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A literature review to evaluate the economic value of ranolazine for the symptomatic treatment of chronic angina pectoris

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ABSTRACT

To conduct a systematic review of the evidence regarding the economic value of ranolazine relative to standard-of-care (SOC) for the treatment of symptomatic chronic stable angina (CSA).
Electronic databases were searched using relevant keywords. The identified studies were independently reviewed by two investigators against pre-determined inclusion and exclusion criteria. Their data were extracted using a relevant form and consequently were synthesized. Studies were also evaluated using the Quality of Health Economic Studies scale. The main outcomes considered were the cost and effectiveness for each comparator and the incremental cost per quality-adjusted-life year (QALY) gained.
Six studies were included in the review. Five of these assessed the cost-utility of ranolazine added to SOC, compared to SOC alone, using decision trees or Markov models whereas one was a retrospective cost evaluation study. The analysis was conducted from a payer perspective in five studies and from a societal perspective in one study with the time horizon varying between six months and a year. The incremental cost-effectiveness ratio (ICER), ranged from €4000 to €15,000 per QALY gained. Ranolazine appears to be dominant or cost-effective, mainly due to its ability to decrease angina-related hospitalizations and also due to a marginal improvement in quality of life. The acquisition cost of ranolazine was the variable with the greatest impact upon the ICER. The existing evidence, although limited, indicates that ranolazine may be a dominant or cost-effective therapy option, for the treatment of patients with symptomatic CSA. Further research is required to evaluate the cost-effectiveness of ranolazine.

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1. Background

Stable angina is the most common manifestation of coronary heart disease. The condition exerts a major impact on quality of life and ability to work [1] and is associated with an increase of the risk of cardiovascular events, as events in this population are higher than those observed in the general population, with average annual mortality rates reaching 1 to 2% [2]. Despite the remarkable advances in cardiovascular therapeutics in recent years and the declining incidence of myocardial infarction, the prevalence of chronic stable angina (CSA) in the industrialized world is considerably high, although it varies significantly throughout populations [1,3,4].

In the USA, its prevalence was estimated at 7.8 million people (3.2% of the population) [5] and in European populations, it reaches 10% to 20% in patients aged >70 years [1]. Hemingway et al., (2008) reported higher prevalence in women than in men (pooled sex ratio: 1.20) [6]. The annual rates per 1000 population of new episodes of CSA for non-black men have been estimated at 28.3 for those aged 65–74 years, 36.3 for those aged 75–84 years, and 33.0 for those aged > = 85 years [5]. Finally, the fact that patients with CSA present increased morbidity and hospitalizations increases the economic cost of ischemic heart disease for the health payers. In USA, direct costs for CSA have been estimated up to $75 billion, in 2000 [7].

In this context, it is clear that the appropriate management of chronic stable angina is important both for clinical and economic reasons. Effective treatment of chronic stable angina should aim towards reducing or ideally abolishing symptoms and improving quality of life and prognosis. Lifestyle changes, pharmacological therapy and revascularization procedures have important roles in the management of stable angina [1,8,9]. The current standard-of-care (SOC) pharmacological treatment of CSA, in Europe, comprises the use of beta blockers (BBs), calcium channel blockers (CCBs) and short-acting nitrates [10]. Nonetheless, despite the aggressive use of conventional anti-anginal therapies, many patients experience persistent angina [11,12]. Long acting nitrates, ivabradine, nicorandil and ranolazine can be added to SOC, as a second line treatment. Event prevention agents, such as

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antiplatelets, lipid – lowering agents, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are also recommended for the treatment of CSA [10].

According to the European Medicines Agency (EMA), ranolazine is indicated as an add-on therapy for the treatment of adult patients with symptomatic CSA, who are inadequately controlled or are intolerant to first-line anti-anginal therapies, such as BBs and/or CCBs [13]. In patients with ischemic heart disease, the use of ranolazine has been evaluated in several randomized, placebo-controlled trials, which overall are comprising data from 8129 patients, including: MARISA [14], ERICA [15], CARISA [16], TERISA [17], and MERLIN-TIMI 36 [18]. All the above studies confirm the anti-ischemic effects of ranolazine when added to BBs and CCBs [14–17] and the significant reduction in recurrent ischemia [18].

A combination of increased therapeutic options, over a range of clinical areas, coupled with limited health care budgets, has led to the need of efficient use of scarce resources and to the search for optimizing the relationship between costs and results. Economic evaluation studies help decision-makers to select more efficient options (with a good cost/effect relationship), aiming to maximise patient benefit within available health care budgets [19]. Ranolazine has been extensively studied in terms of both costs and health benefits. The primary objective of the present review was to systematically examine, synthesize and present the available evidence on the economic value of ranolazine, in adult patients with poorly controlled angina.

2. Materials and methods

The present systematic review was conducted using the methodology developed by the Centre for Reviews and Dissemination (CRD) at the University of York [20], to search, retrieve, appraise and synthesize findings from a range of different studies. This methodology is recommended as a good practice by agencies such as the National Institute for Health and Clinical Excellence (NICE) and is in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [21].

2.1. Search Strategy

In order to identify all published studies investigating the pharmacoeconomic value of ranolazine in patients with CSA, the following electronic databases were searched: Medline, Cochrane Library, and the Cost – Effectiveness registry, without any time limits. The following keywords on the title and abstract were used: economic evidence related (i.e. cost, economic), drug related (i.e. ranexa, ranolazine), angina pectoris related (i.e. angina, coronary). These three categories were combined by the Boolean 'AND' and the terms utilized within these search categories were combined by the Boolean 'OR'. The Medical Subject Headings (MeSH) database was used for identification of synonyms. Appendix 1 illustrates the full search strategy used for MEDLINE, which was adapted appropriately for the rest of databases.

Additionally, the reference lists of all relevant articles originally selected for inclusion in the review and relevant reviews were also searched manually to identify potentially relevant articles that were not identified by the original electronic search. Finally, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) database for abstracts was searched with the aforementioned keywords and one abstract was retrieved [22] which, in turn, was excluded since substantial information on methodology and effectiveness was lacking.

2.2. Study Selection

Following the literature search, identified studies were checked to exclude duplicates. Remaining articles were independently screened by two researchers (K.V. and G.K.) to identify studies that met the predetermined inclusion criteria, presented in Fig. 1. A two-stage study selection process was followed. Initially, all the identified studies were evaluated on the basis of titles and/or abstracts against the eligibility criteria. Rejected studies fell into two main categories: those that were clearly not relevant for the review and those that, although they addressed the topic of interest, failed to meet one or more inclusion criteria, for instance the abstract being in English.

In the second stage, when the information provided in titles/abstracts was insufficient to decide on inclusion/exclusion or when the titles/abstracts indicated that the specific studies met the inclusion criteria, the full articles were retrieved for further screening. In cases where the amount of information reported in the full text continued to be insufficient to make a decision about inclusion, the studies were excluded. Finally, a check for double reporting of research results among the selected studies was undertaken to ensure that duplicates were not included. The study selection process is documented through the flow chart showing the number of studies/articles considered at each stage.

2.3. Data Extraction

The aforementioned researchers independently extracted data using a standardized data extraction form, which was developed for the purposes of the review. Potential disagreements in data extracted from the two reviewers were resolved by consensus among researchers. This extraction form was designed to capture the characteristics and the results of the studies considered in a systematic way. It included general information regarding the authors, publication year, the type of analysis, the country concerned, the sample size, participant characteristics (i.e. type of patients, age, if any subgroups), the perspective, and the time horizon of the analysis undertaken. Moreover, data were extracted regarding the model (if any) used in the analysis, its type, the cycles and health states (if available), the comparison groups, and the efficacy outcomes assessed, such as: angina frequency, hospitalization rate, revascularization rate, quality of life. Information on the resources assessed, the costing methodologies (if available), and cost data used was also extracted. The main outcomes of interest were related to the mean and incremental health and economic outcomes alone and the incremental cost – effectiveness ratio (ICER). Finally, results of any sensitivity analysis (deterministic and probabilistic), if conducted, were also extracted and the funding source of each study was recorded. The consistency of the data extracted was assessed to make sure that the reviewers were interpreting the forms, the draft instructions and the decision rules about coding data, in an identical way, in order to reduce data extraction discrepancies and errors.

2.4. Data Synthesis

In this narrative systematic review, the results reported in primary research are summarized in a qualitative manner and any meta-analysis has not been conducted. Relevant available data are synthesized and presented in a systematic manner, on grounds of the review question and the inclusion and exclusion criteria. In turn, the quality of the studies was critically appraised with the use of established standards.

2.5. Quality Assessment

The two reviewers independently assessed each of the studies to determine whether they met the pre-specified quality criteria. Reviewers were not blinded to study identifiers (e.g. author names, institutions, journals). The quality of studies evaluating the pharmacoeconomic value of ranolazine was assessed using the Quality Health Economic Scale (QHES) [23] which is used to appraise the health economic evaluation studies. The QHES comprises of 16 criteria, each of which has a weighted point value. The quality score for a study can be calculated by adding up all of the points for questions answered "yes", with

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