

British Journal of Medicine & Medical Research 6(2): 173-199, 2015, Article no.BJMMR.2015.194 ISSN: 2231-0614



SCIENCEDOMAIN international www.sciencedomain.org

Adding a New Anticoagulant or Antiplatelet Agent for Patient Receiving Aspirin after an Acute Coronary Syndrome?--Results from a Pairwise and Network Meta-Analysis of Randomized-Controlled Trials

Lan Gao^{1,2} and Shu-Chuen Li^{1*}

¹School of Biomedical Sciences and Pharmacy, The University of Newcastle, Callaghan, NSW, Australia. ²Deakin Health Economics, Population Health Strategic Research Centre, Faculty of Health, Deakin University, VIC, Australia.

Authors' contributions

This work was carried out in collaboration between all authors. Authors LG and SCL designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author LG managed the literature searches, performed the analysis. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/14423 <u>Editor(s):</u> (1) Gaetano Santulli, College of Physicians & Surgeons, Columbia University Medical Center, New York, NY, USA. <u>Reviewers:</u> (1) Pedro Beraldo de Andrade, Invasive Cardiology, Santa Casa de Marília, São Paulo, Brazil. (2) Anonymous, Lausanne University Hospital, Switzerland. Complete Peer review History: <u>http://www.sciencedomain.org/review-history.php?iid=721&id=12&aid=7263</u>

> Received 29th September 2014 Accepted 25th November 2014 Published 15th December 2014

Original Research Article

ABSTRACT

Objectives: To synthesize the efficacy and safety outcomes from randomized-controlled trials (RCTs) regarding new oral anticoagulant, protease-activated receptor-1 (PAR-1) antagonist, and warfarin adjunctive to aspirin for patients after acute coronary syndrome (ACS) via pair-wise and network meta-analyses.

Methods: A comprehensive literature search was performed in Embase, Medline, Cochrane Library Web of Knowledge, and Scopus. The pair-wise meta-analysis was undertaken respectively to each agent/treatment category via Revmen 5.1. In order to estimate the relative efficacy of each agent/treatment category whilst preserving the randomized comparisons within each trial, a

^{*}Corresponding author: Email: ShuChuen.Li@newcastle.edu.au;

Bayesian network meta-analysis was conducted in WinBUGS using both fixed- and random-effects model. Covariate analysis was performed to explore the effects of length of follow-up and age of subject on the final results.

Results: In total, 23 RCTs were included in the meta-analysis. As shown by the results (OR,95%CI) for the pair-wise meta-analysis, new oral anticoagulants (0.85, [0.78, 0.93] and 3.04, [2.21, 4.19]), PAR-1 antagonists (0.80, [0.52, 1.22] and 1.55, [1.25, 1.93]) and warfarin (0.87, [0.74, 1.02] and 1.77, [1.46, 2.14]) might be able to provide better outcome in the incidences of major adverse events (MAE) but with higher bleeding risk comparing to aspirin treatment alone. Based on the model fit assessment, the random-effects model was adopted. The network meta-analysis (treatment effect comparing to aspirin lone) identified ximelagatran (-0.3044, [-0.8601, 0.2502]), dabigatran (-0.2144, [-0.8666, 0.4525]), rivoroxaban (-0.2179, [-0.5986, 0.1628]) and vorapaxar (-0.2272, [-0.81, 0.1664]) produced better improvements in MAE incidences whereas vorapaxar (0.3764, [-0.4444, 1.124]), warfarin (0.663, [0.3375, 1.037]), ximelagatran (0.7509, [-0.4164, 2.002]) and apixaban (0.8594, [-0.0049, 1.7]) produced less major bleeding events. The indirect comparisons among drug category (difference in incidence comparing to aspirin lone) showed new oral anticoagulants (-0.1974, [-0.284, -0.111]) and PAR-1 antagonists (-0.1239, [-0.215, -0.033]) to besuperior to warfarin (-0.1004, [-0.166, -0.035]) in the occurrences of MAE whereas PAR-1 antagonists (0.4292, [0.2123, 0.6476]) afforded better outcomes in major bleeding events against warfarin (0.5742, [0.3889, 0.7619]) and new oral anticoagulants (1.169, [0.8667, 1.485]). **Conclusion:** Based on the study results, we cannot recommend the routine administration of new oral anticoagulant as add-on treatment for patients after ACS. However, for ACS patients comorbid with atrial fibrillation, new oral anticoagulant might be superior to warfarin in both efficacy and safety outcomes.

Keywords: New oral anticoagulant; protease-activated-receptor; randomized controlled trial; network meta-analysis; acute coronary syndrome.

1. INTRODUCTION

Cardiovascular disease is the number one cause of death globally (WHO). In particular, the Global Burden of Disease Study classified ischemic heart disease as the leading cause of global mortality, accounting for 1.4 million deaths in the developed world and 5.7 million deaths in the developing regions [1]. At the same time, antiplatelet therapy is the foundation therapy for the prevention and treatment for arterial thrombosis. Aspirin is known to reduce, by approximately 25%, the risk of any serious vascular accident, with greatest protection among patients with Acute Coronary Syndromes (ACS) [2]. Besides aspirin, clopidogrel [3-6], glycoprotein IIb/IIIa inhibitors [7,8] and new antiplatelet agents [such as prasugrel [9] and ticagrelor [10] are also effective in the management of patients with ACS. However, even with these powerful antithrombotic treatments (deactivation of P2Y12 ADP receptor and TxA2-related activation pathways at the same time), the recurrent ischemic events in ACS patients are still high) with an occurrence of greater than 11% [9,10]. This is in spite of the fact that P2Y12 receptor has a well-established role as antithrombotic agents in treating cardiovascular diseases [11], although the potent

platelet inhibition by P2Y12 receptor might be associated with increased level of miR-223 [12]. Furthermore, a few studies also indicated that some polymorphisms are linked to the action of antiplatelet drugs that might increase the risk of cardiovascular and cerebrovascular events [13,14]; and a series of risk factors has been identified to be associated with the increased risk of acute coronary syndrome [15].

Meanwhile, it was reported that excess thrombin generation persists beyond the acute presentation after an ACS [16]. As a result, anticoagulants have been shown to be as effective as antiplatelet therapy in the long-term management of coronary artery disease [17]. Most importantly, the effectiveness of combination therapy (antiplatelet and anticoagulant) has been demonstrated for both initial and long-term therapy for ACS patients [18].

In recent years, the efficacy and safety of several new oral antiplatelet Thrombin-receptor antagonist, [TRA or protease-activated-receptor [PAR-1] antagonist [19-22]] and anticoagulant agents [23-29] have been assessed in a series of phase II and III clinical trials. While majority of the trials claimsa more desirable improvement in recurrent ischemic events after an ACS, the safety results, primarily the bleeding risks, are not consistent across studies. Furthermore, two meta-analyses of new oral anticoagulants suggested that the increased risk of major bleeding might offset the benefits in reduction of ischemic events [30,31]; while another metaanalysis concluded that new oral anticoagulant may be the optimal antithrombotic regime for patients with ACS [32]. Hence, the inconsistency in the safety outcome needs to be ascertained when adding new antithrombotic agent after an ACS.

Beyond the safety concern, clinicians would also need knowledge on how to choose among these competing antithrombotic agents. Nevertheless, the results from those clinical trials are heterogeneous in terms of different efficacy outcomes or they are under power (e.g. phase II trials) to detect the statistically significant difference. Furthermore, there is no head-tohead comparison between these newly invented antiplatelet and anticoagulant agents. Last but not least, the efficacy and safety of newer generation oral anticoagulants were unanimously investigated based on placebo-controlled trials rather than warfarin-controlled ones. In order to address all these, we performed a pairwise and indirect meta-analysis comparing a series of new antithrombotic agents to ascertain the therapeutic and safety outcomes and to aid clinicians to optimize the treatment for patients with ACS history.

2. METHODS

2.1 Data Sources

We conducted an electronic literature search for all prospective randomized controlled trials evaluating the efficacy and safety of a newly invented anticoagulant or antiplatelet agent for patients receiving aspirin after an ACS in Medline, Embase, Cochrane Library, Web of Knowledge, and Scopus from inception to 25th June 2013. In addition, the reference list of identified articles was manually searched as well. The following key search terms were used: acute coronary syndrome or myocardial infarction, randomized controlled trial or (double-blind) controlled trial with one of the following terms: factor antithrombins, Ха inhibitor, oral anticoagulation, apixaban or edoxaban or darexaban or rivaroxaban or otamixaban, and dabigatran or argatroban or ximelagatran or warfarin or thrombin-receptor antagonist, protease-activated-receptor (PAR-1) antagonist, atopaxar, vorapaxar.

2.2 Inclusion Criteria

- 1. Studies should be reported in English and the full text could be retrieved.
- 2. All participants in the study should be explicitly diagnosed with ACS or at least included a subgroup of patients diagnosed with ACS.
- 3. Double-blind study should contain a placebo-controlled arm.
- 4. Patients were treated with aspirin or plus another thienopyridine.
- Study should at least present the results regarding the Major Adverse Events (a composite of death, severe recurrent ischemia, myocardial infarction, and ischemic stroke) and incidences of major bleeding in each arm.

2.3 Data Extraction

Two reviewers independently extracted the data from each retrieved study. Discrepancy was resolved by thorough discussion and only agreed data were incorporated into the meta-analysis. The primary efficacy outcome was defined as the major adverse events (MAE), including a composite of all cause death, severe recurrent ischemia, myocardial infarction and ischemic stroke. The main safety endpoint was the major bleeding events (MB), according to the definition of each trial. The efficacy outcome was estimated based on Intention-to-Treat population, and the safety outcome assessed on safety population.

2.4 Data Analysis

2.4.1 Direct meta-analysis

Both pairwise and indirect meta-analyses were performed to pool the efficacy and safety data. For the pairwise meta-analysis, given the different drugs and treatment effects, random-effects model was adopted to assess the effect size. The reported event frequencies were used to calculate Odds Ratios (OR) with 95% Confidence Interval (95% Cls). Log odds ratios were pooled with inverse variance weighting. The degree of inconsistency across studies was quantified using the l^2 statistic [33]. The Cochrane Q heterogeneity test (X^2 test) was also applied. These data were reported as l^2 percentages, along with *P* values from the X^2 test. The pairwise meta-analysis was performed via Revman 5.1.

2.4.2 Network meta-analysis

In a network meta-analysis, treatment effects are calculated for all treatments using all available evidence in one simultaneous analysis. This method builds on the principles of indirect comparisons and preserves the randomized comparisons within each trial. Particularly, at first, the models were fitted to the data using the Bayesian Markov chain Monte Carlo simulations, utilizing the WinBUGS 1.4.3 (MRC Biostatistic Unit, Cambridge, UK) via both fixed- and random-effects models. WinBUGS code for network meta-analysis of dichotomous and standard Bayesian random-effects meta-analysis was adapted from code developed by the NICE Decision Support Unit [34].

Since all the clinical trials recruited patients receiving aspirin alone or aspirin plus another thienopyridine at the baseline, all the treatment comparisons could be viewed as anchored on treatment aspirin against another anticoagulant/antiplatelet agent and therefore formed the comparison network, subsequently enabling the indirect comparisons among those drugs. Comparisons were presented throughout aspirin reference treatment usina as (Supplementary Fig. 1).

The likelihood of publication bias was assessed visually by generating a funnel plot for the primary efficacy end point. A *p* value<0.05 was considered statistically significant.

2.4.3 Model fit

Since the mean residual deviances provided an estimate of how well the values predicted by the model fit the observed dataset, for an adequate model fit, the sum of the residual deviances should be approximately equal to the total number of study arms in the observed the dataset. In addition, deviance information criterion (DIC) was recorded by the WinBUGS to appraise the model as well. The model with the lowest value of DIC would best predict a replicate dataset of the same structure as currently observed.

2.4.4 Baseline treatment effect

To assess the absolute effect of each treatment, a baseline model that represents the absolute natural history under a standard treatment in the comparator setting was developed separately. Thus, both the posterior and predictive distributions of baseline treatment effect could be obtained to model the baseline response. It has been reported that predictive distribution for a new baseline incorporates the uncertainty about the value a new observation might take, as well as the observed variation in the data [34]. It is however important to ensure that the uncertainty conveyed by the predictive distribution reflects genuine uncertainty in the baseline. Therefore, the baseline effect was drawn from both posterior and predictive distribution, whereas the results from the predictive distribution were adopted in the subsequent computation.

2.4.5 Effect of covariates

As various follow-up times and ages of subjects in the included RCTs might have influenced on the treatment, these two factors were modelled as covariates in the network meta-analysis. The study-level data were taken into account by the following three constructed models: (I) follow-up times and baseline age of subjects: the model encompassed two study level continuous variables to adjust for the effects they may have. X years was a covariate centred at mean followup across the studies, thus the coefficient βyears estimated the incremental difference (above or below) in (log) treatment effect for each year from the average follow-up across studies. Similarly, the Xage was covariate centred at mean age, such that the coefficient ßage estimated the incremental difference (above or below) in the (log) treatment effect for each year from the average age across studies [35]. (II)Follow-up times: the model only included this variable to adjust for the time point at which the response was measured (in years). (III) Baseline age of subjects: this covariate model included this continuous variable to adjust for differences in patient age across studies. Again, the fixedand random-effects models were both utilized to examine the difference in results.

2.4.6 Indirect comparison between warfarin, new oral anticoagulants and antiplatelet agents (PAR-1 antagonist)

The effect of each treatment category (grouped into warfarin, new oral anticoagulants and PAR-1 antagonists) was first synthesized individually via pairwise meta-analysis. Then the probability that each treatment strategy has the most preferable incidences in terms of MAE or major bleeding was estimated via network meta-analysis using aspirin as the reference treatment. Likewise, the baseline treatment effect was computed based on the afore-mentioned method. Thus, the absolute effect of specific treatment strategy could be calculated subsequently.

3. RESULTS

The electronic literature search identified 356 articles, of which 36 were read in full text after scanning the titles and abstracts. Among these, seven RCTs were for five new oral anticoagulants (apixaban, ximelagatran. rivaroxaban, dabigatran, and darexaban) [23-29], another four investigated two newer antiplatelet agents—PAR-1 antagonists (atopaxar and vorapaxar) [19-22], and 13 compared the therapeutic effects between warfarin add-on to aspirin and aspirin alone [36-48]. Consequently, these 24 RCTs were included in the metaanalysis (Fig. 1). The characteristics of the included studies were presented in Table 1.

3.1 Description of the Included Studies

Publication bias was assessed via the funnel plot, except for PAR-1, the other two antithrombotic agents did not show significant publication biases based on the results of major adverse events (Appendix-Figs. 1 to 3).

Regarding concurrent antithrombotic agents' uses, single antiplatelet therapy with aspirin was allowed in 14 studies [29, 36-48], while the other RCTs recruited patients either on single (aspirin) or dual antiplatelet therapy with aspirin and a thienopyridine [19-28].

For the studies assessing new oral anticoagulants, number of subjects varied from 1279 [28] to 15526 [26], and average age from 57 [25] to 68 years [29]. All the included studies were with at least 6 months of follow-up and recruited more male than female patients. In defining bleeding events, four out of seven studies defined the major bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) [23,27-29] whereas the other three used the definition based on the Thrombosis in Myocardial Infarction (TIMI) Trial [24-26].

Four RCTs investigated the efficacy and safety effect of PAR-1 antagonist (atopaxar and vorapaxar) with sample sized varying from 117 [20] to 12944 [22] and follow-up times ranging from 8 weeks [20] to 502 days [22]. All four studies utilized the TIMI criteria to define the key safety endpoint.

Eleven RCTs assessed warfarin against aspirin alone for ACS patients. Specifically, the number of subjects varied from 57 [47] to 8803 [36] with mean age from 57 [47] to 67 years [45]. The length of follow-up was between 2.5 months [47] and 5 years [43]. Each study defined the major and minor bleeding based on their own criteria (other than TIMI and ISTH).

3.2 Pairwise Meta-Analysis

3.2.1 New oral anticoagulant vs Placebo

For the primary efficacy endpoint, the new oral anticoagulant produced moderately better outcomes than placebo, with OR of 0.85 (95% confidence interval: 0.78, 0.93). However, the major bleeding incidence was considerably higher than the placebo, with OR of 3.04 (95%CI: 2.21, 4.19). No heterogeneity was detected in the efficacy and safety outcomes, with I² of 0% respectively (Table 2).

Except for overall synthesis, we also estimated the OR for each kind of the oral anticoagulant in order to compare with the result from the indirect comparisons where applicable. As a result, the ORs (95% CI) of MAE for individual oral anticoagulant were: ximelagatran 0.74 (0.57, 0.95), apixaban 0.97 (0.85, 1.11), dabigatran 0.80 (0.51, 1.24), rivaroxban 0.81 (0.73, 0.89), and darexaban 1.29 (0.73, 2.28). Likewise, the bleeding profile unanimously favoured placebo against new oral anticoagulant with the ORs varied from 1.75 (95%CI: 0.21, 14.24) for dabigatran to 5.60 (95%CI: 1.67, 18.79) for rivaroxban (Appendix).

3.2.2 PAR-1 antagonist vs Placebo

When comparing the PAR-1 antagonist with placebo, the ORs (95% Cl) for MAE was 0.80 (0.52, 1.22), and MB was 1.55 (1.25, 1.93) respectively. Similarly, the ORs (95% Cl) for each drug were calculated. For atopaxar, the OR was 0.96 (0.52, 1.76) for MAE and 1.02 (0.63, 1.67) for MB; and for vorapaxar, the ORs were 0.56 (0.17, 1.83) and 1.49 (1.35, 1.65) for MAE and MB respectively. Nonetheless, medium heterogeneity was observed for the primary efficacy end point (I^2 =60%) [33] (Table 2).

3.2.3 Warfarin vs Placebo

The pairwise meta-analysis for warfarin showed that the OR for MAE was similar to that for new anticoagulants of 0.87 (95% CI: 0.74, 1.02), while



Fig. 1. Flow diagram of study selection

generating a moderate increase in MB with OR of 1.77 (95%CI: 1.46, 2.14). Again, for the efficacy outcome, medium heterogeneity was detected (I^2 =62%) (Table 2).

3.3 Network Meta-Analysis

3.3.1 Major adverse events

In terms of the absolute effect, both the randomand fixed-effects models showed similar results. More specifically, ximelagatran (ORs: 0.1243 and 0.1227 respectively) afforded the best profile in the incidences of MAE, whereas darexaban (0.1918 and 0.1903 respectively) had the highest occurrences in this outcome. In addition, dabigatran, rivaroxban and vorapaxar also generated lower MAE incidence compared to the other antithrombotic agents from those two models. The comparative effects were consistent with the absolute effects as well. For instance, ximelagatran (-0.3044 and -0.3039), dabigatran (-0.2144 and -0.2173) and rivaroxban (-0.2179 and -0.2161) were superior to darexaban (0.2777 and 0.2788) in lowering the MAE incidences. From the random-effects model, ximelagatran (32.3%) followed by dabigatran (24.0%) might have higher probability than the other drugs in reducing the incidences of MAE.

The total residual deviance and DIC values both favoured random-effects model for the indirect comparisons, with lower values in DIC (365.89) and total residual deviance (57.8) than the fixed-effects model (374.11 and 73.09 respectively) (Table 3).

3.3.2 MB

Both the random and fixed effects models showed darexaban generated the highest risk of major bleeding, whereas vorapaxar followed by warfarin, ximelagatran and apixaban produced improvement for the same outcome. After adjusted for baseline treatment effect, the absolute effect also produced identical results, with vorapaxar having the lowest risk of major bleeding (other than aspirin alone). However, in terms of the total residual deviance and DIC, these two values in the random effects model (mean 44.11 and 262.76) were substantially lower than those from the fixed effects model (51.5 and 265.40), indicating the results from the former model should be adopted. Additionally, except for the aspirin treatment alone, dabigatran (17.0%) and atopaxar (16.8%) might be more likely to have the best profile of major bleeding risk (Table 4).

3.4 Effects of Covariates

3.4.1 Major adverse events

Three models were constructed to investigate the impact of covariate on the MAE incidences. However, the results did not change substantially when adjusted for these factors together or separately. Again, according to the DIC and total residual deviance, the results from the random-effect models should be preferred (Appendix).

3.4.2 Major bleeding

Similarly, the results from the three models did not contradict each other, but unanimously indicated vorapaxar as having the best major bleeding risk profile and darexaban having the highest major bleeding risk. Again, the results favour the random-effects model (Appendix).

Indirect comparison among aspirin, new oral anticoagulants, warfarin and new antiplatelet agents

Results from both absolute and comparative effects favoured new oral anticoagulants and PAR-1 antagonists over warfarin or aspirin alone in terms of MAE. However, the major bleeding incidences showed the PAR-1 antagonist as superior to either new oral anticoagulants or warfarin, with the highest bleeding risk borne by new oral anticoagulants. Though with slightly different results, the DIC and total residual deviance did not vary substantially between random- and fixed-effects models for both MAE and major bleeding results. Both models unanimously showed new oral anticoagulants having the highest probability of being the best (85.4% vs 32.8%) in terms of efficacy end point, and treatment with aspirin alone being the best as to the safety outcome (100% vs 33%) (Tables 5 and 6).

4. DISCUSSION

Overall, both pair-wise and network metaanalyses showed add-on newer antithrombotic agent might be more preferable to aspirin treatment alone but with higher risk of major bleeding. The main findings from the present study were, first, when considering MAE and MB together, vorapaxar and rivaroxban were associated with lower incidences of these two events than the other antithrombotic agents included in the study. Although ximelagatran also showed improved occurrences, the potential liver toxicity refuted its further use in the market [29]. Second, from the indirect comparisons between all the new oral anticoagulants, warfarin and PAR-1 antagonists, the new oral anticoagulants were more likely to decrease the MAE incidences but with highest risk of MB. Alternatively, PAR-1 antagonists were able to lower the occurrences of MAE with lowest risk of MB. Nonetheless, it was worth noting that there was a slight difference in the baseline antiplatelet treatment. For majority of the RCTs, dual antiplatelet treatment was allowed whereas all the studies for warfarin and one RCT for ximelagatran [29] only enrolled subjects on single antiplatelet therapy (aspirin). This would introduce a confounding factor for the final result as it is recommended that all the post-ACS patients should receive dual antiplatelet treatment up to 12 months [49].

Since the absolute effect of each treatment/category in terms of MAE and MB was in the network meta-analysis estimated simultaneously, the risk-benefit analysis could be conducted subsequently. In consistent with the results from the meta-analyses, except for ximelagatran and vorapxar, all the other antithrombotic agents did not achieve a positive net benefit per 10000 ACS patients treated. This revealed the substantial increase in bleeding risk compared to the decrease in MAE when adding the antithrombotic agent to aspirin. Particularly, compared to aspirin alone, each treatment strategy would generate more major bleeding events than the avoided major adverse events (Net bleeding events: 144 for all the new oral anticoagulant, 42 for PAR-1 antagonist and 130 for warfarin per 10000 ACS patients treated). In terms of the MB specifically, the increase in MB incidences varied from 37.6% for vorapaxar to 119% for deraxaban when using aspirin as comparator, which was fairly discouraging. In contrast, the relative increase in annual rate of non-CABG TIMI bleeding events was approximately 25% with the introduction of new P2Y12 ADP-receptor antagonist [9,10]. Since the prognostic significance of bleeding complications is as serious as the occurrence of ischemic events after percutaneous coronary intervention,

these results would partly discourage its future extensive use in the clinical setting.

Covariates exerted little impact on the final results according to the covariate analysis. It is important that network meta-analysis has the underlying assumption that trails and outcomes are sufficiently similar to allow the data to be pooled, and the consistency assumption relies on there being no imbalance in modifiers of relative treatment effects across studies. In our network meta-analysis, the similarity assumption was supported by the inclusion criteria for study selection and also the adjustment of the results by way of covariate analyses for the potential effect modifiers, e.g. length of follow-up, baseline age of subjects. Specifically, the covariate analysis aimed to reduce the impact of any bias due to similarity and/or consistency violations [35]. The results of our covariate analyses showed the assumptions for network metaanalysis were not violated even with different follow-up times and baseline age of subjects across studies.

At present, the use of oral anticoagulants in patients with ischemic heart disease is commonly restricted to individuals at high risk of thromboticcomplications. those embolic with atrial fibrillation. valve prostheses. intracardiac thrombi, recurrent thrombo-embolism, or antiphospholipid syndrome [7,50,51]. As demonstrated in a couple of RCTs, the use of apixaban or dabigatran was associated with a decreased risk for thromboembolic events compared with warfarin or low-molecular-weight heparins [52,53]. Nevertheless, the use of new oral anticoagulant on the top of antiplatelet treatment for patients without aforementioned comorbidities after ACS is not recommended yet [54]. From our present study, the excess bleeding risk of new oral anticoagulant refutes its unrestricted use in combination with other antiplatelet therapy (although ximelagatran vielded a positive net benefit, its liver toxicity has rendered discontinuation of further investigation).

Except for warfarin, it should be noted that the large majority of RCTs were phase II trials (8 out of 11). However, the primary results from the phase II trials were in agreement with the phase III trials for the particular agent. The bleeding incidences in these three large trials were similar to the phase II experiments corresponding to each drug. Furthermore, the bleeding outcomes were also consistent between two phase III trials for apixaban (2.55 [1.48, 4.41]) and rivaroxaban (3.92 [2.43, 6.33]). Even with nominally larger

relative increase in bleeding in rivaroxaban trial [26] than the prematurely discontinued apixaban trial [24], these were substantially greater than the results derived from another phase III trial pertaining to vorapaxar (1.55 [1.24, 1.92]) [22]. Considering the statistical power and longer follow-up of phase III trials, this could be viewed as evidence to support the results from our network meta-analysis.

Since the occurrences of recurrent ischemic events are still strikingly high for patients after ACS even with standard dual antiplatelet therapy. it is imperative to consider more potent antiplatelet/anticoagulant agent to reduce these events. With the availability of newly invented oral anticoagulant and antiplatelet, clinicians would need the evidence to assist them to choose among a variety of options. As efficacy and safety endpoints are of equal importance for this cohort, decision should be made to optimize these two outcomes. From the evidences of our present study, adding an antiplatelet agent (e.g. vorapaxar) would be much better than adding an anticoagulant to improve both the incidences of recurrent ischemic and major bleeding events for patient with ACS history. This is supported by the consistency in results between pairwise and network meta-analyses. For patients with a combination of ACS and atrial fibrillation, where a of anticoagulant combination and dual antiplatelet treatment is currently recommended, the information from our present study might be very helpful. First of all, from our network metaanalysis, it was indicated that ximelagatran, dabigatran and rivaroxaban were superior to warfarin in improving MAE. Additionally, the profile of major bleeding was comparable among ximelagatran, apixaban. rivoroxaban and warfarin. But the new oral anticoagulants are able to provide more reliable effect without the need for laboratory monitoring, and might be an ideal replacement of warfarin. Hence, for ACS patient comorbid with atrial fibrillation, new oral anticoagulant like dabigatran, apixaban and rivoroxban might be more appropriate to be prescribed.

However, several study limitations needed to be addressed. Firstly, large numbers of studies were excluded due to shorter follow-up times and small sample size. Second, lack of head-to-head comparisons between the included agents also necessitates caution in interpretation of our results. Third, the definitions of MAE and major bleeding events were heterogeneous across studies, which may explain the heterogeneity of efficacy endpoint in the pair-wise meta-analysis.

| Study | Design of trial | Follow-up | Drugs | Number of subjects | Baseline age | Male (%) | Aspirin use/ thienopyridine use | Definition of composite Ischemic events | Definition of major bleeding events |
|-------------------------------|--------------------|-----------------------|---|-----------------------|-----------------|-------------|------------------------------------|--|---|
| Wallentine et al. 2003 | Phase II | 6 months | Ximelagatran 24, 36, 48, or 60 mg bid or placebo | 1900 | 60.7 | 68 | 100/0 | MI, severe recurrent ischemia, overall mortality | ISTH major and clinically relevant non-major bleeds |
| Mega et al. 2009 [25] | Phase II | 6 months | Rivaroxban 5 mg od, 5 mg bid, 10mg od or placebo | 3462 | 57.4 | 77 | 99.0/80.7 | MI, stroke, severe recurrent ischemia, overall mortality | TIMI clinically significant bleeding |
| Mega et al. 2012 [26] | Phase III | 13 months | Rivaroxban 2.5 or 5 mg bid or placebo | 15526 | 61.5 | 75 | 98.6/92.8 | MI, stroke, cardiovascular mortality | TIMI clinically significant bleeding |
| Alexander et al. 2009 [23] | Phase II | 6 months | Apixaban 2.5 mg bid, 10mg od or placebo | 1715 | 60.7 | 76 | 99.7/75.7 | MI, severe recurrent ischemia, ischemic stroke, cardiovascular mortality | ISTH major and clinically relevant non-major bleeds |
| Alexander et al. 2011 [24] | Phase III | 8 months | Apixaban 5 mg (or 2.5 mg) bid, or placebo | 7392 | 67.0 | 68 | 97.0/65.1 | MI, ischemic stroke, cardiovascular mortality | TIMI major bleeds and ISTH major and clinically relevant none- major bleeds |
| Oldgren et al. 2011 [27] | Phase II | 6 months | Dabigatran 50, 75, 110 or 150 mg bide or placebo | 1878 | 61.2 | 76 | 98.7/83.8 | MI, non-haemorrhagic stroke, overall mortality | ISTH major and clinically relevant non-major bleeds |
| Steg et al. 2011 [28] | Phase II | 6 months | Darexaban 5, 15 or 30 mg bid, or 10, 30 or 60 mg od, or placebo | 1279 | 56.9 | 80 | 100/96.6 | MI, stroke, severe recurrent ischemia, overall mortality | ISTH major and clinically relevant non-major bleeds |
| Goto et al. 2010 [19] | Phase II | 16 weeks | Atopaxar 400mg LD, 50, 100, 200 mg or placebo | 241 | 66.3 | 87 | 96.0/88.5 | MI, stroke, recurrent ischemia cardiovascular death | TIMI bleeding |
| O' Donoghue et al 2011 | Phase II | 16 weeks | Atopaxar 400mg LD, 50, 100, 200 mg or placebo | 603 | 62.3 | 72 | 94.0/78.0 | MI, stroke, recurrent ischemia cardiovascular death | TIMI bleeding, CURE bleeding |
| Goto et al. 2010 [20] | Phase II | 8 weeks | Vorapxar 20, 40mg LD, 1.0, 2.5mg or placebo | 117 | 65.0 | 80 | 100/100 | Non-fatal MI, non-fatal stroke, hospitalization for recurrent ischemia, urgent coronary revascularization | TIMI bleeding |
| Tricoci et al. 2012 [22] | Phase III | 30 months (Median) | Vorapaxar 2.5mg or placebo | 12944 | NA | 72 | 96.0/87.0 | Cardiovascular death, MI, stroke, recurrent ischemia | TIMI bleeding |
| Cohen et al. 1990 [40] | 1 | 3 months | Warfarin with INR target of 3.0-4.5 s | 69 | 62.0 | 60 | 100/0 | All death, recurrent chest pain, revascularisation with coronary angioplasty or bypass surgery | Major bleeding was defined as bleeding requiring a transfusion of ≥2units of blood or corrective surgery, or as bleeding that resulted in death, disability, intracranial or retroperitoneal |

Table 1. Characteristics of included trials

Gao and Li; BJMMR, 6(2): 173-199, 2015; Article no.BJMMR.2015.194

| Study | Design of trial | Follow-up | Drugs | Number of subjects | Baseline age | Male (%) | Aspirin use/ thienopyridine use | Definition of composite Ischemic events | Definition of major bleeding events |
|------------------------------|--------------------|------------|---|-----------------------|-----------------|-------------|------------------------------------|---|--|
| | | | | | | | | | haemorrhage. |
| Cohen et al. 1994 [41] | 1 | 3 months | Warfarin with INR target of 2.0-3.0 s | 214 | 61.5 | 68 | 100/0 | Recurrent angina, myocardial infarction, total death | Major bleeding was defined as bleeding requiring a transfusion of ≥2units of blood or corrective surgery, retroperitoneal or intracranial haemorrhage, or bleeding that resulted in death, or permanent disability, intracranial. |
| Williams et al. 1997 [47] | 1 | 2.5 months | Warfarin with the target INR of 2.0-2.5 s | 57 | 57 | 86 | 100/0 | Death, MI, revascularization | Major bleeding defined as required transfusion or surgical intervention |
| CARS 1997 [36] | 1 | 14 months | INR in Warfarin arm <1.5 s (measured) Target INR was not reported | 8803 | NA | 77 | 100/0 | Non-fatal myocardial re- infarction, non-fatal ischemic stroke, and cardiovascular death | Major bleeding included intracranial hemorrhage or a spontaneous bleeding episode that required surgical intervention during the stay in hospital, that decreased hemoglobin by more than 2 g/dL, contributed to death, or disability |
| Anand et al. 1998 [38] | 1 | 6 months | Warfarin with the target INR of 2.5 s | 309 | 64 | 67 | 100/0 | All cause death, MI, refractory angina, readmission for unstable angina, major bleed, and stroke | Major bleeding defined as if the event was fatal or life threatening, was permanently or significantly disabling, or required transfusion of packed red blood cells or surgical treatment |
| Huyhn et al 2001 | 1 | 1 year | Warfarin with the target INR of 2.0-2.5 s | 90 | 67 | 77 | 100/0 | All cause death, myocardial infarction, or unstable angina requiring a new hospitalization | Major bleeding was defined as a fall in hemoglobin of \$2 g/L or requiring blood product transfusion |
| OASIS-2 2001 | 1 | 5 months | Warfarin with the target INR of 2.5 s | 3712 | 64 | 61 | 100/0 | Cardiovascular death, MI or strokes | Major bleeding defined as if the event was fatal or life threatening, was permanently or significantly disabling, or required transfusion of packed red blood cells or surgical treatment |

Gao and Li; BJMMR, 6(2): 173-199, 2015; Article no.BJMMR.2015.194

| Study | Design of trial | Follow-up | Drugs | Number of subjects | Baseline age | Male (%) | Aspirin use/ thienopyridine use | Definition of composite Ischemic events | Definition of major bleeding events |
|----------------------------------|--------------------|------------|---|-----------------------|-----------------|-------------|------------------------------------|---|--|
| Van ES et al. 2002 [46] | 1 | 1 year | Warfarin with the target INR of 2.0-2.5 s | 668 | 61 | 78 | 100/0 | Death, myocardial infarction, or stroke. | Major bleeding defines as fatal bleeding, intracranial hemorrhage, or any bleeding requiring admission, irrespective of interventions |
| Brouwer et al. 2002 [39] | / | 3 months | Warfarin with the target INR of 2.0-3.0 s | 274 | 58 | 82 | 100/0 | Death, re-infarction, revascularization | TIMI major bleeding |
| Fiore et al. 2002 [42] | 1 | 2.7 months | Warfarin with the target INR of 2.0-3.0 s | 5059 | 64 | 98 | 100/0 | All-cause mortality, recurrent myocardial infarction and stroke | Major hemorrhage was defined as any fatal, intracranial, or retroperitoneal bleed or any bleed that led to a hospitalization or transfusion and was accompanied by a fall in the hemoglobin of at least 2 g/dL |
| Hurlen et al. 2002 [44] | 1 | 4 years | Warfarin with the target INR of 2.0-2.5 s | 2414 | 61 | 76 | 100/0 | All cause death, re-infarction, stroke | Major bleeding were defined as nonfatal cerebral hemorrhage or bleeding necessitating surgical intervention or blood transfusion |
| Herliz et al. 2004 | / | 5 years | Warfarin with the target INR of 2.0-2.5 s | 3300 | 66 | 75 | 100/0 | Cardiovascular death, re- infarction | Major bleeding was defines as transfusion or a bleed requiring hospitalization. |
| Zibaeenezhad et al. 2004 [48] | 1 | 12 months | Warfarin with the target INR of 2.0-3.0 s | 140 | 61 | 76 | 100/0 | Angina pectoris, cerebrovascular accident, re- hospitalization, re-infarction, death | Major bleeding was defined as gastrointestinal hemorrhage, bleeding leading to shock or the need for blood transfusion |

Table 2. Pairwise meta-analysis

| | New oral anticoagulants | | | PA | nist | Warfarin | | | |
|----------------------|-------------------------|--------------------|-------------------|-------------------|--------------------|-------------------|-------------------|--------------------|-------------------|
| | OR (95% CI) | l ² (%) | Z -test (p-value) | OR (95% CI) | l ² (%) | Z -test (p-value) | OR (95% CI) | l ² (%) | Z -test (p-value) |
| Major adverse events | 0.85 (0.78, 0.93) | 0 | 3.61(0.0003) | 0.80 (0.52, 1.22) | 60 | 1.84(0.07) | 0.87 (0.74, 1.02) | 62 | 1.79(0.09) |
| Major bleeding | 3.04 (2.21, 4.19) | 0 | 6.85(<0.00001) | 1.55 (1.25, 1.93) | 0 | 3.90(<0.00001) | 1.77 (1.46, 2.14) | 0 | 5.79(<0.00001) |

Table 3. Network meta-analysis results- major adverse events

| | | | Fi | xed effect model | | | | Ran | dom effect model | |
|------------------|---------|--------|---------|------------------|-----------------------|---------|--------|---------|------------------|-----------------------|
| | Mean | SD | Median | Crl | Probability of best % | Mean | SD | Median | Crl | Probability of best % |
| d ₁₂ | -0.3017 | 0.0352 | -0.0302 | -0.0981, 0.0379 | 1 | -0.1364 | 0.1095 | -0.1218 | -0.3931, 0.0390 | 1 |
| d ₁₃ | -0.3039 | 0.1298 | -0.3044 | -0.5568, -0.0483 | / | -0.3044 | 0.2757 | -0.3042 | -0.8601, 0.2502 | / |
| d ₁₄ | -0.0282 | 0.0678 | -0.0281 | -0.1603, 0.1043 | / | -0.0595 | 0.1943 | -0.0554 | -0.4641, 0.3276 | / |
| d ₁₅ | -0.2173 | 0.2259 | -0.2207 | -0.65, 0.2348 | / | -0.2144 | 0.3328 | -0.2176 | -0.8666, 0.4525 | / |
| d ₁₆ | -0.2161 | 0.0537 | -0.2162 | -0.3202,-0.111 | / | -0.2179 | 0.1857 | -0.2178 | -0.5986, 0.1628 | / |
| d ₁₇ | 0.2788 | 0.2937 | 0.2709 | -0.2746, 0.8773 | / | 0.2777 | 0.379 | 0.273 | -0.4576, 1.039 | / |
| d ₁₈ | -0.0185 | 0.3137 | -0.0246 | -0.6144, 0.6165 | / | -0.0300 | 0.3672 | -0.0349 | -0.7376, 0.7066 | / |
| d ₁₉ | -0.0890 | 0.0476 | -0.0890 | -0.1814, 0.0034 | 1 | -0.2272 | 0.2424 | -0.191 | -0.81, 0.1664 | / |
| T ₁ | 0.1537 | 0.1311 | 0.1134 | 0.0155, 0.5103 | 0 | 0.1537 | 0.1312 | 0.1137 | 0.0154, 0.5113 | 0 |
| T ₂ | 0.1504 | 0.1293 | 0.1105 | 0.0150, 0.5028 | 0 | 0.1392 | 0.1234 | 0.1006 | 0.0133, 0.4796 | 1.5 |
| T ₃ | 0.1227 | 0.1132 | 0.0863 | 0.0113, 0.4382 | 44.4 | 0.1243 | 0.117 | 0.0863 | 0.0106, 0.4526 | 32.3 |
| T_4 | 0.1507 | 0.1297 | 0.1106 | 0.0150, 0.5041 | 0 | 0.1482 | 0.1299 | 0.1077 | 0.0140, 0.5045 | 2.5 |
| T_5 | 0.1322 | 0.1208 | 0.0932 | 0.0119, 0.4689 | 29.7 | 0.1341 | 0.1246 | 0.0937 | 0.0113, 0.482 | 24.0 |
| T ₆ | 0.1308 | 0.1178 | 0.0936 | 0.0124, 0.4568 | 10.4 | 0.1316 | 0.1199 | 0.0934 | 0.0120,0.4647 | 11.6 |
| T ₇ | 0.1903 | 0.1546 | 0.1444 | 0.0190, 0.5997 | 1.3 | 0.1918 | 0.1582 | 0.1447 | 0.0178, 0.6108 | 2.1 |
| T ₈ | 0.1546 | 0.1362 | 0.1117 | 0.0140, 0.5283 | 14.0 | 0.1544 | 0.1381 | 0.1105 | 0.0133, 0.5348 | 11.8 |
| T ₉ | 0.144 | 0.1257 | 0.1048 | 0.0142, 0.4888 | 0.1 | 0.1313 | 0.1204 | 0.0927 | 0.0116, 0.4655 | 14.2 |
| D _{res} | 73.9 | | | | | 57.8 | | | | |
| DIC | 374.108 | | | | | 365.888 | | | | |

| | | | F | ixed effect model | | Random effect model | | | | | |
|------------------|---------|--------|--------|-------------------|-----------------------|---------------------|--------|--------|----------------|-----------------------|--|
| | Mean | SD | Median | Crl | Probability of best % | Mean | SD | Median | Crl | Probability of best % | |
| d ₁₂ | 0.5895 | 0.0961 | 0.5891 | 0.4041, 0.7771 | / | 0.7058 | 0.1878 | 0.692 | 0.3701, 1.114 | / | |
| d ₁₃ | 0.7473 | 0.4770 | 0.7262 | -0.1312, 1.74 | / | 0.741 | 0.6255 | 0.7274 | -0.4624, 2.017 | 1 | |
| d ₁₄ | 0.9035 | 0.2689 | 0.8985 | 0.3905, 1.444 | 1 | 0.857 | 0.4434 | 0.8617 | -0.0454, 1.728 | 1 | |
| d ₁₅ | 1.046 | 1.337 | 0.8624 | -1.034, 4.1811 | 1 | 1.05 | 1.395 | 0.8828 | -1.189, 4.281 | 1 | |
| d ₁₆ | 1.113 | 0.2002 | 1.108 | 0.7346, 1.517 | 1 | 0.9828 | 0.3626 | 0.9941 | 0.229, 1.678 | / | |
| d ₁₇ | 1.179 | 1.337 | 1.001 | -0.9298, 4.33 | 1 | 1.207 | 1.438 | 1.039 | -1.106, 4.57 | / | |
| d ₁₈ | 0.669 | 1.042 | 0.5634 | -1.077, 3.0211 | 1 | 0.6191 | 1.081 | 0.5213 | -1.237, 3.015 | / | |
| d ₁₉ | 0.4357 | 0.1121 | 0.4352 | 0.2185, 0.6557 | 1 | 0.4331 | 0.4049 | 0.4327 | -0.4011, 1.275 | / | |
| T ₁ | 0.01162 | 0.0144 | 0.0072 | 0.0010, 0.0497 | 45.0 | 0.01162 | 0.0144 | 0.0072 | 0.0010, 0.0494 | 34.3 | |
| T_2 | 0.0206 | 0.0245 | 0.0128 | 0.0018, 0.0867 | 0 | 0.0232 | 0.0278 | 0.0144 | 0.0020, 0.0983 | 0 | |
| T ₃ | 0.0262 | 0.0348 | 0.0150 | 0.0017, 0.1208 | 2.8 | 0.0279 | 0.0400 | 0.0149 | 0.0015, 0.1356 | 5.9 | |
| T_4 | 0.0284 | 0.0339 | 0.0175 | 0.0023, 0.1214 | 0 | 0.0286 | 0.0364 | 0.0168 | 0.0020, 0.1278 | 1.3 | |
| T_5 | 0.0597 | 0.1193 | 0.0180 | 0.0011, 0.4353 | 16.9 | 0.0617 | 0.1234 | 0.0182 | 0.0001, 0.4583 | 16.5 | |
| T_6 | 0.0340 | 0.0391 | 0.0215 | 0.0029, 0.1415 | 0 | 0.0313 | 0.0381 | 0.0190 | 0.0024, 0.1357 | 0.3 | |
| T ₇ | 0.0656 | 0.1252 | 0.0206 | 0.0012, 0.4712 | 13.5 | 0.0709 | 0.1362 | 0.0210 | 0.0011, 0.5231 | 13.5 | |
| T ₈ | 0.0354 | 0.0696 | 0.0131 | 0.0001, 0.2232 | 21.8 | 0.0347 | 0.0683 | 0.0126 | 0.0010, 0.2205 | 22.4 | |
| T ₉ | 0.0178 | 0.0215 | 0.0110 | 0.0015, 0.0755 | 0 | 0.0190 | 0.0253 | 0.0110 | 0.0013, 0.0862 | 5.8 | |
| D _{res} | 55.18 | | | | | 46.93 | | | | | |
| DIC | 270.720 | | | | | 267.590 | | | | | |

Table 4. Network meta-analysis results- major bleeding

Table 5. Indirect comparison between new oral anticoagulants, PAR-1 antagonists and Warfarin-major adverse events

| | | | Fix | ced effect model | | | | Rand | lom effect model | |
|------------------|---------|--------|---------|------------------|-------------------------|---------|--------|---------|------------------|-------------------------|
| | Mean | SD | Median | Crl | Probability of best (%) | Mean | SD | Median | Crl | Probability of best (%) |
| d ₁₂ | -0.1974 | 0.0452 | -0.1973 | -0.284, -0.111 | / | -0.1938 | 2.879 | -0.1974 | -6.447, 6.077 | / |
| d ₁₃ | -0.1239 | 0.0468 | -0.1239 | -0.215, -0.033 | / | -0.1229 | 2.882 | -0.1235 | -6.41, 6.152 | / |
| d ₁₄ | -0.1004 | 0.0339 | -0.1004 | -0.166, -0.035 | / | -0.0977 | 2.875 | -0.0990 | -6.385, 6.157 | / |
| Τ ₁ | 0.1589 | 0.1417 | 0.1135 | 0.013, 0.5471 | 0 | 0.1585 | 0.1416 | 0.1133 | 0.0133, 0.548 | 9.8 |
| Τ ₂ | 0.1377 | 0.1292 | 0.0951 | 0.011, 0.498 | 85.4 | 0.2387 | 0.2999 | 0.0947 | 0.0002, 0.987 | 32.8 |
| Τ ₃ | 0.1454 | 0.1338 | 0.1016 | 0.019, 0.516 | 12.1 | 0.2453 | 0.3025 | 0.1011 | 0.0002, 0.9879 | 29.2 |
| Τ ₄ | 0.1478 | 0.1353 | 0.1038 | 0.012, 0.522 | 2.6 | 0.2478 | 0.303 | 0.1036 | 0.0002, 0.9878 | 28.2 |
| D _{res} | 6.086 | | | | | 6.004 | | | | |
| DIC | 65.599 | | | | | 65.577 | | | | |

Footnote: d refers to the treatment effect comparing to aspirin alone; T refers to absolute effect; D res: residual deviance; DIC: deviance information criterion

Table 6. Indirect comparison between new oral anticoagulants, PAR-1 antagonists and Warfarin-major bleeding

| | | | F | ixed effect model | | Random effect model | | | | | |
|-----------------|--------|--------|--------|-------------------|-------------------------|---------------------|--------|--------|----------------|-------------------------|--|
| | Mean | SD | Median | Crl | Probability of best (%) | Mean | SD | Median | Crl | Probability of best (%) | |
| d ₁₂ | 1.243 | 0.1578 | 1.241 | 0.9431, 1.557 | / | 1.237 | 2.879 | 1.241 | -5.035, 7.507 | 1 | |
| d ₁₃ | 0.4001 | 0.1112 | 0.3998 | 0.1839, 0.618 | / | 0.4077 | 2.861 | 0.3992 | -5.843, 6.694 | 1 | |
| d ₁₄ | 0.5741 | 0.0961 | 0.5738 | 0.389, 0.7619 | 1 | 0.5684 | 2.883 | 0.5711 | -5.723, 6.839 | 1 | |
| Τ ₁ | 0.0116 | 0.0143 | 0.0072 | 0.0001, 0.0495 | 100 | 0.0116 | 0.0143 | 0.0071 | 0.0002, 0.0494 | 32.7 | |
| T ₂ | 0.0382 | 0.0426 | 0.0244 | 0.0034, 0.1561 | 0 | 0.1296 | 0.2389 | 0.0243 | 0.0004, 0.9432 | 15.6 | |
| Τ ₃ | 0.0172 | 0.0208 | 0.0107 | 0.0015, 0.0729 | 0 | 0.0903 | 0.2056 | 0.0107 | 0.0002, 0.8802 | 27.6 | |
| T ₄ | 0.0203 | 0.0241 | 0.0127 | 0.0017, 0.0853 | 0 | 0.0967 | 0.2115 | 0.0126 | 0.0002, 0.8941 | 24.2 | |
| D res | 6.038 | | | | | 6.00 | | | | | |
| DIC | 53.574 | | | | | 53.695 | | | | | |

5. CONCLUSION

From the results of the network meta-analysis, ximelagatran, dabigatran, rivoroxaban and vorapaxar were identified to be superior to the other antithrombotic agents in MAE incidences for patients with ACS histories. The combined comparisons showed new oral anticoagulants and PAR-1 antagonists to be superior to warfarin in the occurrences of MAE for the same cohort whereas PAR-1 antagonists afforded optimum outcomes in the events of major bleeding against warfarin and new oral anticoagulants. Therefore, routine administration of new oral the anticoagulant as add-on treatment for patients after ACS might not be recommendable due to its increased bleeding risk. Nonetheless, for ACS patient comorbid with atrial fibrillation, new oral anticoagulant might be superior to warfarin in both efficacy and safety outcomes. Future headto-head RCT comparing new oral anticoagulant with new antiplatelet is needed to testify the results from our network meta-analysis.

CONSENT

Not applicable.

ETHICAL APPROVAL

As the current systematic review and metaanalysis was based on published data sources with original approval from individual ethical committees, no ethical issue was involved.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

- Pagidipati NJ, Gaziano TA. Estimating deaths from cardiovascular disease: a review of global methodologies of mortality measurement. Circulation. 2013;127(6): 749-756.
- Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324(7329):71-86.
- Yusuf S, Fox KAA, Tognoni G, Mehta SR, Chrolavicius S, Anand S, Avezum A, Awan N, Bertrand M, Budaj A, et al. Effects of

clopidogrel in addition to aspirin in patients with acute coronary syndromes without STsegment elevation. N Engl J Med. 2001;345(7):494-502.

- Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, Lewis BS, Murphy SA, McCabe CH, Braunwald E, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with STelevation myocardial infarction treated with fibrinolytics - The PCI-CLARITY study. JAMA. 2005;294(10):1224-1232.
- Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, Claeys MJ, Cools F, Hill KA, Skene AM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med. 2005;352(12):1179-1189.
- Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, Collins R, Liu LS, Chen ZM, Liu LS, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebocontrolled trial. Lancet. 2005;366(9497): 1607-1621.
- Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van de Werf F, de Torbal A, Armstrong PW, Wallentin LC, Wilcox RG, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. Lancet. 2002; 359(9302):189-198.
- De Luca G, Navarese E, Marino P. Risk profile and benefits from Gp IIb-IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials. Eur Heart J. 2009;30(22):2705-2713.
- Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20): 2001-2015.
- Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045-1057.
- 11. Liverani E, Kilpatrick LE, SP K. P2Y12 Receptor in Cardiovascular Diseases.

Journal of Cardiovascular Disease. 2014;2(4):203-208.

- Chyrchel B, Toton-Zuranska J, Kruszelnicka O, Chyrchel M, Mielecki W, Kolton-Wroz M, Wolkow P, Surdacki A. Association of plasma miR-223 and platelet reactivity in patients with coronary artery disease on dual antiplatelet therapy: A preliminary report. Platelets. 2014;1-5.
- Lanni F, Santulli G, Izzo R, Rubattu S, Zanda B, Volpe M, Iaccarino G, Trimarco B. The PIA1/A2 polymorphism of glycoprotein IIIa and cerebrovascular events in hypertension: increased risk of ischemic stroke in high-risk patients. Journal of Hypertension. 2007;25(3):551-556.

510.1097/HJH.1090b1013e328013cd3280 67.

- Galasso G, Santulli G, Piscione F, De Rosa R, Trimarco V, Piccolo R, Cassese S, laccarino G, Trimarco B, Chiariello M. The GPIIIA PIA2 polymorphism is associated with an increased risk of cardiovascular adverse events. BMC Cardiovascular Disorders. 2010;10(1):41.
- 15. Gaetano S. Coronary Heart Disease Risk Factors and Mortality. JAMA. 2012; 307(11):1137-1138.
- Merlini PA, Bauer KA, Oltrona L, Ardissino D, Cattaneo M, Belli C, Mannucci PM, Rosenberg RD. Persistent activation of coagulation mechanism in unstable angina and myocardial infarction. Circulation. 1994;90(1):61-68.
- 17. Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. JAMA. 1999;282(21):2058-2067.
- Becker RC, Meade TW, Berger PB, Ezekowitz M, O'Connor CM, Vorchheimer DA, Guyatt GH, Mark DB, Harrington RA. The Primary and secondary prevention of coronary artery disease american college of chest physicians evidence-based clinical practice guidelines. CHEST Journal. 2008;133(6_suppl):776S-814S.
- Goto S, Ogawa H, Takeuchi M, Flather MD, Bhatt DL. Double-blind, placebocontrolled Phase II studies of the proteaseactivated receptor 1 antagonist E5555 (atopaxar) in Japanese patients with acute coronary syndrome or high-risk coronary artery disease. Eur Heart J. 2010;31(21):2601-2613.
- 20. Goto S, Yamaguchi T, Ikeda Y, Kato K, Yamaguchi H, Jensen P. Safety and

exploratory efficacy of the novel thrombin receptor (PAR-1) antagonist SCH530348 for non-ST-segment elevation acute coronary syndrome. J Atheroscler Thromb. 2010;17(2):156-164.

- 21. O'Donoghue ML, Bhatt DL, Wiviott SD, Goodman SG, Fitzgerald DJ, Angiolillo DJ, Goto S, Montalescot G, Zeymer U, Aylward PE, et al. Safety and tolerability of atopaxar in the treatment of patients with acute coronary syndromes: the lessons from antagonizing the cellular effects of Thrombin-Acute Coronary Syndromes Trial. Circulation. 2011;123(17):1843-1853.
- Tricoci P, Huang Z, Held C, Moliterno DJ, Armstrong PW, Van de Werf F, White HD, Aylward PE, Wallentin L, Chen E, et al. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. N Engl J Med. 2012;366(1):20-33.
- Alexander JH, Becker RC, Bhatt DL, Cools F, Crea F, Dellborg M, Fox KA, Goodman SG, Harrington RA, Huber K, et al. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. Circulation. 2009; 119(22):2877-2885.
- 24. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, Bhatt DL, Goodman S, Verheugt FW, Flather M, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med. 2011;365(8):699-708.
- Mega JL, Braunwald E, Mohanavelu S, Burton P, Poulter R, Misselwitz F, Hricak V, Barnathan ES, Bordes P, Witkowski A, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet. 2009;374(9683):29-38.
- Mega JL, Braunwald E, Wiviott SD, Bassand J-P, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366(1):9-19.
- Oldgren J, Budaj A, Granger CB, Khder Y, Roberts J, Siegbahn A, Tijssen JG, Van de Werf F, Wallentin L. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J. 2011;32(22):2781-2789.

- Steg PG, Mehta SR, Jukema JW, Lip GY, Gibson CM, Kovar F, Kala P, Garcia-Hernandez A, Renfurm RW, Granger CB. RUBY-1: a randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome. Euro Heart J. 2011;32(20):2541-2554.
- 29. Wallentin L, Wilcox RG, Weaver WD, Emanuelsson H, Goodvin A, Nystrom P, Bylock A. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. Lancet. 2003;362(9386):789-797.
- Komocsi A, Vorobcsuk A, Kehl D, Aradi D. Use of New-generation oral anticoagulant agents in patients receiving antiplatelet therapy after an acute coronary syndrome systematic review and meta-analysis of randomized controlled trials. Archives of Internal Medicine. 2012;172(20):1537-1545.
- Oldgren J, Wallentin L, Alexander JH, James S, Jonelid B, Steg G, Sundstrom J. New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis. Eur Heart J. 2013;34(22):1670-1680.
- Ye Y, Xie H, Zeng Y, Zhao X, Tian Z, Zhang S. Optimal oral antithrombotic regimes for patients with acute coronary syndrome: a network meta-analysis. PloS One. 2014;9(3):e90986.
- 33. Cochrane Handbook for Systematic Reviews of Interventions: The Cochrane Collaboration; 2011.
- 34. Dias S, Welton NJ, Sutton AJ, Ades AE: NICE DSU Technical Support Document 5: Evidence synthesis in the baseline natural history model; 2011. Last updated April 2012; available from: http://wwwnicedsuorguk.
- 35. Orme ME, Macgilchrist KS, Mitchell S, Spurden D, Bird A. Systematic review and network meta-analysis of combination and monotherapy treatments in diseasemodifying antirheumatic drug-experienced patients with rheumatoid arthritis: analysis of American College of Rheumatology criteria scores 20, 50, and 70. Biologics. 2012;6:429-464.
- Coumadin Aspirin Reinfarction Study (CARS) Investigators. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction.

Coumadin Aspirin Reinfarction Study (CARS) Investigators. Lancet 1997; 350(9075):389-396.

- Effects of long-term, moderate-intensity oral anticoagulation in addition to aspirin in unstable angina. The Organization to Assess Strategies for Ischemic Syndromes (OASIS) Investigators. J Am Coll Cardiol. 2001;37(2):475-484.
- Anand SS, Yusuf S, Pogue J, Weitz JI, Flather M. Long-term oral anticoagulant therapy in patients with unstable angina or suspected non-Q-wave myocardial infarction: organization to assess strategies for ischemic syndromes (OASIS) pilot study results. Circulation. 1998;98(11): 1064-1070.
- 39. Brouwer MA, van den Bergh PJ, Aengevaeren WR, Veen G, Luijten HE, Hertzberger DP, van Boven AJ, Vromans RP, Uijen GJ, Verheugt FW. Aspirin plus coumarin versus aspirin alone in the prevention of reocclusion after fibrinolysis for acute myocardial infarction: results of the Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT)-2 Trial. Circulation. 2002; 106(6):659-665.
- 40. Cohen M, Adams PC, Hawkins L, Bach M, Fuster V. Usefulness of antithrombotic therapy in resting angina pectoris or non-Q-wave myocardial infarction in preventing death and myocardial infarction (a pilot study from the Antithrombotic Therapy in Acute Coronary Syndromes Study Group). Am J Cardiol. 1990;66(19):1287-1292.
- 41. Cohen M, Adams PC, Parry G, Xiong J, Chamberlain D, Wieczorek I, Fox KA, Chesebro JH, Strain J, Keller C, et al. Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users. Primary end points analysis from the ATACS trial. Antithrombotic Therapy in Acute Coronary Syndromes Research Group. Circulation. 1994;89(1):81-88.
- 42. Fiore LD, Ezekowitz MD, Brophy MT, Lu D, Sacco J, Peduzzi P. Department of Veterans Affairs Cooperative Studies Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study. Circulation. 2002;105(5):557-563.
- 43. Herlitz J, Holm J, Peterson M, Karlson BW, Haglid Evander M, Erhardt L. Effect of fixed low-dose warfarin added to aspirin in

the long term after acute myocardial infarction; the LoWASA Study. Eur Heart J. 2004;25(3):232-239.

- 44. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med. 2002;347(13):969-974.
- 45. Huynh T, Theroux P, Bogaty P, Nasmith J, Solymoss S. Aspirin, warfarin, or the combination for secondary prevention of coronary events in patients with acute coronary syndromes and prior coronary artery bypass surgery. Circulation. 2001;103(25):3069-3074.
- van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet 2002;360(9327): 109-113.
- Williams MJ, Morison IM, Parker JH, Stewart RA: Progression of the culprit lesion in unstable coronary artery disease with warfarin and aspirin versus aspirin alone: preliminary study. J Am Coll Cardiol 1997, 30(2):364-369.
- Zibaeenezhad MJ, Mowla A, Sorbi MH. Warfarin and aspirin versus aspirin alone in patients with acute myocardial infarction: a pilot study. Angiology. 2004;55(1):17-20.
- 49. Yusuf S. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation (vol 345, pg 494, 2001). N Engl J Med. 2001;345(23):1716-1716.
- 50. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, et al. ACC/AHA guidelines for the

management of patients with ST-elevation myocardial infarction--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation. 2004; 110(5):588-636.

- 51. Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy1. J Am Coll Cardiol. 2003;41(9):1633-1652.
- 52. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11): 981-992.
- Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt Gn, Halperin JL, Hankey GJ, Piccini JP. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365(10):883-891.
- 54. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on the management of patients with unstable angina). Circulation. 2000;102(10):1193-1209.

APPENDIX

Appendix Table 1. Odds ratio of individual antithrombotic agent (major adverse events)

| Antithrombotic agent | Odds ratio |
|----------------------|-------------------|
| Warfarin | 0.87 (0.74, 1.02) |
| Ximelagatran | 0.74 (0.57, 0.95) |
| Apixaban | 0.97 (0.85, 1.11) |
| Dabigatran | 0.80 (0.51, 1.24) |
| Rivaroxban | 0.81 (0.72, 0.92) |
| Darexaban | 1.29 (0.73, 2.28) |
| Atopaxar | 0.96 (0.52, 1.76) |
| Vorapaxar | 0.56 (0.17, 1.83) |

Appendix Table 2. Odds ratio of individual antithrombotic agent (major bleeding)

| Antithrombotic agent | odds ratio |
|----------------------|--------------------|
| Warfarin | 1.77 (1.46, 2.14) |
| Ximelagatran | 1.98 (0.80, 4.89) |
| Apixaban | 2.43(1.44, 4.10) |
| Dabigatran | 1.75 (0.21, 14.24) |
| Rivaroxban | 5.60 (1.67, 18.79) |
| Darexaban | 2.05 (0.25, 17.05) |
| Atopaxar | 1.83 (0.22, 15.34) |
| Vorapaxar | 1.55 (1.24, 1.92) |

| | | Fixed | effect mo | del | | Random | n effect mod | lel |
|------------------|---------|-----------|-----------|----------------|-----------|-----------|--------------|----------|
| | Mean | SD | Median | Crl | Mean | SD | Median | Crl |
| d ₁₂ | -0.0300 | 0.0347 | -0.0300 | -0.0978, | -0.1354 | 0.1098 | -0.1207 | -0.3934, |
| | | | | 0.0379 | | | | 0.0394 |
| d ₁₃ | -0.3041 | 0.1299 | -0.3047 | -0.557, - | -0.3041 | 0.2754 | -0.3047 | -0.8606, |
| | | | | 0.0481 | | | | 0.252 |
| d ₁₄ | -0.0284 | 0.0676 | -0.0285 | -0.1609, | -0.0600 | 0.1933 | -0.0553 | -0.4641, |
| | | | | 0.1043 | | | | 0.3235 |
| d ₁₅ | -0.2157 | 0.2264 | -0.2197 | -0.6492, 0.239 | -0.215 | 0.3319 | -0.2165 | -0.8689, |
| | | | | | | | | 0.4446 |
| d ₁₆ | -0.2163 | 0.0534 | -0.2165 | -0.3205, - | -0.2186 | 0.1846 | -0.2189 | -0.5967, |
| | | | | 0.1115 | | | | 0.1581 |
| d ₁₇ | 0.2814 | 0.2928 | 0.274 | -0.2704, | 0.2807 | 0.3801 | 0.2763 | -0.4542, |
| | | | | 0.8778 | | | | 1.041 |
| d ₁₈ | -0.0173 | 0.313 | -0.0245 | -0.6121, | -0.0318 | 0.3655 | -0.0362 | -0.7352, |
| | | | | 0.6161 | | | | 0.7001 |
| d ₁₉ | -0.0891 | 0.0479 | -0.0891 | -0.1819, | -0.2266 | 0.2424 | -0.19 | -0.8103, |
| _ | | | | 0.0035 | | | | 0.1656 |
| I ₁ | 0.154 | 0.1314 | 0.1136 | 0.0154, | 0.1539 | 0.1312 | 0.1138 | 0.0155, |
| - | | | | 0.5116 | | | | 0.5106 |
| I ₂ | 0.1507 | 0.1296 | 0.1107 | 0.0150, | 0.1395 | 0.1234 | 0.1009 | 0.0134, |
| - | 0 4 0 0 | 0 4400 | 0.0000 | 0.5043 | 0 4045 | 0 44 00 | 0.0005 | 0.4799 |
| I ₃ | 0.123 | 0.1136 | 0.0863 | 0.0113, | 0.1245 | 0.1169 | 0.0865 | 0.0107, |
| т | 0 151 | 0 1 2 0 0 | 0 1100 | 0.4409 | 0 1 1 0 1 | 0 1 2 0 0 | 0 1070 | 0.4534 |
| 14 | 0.151 | 0.1299 | 0.1100 | 0.0150, | 0.1404 | 0.1299 | 0.1079 | 0.0141, |
| т. | 0 1326 | 0 1212 | 0 0036 | 0.0002 | 0 13/2 | 0 1244 | 0 0038 | 0.0004 |
| 15 | 0.1520 | 0.1212 | 0.0350 | 0.0119, | 0.1342 | 0.1244 | 0.0950 | 0.0114, |
| Т | 0 1311 | 0 118 | 0.0936 | 0.4000 | 0 1317 | 0 1196 | 0 0935 | 0.4013 |
| •6 | 0.1011 | 0.110 | 0.0000 | 0.4583 | 0.1017 | 0.1100 | 0.0000 | 0.4645 |
| Τ- | 0 1909 | 0 155 | 0 1451 | 0.0190 | 0 1925 | 0 1584 | 0 1451 | 0.0180 |
| • / | 0.1000 | 0.100 | 0.1101 | 0.6006 | 0.1020 | 0.1001 | 0.1101 | 0.6107 |
| T ₈ | 0.1551 | 0.1368 | 0.1117 | 0.0140. | 0.1544 | 0.1378 | 0.1106 | 0.0134. |
| 0 | | | | 0.5301 | | | | 0.5333 |
| Τq | 0.1443 | 0.1259 | 0.105 | 0.0141, 0.49 | 0.1316 | 0.1203 | 0.0931 | 0.0117, |
| U U | | | | , - | | | | 0.4657 |
| D _{res} | 73.06 | | | | 57.87 | | | |
| DIC | 374.140 | | | | 366.020 | | | |

Appendix Table 3. Effect of covariates (follow-up times and age of subjects)—major adverse events

| | _ | Fixed | effect mod | el | Random effect model | | | | | |
|-----------------|-----------|--------|------------|--------------|---------------------|-----------|--------|----------|--|--|
| | Mean | SD | Median | Crl | Mean | SD | Median | Crl | | |
| d ₁₂ | 0.6011 | 0.0958 | 0.6007 | 0.4148, | 0.7613 | 0.2109 | 0.7407 | 0.4007, | | |
| | | | | 0.7906 | | | | 1.234 | | |
| d ₁₃ | 0.748 | 0.4794 | 0.7257 | -0.1315, | 0.7539 | 0.6609 | 0.7405 | -0.5228, | | |
| | | | | 1.752 | | | | 2.096 | | |
| d ₁₄ | 0.9071 | 0.2687 | 0.9022 | 0.3929,1.448 | 0.8517 | 0.4737 | 0.8573 | -0.1196, | | |
| | | | | | | | | 1.786 | | |
| d ₁₅ | 1.075 | 1.365 | 0.8777 | -1.027, 4.32 | 1.054 | 1.456 | 0.8754 | -1.263, | | |
| | | | | | | | | 4.34 | | |
| d ₁₆ | 1.112 | 0.1996 | 1.108 | 0.734, 1.516 | 0.9713 | 0.3916 | 0.9839 | 0.1538, | | |
| | | | | | | | | 1.721 | | |
| d ₁₇ | 1.206 | 1.353 | 1.024 | -0.9197, | 1.219 | 1.428 | 1.049 | -1.117, | | |
| | | | | 4.4141 | | | | 4.522 | | |
| d ₁₈ | 0.2776 | 0.8961 | 0.2086 | -1.286, | 0.2549 | 0.9782 | 0.1936 | -1.505, | | |
| -l | 0 4 4 4 0 | 0.440 | 0.4400 | 2.252 | 0 5044 | 0 4554 | 0.400 | 2.35 | | |
| a ₁₉ | 0.4412 | 0.112 | 0.4406 | 0.2235, | 0.5044 | 0.4554 | 0.482 | -0.3802, | | |
| т | 0.0116 | 0.0144 | 0.0072 | 0.0014 | 0.0116 | 0 0142 | 0.0072 | 1.501 | | |
| I ₁ | 0.0116 | 0.0144 | 0.0072 | 0.0010, | 0.0110 | 0.0145 | 0.0072 | 0.0010, | | |
| т | 0 0208 | 0 0247 | 0.0130 | 0.0493 | 0.0246 | 0 0 2 0 4 | 0.0152 | 0.0492 | | |
| 12 | 0.0200 | 0.0247 | 0.0150 | 0.0010, | 0.0240 | 0.0294 | 0.0152 | 0.0021, | | |
| т. | 0 0262 | 0 0348 | 0.0150 | 0.0074 | 0.0286 | 0 0417 | 0.0151 | 0.0015 | | |
| 13 | 0.0202 | 0.0040 | 0.0100 | 0.0017, | 0.0200 | 0.0417 | 0.0101 | 0.0010, | | |
| т₄ | 0 0285 | 0 0340 | 0.0176 | 0.0023 | 0 0287 | 0 | 0.0167 | 0.1400 | | |
| • 4 | 0.0200 | 0.0010 | 0.0170 | 0.1215 | 0.0207 | 0371 | 0.0107 | 0.0013 , | | |
| T, | 0.0621 | 0 1238 | 0.0183 | 0.0011 | 0.0638 | 0 129 | 0.0181 | 0.0010 | | |
| • 5 | 0.0021 | 0.1200 | 0.0100 | 0.4599 | 0.0000 | 0.120 | 0.0101 | 0.4818 | | |
| Te | 0.0340 | 0.0390 | 0.0215 | 0.0029 | 0.0312 | 0.0384 | 0.0188 | 0.0023 | | |
| - 0 | 0.0010 | | 0.02.0 | 0.1414 | 0.00.2 | | 0.0.00 | 0.1363 | | |
| T_7 | 0.0675 | 0.1283 | 0.0211 | 0.0012, | 0.0714 | 0.1336 | 0.0214 | 0.0011, | | |
| | | | | 0.4871 | | | | 0.5106 | | |
| T ₈ | 0.0222 | 0.0428 | 0.0091 | 0.0001, | 0.0229 | 0.0455 | 0.0090 | 0.0001, | | |
| 5 | | | | 0.1294 | | | | 0.1374 | | |
| T ₉ | 0.0179 | 0.0216 | 0.0111 | 0.0015, | 0.0208 | 0.0287 | 0.0118 | 0.0014, | | |
| - | | | | 0.0756 | | | | 0.0955 | | |
| D res | 61.72 | | | | 52.1 | | | | | |
| DIC | 270.612 | | | | 266.399 | | | | | |

Appendix Table 4. Effect of covariates (follow-up times and age of subjects)-major bleeding

| | _ | Fixed | effect mod | lel | Random effect model | | | |
|-----------------|----------|---------|------------|------------|---------------------|--------|---------|----------|
| | Mean | SD | Median | Crl | Mean | SD | Median | Crl |
| d ₁₂ | - | 0.0346 | -0.0302 | -0.0978, | -0.1352 | 0.1096 | -0.1203 | -0.3932, |
| | 0.0301 | | | 0.0379 | | | | 0.0388 |
| d ₁₃ | - | 0.1305 | -0.304 | -0.5581, - | -0.3037 | 0.2745 | -0.3039 | -0.8582, |
| | 0.3037 | | | 0.0470 | | | | 0.2481 |
| d ₁₄ | - | 0.0676 | -0.0287 | -0.1606, | -0.0596 | 0.1929 | -0.0555 | -0.4615, |
| | 0.0286 | | | 0.1041 | | | | 0.3237 |
| d ₁₅ | - | 0.2258 | -0.2204 | -0.649, | -0.217 | 0.3295 | -0.22 | -0.8624, |
| | 0.2167 | | | 0.2357 | | | | 0.4417 |
| d ₁₆ | - | 0.0534 | -0.2162 | -0.3205, - | -0.2192 | 0.1841 | -0.2187 | -0.5963, |
| | 0.2162 | | | 0.1114 | | | | 0.1564 |
| d ₁₇ | 0.2781 | 0.2934 | 0.2713 | -0.2757, | 0.2784 | 0.3798 | 0.2739 | -0.4573, |
| | | | | 0.8741 | | | | 1.043 |
| d ₁₈ | - | 0.314 | -0.0240 | -0.6118, | -0.029 | 0.366 | -0.0346 | -0.7349, |
| | 0.0170 | | | 0.6197 | | | | 0.7071 |
| d ₁₉ | - | 0.0478 | -0.0891 | -0.1817, | -0.2249 | 0.2408 | -0.1888 | -0.8031, |
| _ | 0.0890 | | | 0.0035 | | | | 0.1672 |
| T ₁ | 0.1541 | 0.1314 | 0.1138 | 0.0155, | 0.1542 | 0.1316 | 0.1137 | 0.0154, |
| _ | | | | 0.5123 | | | | 0.5125 |
| l ₂ | 0.1507 | 0.1296 | 0.1108 | 0.0150, | 0.1398 | 0.1238 | 0.1008 | 0.0133, |
| - | 0.400 | 0 4405 | 0 0005 | 0.5049 | 0.4040 | 0 4474 | | 0.4812 |
| l ₃ | 0.123 | 0.1135 | 0.0865 | 0.0113, | 0.1248 | 0.11/4 | 0.0864 | 0.0107, |
| - | 0 4 5 4 | 0.4000 | 0.444 | 0.4402 | 0 4 4 0 7 | 0 4000 | 0.4070 | 0.4536 |
| 14 | 0.151 | 0.1299 | 0.111 | 0.0150, | 0.1487 | 0.1303 | 0.1079 | 0.0140, |
| т | 0 1225 | 0 1 2 1 | 0.0020 | 0.0004 | 0 12/2 | 0 1247 | 0.0026 | 0.0000 |
| 15 | 0.1525 | 0.121 | 0.0939 | 0.0120, | 0.1342 | 0.1247 | 0.0930 | 0.0113, |
| т | 0 1311 | 0 1191 | 0.0037 | 0.4094 | 0 1318 | 0 12 | 0 0032 | 0.4052 |
| 6 | 0.1311 | 0.1101 | 0.0957 | 0.0124, | 0.1510 | 0.12 | 0.0952 | 0.0121, |
| т_ | 0 1005 | 0 1548 | 0 1449 | 0.4303 | 0 1024 | 0 1585 | 0 1448 | 0.4004 |
| 17 | 0.1303 | 0.1540 | 0.1445 | 0.0105, | 0.1524 | 0.1000 | 0.1440 | 0.0100, |
| T₀ | 0 1552 | 0 1369 | 0 1121 | 0.0139 | 0 155 | 0 1384 | 0 1107 | 0.012 |
| •8 | 0.1002 | 0.1000 | 0.1121 | 0.5311 | 0.100 | 0.1001 | 0.1107 | 0.5356 |
| T _o | 0 1443 | 0 126 | 0 1051 | 0.0142 | 0 1319 | 0 1208 | 0 0932 | 0.0116 |
| - 9 | . | | | 0.4908 | | | | 0.4686 |
| D res | 73.06 | | | | 57.91 | | | |
| DIC | 374.114 | | | | 366.076 | | | |

Appendix Table 5. Effect of covariates (follow-up times)-major adverse events

| | | Fixed | effect mo | del | Random effect model | | | |
|-----------------|---------|--------|-----------|---------------|---------------------|-----------|--------|------------------|
| | Mean | SD | Median | Crl | Mean | SD | Median | Crl |
| d ₁₂ | 0.5897 | 0.0955 | 0.5893 | 0.404, 0.7781 | 0.7073 | 0.1889 | 0.6939 | 0.3708, |
| | | | | | | | | 1.119 |
| d ₁₃ | 0.7482 | 0.4764 | 0.7258 | -0.1246, | 0.7445 | 0.6228 | 0.7257 | -0.4564, |
| | 0.0047 | 0.0007 | 0 0000 | 1.749 | 0.0550 | 0 4 4 4 0 | 0.0504 | 2.038 |
| a ₁₄ | 0.9047 | 0.2687 | 0.9002 | 0.3896, 1.444 | 0.8552 | 0.4448 | 0.8591 | -0.0476, |
| d | 1 044 | 1 333 | 0 8610 | 1 032 1 2 | 1 097 | 1 / 2 | 0 0115 | 1.729 |
| u 15 | 1.044 | 1.555 | 0.0019 | -1.032, 4.2 | 1.007 | 1.42 | 0.9115 | -1.195, 4 352 |
| d 10 | 1 114 | 0 2002 | 1 109 | 0 7351 1 52 | 0 9805 | 0.364 | 0 991 | 0.2217 |
| G 10 | | 0.2002 | | 0.1001, 1.02 | 0.0000 | 0.001 | 0.001 | 1.681 |
| d ₁₇ | 1.227 | 1.372 | 1.036 | -0.9178, | 1.243 | 1.451 | 1.058 | -1.077, |
| | | | | 4.478 | | | | 4.587 |
| d ₁₈ | 0.6846 | 1.048 | 0.5788 | -1.067, 3.055 | 0.6312 | 1.077 | 0.5398 | -1.242, |
| | | | | | | | | 3.009 |
| d ₁₉ | 0.4357 | 0.1143 | 0.435 | 0.2177, | 0.4314 | 0.4058 | 0.432 | -0.4097, |
| – | 0.0440 | 0.0444 | 0.0070 | 0.6562 | 0.0440 | 0.0444 | 0.0070 | 1.27 |
| I ₁ | 0.0116 | 0.0144 | 0.0072 | 0.0010, | 0.0116 | 0.0144 | 0.0072 | 0.0010, |
| т | 0 0206 | 0.0245 | 0 0120 | 0.0495 | 0 0233 | 0 0267 | 0 0144 | 0.0495 |
| 12 | 0.0200 | 0.0245 | 0.0129 | 0.0018, | 0.0255 | 0.0207 | 0.0144 | 0.0020. |
| T₂ | 0.0262 | 0.0347 | 0.0150 | 0.0017 | 0.0280 | 0.0402 | 0.0149 | 0.0015 |
| • 5 | 0.0202 | 0.0011 | 0.0100 | 0.1201 | 0.0200 | 0.0102 | 0.0110 | 0.1367 |
| T ₄ | 0.0284 | 0.0339 | 0.0175 | 0.0023,0.1213 | 0.0286 | 0.0366 | 0.0167 | 0.0020, |
| | | | | | | | | 0.1286 |
| T_5 | 0.0595 | 0.1185 | 0.0180 | 0.0011, | 0.0645 | 0.1272 | 0.0187 | 0.0010, |
| | | | | 0.4375 | | | | 0.4787 |
| Т ₆ | 0.0341 | 0.0390 | 0.0215 | 0.0029, | 0.0312 | 0.0381 | 0.0189 | 0.0024, |
| - | 0.0005 | 0 4040 | 0.0044 | 0.1414 | 0.0700 | 0 4005 | 0.0047 | 0.1361 |
| 1 ₇ | 0.0695 | 0.1318 | 0.0214 | 0.0012, | 0.0732 | 0.1385 | 0.0217 | 0.0011, |
| т. | 0.0361 | 0 0711 | 0.013/ | 0.5056 | 0 0348 | 0.0675 | 0.0128 | 0.5545 |
| 18 | 0.0001 | 0.0711 | 0.0134 | 0.2267 | 0.0540 | 0.0075 | 0.0120 | 0.2198 |
| Τo | 0.0178 | 0.0217 | 0.0110 | 0.0015 | 0.0190 | 0.0254 | 0.0110 | 0.0013 |
| . 9 | 5.0110 | 0.0217 | 5.0110 | 0.0754 | 0.0100 | 0.0201 | 0.01.0 | 0.0858 |
| D res | 55.24 | | | - | 46.95 | | | |
| DIC | 270.808 | 5 | | | 267.558 | | | |

Appendix Table 6. Effect of covariates (follow-up times)-major bleeding

| | | Fixed | effect mod | del | Random effect model | | | |
|------------------|---------|-----------|------------|------------|---------------------|-----------|---------|----------|
| | Mean | SD | Median | Crl | Mean | SD | Median | Crl |
| d ₁₂ | - | 0.0348 | -0.0302 | -0.0981, | -0.1364 | 0.1096 | -0.122 | -0.3932, |
| | 0.0301 | | | 0.0379 | | | | 0.0394 |
| d ₁₃ | - | 0.1308 | -0.304 | -0.5582, - | -0.3044 | 0.2754 | -0.3049 | -0.8611, |
| | 0.3037 | | | 0.0472 | | | | 0.2529 |
| d ₁₄ | - | 0.0674 | -0.0287 | -0.1606, | -0.0596 | 0.1953 | -0.0553 | -0.4657, |
| | 0.0285 | | | 0.1039 | | | | 0.3277 |
| d ₁₅ | - | 0.2258 | -0.2201 | -0.6486, | -0.216 | 0.3329 | -0.2188 | -0.8686, |
| | 0.2165 | | | 0.2357 | | | | 0.45 |
| d ₁₆ | - | 0.0533 | -0.2163 | -0.3204, - | -0.2185 | 0.186 | -0.2184 | -0.5989, |
| | 0.2162 | | | 0.1116 | | | | 0.16 |
| d ₁₇ | 0.2779 | 0.2936 | 0.271 | -0.2771, | 0.2783 | 0.3804 | 0.2736 | -0.4582, |
| | | | | 0.8758 | | | | 1.044 |
| d ₁₈ | - | 0.3143 | -0.0247 | -0.6124, | -0.0297 | 0.3662 | -0.0343 | -0.7349, |
| ما | 0.0176 | 0.0400 | 0.0004 | 0.6192 | 0 0004 | 0 0 4 4 4 | 0 4047 | 0.7064 |
| a ₁₉ | - | 0.0483 | -0.0891 | -0.1815, | -0.2291 | 0.2441 | -0.1917 | -0.8164, |
| т | 0.8904 | 0 1 2 1 4 | 0 1107 | 0.0033 | 0 1 5 1 | 0 1 2 1 2 | 0 1127 | 0.1001 |
| I 1 | 0.154 | 0.1314 | 0.1137 | 0.0154, | 0.134 | 0.1312 | 0.1137 | 0.0154, |
| т | 0 1506 | 0 1206 | 0 1106 | 0.0120 | 0 1205 | 0 1 2 2 4 | 0 1007 | 0.0124 |
| 12 | 0.1500 | 0.1290 | 0.1100 | 0.0149, | 0.1395 | 0.1234 | 0.1007 | 0.0134, |
| т. | 0 1220 | 0 1135 | 0.0864 | 0.0049 | 0 1245 | 0 117 | 0.0865 | 0.4703 |
| 13 | 0.1223 | 0.1155 | 0.0004 | 0.0113, | 0.1245 | 0.117 | 0.0000 | 0.0107, |
| Т | 0 1509 | 0 1299 | 0 1108 | 0.4401 | 0 1485 | 0 1299 | 0 1079 | 0.4313 |
| 14 | 0.1000 | 0.1200 | 0.1100 | 0.5063 | 0.1100 | 0.1200 | 0.1070 | 0.5039 |
| T₅ | 0.1324 | 0.121 | 0.0937 | 0.0119. | 0.1342 | 0.1246 | 0.0936 | 0.0114 |
| - 5 | | | | 0.4691 | | | | 0.4818 |
| Te | 0.131 | 0.118 | 0.0936 | 0.0124. | 0.1317 | 0.1197 | 0.0935 | 0.0121. |
| 0 | | | | 0.4587 | | | | 0.4642 |
| T ₇ | 0.1904 | 0.1548 | 0.1447 | 0.0188, | 0.1922 | 0.1584 | 0.1446 | 0.0180, |
| | | | | 0.5996 | | | | 0.6105 |
| T ₈ | 0.155 | 0.1368 | 0.1119 | 0.0139, | 0.1546 | 0.1377 | 0.1107 | 0.0134, |
| | | | | 0.5308 | | | | 0.5323 |
| T₀ | 0.1442 | 0.1259 | 0.105 | 0.0141, | 0.1314 | 0.1202 | 0.0928 | 0.0116, |
| | | | | 0.4908 | | | | 9,4653 |
| D _{res} | 73.08 | | | | 57.8 | | | |
| DIC | 374.132 | | | | 365.991 | | | |

Appendix Table 7. Effect of covariates (age of subjects)-major adverse events

| | | Fixed | effect mo | del | Random effect model | | | |
|-----------------|---------|--------|-----------|---------------|---------------------|--------|--------|----------|
| | Mean | SD | Median | Crl | Mean | SD | Median | Crl |
| d ₁₂ | 0.5896 | 0.0954 | 0.5892 | 0.4041, | 0.7058 | 0.1872 | 0.6924 | 0.3692, |
| | | | | 0.7772 | | | | 1.114 |
| d ₁₃ | 0.75 | 0.4781 | 0.7264 | -0.126, 1.755 | 0.7487 | 0.6222 | 0.7335 | -0.4429, |
| | | | | | | | | 2.022 |
| d ₁₄ | 0.9067 | 0.269 | 0.902 | 0.3923, 1.448 | 0.8586 | 0.4408 | 0.8644 | -0.0403, |
| | | | | | | | | 1.725 |
| d ₁₅ | 1.05 | 1.331 | 0.87 | -1.032, 4.196 | 1.051 | 1.408 | 0.8712 | -1.206, |
| | | | | | | | | 4.323 |
| d ₁₆ | 1.112 | 0.1995 | 1.107 | 0.7353, 1.518 | 0.9807 | 0.3603 | 0.992 | 0.2285, |
| | | | | | | | | 1.669 |
| d ₁₇ | 1.222 | 1.364 | 1.0344 | -0.9135, 4.27 | 1.199 | 1.386 | 1.047 | -1.073, |
| | 0.0005 | 0.0070 | 0.0404 | 4 005 0 040 | 0 00 10 | 0.0705 | 0.4054 | 4.433 |
| d ₁₈ | 0.2865 | 0.8976 | 0.2181 | -1.285, 2.249 | 0.2646 | 0.9735 | 0.1954 | -1.45, |
| ام | 0 4050 | 0 4440 | 0 40 47 | 0.0470 | 0 4005 | 0 4040 | 0.4000 | 2.397 |
| u ₁₉ | 0.4350 | 0.1118 | 0.4347 | 0.2170, | 0.4295 | 0.4018 | 0.4308 | -0.400 |
| т | 0.0116 | 0.0144 | 0 0070 | 0.0000 | 0.0116 | 0.0142 | 0.0072 | 1.20 |
| I ₁ | 0.0110 | 0.0144 | 0.0072 | 0.0010, | 0.0110 | 0.0143 | 0.0072 | 0.0001, |
| т | 0 0206 | 0.0245 | 0.0128 | 0.0495 | 0 0233 | 0 0278 | 0.0144 | 0.0490 |
| 12 | 0.0200 | 0.0245 | 0.0120 | 0.0010, | 0.0255 | 0.0270 | 0.0144 | 0.0020, |
| т. | 0 0263 | 0 0340 | 0.0150 | 0.0002 | 0 0280 | 0 0300 | 0 0149 | 0.0300 |
| 13 | 0.0200 | 0.0040 | 0.0100 | 0.1206 | 0.0200 | 0.0000 | 0.0145 | 0.1366 |
| T, | 0 0285 | 0 0340 | 0 0175 | 0.0023 | 0 0286 | 0.0366 | 0.0168 | 0.0019 |
| •4 | 0.0200 | 0.0010 | 0.0110 | 0.1215 | 0.0200 | 0.0000 | 0.0100 | 0.1287 |
| T ₅ | 0.0597 | 0.1184 | 0.0180 | 0.0011. | 0.0627 | 0.1246 | 0.0181 | 0.0001. |
| 5 | | | | 0.4388 | | | | 0.4664 |
| T ₆ | 0.034 | 0.0390 | 0.0214 | 0.0029, | 0.0312 | 0.0379 | 0.0189 | 0.0023, |
| ° | | | | 0.1413 | | | | 0.1356 |
| T_7 | 0.0688 | 0.1302 | 0.0213 | 0.0012, | 0.0683 | 0.1284 | 0.0212 | 0.0011, |
| | | | | 0.4958 | | | | 0.4867 |
| T ₈ | 0.0223 | 0.0430 | 0.0092 | 0.0001, | 0.0233 | 0.047 | 0.0090 | 0.0001, |
| | | | | 0.1289 | | | | 0.1417 |
| T ₉ | 0.0178 | 0.0215 | 0.0110 | 0.0015, | 0.0189 | 0.0251 | 0.0110 | 0.0013, |
| | | | | 0.0753 | | | | 0.0853 |
| D res | 54.57 | | | | 46.33 | | | |
| DIC | 270.707 | | | | 267.480 | | | |

Appendix Table 8. Effect of covariates (age of subjects)—major bleeding



Appendix Fig. 1. Funnel plot for oral anticoagulants







Appendix Fig. 3. Funnel plot for PAR-1 Antagonists

© 2015 Gao and Li; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history: The peer review history for this paper can be accessed here: http://www.sciencedomain.org/review-history.php?iid=721&id=12&aid=7263