Disease Management; Humans; International Normalized Ratio; Randomized Controlled Trials as Topic; Time Factors; Treatment Outcome; Venous Thromboembolism /drug therapy /economics; Vitamin K /antagonists & inhibitors

AccessionNumber
12012046909

Date bibliographic record published
30/01/2013

Date abstract record published
10/05/2013

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.