Meta-Analysis of Oral Anticoagulant Monotherapy as an Antithrombotic Strategy in Patients With Stable Coronary Artery Disease and Nonvalvular Atrial Fibrillation

Lee, So Ryoung; Rhee, Tae Min; Kang, Do Yoon; Choi, Eue Keun; Oh, Seil; Lip, Gregory Y.H.

Published in:
American Journal of Cardiology

DOI (link to publication from Publisher):
10.1016/j.amjcard.2019.05.072

Publication date:
2019

Document Version
Accepted author manuscript, peer reviewed version

Meta-analysis of Oral Anticoagulant Monotherapy as an Antithrombotic Strategy in Patients with Stable Coronary Artery Disease and Non-valvular Atrial Fibrillation

So-Ryoung Lee MD , Tae-Min Rhee , Do-Yoon Kang MD , Eue-Keun Choi MD, PhD , Seil Oh MD, PhD , Gregory Y H Lip MD

PII: S0002-9149(19)30705-2
DOI: https://doi.org/10.1016/j.amjcard.2019.05.072
Reference: AJC 24019

To appear in: *The American Journal of Cardiology*

Received date: 10 April 2019
Revised date: 28 May 2019

Please cite this article as: So-Ryoung Lee MD , Tae-Min Rhee , Do-Yoon Kang MD , Eue-Keun Choi MD, PhD , Seil Oh MD, PhD , Gregory Y H Lip MD , Meta-analysis of Oral Anticoagulant Monotherapy as an Antithrombotic Strategy in Patients with Stable Coronary Artery Disease and Non-valvular Atrial Fibrillation, *The American Journal of Cardiology* (2019), doi: https://doi.org/10.1016/j.amjcard.2019.05.072

Meta-analysis of Oral Anticoagulant Monotherapy as an Antithrombotic Strategy in Patients with Stable Coronary Artery Disease and Non-valvular Atrial Fibrillation

So-Ryoung Lee, MD[a]*, Tae-Min Rhee[a]*, Do-Yoon Kang, MD[b], Eue-Keun Choi, MD, PhD[a], Seil Oh, MD, PhD[a†], and Gregory Y H Lip, MD[c,d†]

[a] Division of Cardiology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [b] Heart Institute, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [c] Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Chest & Heart Hospital, Liverpool, United Kingdom; and [d] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

*Drs. Lee and Rhee contributed equally to this work and are joint first authors.

[†]Drs. Oh and Lip contributed equally to this work and are joint senior authors.

Running title: Antithrombotic strategy in stable coronary artery disease

Corresponding authors

Seil Oh: Phone +82 2 2072 2088/ Fax: +82 2 762 9662; E-mail: seil@snu.ac.kr

Gregory Y H Lip: Phone: +44 151 794 9020; E-mail: Gregory.Lip@liverpool.ac.uk

Abstract

Guidelines recommend oral anticoagulant (OAC) monotherapy without antiplatelet therapy in patients with non-valvular atrial fibrillation (AF) with stable coronary artery disease (CAD) of >1 year after myocardial infarction or percutaneous coronary intervention. More evidences are required for the safety and efficacy of OAC monotherapy compared to OAC plus antiplatelet therapy. PubMed, EMBASE, and Cochrane Database of Systematic Reviews were systematically searched up to February 2019. Nonrandomized studies and randomized clinical trials comparing OAC monotherapy with OAC plus single antiplatelet therapy (SAPT) for patients with stable CAD and non-valvular AF. The primary endpoint was major adverse cardiovascular events (MACEs, composite of ischemic or thrombotic events) and secondary outcomes included major bleeding, stroke, all-cause death, and net adverse events (NAEs, composite of ischemic, thrombotic, or bleeding events). From 6 trials, 8,855 patients were included. There was no significant difference in MACE in AF patients treated using OAC plus SAPT compared to those treated with OAC monotherapy (hazard ratio [HR], 1.09; 95% confidence interval [CI], 0.92-1.29). OAC plus SAPT was associated with a significantly higher risk of major bleeding compared to OAC monotherapy (HR, 1.61; 95% CI, 1.38-1.87), as well as in terms of NAE (HR, 1.21; 95% CI, 1.02-1.43). There were no significant differences in rates of stroke and all-cause death. In conclusion, in this meta-analysis, OAC monotherapy and OAC plus SAPT treatment showed similar effectiveness, but OAC monotherapy was significantly associated with a lower risk of bleeding compared to OAC plus SAPT in patients with non-valvular AF and stable CAD.

Keywords: atrial fibrillation, stable coronary artery disease, oral anticoagulation, meta-analysis

Introduction

Coronary artery disease (CAD) is accompanied in one third of atrial fibrillation (AF) patients.[1] The oral anticoagulant (OAC) and antiplatelet therapy (APT) are essential treatment for AF patients with CAD who have undergone percutaneous coronary intervention (PCI).[2,3] Particularly in AF patients with stable CAD for >1 year after the acute coronary events or PCI, either OAC monotherapy or combined OAC with single antiplatelet therapy (SAPT) is recommended according to their risk of future coronary events.[4-6] Although several observational and prospective registries have evaluated the optimal treatment for patients with stable CAD and AF,[7-10] there are limited data from randomized controlled trials (RCTs) regarding the use of OAC monotherapy. The result of OAC-ALONE trial remains inconclusive due to being under-powered.[11] We thus conducted a systematic review and performed a meta-analysis to compare the efficacy and safety of OAC monotherapy and OAC plus single antiplatelet therapy (SAPT) in AF patients with stable CAD.

Methods

We performed electronic searches of PubMed, EMBASE and the Cochrane Database of Systematic Reviews to identify studies that included specific keywords relevant to this topic. We added manual search results, including references cited in electronically searched articles, recent reviews, editorials, and meta-analyses. We did not apply any restrictions regarding the language, study period, or sample size. A description of the detailed study methods including search strategy are included in the Supplement.

The inclusion criteria for studies in this meta-analysis were as follows: 1) the study should be published before February 2019; 2) clinical endpoints should be clearly reported; 3) the study should include stable CAD (defined as 1 year after any MI or PCI) patients with AF;

4) a comparison of outcomes between OAC monotherapy and OAC plus SAPT should be presented. Two investigators (S-R Lee and T-M Rhee) independently screened titles and abstracts from the search results, removed duplicates, investigated full articles and determined if they should be included in the analysis. The primary endpoint was a major adverse cardiovascular event (MACE, a composite of ischemic or thrombotic events) and secondary outcomes included major bleeding, stroke or systemic thromboembolism, all-cause death, and net adverse events (NAEs, a composite of ischemic, thrombotic, or bleeding events).

We acquired the data for analysis and the description of study characteristics using a standardized extraction form. We assessed the quality of eligible studies using the Cochrane Collaboration's tool for assessing the risk of bias, the Newcastle-Ottawa Scale (NOS) and the strengthening the reporting of observational studies in epidemiology (STROBE) checklist.

We applied random-effect models to analyze primary and secondary endpoints and pooled hazard ratios (HR) are presented with 95% confidence intervals (CI) as statistical summaries. Heterogeneity between studies was quantified using I^2 statistics. Publication bias was assessed qualitatively using funnel plot asymmetry and quantitatively using Egger's and Begg's tests.

Subgroup analyses were used to assess differential effects between various subgroups. Two-sided *p*-values <0.05 were considered to statistically significant. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (eTable 1 in the Supplement) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.

Results

Figure 1 presents an overview of the search and selection process used in this meta-analysis. A total of 8,855 patients with stable CAD and non-valvular AF were included in the 6 studies. A summary of important study characteristics can be found in Table 1 and eTable 4 in the Supplement. Only recent publications included DOAC users (27%, 40.6%, and 24.8% of total study population).[9-11] Patients with DOAC accounted for 8.6% of total of 8,855 pooled patients, irrespective of whether they were prescribed OAC monotherapy or OAC plus SAPT. Both aspirin and clopidogrel were included as SAPT therapies. The definitions of major bleeding in included studies were largely consistent with the International Society on Thrombosis and Hemostasis (ISTH) major bleeding criteria.

Risk of bias of each study was assessed using the Cochrane Collaboration's tool for RCT, and the Newcastle-Ottawa Scale for non-randomized studies (eTable 2 and 3 in the Supplement). The bias risk of both RCT and non-randomized studies was low, providing high methodologic quality of this meta-analysis.

In our main analysis, we observed no significant heterogeneity for the all endpoints. In this population of patients with stable CAD and non-valvular AF, OAC plus SAPT was associated with an increased risk of major bleeding (pooled HR, 1.61; 95 % CI, 1.38-1.87) while there was no significant difference in MACE when compared to OAC monotherapy (pooled HR, 1.09; 95 % CI, 0.92-1.29) (Figure 2). Funnel plots, along with the Egger's and the Begg's test, showed no significant publication bias for MACE. Although some asymmetry was observed for major bleeding, the result remained consistent after trim-and-fill method (eFigure 1 in the Supplement).

There was no significant difference in rates of all-cause death (pooled HR, 1.07; 95 % CI, 0.91-1.27) and stroke (pooled HR, 0.99; 95% CI, 0.70-1.40). Compared to OAC

monotherapy, OAC plus SAPT showed a significantly worse outcomes in NAE (pooled HR, 1.21; 95 % CI, 1.02-1.43) (Figure 3).

In general, consistent findings were observed in various subgroup analyses (Figure 4). The subgroup analyses did not reveal any significant heterogeneity in various subgroups. OAC plus SAPT tended to show higher risk of MACE than OAC monotherapy in the subgroup that >60% of total population had previous history of MI (HR, 1.35; 95% CI, 0.96-1.88). Results were consistent in the subgroup by the stent type mainly used in the studies (BMS or DES). OAC plus SAPT tended to show higher risk of bleeding than OAC monotherapy regardless of the subgroup by VKA only versus VKA/DOAC.

Discussion

Our principal findings are as follows: (1) the pooled HR for major bleeding and NAE were significantly higher in the OAC plus SAPT group, while there were no significant differences in MACE, stroke, and death; (2) in general, consistent findings were observed in various subgroup analyses, including BMS and DES studies; (3) OAC monotherapy showed more benefit for MACE in the subgroup with higher proportion of previous MI patients; (4) in the studies after the introduction of DOACs, OAC monotherapy was generally safer and had comparable MACE to that of OAC plus SAPT. This meta-analysis is the first to include data from the OAC-ALONE study, which is the first RCT evaluating safety and efficacy of OAC monotherapy and OAC plus SAPT.[11]

A substantial proportion of patients with AF have concomitant CAD and are at risk of acute coronary events requiring PCI at some point in their lives.[1,12] Irrespective of APT regimens used, omission of OAC is regarded as inadequate for stroke prevention in patients with AF; however, the comorbidities of CAD and concomitant use of APT lead to

underutilization of OAC, often due to concerns about the risk of bleeding.[13-16] A recent report that primary prevention through aspirin is harmful in terms of bleeding without any benefit evokes a need to review the current medical practice of using APT routinely.[17] Also, many physicians have misconception that APT is more mandatorily considered in AF patients with CAD; therefore, OAC is largely underused in these patients or alternatively, such patients receive unnecessary treatment, which can substantially increase the risk of bleeding.[18]

Although guidelines generally recommend OAC monotherapy for AF patients with stable CAD, the evidence that stands for the use of OAC monotherapy has been limited.[5,6,19] A Danish nationwide registry study demonstrated that when compared to other antithrombotic regimen, VKA plus SAPT was not more beneficial for prevention of thromboembolism; however, it significantly increased the risk of bleeding compared to VKA monotherapy.[18] Subsequent prospective studies reported that VKA alone resulted in no difference in MACE, but led to a decreased risk of bleeding compared with VKA plus SAPT.[7,8]

In the PREFER-in-AF and PREFER-in-AF PROLONGATION registries, OAC monotherapy significantly reduced both ACS and major bleeding, leading to a clear net clinical benefit.[10] The benefits of OAC monotherapy in ACS indicate that the OAC plus SAPT group may be at an increased risk of both thromboembolic and bleeding events, which is consistent with the result of the subgroup analysis in this meta-analysis. Notably, in the OAC plus SAPT group, the use of antithrombotic agents is likely to be interrupted by the bleeding events, which may increase the incidence of MACE in high risk patients. Furthermore, since most evidence to date is from non-randomized studies, unmeasured confounders such as physician's discretion cannot be ignored. It is possible that the assignment to either OAC monotherapy or OAC plus SAPT group was affected by the

individual bleeding risk.

Following these cohort studies, the first RCT comparing OAC versus OAC plus SAPT in AF patients with stable CAD was performed,[11] but the patient enrollment was prematurely terminated due to slow enrollment and the number of study patients was smaller than originally planned. The significance of non-inferiority of OAC monotherapy compared to OAC plus SAPT was not achieved for the primary composite outcome (all-cause death + MI + stroke/systemic embolism), while was established for the secondary composite outcome (primary composite outcome + major bleeding) (HR: 0.99; 95% CI: 0.71-1.39; p = 0.016 for non-inferiority). Although the study was under-powered and inconclusive, the findings were consistent with previous cohort studies, demonstrating that OAC plus SAPT had no significant benefit when compared to OAC monotherapy.

In our meta-analysis, OAC plus SAPT treatment was significantly associated with an increased risk of major bleeding as well as NAE, without a significant reduction in cardiac and cerebral ischemic events compared to OAC monotherapy. Our findings are largely consistent with previous studies.

Prescription of DOACs for stroke prevention has been rapidly increasing in patients with non-valvular AF, since their introduction, as an effective, safe, and convenient alternative to VKA.[1,14,20] In this study, a large portion of OAC treatment was performed using VKA, and only recent studies have included patients treated with DOAC or DOAC plus SAPT.[9-11] In the subgroup analysis, the results were consistent for both VKA and VKA/DOAC studies. At the time of the systematic search for the present meta-analysis, we found no clinical trials directly comparing the use of DOAC monotherapy with DOAC plus SAPT in AF patients with stable CAD. Although 2 randomized clinical trials are undergoing with DOACs (NCT 02642419 and NCT 03718559),[21] more evidence are required given the

recent report that worse efficacy may be seen in DOAC compared to VKA.[22] Real-world cohort studies are also warranted to analyze the various factors that affect the practical use of DOAC, such as the dosing regimen, adherence or compliance issue, and the fluctuation of renal function.

This study has several limitations. First, the treatment quality of VKA, represented as time in therapeutic range, was not thoroughly evaluated in all studies included in this analysis. Second, some studies in this meta-analysis reported the mean CHA_2DS_2-VASc score (4.7-4.9[8], 4.7[9], and 4.6[11]) and HAS-BLED score (3.1[9]) of the total study population, but the reporting methods for CHA_2DS_2-VASc and HAS-BLED scores varied between the studies. Therefore, we could not explore whether significant interactions exist among subgroups stratified by these scores. Third, we could not analyze whether there was a particular clinical subgroup in which OAC plus SAPT treatment may be beneficial. The procedural characteristics were not available for most of the studies included, thus limiting the scope of this analysis. Lastly, since many of included studies were performed in the VKA era,[7,8,18] further studies are required, particularly those including DOACs as the OAC therapy used. In addition, subsequent studies should include comparisons with new antiplatelet drugs that have not been adequately addressed in previous studies.

In conclusion, OAC monotherapy and OAC plus SAPT treatment showed similar effectiveness, but OAC monotherapy was significantly associated with a lower risk of bleeding compared to OAC plus SAPT in patients with non-valvular AF and stable CAD.

Acknowledgements

None

Funding source

This study was supported by a SoonChunHyang University Research Fund.

Disclosures

SRL, TMR, DYK: None; EKC: Research grant from Daiichi-Sankyo, BMS/Pfizer, and Biosense Webster; SO: Research grant from Bayer Korea, BMS Korea, Boehringer-Ingelheim Korea, Daiichi Sankyo Korea, Pfizer Korea. No fees are received personally; GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are received personally.

References

1. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955-962.

2. Sibbing D, Angiolillo DJ, Huber K. Antithrombotic therapy for acute coronary syndrome: Past, present and future. *Thromb Haemost* 2017;117:1240-1248.

3. Lip G, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: Past, present and future. Comparing the guidelines and practical decision-making. *Thromb Haemost* 2017;117:1230-1239.

4. Lip GYH, Collet JP, Haude M, Byrne R, Chung EH, Fauchier L, Halvorsen S, Lau D, Lopez-Cabanillas N, Lettino M, Marin F, Obel I, Rubboli A, Storey RF, Valgimigli M, Huber K. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). *Europace* 2019;21:192-193.

5. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893-2962.

6. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;39:213-260.

7. Hamon M, Lemesle G, Tricot O, Meurice T, Deneve M, Dujardin X, Brufau JM, Bera J, Lamblin N, Bauters C. Incidence, source, determinants, and prognostic impact of major bleeding in outpatients with stable coronary artery disease. *J Am Coll Cardiol* 2014;64:1430-1436.

8. Lemesle G, Ducrocq G, Elbez Y, Van Belle E, Goto S, Cannon CP, Bauters C, Bhatt DL, Steg PG. Vitamin K antagonists with or without long-term antiplatelet therapy in outpatients with stable coronary artery disease and atrial fibrillation: Association with ischemic and bleeding events. *Clin Cardiol* 2017;40:932-939.

9. Fischer Q, Georges JL, Le Feuvre C, Sharma A, Hammoudi N, Berman E, Cohen S, Jolivet I, Silvain J, Helft G. Optimal long-term antithrombotic treatment of patients with stable coronary artery disease and atrial fibrillation: "OLTAT registry". *Int J Cardiol* 2018;264:64-69.

10. Patti G, Pecen L, Lucerna M, Huber K, Rohla M, Renda G, Siller-Matula J, Schnabel

RB, Cemin R, Kirchhof P, De Caterina R. Outcomes of anticoagulated patients with atrial fibrillation treated with or without antiplatelet therapy - A pooled analysis from the PREFER in AF and PREFER in AF PROLONGATON registries. *Int J Cardiol* 2018;270:160-166.

11. Matsumura-Nakano Y, Shizuta S, Komasa A, Morimoto T, Masuda H, Shiomi H, Goto K, Nakai K, Ogawa H, Kobori A, Kono Y, Kaitani K, Suwa S, Aoyama T, Takahashi M, Sasaki Y, Onishi Y, Mano T, Matsuda M, Motooka M, Tomita H, Inoko M, Wakeyama T, Hagiwara N, Tanabe K, Akao M, Miyauchi K, Yajima J, Hanaoka K, Morino Y, Ando K, Furukawa Y, Nakagawa Y, Nakao K, Kozuma K, Kadota K, Kimura K, Kawai K, Ueno T, Okumura K, Kimura T. Open-Label Randomized Trial Comparing Oral Anticoagulation With and Without Single Antiplatelet Therapy in Patients With Atrial Fibrillation and Stable Coronary Artery Disease Beyond 1 Year After Coronary Stent Implantation. *Circulation* 2019;139:604-616.

12. Lee SR, Choi EK, Han KD, Cha MJ, Oh S. Trends in the incidence and prevalence of atrial fibrillation and estimated thromboembolic risk using the CHA2DS2-VASc score in the entire Korean population. *Int J Cardiol* 2017;236:226-231.

13. Gadsboll K, Staerk L, Fosbol EL, Sindet-Pedersen C, Gundlund A, Lip GYH, Gislason GH, Olesen JB. Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. *Eur Heart J* 2017;38:899-906.

14. Lee SR, Choi EK, Han KD, Cha MJ, Oh S, Lip GYH. Temporal trends of antithrombotic therapy for stroke prevention in Korean patients with non-valvular atrial fibrillation in the era of non-vitamin K antagonist oral anticoagulants: A nationwide population-based study. *PLoS One* 2017;12:e0189495.

15. Verheugt FWA, Gao H, Al Mahmeed W, Ambrosio G, Angchaisuksiri P, Atar D, Bassand JP, Camm AJ, Cools F, Eikelboom J, Kayani G, Lim TW, Misselwitz F, Pieper KS, van Eickels M, Kakkar AK. Characteristics of patients with atrial fibrillation prescribed antiplatelet monotherapy compared with those on anticoagulants: insights from the GARFIELD-AF registry. *Eur Heart J* 2018;39:464-473.

16. Ono F, Tanaka S, Nakao YM, Kawakami K. Utilization of Anticoagulant and Antiplatelet Agents Among Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention- Retrospective Cohort Study Using a Nationwide Claims Database in Japan. *Circ J* 2018;82:361-368.

17. McNeil JJ, Nelson MR, Woods RL, Lockery JE, Wolfe R, Reid CM, Kirpach B, Shah RC, Ives DG, Storey E, Ryan J, Tonkin AM, Newman AB, Williamson JD, Margolis KL, Ernst ME, Abhayaratna WP, Stocks N, Fitzgerald SM, Orchard SG, Trevaks RE, Beilin LJ, Donnan GA, Gibbs P, Johnston CI, Radziszewska B, Grimm R, Murray AM. Effect of Aspirin on All-Cause Mortality in the Healthy Elderly. *N Engl J Med* 2018;379:1519-1528.

18. Lamberts M, Gislason GH, Lip GY, Lassen JF, Olesen JB, Mikkelsen AP, Sorensen R, Kober L, Torp-Pedersen C, Hansen ML. Antiplatelet therapy for stable coronary artery disease in atrial fibrillation patients taking an oral anticoagulant: a nationwide cohort study. *Circulation* 2014;129:1577-1585.

19. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, Lane DA, Ruff CT, Turakhia M, Werring D, Patel S, Moores L. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. *Chest* 2018;154:1121-1201.

20. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, Halperin

JL, Ma CS, Zint K, Elsaesser A, Bartels DB, Lip GY. The Changing Landscape for Stroke Prevention in AF: Findings From the GLORIA-AF Registry Phase 2. *J Am Coll Cardiol* 2017;69:777-785.

21. Yasuda S, Kaikita K, Ogawa H, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K. Atrial fibrillation and ischemic events with rivaroxaban in patients with stable coronary artery disease (AFIRE): Protocol for a multicenter, prospective, randomized, open-label, parallel group study. *Int J Cardiol* 2018;265:108-112.

22. Shpak M, Ramakrishnan A, Nadasdy Z, Cowperthwaite M, Fanale C. Higher Incidence of Ischemic Stroke in Patients Taking Novel Oral Anticoagulants. *Stroke* 2018;49:2851-2856.

Figure legends

Figure 1. Study flow

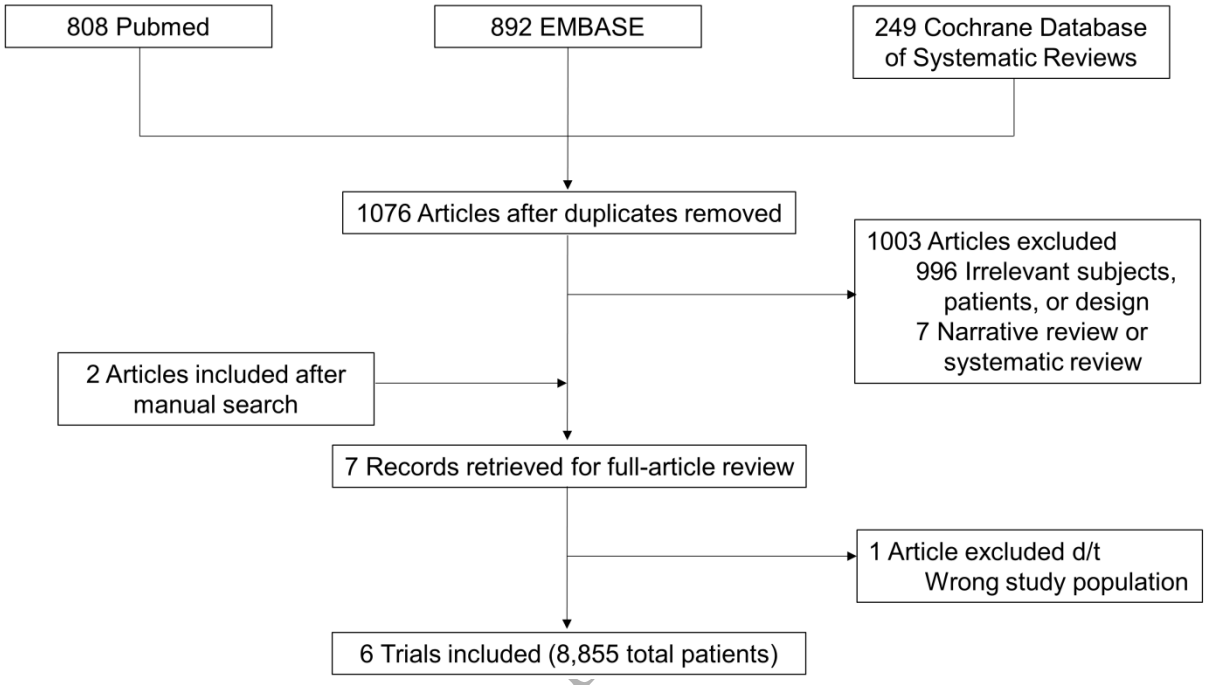
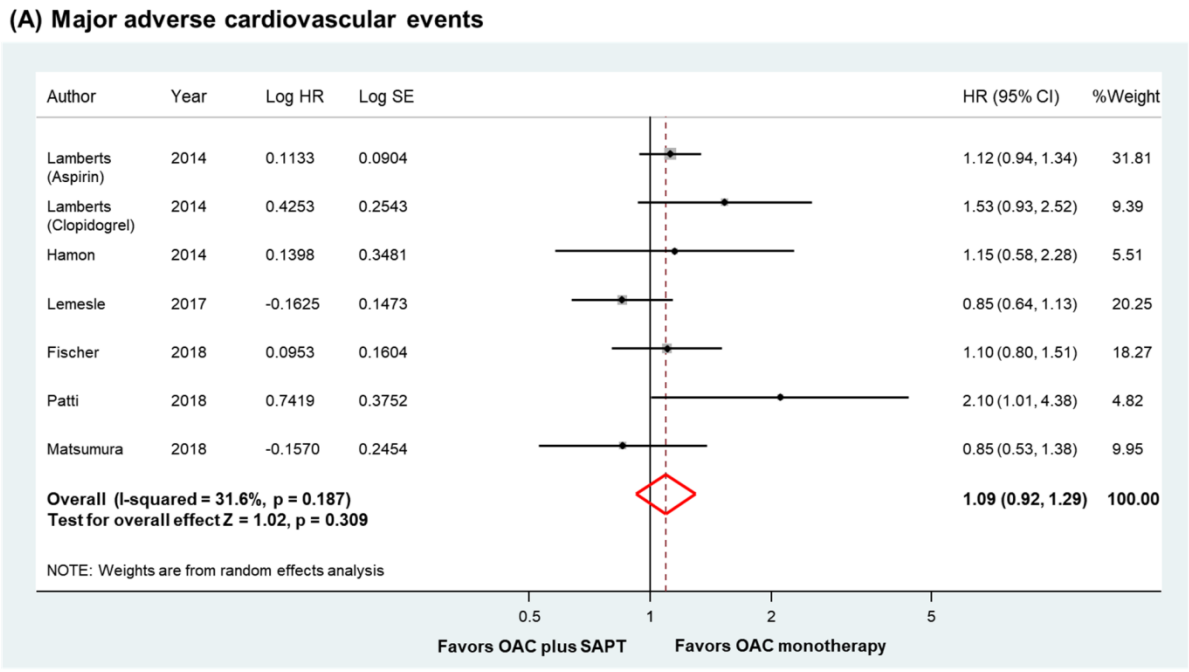
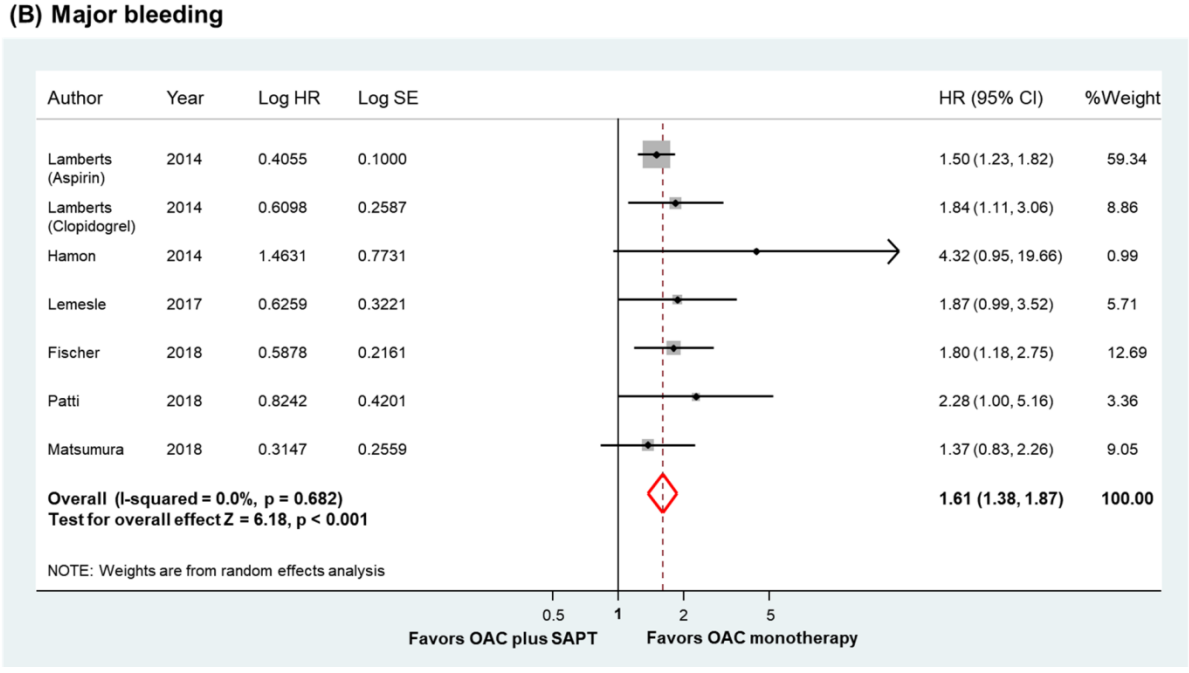


Figure 2. Pooled hazard ratio of MACE and major bleeding comparing OAC monotherapy versus OAC plus SAPT

(A) Major adverse cardiovascular events

(B) Major bleeding





Abbreviation: MACE, major adverse cardiovascular events; OAC, oral anticoagulant; SAPT, single antiplatelet therapy.

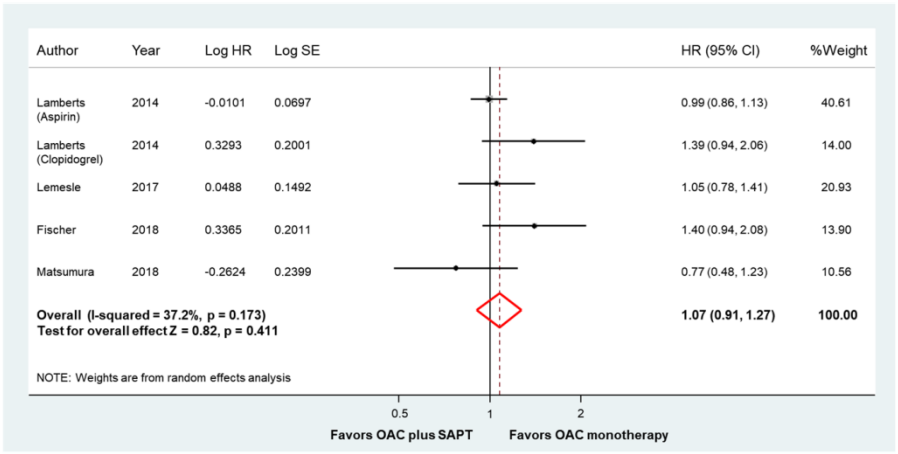
Figure 3. Pooled hazard ratio of all-cause death, stroke, and net adverse events comparing OAC monotherapy versus OAC plus SAPT

(A) All-cause death

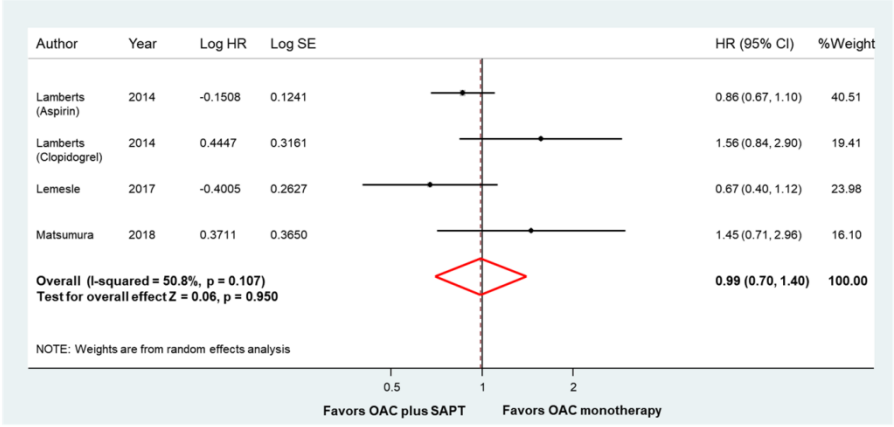
(B) Stroke

(C) Net adverse events

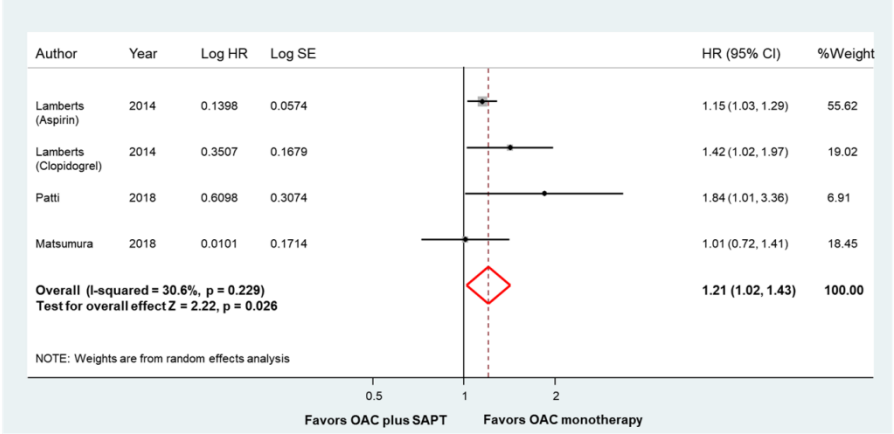
(A) All-cause death



(B) Stroke



(C) Net adverse events



Abbreviation: OAC, oral anticoagulant; SAPT, single antiplatelet therapy.

Figure 4. Subgroup analyses for MACE and major bleeding

Abbreviation: MACE, major adverse cardiovascular events.

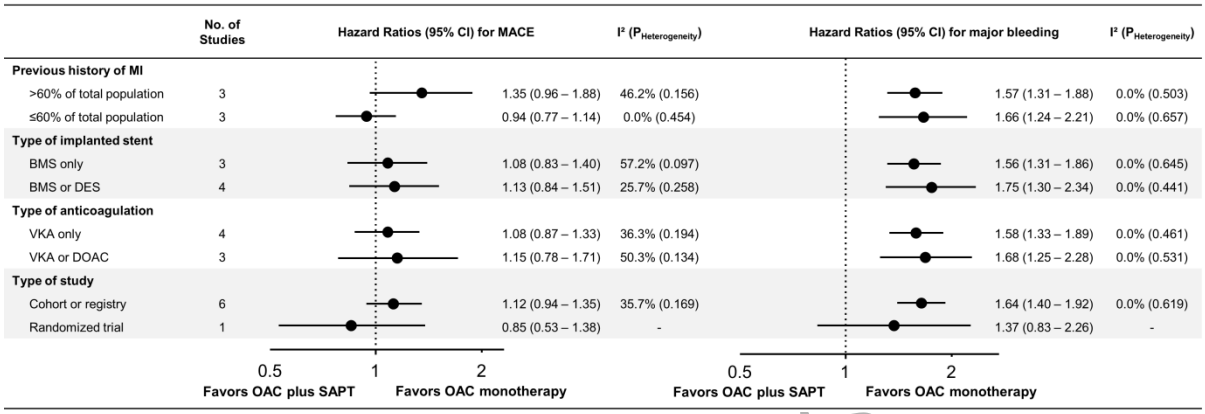


Table 1. Characteristics of Studies Selected for Analysis

			Number of patients				Demographics of overall population			
First author of study	**Study period**	**Study design**	**OAC alone**	**OAC + APT**	**Type of OAC**	**Type of APT**	**Mean age (Years)**	**Male**	**MI**	**Type of stent**
Lamberts (2014) (Aspirin)	2002-2011	Observational registry	950	1471	VKA	Aspirin	73.4	66.1%	78.8%	NR
Lamberts (2014) (Clopidogrel)	2002-2011	Observational registry	950	322	VKA	Clopidogrel	73.0	64.2%	74.3%	NR
Hamon (2014)	2010-2011	Prospective cohort	119	342	VKA	Aspirin or clopidogrel	NR	NR	NR	NR
Lemesle (2017)	2003-2004	Prospective cohort	1481	866	VKA	Aspirin or clopidogrel	73.2	71.2%	54.8%	NR
Fischer (2018)	2010-2015	Observational registry	172	434	VKA or DOAC	Aspirin or clopidogrel	76.0	68.9%	45.3%	BMS or DES
Patti (2018)	2012-2016	Observational registry	710	348	VKA or DOAC	Aspirin or clopidogrel	74.1	78.6%	68.3%	BMS or DES
Matsumura-Nakano (2018)	2013-2016	Randomized trial	344	346	VKA or DOAC	Aspirin or clopidogrel	75.1	85.2%	38.6%	BMS or DES

Abbreviations: APT, antiplatelet therapy; BMS, bare-metal stent; DES, drug-eluting stent; DOAC, direct oral anticoagulant; MI, myocardial infarction; NR, not reported; OAC, oral anticoagulant; VKA, vitamin K antagonist.

Highlights

- Evidence for optimal antithrombotic regimen for AF with stable CAD is limited.
- This meta-analysis compared outcomes between OAC monotherapy and OAC plus SAPT.
- OAC monotherapy showed similar efficacy but significantly lower risk of bleeding.
- Further evidence regarding DOAC in AF patients with stable CAD is required.