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Efficacy and safety of antithrombotic regimens after coronary intervention in patients on oral anticoagulation: Traditional and Bayesian meta-analysis of clinical trials

Jian Liu [a,1], Meida Fan [b,1], Jingjing Zhao [a], Bingcheng Zhao [c], Chongyu Zhang [a], Chen Liu [a], Yugang Dong [a,*]

[a] Department of Cardiology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, China
[b] Department of Rheumatology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, China
[c] Department of Anesthesiology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, China

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ABSTRACT

Objective: To perform a systematic review and meta-analysis to assess the efficacy and safety of diverse antithrombotic regimens in patients on long-term anticoagulation after percutaneous coronary intervention (PCI).
Methods: After searching electronic database (up to 27 June 2015), we included trials comparing dual antiplatelet therapy (aspirin plus clopidogrel), oral anticoagulant (OAC) plus clopidogrel, OAC plus aspirin, or triple therapy (OAC with clopidogrel and aspirin). Efficacy outcomes were major adverse cardiovascular event (MACE), ischemic stroke, myocardial infarction (MI), and all-cause mortality; safety outcomes included major bleeding and any bleeding. We conducted both traditional and Bayesian network meta-analysis, computing pooled odds ratio (OR) with 95% confidence intervals (CI) to compare diverse antithrombotic therapies simultaneously.
Results: Eighteen trials were included in the quantitative analysis. OAC plus clopidogrel and triple therapy were associated with a lower risk of MACE, ischemic stroke, MI and all-cause mortality compared with dual antiplatelet or OAC plus aspirin regimens. OAC plus clopidogrel was ranked the most efficacious option without an increase in bleeding episodes. However, triple therapy improved the efficacy outcomes at the expense of increasing hemorrhage. For the initial short-term outcomes, OAC plus clopidogrel inconclusively reduced the risk of MACE and had a significantly lower risk of any bleeding.
Conclusions: OAC plus clopidogrel may be the optimal antithrombotic therapy in patients on oral anticoagulation undergoing PCI, which has equal or better efficacy outcomes without increasing the rates of bleeding episodes. Moreover, we found initial triple therapy to be unnecessary as it increased the risk of bleeding.

1. Introduction

Current guidelines recommend dual antiplatelet therapy (DAPT) with aspirin and clopidogrel in patients undergoing percutaneous coronary intervention (PCI) for thromboprophylaxis [1,2]. However, approximately 10% of the patients undergoing PCI suffer atrial fibrillation (AF), prosthetic heart valves, systemic/venous thromboembolism or other conditions, which require long-term oral anticoagulants (OAC), resulting in a combination of DAPT and OAC [3]. Nevertheless, this regimen, also known as triple therapy, is associated with a high annual risk (4–16%) of bleeding episodes, which are consistently linked with hospitalization, increased morbidity and death [4–7]. Antithrombotic strategies remain problematic under this circumstance. Recently, several registries [8–11] and the *What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting* (WOEST) [12] study have demonstrated that OAC plus clopidogrel may be of superior safety than triple therapy without reducing efficacy. Thus, we performed a systematic review and meta-analysis to quantify, summarize, and compare the efficacy and safety of various antithrombotic regimens after coronary intervention in patients on long-term oral anticoagulation.

2. Methods

2.1. Literature search and study selection

We searched the electronic database of PubMed, Embase and the Cochrane Library database (from inception until 27 June 2015) without restrictions on language, publication year, or type of publication. The systematic search strategy is described in Appendix S1 in the supplementary material. In addition, references of included studies and narrative reviews were manually searched for potential studies. Two investigators (J.L, M.D.F) assessed reports for eligibility. Included studies

* Corresponding author at: Department of Cardiology, The First Affiliated Hospital of Sun Yat-sen University, 58 Zhongshan Road 2, Guangzhou 510080, China.
E-mail address: dongxg@mail.sysu.edu.cn (Y. Dong).
[1] Jian Liu and Meida Fan contributed equally to the manuscript.

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met the following criteria: (1) patients with an indication for long-term oral anticoagulation undergoing PCI; (2) studies comparing dual therapy (DAPT, OAC plus clopidogrel, or OAC plus aspirin) with triple therapy; (3) clinical follow-up duration no less than 4 weeks; and (4) studies reporting the outcomes of interest (*see below*). Studies were excluded if met any one of the following criteria: (1) duplicate publication (latest report was selected in that case); (2) ongoing/unpublished studies; and (3) less than 30 patients per trial arm.

2.2. Data extraction and quality assessment

Two investigators (J.L, M.D.F) independently extracted data and appraised studies, with divergences resolved by consensus. Data were extracted for each eligible clinical trial on study design, patient characteristics and outcomes. Major adverse cardiovascular event (MACE), ischemic stroke, myocardial infarction (MI), and all-cause mortality were evaluated as efficacy outcomes; major bleeding and any bleeding were applied as safety endpoints. We accepted the outcome definitions adopted by the original articles though there were slight differences across trials. The corresponding authors of studies were contacted if original outcomes could not be extracted from the published article. The methodological quality of observational trials was appraised by the Newcastle-Ottawa scale [13], which consists of three factors: patient selection, comparability of the study groups, and assessment of outcome. The methodological quality of randomized controlled trials (RCT) was assessed by the Cochrane Collaboration's tool for assessing risk of bias [14]. A score of 0–9 stars was allocated to each study except RCTs. RCTs and observational studies achieving six or more stars were considered to be of high quality.

2.3. Data synthesis and analysis

We performed traditional meta-analysis using RevMan version 5.3.3 (Cochrane Collaboration, Nordic Cochrane Centre, Denmark). The odds ratios (OR) and the correspondent 95% confidence intervals (CI) were calculated for various antithrombotic regimens. Heterogeneity between studies was evaluated using I^2statistics [14] ($I^2 > 50\%$ was considered heterogeneous).

Meanwhile, we conducted Bayesian network meta-analysis using winBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) and Stata 12.0 (StataCorp LP, College Station, TX) on all available treatment comparisons to provide the most comprehensive evidence. The binomial likelihood model for multi-arm trials was used, allowing for synthesis of direct and indirect evidences by incorporating the indirect comparisons from trials having one treatment in common. Our model adopted a random effect rather than a fixed effect model as it is perhaps the most appropriate and conservative analysis to account for variance among studies. We estimated odds ratios (OR) and corresponding 95% credible intervals (CrI) from the 2.5th and 97.5th centiles of the posterior distribution. Furthermore, the probability of being the best for each treatment was estimated based on their ranks in each iteration of Markov chain. Using these probability values, we constructed cumulative probability plots and calculated the surface under the cumulative ranking curve (SUCRA), which simply presents the mean rank [15]. Heterogeneity between studies was defined as variability of results across studies, which was estimated from the posterior median between-study variance τ^2, with $\tau^2 < 0.04$ being interpreted as a low level and $\tau^2 > 0.40$ as a high level [16]. The goodness of fit of the model was assessed using residual deviances. We also evaluated the inconsistency of the network by calculating the ratio of two odds ratios (RoR) from direct and indirect evidence in each closed loop in the network of interventions [17]. Further, meta-regression analysis with prospective versus retrospective trials was performed by calculating the subgroup interaction term β. Additionally, we conducted sensitivity analysis for high quality studies, trials enrolled only atrial fibrillation patients or trials with follow-up duration of 6–12 months.

3. Results

3.1. Study selection and characteristics of included trials

As shown in Fig. 1, a total of 1574 potentially eligible records were identified, of which 1542 were excluded by screening titles and abstracts. Then, the full text of the remaining 32 articles were examined. Notably, five case–control studies were further excluded for including patients undergoing PCI without indication for OAC [18–22]. Eventually, 18 articles (1 RCT [12] and 17 observational registries [5,8–11,23–34]) including a total of 17,708 patients met the inclusion criteria. Two trials were four-arm trials, four trials were three-arm trials while the rest were two-arm trials. The network diagram of treatment comparisons is illustrated in Fig. 2. The included studies evaluated four diverse antithrombotic regimens: triple therapy (18 trials), DAPT (15 trials), OAC plus clopidogrel (6 trials), and OAC plus aspirin (5 trials). Table 1 summarizes the main characteristics of the included trials. Quality assessment of the trials indicated that comparability between groups was the main cause of potential bias in majority of trials.

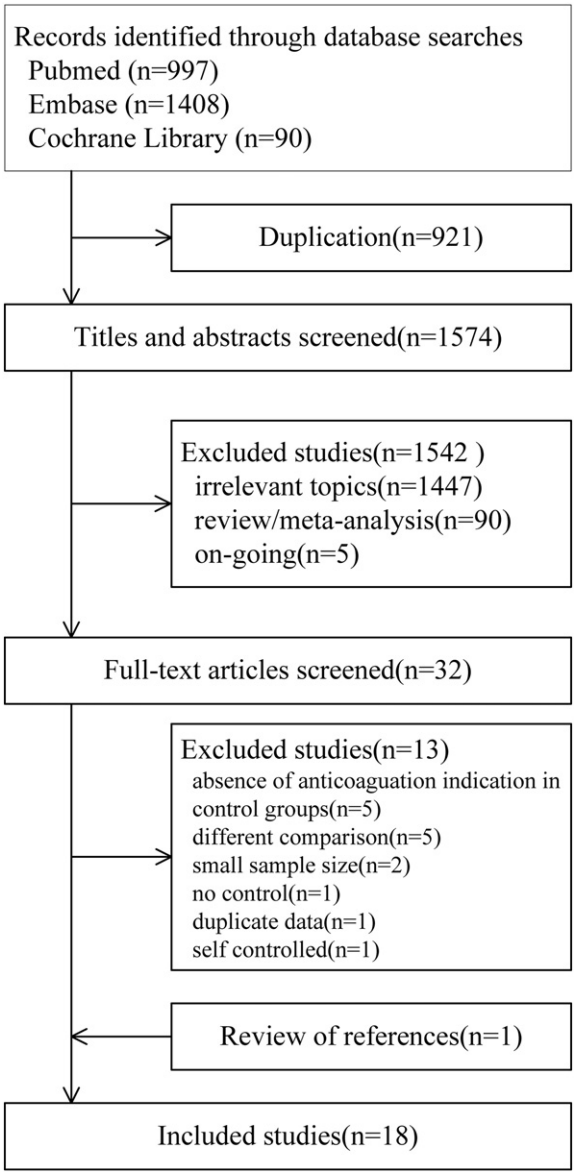

Fig. 1. Flow chart of the selection process.