VALUE IN HEALTH 18 (2015) 234–249

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/jval

Comparative Effectiveness Research/Health Technology Assessment (HTA)

Critical Appraisal of Network Meta-Analyses Evaluating the Efficacy and Safety of New Oral Anticoagulants in Atrial Fibrillation Stroke Prevention Trials

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ABSTRACT

Objectives: To critically appraise published network meta-analyses (NMAs) evaluating the efficacy or safety of the new oral anticogulants (NOACs) dabigatran, rivaroxaban, and apixaban for the prevention of stroke in patients with nonvalvular atrial fibrillation (AF). **Methods:** A systematic literature review was performed to identify the relevant NMAs using MEDLINE, EMBASE, Cochrane Library, Database of Abstracts of Reviews of Effects, and Health Technology Assessment. The synthesis studies were evaluated using the "Questionnaire to assess the relevance and credibility of the NMA." **Results:** Eleven NMAs evaluating NOACs among adults with nonvalvular AF were identified. Most NMAs included three large phase III randomized controlled trials, comparing NOACs to adjusted-dose warfarin (Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY], Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [ROCKET-AF], and Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation [ARISTOTLE]). The main differences identified related to potential treatment effect modifiers regarding the mean time spent in therapeutic range (TTR) in the warfarin arm, the risk of stroke or systemic embolism across the trials (mean $CHADS_2$ score: C = congestive heart failure, H = hypertension, A = older than age 75 years, D = diabetes mellitus, S2 = prior stroke or history of transient ischemic attack) or primary versus secondary prevention, and type of populations used in the analysis. Kansal et al. [Kansal AR, Sharma M, Bradley-Kennedy C, et al. Dabigatran versus rivaroxaban for the prevention of stroke and systemic embolism in atrial fibrillation in Canada: comparative efficacy and cost-effectiveness. Thromb Haemost 2012;108:672–82] appropriately adjusted the ROCKET-AF TTR to match the RE-LY population on the basis of individual patient data. Meta-regressions are not expected to minimize confounding bias given limited data, whereas subgroup analyses had some impact on the point estimates for the treatment comparisons. **Conclusions:** Results of the synthesis studies were generally comparable and suggested that the NOACs had similar efficacy, although some differences were identified depending on the outcome. The extent to which differences in the distribution of TTR, $CHADS_2$ score, or primary versus secondary prevention biased the results remains unclear.

Keywords: atrial fibrillation, network meta-analysis, new oral anticoagulant, systematic review.

Introduction

Atrial fibrillation (AF) is the most common chronic cardiac rhythm abnormality. The worldwide prevalence of AF is 1% to 2% overall [1], but it increases with age to up to 17.8% among those 85 years or older [2]. AF is associated with a fivefold increase in the risk of a stroke [3] and leads to a 30-day stroke mortality of 24% in the absence of treatment [4]. Patients with AF who experience a stroke are at a higher risk of mortality, morbidity, disability, and longer hospital stays than are patients with stroke without AF [5].

Stroke prevention is the main goal for managing patients with AF. The vitamin K antagonist warfarin has long been the mainstay of treatment to prevent stroke in patients with AF [6,7]. However, it is associated with bleeding complications, as well as several food and drug interactions, and therefore requires coagulation monitoring for dose adjustments to maximize the amount of time spent in therapeutic range (TTR) of international normalized ratio (2–3) [8–12]. These limitations have restricted the use of warfarin [13] and have led to the development of new oral anticoagulants (NOACs), which provide predictable

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1098-3015$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2014.10.012

anticoagulation using a fixed-dose administration, thereby eliminating the need for routine monitoring.

Dabigatran etexilate (dabigatran), a reversible direct thrombin inhibitor, was the first NOAC approved on the basis of a landmark study in 2009 (Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY] [14,15]). Two additional large randomized controlled trials (RCTs) assessing the orally administered directly activated coagulation factor Xa inhibitors rivaroxaban and apixaban were recently published (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [ROCKET-AF] [16] and Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation [ARISTOTLE] [17]). These trials demonstrated that each NOAC was noninferior or superior to warfarin for the prevention of stroke among patients with nonvalvular AF and was comparable or more favorable in terms of major bleeding complications, which led to the approval of these drugs in the United States and Europe.

For decision makers to assess the comparative efficacy and safety of the alternative NOACs in the absence of a head-to-head RCT comparing these treatments, an indirect treatment comparison or network meta-analysis (NMA) using warfarin as a common comparator can be performed. NMA is an extension of pairwise meta-analysis and includes multiple different pairwise comparisons assessed in RCTs, in which each RCT has at least one intervention in common with another trial [18–21]. Health technology assessment agencies are increasingly using these methods [22–25]. Despite the limited number of phase III RCTs evaluating NOACs for stroke prevention among patients with AF, numerous (network) meta-analyses have been published. Given the increasing number of NMAs [26], it is increasingly important to assess whether synthesis studies provide a fair reflection of the existing evidence base, whether they include reasonable and adequately justified assumptions, and whether they are a reasonable basis for decision making [27]. Therefore, the aim of this study was to critically appraise the published NMAs evaluating the efficacy or safety of the NOACs dabigatran, rivaroxaban, and apixaban for the prevention of stroke in patients with nonvalvular AF, using a questionnaire to assess the relevance and validity of NMAs recently developed by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) [28].

Methods

Identification and Study Selection

A systematic literature search of MEDLINE, MEDLINE In-Process, and EMBASE databases from inception to November 2012 (see Search strategy in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2014.10.012 for search terms) was performed. The Cochrane Library, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment publications were also searched using a simplified strategy. The relevance of each citation identified was based on title and abstract (or full-text article) according to the following selection criteria predefined in a protocol:

1. *Population*: Adults aged 18 years and older with nonvalvular AF.
2. *Interventions*: NOACs, including dabigatran, rivaroxaban, and apixaban.
3. *Comparators*: NOACs, warfarin, anticoagulants, antiplatelets, direct thrombin inhibitors and factor Xa inhibitors, or placebo.
4. *Outcomes*: Stroke or systemic embolism (SE), myocardial infarction (MI), overall mortality, cardiovascular (CV) death, major hemorrhage, and intracranial hemorrhage.
5. *Study design*: NMA of RCTs.

Full-text publications in English, French, and German were obtained and reference lists were hand searched. The NMAs included in the systematic review will be referred to as "synthesis studies."

Data Extraction of Synthesis Studies

For each synthesis study, details were extracted regarding the research question, method of review and synthesis, method to identify and evaluate potential treatment effect modifiers, results and conclusions for outcomes of interest, and conflicts of interest.

Critical Appraisal of Synthesis Studies

Each synthesis study was critically appraised using the "Questionnaire to assess the relevance and credibility of a network meta-analysis" [28]. Questionnaire items related to the relevance of the studies or the usefulness of the NMA to inform health care decision making were not scored but can be assessed by each decision maker on the basis of information summarized. The questionnaire items related to the validity of the analysis were scored with yes/no/not reported and discussed in a narrative summary.

Results

Identification and Study Selection

The database search identified 833 records, and a hand search identified an additional 10 records [29–38] (Appendix Figure 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2014.10.012 illustrates the selection process). Meta-analyses were not of interest, even if considering NOACs of interest as a class versus warfarin [29,32,33,35,39–41], because decision makers are faced with a choice regarding the individual NOACs and differences between NOACs in terms of the mode of action, pharmacology, pharmacokinetics, and drug interactions suggest that they should be regarded as distinct treatments [42]. Eleven synthesis studies were identified that combined RCTs using an NMA evaluating one or more of the NOACs of interest among adults with nonvalvular AF [31,34,36,43–50]. The Evidence Review Group report by Spackman et al. [37] related to the publication by Roskell et al. [48], which was used as the primary source.

Summary of the Synthesis Studies

All synthesis studies were based on RCTs that included adults with nonvalvular AF and evaluated dabigatran (n = 11), rivaroxaban (n = 10), and apixaban (n = 8) against adjusted-dose warfarin. Both doses of dabigatran (dabigatran 110 mg and dabigatran 150 mg) were included in the synthesis studies with the exception of Edwards et al. [34], which excluded dabigatran 110 mg. Two synthesis studies also included ximelagatran (Edwards et al. [34] and Roskell et al. [48]), which reflects an NOAC that is no longer approved because of safety concerns and therefore is not relevant for the decision problem. Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2014.10.012 summarizes the outcomes assessed, which included overall mortality, stroke or SE, and MI most commonly. A summary of the questionnaire items is presented in Table 1, and the main differences and similarities are discussed in the following sections.

Evidence Base Used in the Synthesis Studies

Methods used by the synthesis studies to identify and select RCTs

A systematic literature review to identify the relevant RCTs was performed by all synthesis studies except for four studies