Rev Esp Cardiol. 2019;72(4):305–316

Original article

Direct Oral Anticoagulants Versus Vitamin K Antagonists in Real-life Patients With Atrial Fibrillation. A Systematic Review and Meta-analysis

Carlos Escobar,[a,*] Julio Martí-Almor,[b] Alejandro Pérez Cabeza,[c] and M. José Martínez-Zapata[d]

[a] Departamento de Cardiología, Hospital La Paz, Madrid, Spain
[b] Servicio de Cardiología, Hospital del Mar, Barcelona, Spain
[c] Servicio de Cardiología, Hospital Costa del Sol, Marbella, Málaga, Spain
[d] Institut d'Investigació Biomèdica Sant Pau (IIB Sant Pau), CIBER Epidemiología y Salud Pública CIBERESP, Barcelona, Spain

Article history:
Received 27 October 2017
Accepted 2 March 2018
Available online 30 March 2018

Keywords:
Apixaban
Atrial fibrillation
Clinical practice
Dabigatran
Direct oral anticoagulants
Meta-analysis
Rivaroxaban
Warfarin

ABSTRACT

Introduction and objectives: To assess the effectiveness of direct oral anticoagulants vs vitamin K antagonists in real-life patients with atrial fibrillation.
Methods: A systematic review was performed according to Cochrane methodological standards. The results were reported according to the PRISMA statement. The ROBINS-I tool was used to assess risk of bias.
Results: A total of 27 different studies publishing data in 30 publications were included. In the studies with a follow-up up to 1 year, apixaban (HR, 0.93; 95%CI, 0.71-1.20) and dabigatran (HR, 0.95; 95%CI, 0.80-1.13) did not significantly reduce the risk of ischemic stroke vs warfarin, whereas rivaroxaban significantly reduced this risk (HR, 0.83; 95%CI, 0.73-0.94). Apixaban (HR, 0.66; 95%CI, 0.55-0.80) and dabigatran (HR, 0.83; 95%CI, 0.70-0.97) significantly reduced the major bleeding risk vs warfarin, but not rivaroxaban (HR, 1.02; 95%CI, 0.95-1.10), although with a high statistical heterogeneity among studies. Apixaban (HR, 0.56; 95%CI, 0.42-0.73), dabigatran (HR, 0.45; 95%CI, 0.39-0.51), and rivaroxaban (HR, 0.66; 95%CI, 0.49-0.88) significantly reduced the risk of intracranial bleeding vs warfarin. Reduced doses of direct oral anticoagulants were associated with a slightly better safety profile, but with a marked reduction in stroke prevention effectiveness.
Conclusions: Data from this meta-analysis suggest that, vs warfarin, the stroke prevention effectiveness and bleeding risk of direct oral anticoagulants may differ in real-life patients with atrial fibrillation.

Anticoagulantes orales directos frente a antagonistas de la vitamina K en pacientes con fibrilación auricular de la práctica clínica: revisión sistemática y metanálisis

Palabras clave:
Apixabán
Fibrilación auricular
Práctica clínica
Dabigatrán
Anticoagulantes orales directos
Metanálisis
Rivaroxabán
Warfarina

RESUMEN

Introducción y objetivos: Determinar la efectividad de los anticoagulantes orales directos frente a los antagonistas de la vitamina K en pacientes con fibrilación auricular de la práctica clínica.
Métodos: Se realizó una revisión sistemática acorde con los estándares metodológicos de Cochrane. Los resultados de la revisión se publicaron según la declaración PRISMA. Se empleó la herramienta ROBINS-I para determinar el riesgo de sesgos.
Resultados: Se incluyeron datos de 27 estudios diferentes provenientes de 30 publicaciones. En los estudios con seguimiento hasta 1 año, el apixabán (HR = 0,93; IC95%, 0,71-1,20) y dabigatrán (HR = 0,95; IC95%, 0,80-1,13) no se redujo significativamente el riesgo de ictus isquémico frente a la warfarina, pero sí el rivaroxabán (HR = 0,83; IC95%, 0,73-0,94). Con respecto al riesgo de hemorragias mayores, el apixabán (HR = 0,66; IC95%, 0,55-0,80) y el dabigatrán (HR = 0,83; IC95%, 0,70-0,97) lo redujeron significativamente frente a la warfarina, pero no el rivaroxabán (HR = 1,02, IC95%, 0,95-1,10), aunque con heterogeneidad entre los estudios. El apixabán (HR = 0,56; IC95%, 0,42-0,73), el dabigatrán (HR = 0,45; IC95%, 0,39-0,51) y el rivaroxabán (HR = 0,66; IC95%, 0,49-0,88) redujeron significativamente el riesgo de hemorragia intracraneal frente a la warfarina. El empleo de dosis bajas de anticoagulantes orales directos se asoció con una ligera mejoría del perfil de seguridad, pero con una marcada reducción de la efectividad en la prevención de ictus.

* Corresponding author: Departamento de Cardiología, Hospital La Paz, Paseo de la Castellana 261, 28046 Madrid, Spain.
E-mail address: escobar_cervantes_carlos@hotmail.com (C. Escobar).

https://doi.org/10.1016/j.rec.2018.03.009
1885-5857/

Conclusiones: Los resultados de este metanálisis indican que, en comparación con la warfarina, la efectividad para prevenir el riesgo de ictus y de hemorragias de los anticoagulantes orales directos en los pacientes con fibrilación auricular de la práctica clínica real puede ser diferente.

Abbreviations

AF: atrial fibrillation
DOACs: direct oral anticoagulants
VKAs: vitamin K antagonists

INTRODUCTION

Atrial fibrillation (AF), the most common arrhythmia in clinical practice,[1] is associated with a markedly increased risk of stroke. AF-associated stroke has a higher risk of death, disability, and recurrence.[2] A cornerstone in the prevention of thromboembolic complications in patients with AF is anticoagulation.[3] Although vitamin K antagonists (VKAs) are associated with a 60% reduction in the risk of stroke in AF patients,[4] they have many disadvantages that have limited their use in clinical practice, including a narrow therapeutic window, multiple interactions with other drugs and foods, and the need for frequent monitoring of anticoagulant activity and for dosage adjustments.[5]

Direct oral anticoagulants (DOACs) overcome most of these limitations. In addition, a number of phase III clinical trials have shown that DOACs are at least as effective as VKAs for the prevention of stroke or systemic embolism, but have a better safety profile, particularly regarding the risk of intracranial bleeding.[6–8]

The introduction of DOACs to routine clinical practice has been associated with improved rates of overall oral anticoagulation use in patients with AF.[9] Due to strict clinical trial inclusion and exclusion criteria and closer patient follow-up, patients with AF participating in clinical trials frequently differ from those in clinical practice. Thus, the information reported in randomized clinical trials is not always valid for real-life patients.[10,11] In the last few years, many claims database studies have analyzed the use of DOACs in AF in clinical practice. However, discrepancies between data sources, the statistical analysis approach, and patient characteristics can lead to conflicting results. In this context, a comprehensive analysis of all published information on the use of DOACs in patients with AF vs VKAs is of great interest. The aim of this systematic review and meta-analysis was to assess the effectiveness and safety of DOACs (apixaban, dabigatran, and rivaroxaban) vs VKAs in real-life patients with nonvalvular AF.

METHODS

A systematic review was performed according to Cochrane methodological standards.[12] Results were reported according to the PRISMA statement.[13] The review protocol is detailed in the Methods section of the supplementary material. C. Escobar and J. Martí-Almor selected the articles to be included. If there was disagreement, a third researcher, A. Pérez Cabeza, was consulted. All authors were responsible for data extraction. M.J. Martínez-Zapata was responsible for data analysis. All authors were involved in writing the manuscript.

Eligibility Criteria

We included observational controlled studies in patients diagnosed with nonvalvular AF comparing any DOAC (apixaban, dabigatran, or rivaroxaban; any dose) vs VKAs (focusing on warfarin). Only studies that reported rates and effect measures (hazard ratios [HRs]) were included in this meta-analysis. Inclusion was limited to observational studies (either prospective or retrospective) reporting on any of the abovementioned efficacy and safety outcomes from routinely collected health data. Studies with national or regional registries or registries covering a large population across multiple sites were included. Single-center studies using local registries were excluded unless they had more than 1000 patients. For studies that used the same registry and were conducted in the same period (or with substantial overlap), the most complete publication was selected. Only when the degree of overlap between studies was minimal were all publications included.

Outcomes

The outcomes of interest are detailed in the protocol described in the Methods section of the supplementary material. We prioritized ischemic stroke and the composite end point of stroke/systemic embolism for efficacy and major and intracranial bleeding for safety. All outcomes were assessed according to follow-up duration (up to 1 year, as well as longer) and anticoagulant dose (standard vs reduced).

Search Strategy

To retrieve studies of interest, a MEDLINE (via PubMed) and EMBASE (via Ovid) search was performed up to March 2017. Search algorithms adapted to the requirements of each database were designed; these algorithms included a combination of controlled vocabulary search terms and filters to retrieve clinical trials and cohort studies (Table 1 of the supplementary material). In addition, the bibliography sections of the retrieved eligible studies were further used to identify additional relevant studies. No temporal or linguistic limitations were applied to the searches.

For the study selection, search results were screened based on the title and abstract independently. Full-text versions of the articles deemed to be eligible were retrieved and eligibility was independently confirmed based on the inclusion criteria. Disagreements were resolved by reaching consensus or by consulting a third researcher. Results were imported into a PRISMA flowchart. For data collection, relevant data from eligible studies were extracted and crosschecked for accuracy.

Risk of Bias Assessment

The ROBINS-I tool was used to assess the risk of bias of the included studies.[14] For each study, the confounding bias was assessed regarding the selection, measurement interventions, deviations from intended interventions, missing data, outcome assessment, and selection of reported results. The original ROBINS-I tool was adapted to fit the design and specificities of the included studies (Table 2 of the supplementary material).

Data Analysis and Summary of Findings

When feasible, a pooled analysis was conducted by applying the Cochran-Mantel-Haenszel method under a random-effects model

using Review Manager Software (version 5.3.5). Heterogeneity and sources of variation between studies were assessed through the I^2 statistic. Findings were reported according to a narrative synthesis for each outcome of interest and its effect estimate.

RESULTS

The PRISMA flowchart is shown in Figure 1. A total of 4244 references were obtained from MEDLINE and EMBASE searches. After duplicate elimination, 3391 unique references were screened. Of the 3391 unique references, 3312 were excluded based on their title or abstract because they had no relationship with the outcomes of this systematic review. Of these, full texts were obtained for 79 studies. After a detailed assessment of the full texts, 49 studies were excluded. Finally, 27 different studies with published data in 30 publications were included (3 studies published relevant data in 2 separate articles).[15–45] The characteristics of the included studies are summarized in Table 3 of the supplementary material.

Data from AF patients treated with DOACs vs VKAs up to about 1 year are shown in Figure 2.

Ischemic Stroke

Apixaban and dabigatran did not reduce the risk of ischemic stroke vs warfarin (HR, 0.93; 95% confidence interval [95%CI], 0.71-1.20; HR, 0.95; 95%CI, 0.80-1.13; respectively). Statistical heterogeneity was high among studies. In contrast, rivaroxaban significantly reduced the risk of ischemic stroke vs warfarin (HR, 0.83; 95%CI, 0.73-0.94). This finding was highly consistent among studies (Figure 2A).

Ischemic Stroke Plus Systemic Embolism

Apixaban did not reduce the risk of an ischemic event (stroke/systemic embolism) vs warfarin (HR, 0.88; 95%CI, 0.64-1.21). Statistical heterogeneity was high among studies yielding conflicting results. Dabigatran did not reduce the risk of an ischemic event (stroke/systemic embolism) vs warfarin (HR, 0.92; 95%CI, 0.76-1.11). Rivaroxaban significantly reduced the risk of an ischemic event vs warfarin (HR, 0.80; 95%CI, 0.69-0.93), a finding consistent among studies. Overall, only 1 small study compared DOACs with warfarin with regard to ischemic events, with no significant differences between the 2 groups (HR, 0.44; 95%CI, 0.09-2.04) (Figure 2B).

Major Bleeding

A risk reduction was observed in major bleeding with apixaban and dabigatran vs warfarin (HR, 0.66; 95%CI, 0.55-0.80; HR, 0.83; 95%CI, 0.70-0.97; respectively), but statistical heterogeneity was

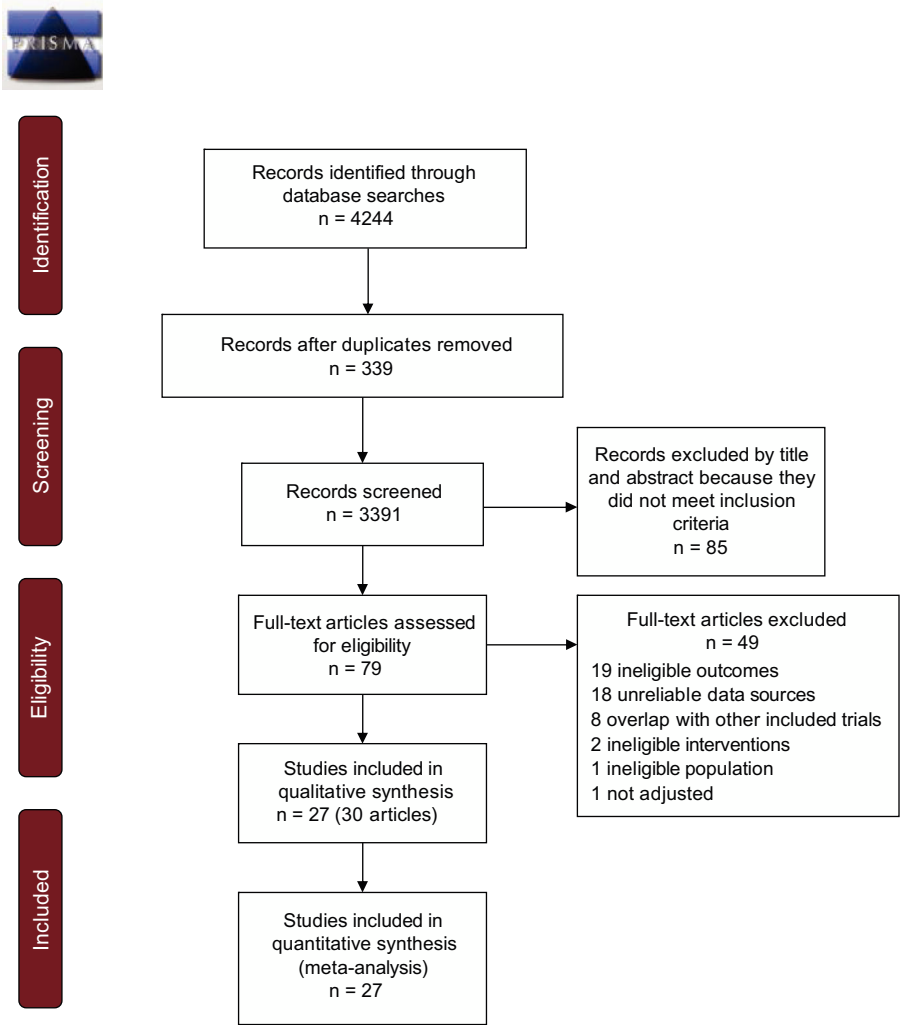

Figure 1. PRISMA eligibility flowchart.

high among studies. Rivaroxaban did not show a reduction in the risk of major bleeding vs warfarin (HR, 1.02; 95%CI, 0.95-1.10) (Figure 2C).

Intracranial Hemorrhage

Apixaban, dabigatran, and rivaroxaban (HR, 0.56; 95%CI, 0.42-0.73; HR, 0.45; 95%CI, 0.39-0.51; HR, 0.66; 95%CI, 0.49-0.88; respectively) significantly reduced the risk of intracranial bleeding vs warfarin (Figure 2D).

Only 4 studies reported results from more than 1 year (Larsen et al.,[36] Nielsen et al.,[39] Li et al.,[37] Avgil-Tsadok et al.[16]). Larsen et al.[36] and Nielsen et al.[39] reported data on all of the above outcomes but Li et al.[37] and Avgil-Tsadok et al.[16] only considered some of them. Compared with studies up to about 1 year of follow-up, the results were unchanged except for apixaban in the outcome "intracranial hemorrhage" and for dabigatran in the outcome "major bleeding"; in these instances, the initially observed significant risk reduction was lost (Figure of the supplementary material).

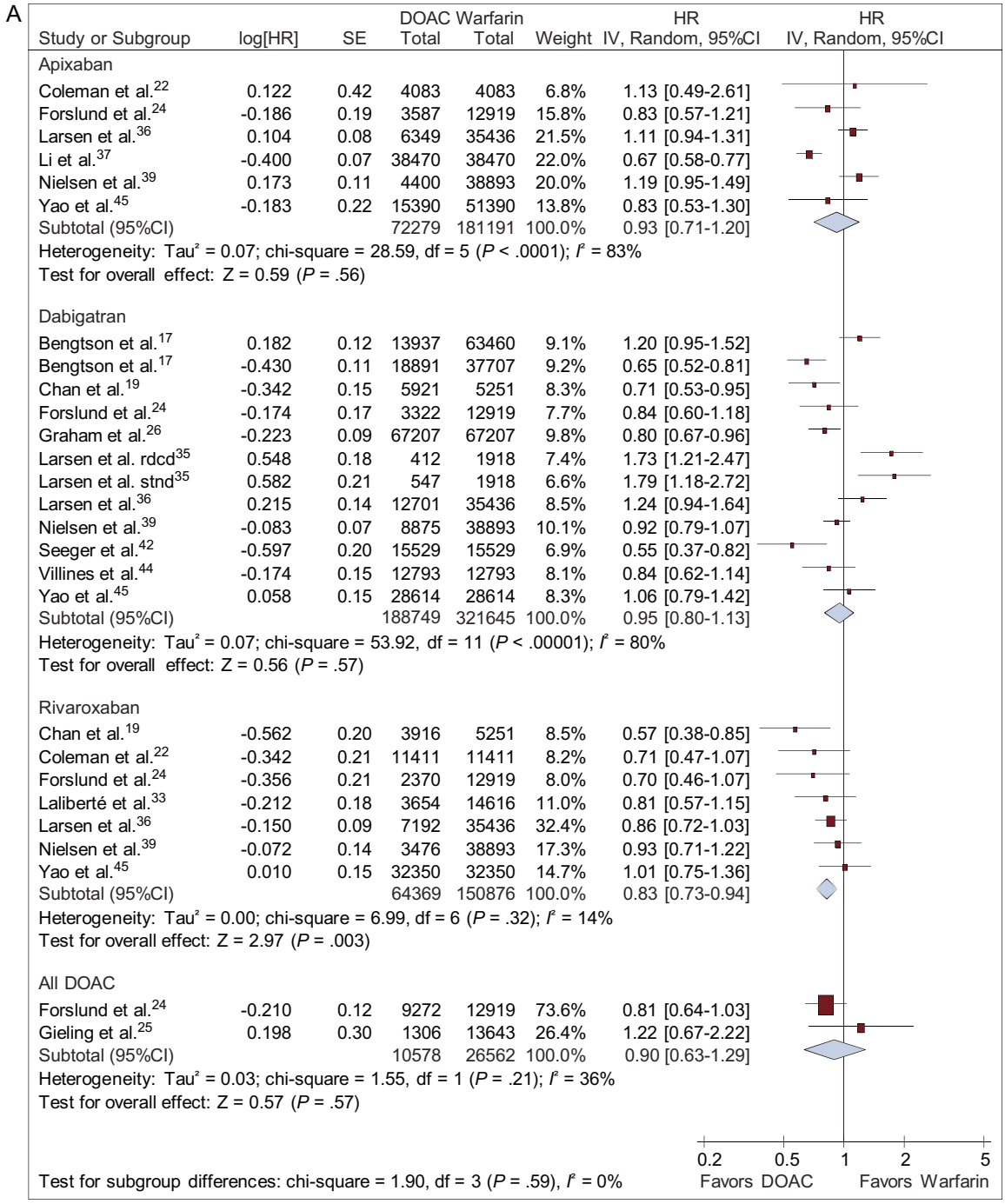

Figure 2. HRs with 95%CIs for ischemic stroke (A), ischemic stroke plus systemic embolism (B), major bleeding (C), and intracranial hemorrhage (D) in patients with AF treated with DOACs vs VKAs up to about 1 year. 95%CI, 95% confidence interval; AF, atrial fibrillation; DOACs, direct oral anticoagulants; HR, hazard ratio; IV, interval variable; SE, systemic embolism.

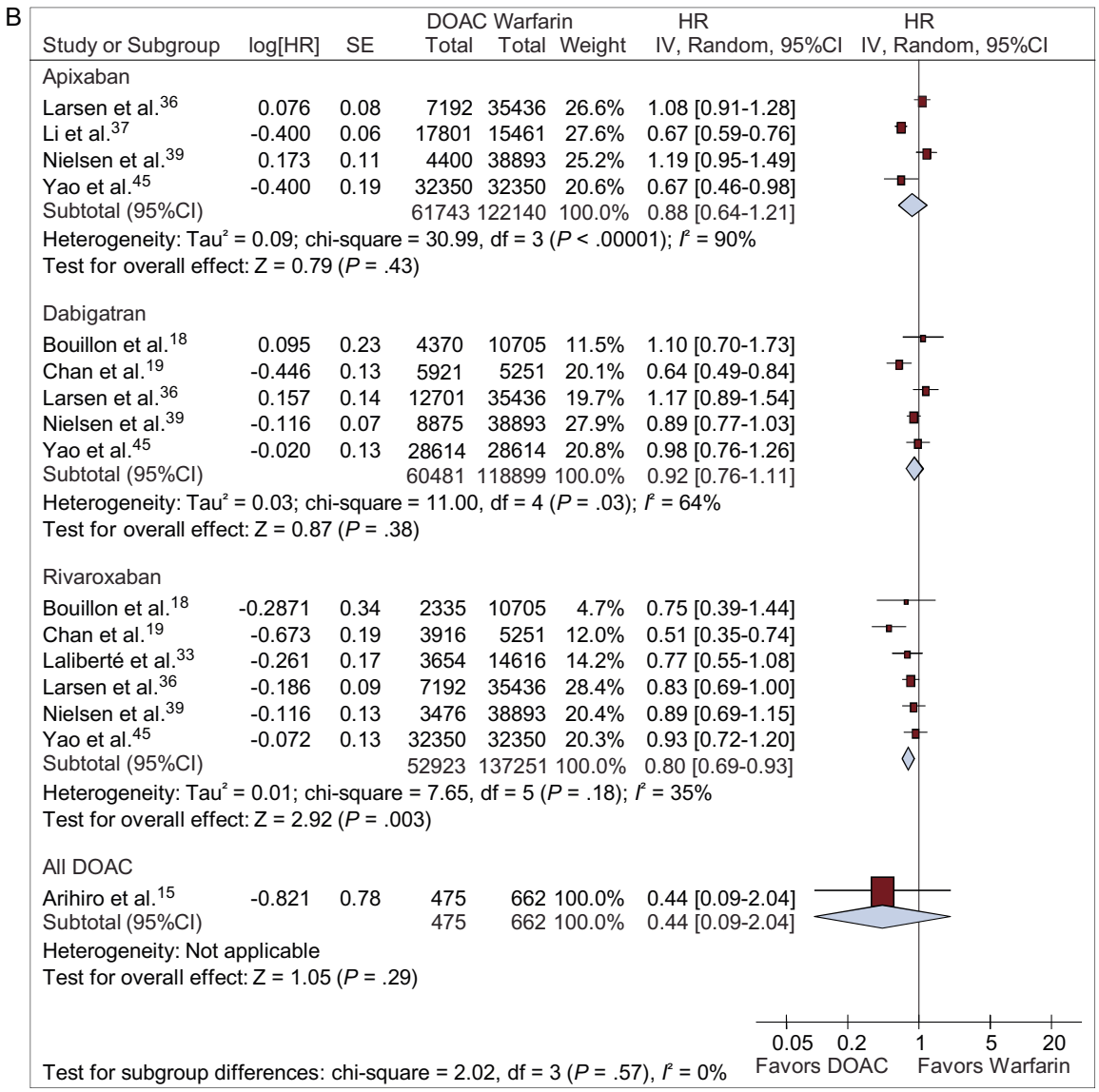

Figure 2. (*Continued*).

Data on ischemic stroke, major bleeding, and intracranial hemorrhage in patients with AF and treated with DOACs vs VKAs are shown in Figure 3 according to DOAC dose (standard and reduced).

Ischemic Stroke

Standard Dose

Compared with warfarin, treatment with standard doses of apixaban did not reduce the risk of ischemic stroke (HR, 1.11; 95%CI, 0.94-1.31). In addition, treatment with standard doses of dabigatran did not reduce the risk of ischemic stroke (HR, 0.97; 95%CI, 0.68-1.38). However, statistical heterogeneity was high among studies. Treatment with standard doses of rivaroxaban reduced the risk of ischemic stroke vs warfarin (HR, 0.86; 95%CI, 0.72-1.03) (Figure 3A).

Reduced Dose

Compared with warfarin, reduced doses of apixaban, dabigatran, or rivaroxaban did not decrease the risk of ischemic stroke (HR, 1.19; 95%CI, 0.95-1.49; HR, 0.94; 95%CI, 0.66-1.36; HR, 0.93; 95%CI, 0.71-1.22; respectively) (Figure 3A).

Major Bleeding

Standard Dose

Compared with warfarin, standard doses of apixaban reduced the risk of major bleeding (HR, 0.55; 95%CI, 0.45-0.66). Treatment with standard doses of dabigatran and rivaroxaban did not reduce the risk of major bleeding (HR, 0.85; 95%CI, 0.61-1.19; HR, 1.02; 95%CI, 0.92-1.12; respectively) (Figure 3B).

Reduced Dose

Compared with warfarin, reduced doses of apixaban did not reduce the risk of major bleeding (HR, 0.75; 95%CI, 0.49-1.15). However, statistical heterogeneity was high among studies. Reduced doses of dabigatran did not diminish the risk of major bleeding (HR, 0.96; 95%CI, 0.78-1.17). No risk reduction in

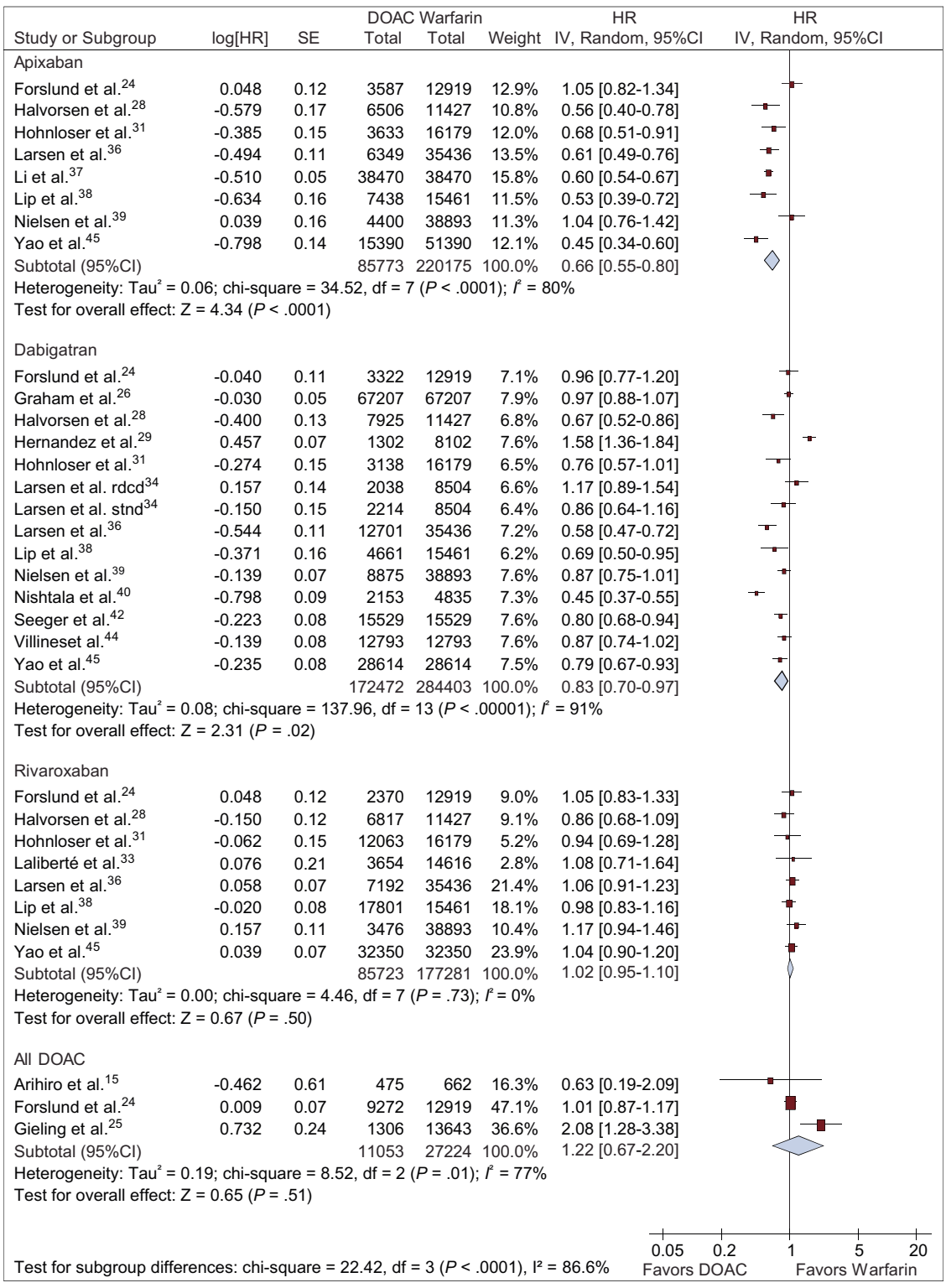

Figure 2. (*Continued*).

major bleeding was observed between reduced doses of rivaroxaban and warfarin (HR, 1.16; 95%CI, 0.98-1.38) (Figure 3B).

Intracranial Hemorrhage

Standard Dose

No differences in the risk reduction of intracranial bleeding were observed between standard doses of apixaban and warfarin (HR, 0.72; 95%CI, 0.42-1.23). Standard doses of dabigatran (HR, 0.39; 95%CI, 0.30-0.52) and rivaroxaban (HR, 0.56; 95%CI, 0.34-0.92) did reduce the risk of intracranial bleeding over time (Figure 3C).

Reduced Dose

No studies compared the incidences of intracranial bleeding between reduced doses of apixaban and warfarin. Reduced doses of

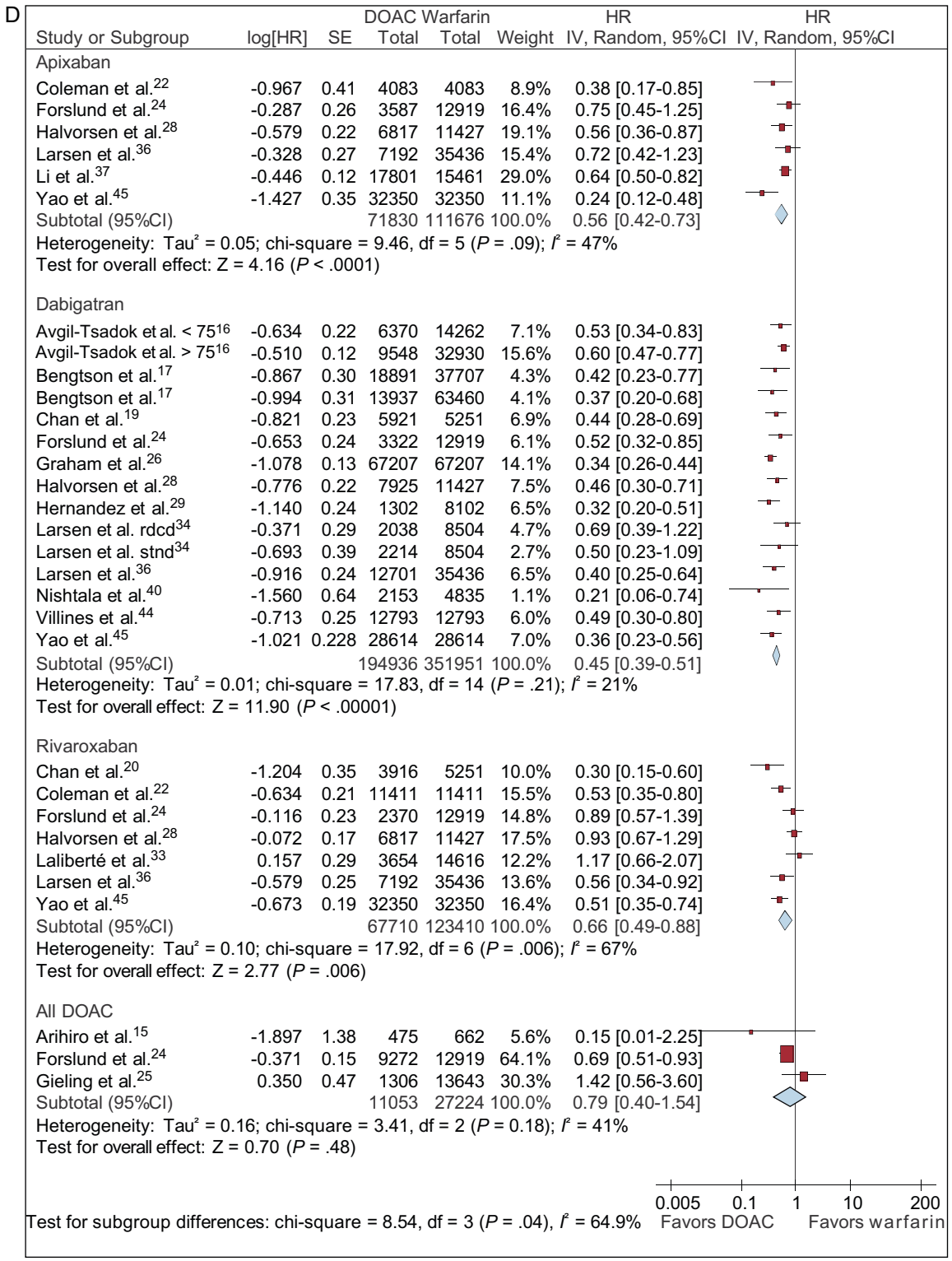

Figure 2. (*Continued*).

dabigatran (HR, 0.47; 95%CI, 0.39-0.56) and rivaroxaban (HR, 0.33; 95%CI, 0.16-0.68) significantly reduced the risk of intracranial bleeding vs warfarin (Figure 3C).

DISCUSSION

The results provided by this meta-analysis aid in the understanding of the effectiveness and safety of DOACs in real-life patients. Unlike noncomparative studies, which only include absolute rates,[46] this study allows determination of the relative effectiveness and safety of DOACs vs VKAs.

The RE-LY study[6] showed that, after a median follow-up of 2.0 years, 150 mg dabigatran was associated with a lower risk of stroke or systemic embolism vs warfarin, with a similar risk of major bleeding, whereas 110 mg dabigatran was associated with a similar risk of stroke or systemic embolism, but with a lower risk of

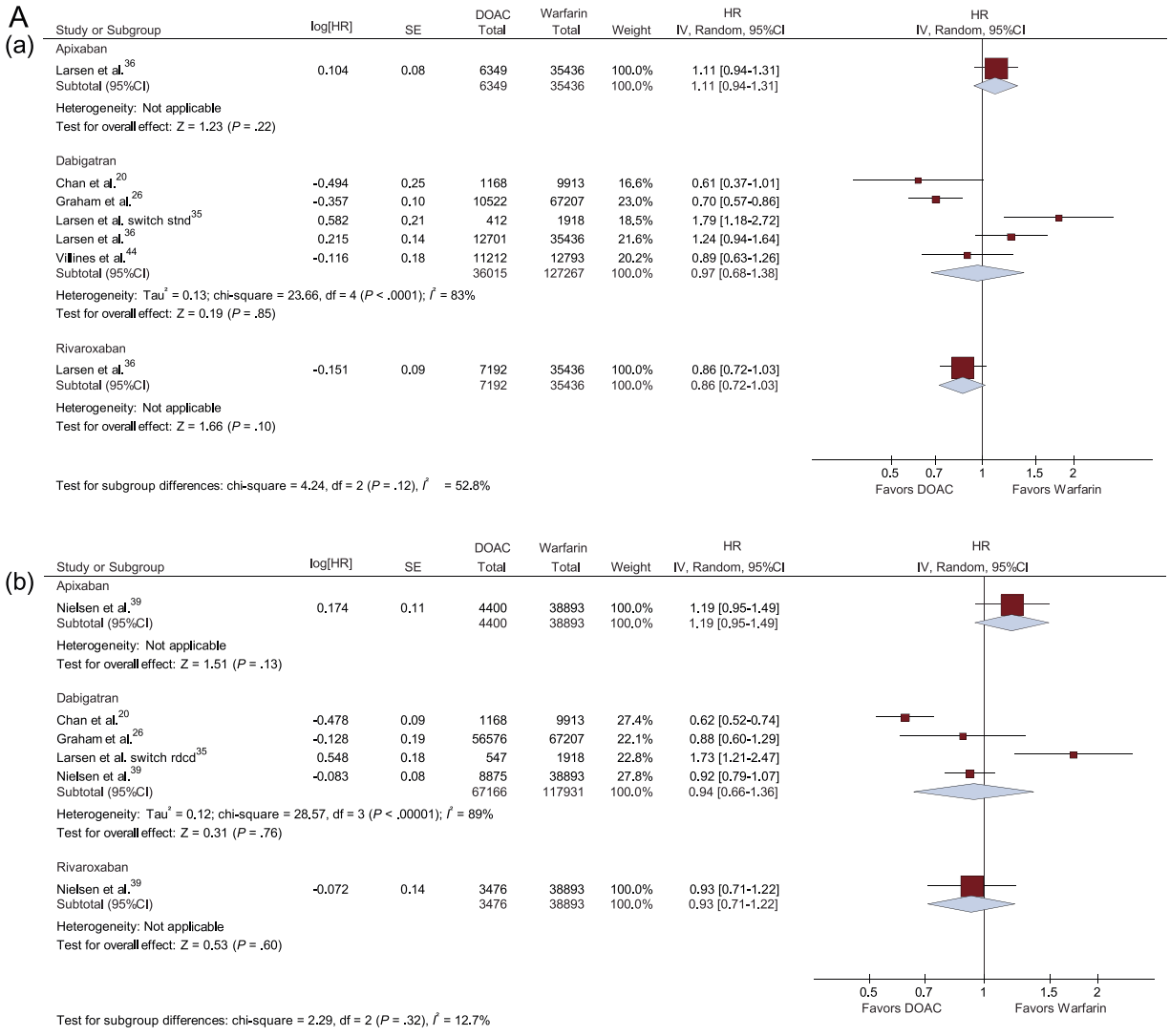

Figure 3. HRs with 95% confidence intervals for ischemic stroke, major bleeding, and intracranial hemorrhage in patients with AF treated with DOACs vs VKAs according to the DOAC dosage (standard/reduced) used in each study. A: ischemic stroke (Aa: Standard dose; Ab: Reduced dose); B: major bleeding (Ba: standard dose; Bb: reduced dose); and C: intracranial bleeding (Ca: standard dose; Cb: reduced dose). 95%CI, 95% confidence interval; AF, atrial fibrillation; DOACs, direct oral anticoagulants; HR, hazard ratio; IV, interval variable; SE, systemic embolism.

major bleeding. In the ROCKET-AF trial,[7] after a median follow-up of 707 days, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism, with a similar risk of major bleeding and a lower risk of intracranial and fatal bleeding. In the ARISTOTLE trial, after a median follow-up of 1.8 years, apixaban was superior to warfarin in preventing stroke or systemic embolism, with less bleeding.[8] Although these 3 studies were head-to-head with warfarin, the patient populations included were different; thus, no direct comparisons can be made. The characteristics of the included studies are summarized in Table 3 of the supplementary material. As shown in Table 3 of the supplementary material, there were some relevant differences in the clinical characteristics of the patients included in these studies, not only among them, but also among the pivotal clinical trials. As a result, the information provided by this meta-analysis is relevant because it allows determination of the relative effectiveness and safety of DOACs vs VKAs in the full spectrum of real-life patients.

This meta-analysis showed that apixaban and dabigatran did not reduce the risk of ischemic stroke vs warfarin in retrospective claims database studies with a follow-up up to 1 year or with longer-term data. However, rivaroxaban significantly reduced this risk vs warfarin. This significant reduction also occurred with the composite variable of ischemic stroke and systemic embolism. Apixaban and dabigatran significantly reduced major bleeding risk vs warfarin, but not vs rivaroxaban. Notably, statistical heterogeneity was high among studies. However, apixaban, dabigatran, and rivaroxaban significantly reduced the risk of intracranial bleeding vs warfarin. The main objective of anticoagulation in AF patients is to prevent stroke with an acceptable bleeding risk.[3] Our data showed that, vs warfarin, the most effective drug to reduce the risk of stroke in clinical practice was rivaroxaban, with a similar risk of major bleeding.

One of the main advantages of DOACs vs warfarin is that DOACs do not require continuous dosage adjustments. DOAC dosages are adjusted according to specific clinical conditions that differ markedly among each drug.[6–8] In our meta-analysis, the effectiveness and safety of DOACs was specifically analyzed according to dosage. Standard doses of dabigatran and particularly rivaroxaban, but not apixaban, tended to reduce the risk of ischemic stroke,

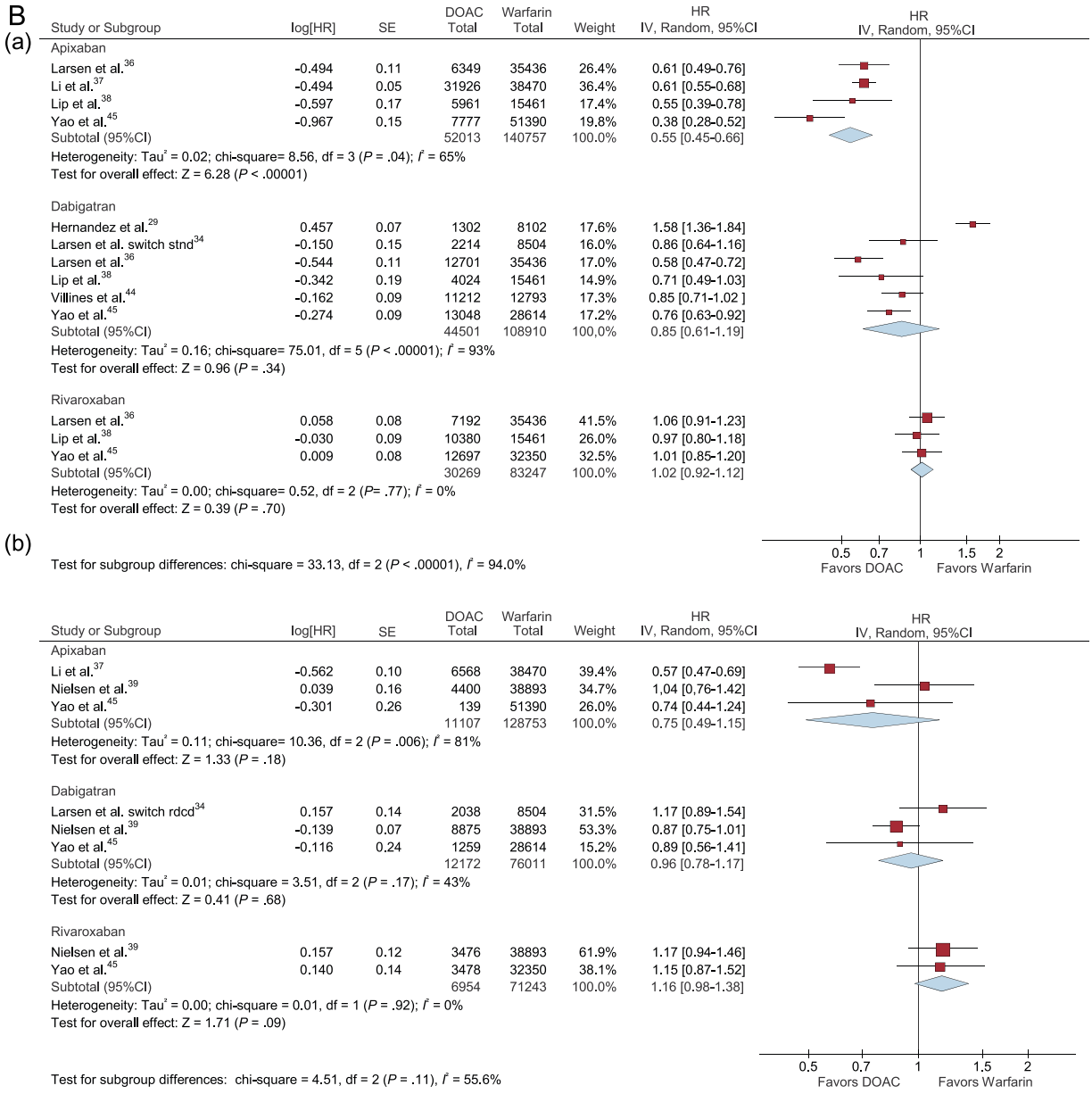

Figure 3. (*Continued*).

whereas reduced doses of all DOACs did not decrease the risk of stroke. Reduced doses of DOACs tended to be safer than standard doses in terms of bleeding risk. The main limitation of the observational studies that reported the DOAC doses is that the information regarding the dosage adequacy according to patients' clinical characteristics was not reported. Our meta-analysis showed that, overall, DOACs at reduced doses were associated with a slightly better safety profile, but with a marked reduction in the effectiveness of stroke prevention. In fact, the prescription of inadequate doses of DOACs is associated with worse safety and no benefit in effectiveness.[39,47] This suggests that reduced doses of DOACs should only be used when indicated according to drug labeling and not when physicians perceive an increased risk of bleeding. Unfortunately, inappropriate drug use is reportedly frequent.[48–50]

A meta-analysis of the effectiveness and safety of DOACs vs VKAs for stroke prevention in AF was recently published.[51] However, there are important differences between our systematic review and that published by Ntaios et al.[51] Our work included a greater number of studies and a higher number of patients. In addition, the inclusion/exclusion criteria were stricter in our systematic review. Indeed, in our systematic review, studies that exhibited a substantial overlap were excluded. In addition, when data were duplicated, the most recent studies or those with the highest number of patients were selected. Moreover, our search was more up-to-date and we included 11 additional studies vs Ntaios et al.[51] Importantly, specific analyses according to follow-up time and DOAC dosage were performed, increasing the validity and generalizability of our results. Accordingly, our systematic review is more complete and exhaustive and has a higher statistical power. For example, due to its higher statistical power and in contrast to the study by Ntaios et al.,[51] our work found that dabigatran significantly reduced the risk of major bleeding vs warfarin and that rivaroxaban decreased the risk of ischemic stroke and systemic embolism.

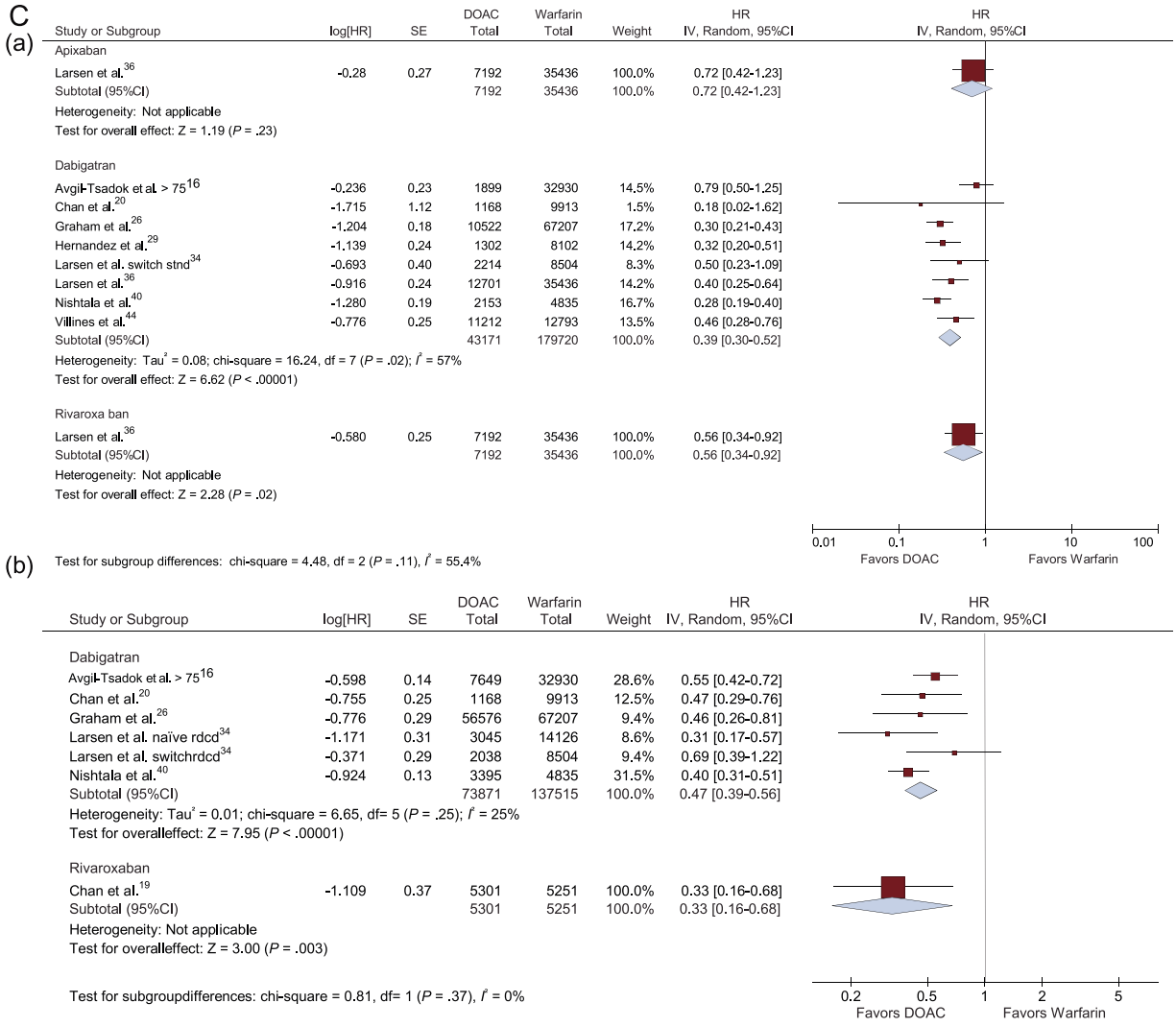

Figure 3. (*Continued*).

Limitations

Some limitations should be mentioned. Observational studies have a higher risk of bias than clinical trials. We found a moderate risk of bias with the ROBINS-I tool. Vitamin K antagonists were the key comparator arm. However, time in therapeutic range and data adjusted according to this parameter were not disclosed in any studies. Analyses were limited to some outcomes, such as stroke, major bleeding, or intracranial bleeding, but not others. In some comparisons, statistical heterogeneity was high among studies, limiting the validity and the generalizability of the results. No significant clinical information was available for edoxaban.

CONCLUSIONS

In conclusion, in studies with a follow-up up to 1 year or with longer-term data, rivaroxaban significantly reduced the risk of ischemic stroke vs warfarin, unlike apixaban and dabigatran. Apixaban and dabigatran significantly reduced the risk of major bleeding, whereas rivaroxaban showed similar risk to warfarin. Compared with warfarin, DOACs significantly reduced the risk of intracranial bleeding. Reduced doses of DOACs were associated with a marked reduction in the effectiveness of stroke prevention and with a slightly better safety profile. Data from this meta-analysis suggest that, vs warfarin, the effectiveness and safety of some DOACs may differ in real-life AF patients.

ACKNOWLEDGMENTS

Editorial assistance was provided by Content Ed Net, Madrid, Spain.

FUNDING

Bayer Hispania S.L.

CONFLICTS OF INTEREST

C. Escobar reports personal fees from Bayer, Boehringer, Bristol-Myers Squibb, Daiichi-Sankyo, and Pfizer outside the submitted work. J. Martí-Almor reports personal fees from Bayer, Daiichi-Sankyo, Pfizer, and Boehringer outside the submitted work. A. Pérez Cabeza reports personal fees from Bayer and Daiichi-Sankyo outside the submitted work. M.J. Martínez-Zapata has nothing to disclose.

WHAT IS KNOWN ABOUT THE TOPIC?

- Data from clinical trials are not always valid for real-life patients.
- In recent years, many studies with different designs, analyses, and patient characteristics have analyzed the use of DOACs in AF patients in clinical practice.
- This systematic review assessed the effectiveness of DOACs vs VKAs in nonvalvular AF patients.

WHAT DOES THIS STUDY ADD?

- In contrast to apixaban and dabigatran, rivaroxaban significantly reduced the risk of ischemic stroke vs warfarin.
- Apixaban and dabigatran significantly reduced the risk of major bleeding vs warfarin, unlike rivaroxaban, but with a high statistical heterogeneity among studies. All DOACs significantly reduced the risk of intracranial bleeding vs warfarin.
- Reduced doses of DOACs were associated with a slightly better safety profile, but with a marked reduction in effectiveness for stroke prevention.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version available at https://doi.org/10.1016/j.rec.2018.03.009.

REFERENCES

1. Ceornodolea AD, Bal R, Severens JL. Epidemiology and Management of Atrial Fibrillation and Stroke: Review of Data from Four European Countries. *Stroke Res Treat.* 2017;2017:8593207.
2. Masjuán J, Álvarez-Sabín J, Blanco M, et al. Current management of antithrombotic treatment in patients with non valvular atrial fibrillation and prior history of stroke or transient ischemic attack. *Rev Neurol.* 2014;59:25–36.
3. Kirchhof P, Benussi S, Kotecha D, et al.2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37:2893–2962.
4. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med.* 2007;146:857–867.
5. Barrios V, Escobar C, Calderón A, et al. Use of antithrombotic therapy according to CHA_2DS_2-VASc score in patients with atrial fibrillation in primary care. *Rev Esp Cardiol.* 2014;67:150–151.
6. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139–1151.
7. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365:883–891.
8. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med.* 2011;365:981–992.
9. Marzec LN, Wang J, Shah ND, et al. Influence of Direct Oral Anticoagulants on Rates of Oral Anticoagulation for Atrial Fibrillation. *J Am Coll Cardiol.* 2017;69:2475–2484.
10. Barón-Esquivias G, Marín F, Sanmartín Fernandez M. Rivaroxaban in patients with atrial fibrillation: from ROCKET AF to everyday practice. *Expert Rev Cardiovasc Ther.* 2017;15:403–413.
11. Russo V, Rago A, Proietti R, et al. Efficacy and safety of the target-specific oral anticoagulants for stroke prevention in atrial fibrillation: the real-life evidence. *Ther Adv Drug Saf.* 2017;8:67–75.
12. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at: www.handbook.cochrane.org. Accessed 7 Jan 2018.
13. Moher D, Liberati A, Tetzlaff J, et al. PRISMA Group Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.
14. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* 2016;355:i4919.
15. Arihiro S, Todo K, Koga M, et al. Three-month risk-benefit profile of anticoagulation after stroke with atrial fibrillation: The SAMURAI-Nonvalvular Atrial Fibrillation (NVAF) study. *Int J Stroke.* 2016;11:565–574.
16. Avgil-Tsadok M, Jackevicius CA, Essebag V, et al. Dabigatran use in elderly patients with atrial fibrillation. *Thromb Haemost.* 2016;115:152–160.
17. Bengtson LGS, Lutsey PL, Chen LY, et al. Comparative effectiveness of dabigatran and rivaroxaban versus warfarin for the treatment of non-valvular atrial fibrillation. *J Cardiol.* 2017;69:868–876.
18. Bouillon K, Bertrand M, Maura G, et al. Risk of bleeding and arterial thromboembolism in patients with nonvalvular atrial fibrillation either maintained on a vitamin K antagonist or switched to a non-vitamin K-antagonist oral anticoagulant: a retrospective, matched-cohort study. *Lancet Haematol.* 2015;2:e150–e159.
19. Chan YH, Kuo CT, Yeh YH, et al. Thromboembolic, bleeding, and mortality risks of rivaroxaban and dabigatran in Asians with nonvalvular atrial fibrillation. *J Am Coll Cardiol.* 2016;68:1389–1401.
20. Chan YH, Yen KC, See LC, et al. Cardiovascular, Bleeding, and Mortality Risks of Dabigatran in Asians With Nonvalvular Atrial Fibrillation. *Stroke.* 2016;47:441–449.
21. Chang HY, Zhou M, Tang W, et al. Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study. *BMJ.* 2015;350:h1585.
22. Coleman CI, Antz M, Bowrin K, et al. Real-world evidence of stroke prevention in patients with nonvalvular atrial fibrillation in the United States: the REVISIT-US study. *Curr Med Res Opin.* 2016;32:2047–2053.
23. Ellis MH, Neuman T, Bitterman H, et al. Bleeding in patients with atrial fibrillation treated with dabigatran, rivaroxaban or warfarin: A retrospective population-based cohort study. *Eur J Intern Med.* 2016;33:55–59.
24. Forslund T, Wettermark B, Andersen M, et al. Stroke and bleeding with nonvitamin K antagonist oral anticoagulant or warfarin treatment in patients with nonvalvular atrial fibrillation: a population-based cohort study. *Europace.* 2017. http://dx.doi.org/10.1093/europace/euw416.
25. Gieling EM, van den Ham HA, van Onzenoort H, et al. Risk of major bleeding and stroke associated with the use of vitamin K antagonists, nonvitamin K antagonist oral anticoagulants and aspirin in patients with atrial fibrillation: a cohort study. *Br J Clin Pharmacol.* 2017. http://dx.doi.org/10.1111/bcp.13265.
26. Graham DJ, Reichman ME, Wernecke M, et al. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation.* 2015;131:157–164.
27. Graham DJ, Reichman ME, Wernecke M, et al. Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation. *JAMA Intern Med.* 2016;176:1662–1671.
28. Halvorsen S, Ghanima W, Fride Tvete I, et al. A nationwide registry study to compare bleeding rates in patients with atrial fibrillation being prescribed oral anticoagulants. *Eur Heart J Cardiovasc Pharmacother.* 2017;3:28–36.
29. Hernandez I, Baik SH, Pinera A, et al. Risk of bleeding with dabigatran in atrial fibrillation. *JAMA Intern Med.* 2015;175:18–24.
30. Hernandez I, Zhang Y. Comparing Stroke and Bleeding with Rivaroxaban and Dabigatran in Atrial Fibrillation: Analysis of the US Medicare Part D Data. *Am J Cardiovasc Drugs.* 2017;17:37–47.
31. Hohnloser SH, Basic E, Nabauer M. Comparative risk of major bleeding with new oral anticoagulants (NOACs) and phenprocoumon in patients with atrial fibrillation: a postmarketing surveillance study. *Clin Res Cardiol.* 2017;106:618–628.
32. Lai CL, Chen HM, Liao MT, et al. Comparative Effectiveness and Safety of Dabigatran and Rivaroxaban in Atrial Fibrillation Patients. *J Am Heart Assoc.* 2017;6:e005362.
33. Laliberte F, Cloutier M, Nelson WW, et al. Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. *Curr Med Res Opin.* 2014;30:1317–1325.
34. Larsen TB, Gorst-Rasmussen A, Rasmussen LH, et al. Bleeding events among new starters and switchers to dabigatran compared with warfarin in atrial fibrillation. *Am J Med.* 2014;127:650–656e5.
35. Larsen TB, Rasmussen LH, Gorst-Rasmussen A, et al. Dabigatran and warfarin for secondary prevention of stroke in atrial fibrillation patients: a nationwide cohort study. *Am J Med.* 2014;127:1172–1178e5.
36. Larsen TB, Skjoth F, Nielsen PB, et al. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ.* 2016;353:i3189.
37. Li XS, Deitelzweig S, Keshishian A, et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in "real-world" clinical practice. A propensity-matched analysis of 76,940 patients. *Thromb Haemost.* 2017;117:1072–1082.
38. Lip GY, Keshishian A, Kamble S, et al. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients 136 initiated on apixaban, dabiga-

tran, rivaroxaban, or warfarin. A propensity score matched analysis. *Thromb Haemost.* 2016;116:975–986.
39. Nielsen PB, Skjoth F, Sogaard M, et al. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ.* 2017; 356:j510.
40. Nishtala PS, Gnjidic D, Jamieson HA, et al. 'Realworld' haemorrhagic rates for warfarin and dabigatran using population-level data in New Zealand. *Int J Cardiol.* 2016;203:746–752.
41. Noseworthy PA, Yao X, Abraham NS, et al. Direct Comparison of Dabigatran, Rivaroxaban, and Apixaban for Effectiveness and Safety in Nonvalvular Atrial Fibrillation. *Chest.* 2016;150:1302–1312.
42. Seeger JD, Bykov K, Bartels DB, et al. Safety and effectiveness of dabigatran and warfarin in routine care of patients with atrial fibrillation. *Thromb Haemost.* 2015;114:1277–1289.
43. Vaughan Sarrazin MS, Jones M, Mazur A, et al. Bleeding rates in Veterans Affairs patients with atrial fibrillation who switch from warfarin to dabigatran. *Am J Med.* 2014;127:1179–1185.
44. Villines TC, Schnee J, Fraeman K, et al. A comparison of the safety and effectiveness of dabigatran and warfarin in non-valvular atrial fibrillation patients in a large healthcare system. *Thromb Haemost.* 2015;114:1290–1298.
45. Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. *J Am Heart Assoc.* 2016;5:e003725.
46. Camm AJ, Amarenco P, Haas S, et al. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J.* 2016;37:1145–1153.
47. Yao X, Shah ND, Sangaralingham LR, et al. Non-Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction. *J Am Coll Cardiol.* 2017;69:2779–2790.
48. Basaran O, Filiz Basaran N, Cekic EG, et al. PRescriptiOn PattERns of Oral Anticoagulants in Nonvalvular Atrial Fibrillation (PROPER study). *Clin Appl Thromb Hemost.* 2017;23:384–391.
49. Larock AS, Mullier F, Sennesael AL, et al. Appropriateness of prescribing dabigatran etexilate and rivaroxaban in patients with nonvalvular atrial fibrillation: a prospective study. *Ann Pharmacother.* 2014;48:1258–1268.
50. Whitworth MM, Haase KK, Fike DS, et al. Utilization and prescribing patterns of direct oral anticoagulants. *Int J Gen Med.* 2017;10:87–94.
51. Ntaios G, Papavasileiou V, Makaritsis K, Vemmos K, Michel P, Lip GYH. Real-World Setting Comparison of Nonvitamin-K Antagonist Oral Anticoagulants Versus Vitamin-K Antagonists for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Meta-Analysis. *Stroke.* 2017;48:2494–2503.