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Searching for Indirect Evidence and Extending the Network of Studies for Network Meta-Analysis: Case Study in Venous Thromboembolic Events Prevention Following Elective Total Knee Replacement Surgery

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ABSTRACT

Objective: To evaluate the effect of study identification methods and network size on the relative effectiveness and cost-effectiveness of recommended pharmacological venous thromboembolic events (VTEs) prophylaxis for adult patients undergoing elective total knee replacement surgery in the United Kingdom. **Methods:** A stepwise literature search specifically designed to identify indirect evidence was conducted to extend the original clinical review from the latest National Institute for Health and Care Excellence (NICE) VTE technology appraisal. Different network sizes or network orders, based on the successive searches, informed three network meta-analyses (NMAs), which were compared with a replicated base case. The resulting comparative estimates were inputted in an economic model to investigate the effect of network size on cost-effectiveness probabilities. **Results:** Searches increased the number of indirect comparisons between VTE interventions, progressively widening the relevant network of studies for NMA. Precision around mean relative treatment effects was increased as the network was extended from the base case to first-order NMA, but further extensions had limited effect. Cost-effectiveness analysis results were largely insensitive to variation in clinical inputs from the different NMA orders. **Conclusions:** No standard methodology is currently recommended by NICE to identify the most relevant network of studies for NMA. Our study showed that optimizing the identification of studies for NMA can extend the evidence base for analysis and reduce the uncertainty in relative effectiveness estimates. Although in our example network extensions did not affect the acceptability of available treatments in VTE prevention based on cost-effectiveness results, it may in other applications.

Keywords: evidence synthesis, indirect treatment comparison, network meta-analysis, relative effectiveness, venous thromboembolism.

Introduction

The quantitative synthesis of clinical data is a key and often necessary step to the relative effectiveness assessment of medical interventions both premarket and postmarket launch. Meta-analysis is widely used to combine results from multiple clinical studies and considered best practice by many regulatory and health technology assessment bodies in Europe and worldwide [1]. The potential advantages, as well as standard methodology for conducting meta-analysis, are well established in the scientific community with acknowledged guidelines by the Cochrane Collaboration and the Centre for Reviews and Dissemination [2,3]. Recent statistical developments are extending this analytical approach to networks of studies, synthesizing evidence from both direct and indirect treatment comparisons [4–6].

When no head-to-head trial is available, studies evaluating A versus B and B versus C can be used to compare A and C indirectly using network meta-analysis (NMA). Indirect comparisons must be connected by at least one common comparator, that is, treatment B. Additional intermediate links may be required to connect two treatments of interest, thereby increasing the degree of "removal" or "separation" between comparisons and decreasing the degree of influence on the analysis [7]. A number of methodological concerns have been raised when extending an evidence base to include indirect comparisons within a network of studies such as how to best identify indirect evidence. The ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices published guidance on how to conduct NMA and recommended Hawkins et al.'s iterative search strategy to identify indirect evidence [7,8]. Although this search methodology can maximize the NMA network by efficiently identifying indirect evidence, authors warn that if more than a few links separate treatments (e.g., A and C), results may be unreliable. Additional links can provide useful information but may also increase between-study heterogeneity, uncertainty around estimates, and inconsistency between direct and indirect comparisons [7–9]. We carried out a case study to evaluate the

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effect of study identification methods and network size on indirect treatment comparisons for the prevention of venous thromboembolic events (VTEs) after total knee replacement (TKR) surgery.

The use of pharmacological, as well as mechanical, prophylaxis for VTE—deep vein thrombosis (DVT) and/or pulmonary embolism—after elective orthopaedic surgery is common practice in the United Kingdom. In 2010, the National Institute for Health and Care Excellence (NICE) published a clinical guideline on reducing the risk of VTE in patients admitted to hospital; at that time, five drugs were recommended: dabigatran etexilate, fondaparinux sodium, low molecular weight heparins, rivaroxaban, and unfractionated heparin for patients with renal failure [10]. Based on relative effectiveness estimates compared with these existing medicines, apixaban was also recommended in 2012 by NICE for use in adult patients scheduled for elective total hip or knee replacement [11]. These drugs were evaluated over time in single technology appraisals and all shown to be cost-effective for their given indication [11–13].

Objectives

We built on the latest NICE VTE technology appraisal TA245 for apixaban [11] to reanalyze the relative effectiveness and cost-effectiveness of recommended pharmacological VTE prophylaxis for adult patients undergoing elective TKR surgery in the United Kingdom using NMA. We sought to evaluate the effect of different network sizes on decision making for VTE prevention.

Methods

Literature Review

A stepwise systematic literature review was conducted in MEDLINE, Medline-in-Process, OLD Medline, EMBASE, and the Cochrane Library in October 2012 to identify relevant studies. The searches were replicated using the reported search strategies for the apixaban appraisal clinical review and adapted using Hawkins et al.'s [7] breadth-first search methodology presented in Table 1 [11,14,15].

Breadth-first searching is based on graph theory; it is an uninformed or "naive" search process that aims to exhaustively search a sequence or a combination of sequences from a "root" node on a graph to all "neighboring" nodes without considering a final limit until it is reached. A parallel can be drawn between nodes on a graph to interventions on a network map and the need to identify all common comparators within a network without knowing the final size or shape of the network. Hawkins et al. [7] refer to search "orders" and associated search comparators to describe each sequential step in the breadth-first search. Treatments directly compared with first-order comparators following first-order searches become second-order comparators, and so on. The sequence of searches in Table 1 progressively include first-, second-, and third-order comparators, allowing us to identify all trials contributing to a network of evidence, until no further comparators are identified. From the set of identifiable trials, all relevant indirect comparisons are also identified at any given order.

Table 1 – Breadth-first search strategy.

Search order	Search iteration	Search comparators
1	i	All first-order comparators *except one*
	ii	First-order comparator previously omitted
2	iii	All second-order comparators *except one*
	iv	Second-order comparator previously omitted
3	v	All third-order comparators *except one*
	vi	Third-order comparator previously omitted

Note. Adapted from Table 1 of Hawkins et al. [7].

In accordance with Hawkins et al. [7], searches were divided further for each order. In Table 1, search orders are numbered 1 to 3 and searches within each order i to vi. For example, in the first-order searches, all but one first-order comparator are included in the search terms (cf. search (1i) in Table 1). The omitted comparator is searched separately in a subsequent search iteration to ensure that all trials including one or more first-order comparators are captured and all possible second-order comparators identified (cf. search (1ii) in Table 1). Search (1i) will identify all trials comparing more than one of the first-order treatments, thus identifying any direct head-to-head evidence, albeit one of the treatments is not included in the search syntax. If the objective is to capture only first-order (i.e. direct) comparisons, the subsequent search (1ii) of the omitted comparator is not required. In this instance, dividing the search into two steps has the potential to reduce the search burden if a particular comparator is associated with a large number of hits. Hawkins et al. [7] thus recommend omitting a widely used comparator such as placebo or best supportive care; however, this is arbitrary. If further search orders are conducted and abstracts reviewed, search (1ii) is redundant and each order comparators could be searched at once. First-order comparators can be arbitrarily selected within or outside the original scope of searches and include treatments not of interest for appraisal. Moreover, study selection is intentionally broadened to include all clinical trials evaluating a first-order comparator without a restriction on comparator criteria, allowing for treatments that may not fall within the scope for appraisal, such as unlicensed drugs, nonrelevant treatments for decision making, or nonpharmacological interventions, to contribute to the network of evidence.

Studies were selected at the abstract and publication level on the basis of the indicated population for TKR and restricted to prospective, phases II to IV randomized controlled trials. To replicate the search conditions and provide comparable model results to the original technology appraisal, abstracts were further restricted by date to studies published before September 2011 and to English language. Date restrictions were included in the search strategy and exclusion of non-English abstracts and publications took place during the screening phase.

Network Meta-Analysis

Network sizes were based on the studies selected following each search order, thereafter referred to as first-, second-, and third-network orders. The base case was defined a priori in the apixaban appraisal from three pivotal phase III clinical trials comparing apixaban 2.5 mg/bd, dabigatran etexilate 220 mg/qd, and rivaroxaban 10 mg/qd to enoxaparin 40 mg/qd, respectively [16–18]. In accordance with the submitted apixaban economic model [14], these interventions form the decision space for VTE prevention after TKR and are routinely used in clinical practice in the United Kingdom. A comparison with fondaparinux was not considered relevant by manufacturers or the evidence review