Thromboembolic, Bleeding, and Mortality Risks among Patients with Nonvalvular Atrial Fibrillation Treated with Dual Antiplatelet Therapy versus Oral Anticoagulants: A Population-Based Study

Running title: Dual Antiplatelet Therapy versus Oral Anticoagulants in Atrial Fibrillation

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Disclosures

This study was funded by the Hong Kong Research Grants Council. Dr. Chan also received research funding from Bayer, Bristol-Myers Squibb, Janssen, Pfizer, the Narcotics Division, Security Bureau, the Hong Kong Health and Medical Research Fund and National Natural Science Foundation of China for unrelated work. Prof. Wong has received research funding from Bristol-Myers Squibb, Janssen, Pfizer, Bayer, the Hong Kong Research Grants Council, and the Hong Kong Health and Medical Research Fund; Prof. Lip has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo, and has been on the speaker bureaus for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. No personal fees received; Prof. Leung has received speaker fees from Eisai, Ferring, Menarini and Takeda. He also serves on the advisory board of AbbVie, Boehringer-Ingelheim and Janssen; Prof. Cheung has received payment to act as consultant for Pfizer and Roche; no other disclosures were reported.

No. of Tables: 2

No. of Figures: 2

Word count: 4923

Abstract

Background: Dual antiplatelet therapy (DAPT) with aspirin plus clopidogrel is used for stroke prevention in patients with atrial fibrillation (AF) when patients refuse to use oral anticoagulants (OAC) in clinical practice. However, there are limited clinical data comparing these treatments.

Objective: To compare the clinical outcomes between DAPT and OAC in patients with AF.

Methods: Cohort study using a population-wide database of the Hong Kong Hospital Authority. New patients with AF during 2010-2014 and prescribed DAPT or OAC (warfarin or dabigatran) were followed until July 31, 2016. Outcomes were thromboembolism, bleeding, and death. Propensity score (PS) matching at 1:2 ratio was used to select DAPT users with similar characteristics to OAC users, analyzed using Poisson regression.

Results: Among 51,946 new patients with AF, 8,520 users of OAC and DAPT were identified. The likelihood of receiving DAPT over OAC increased with older age and previous intracranial hemorrhage. Among DAPT users, the incidences of thromboembolism, death, and bleeding per 100 patient-years were 15.8, 17.6, and 5.1 respectively. When compared to DAPT users, PS-matched analysis indicated a lower incidence of thromboembolism and/or death among OAC users (incidence rate ratio [IRR]=0.32, 95% confidence interval [CI]=0.19-0.55 for dabigatran and IRR=0.58, 95%CI=0.36-0.95 for warfarin), with no significant differences in bleeding events.

Conclusions: DAPT users were at markedly increased risk of thromboembolism and death compared to OAC users. These findings indicate the need for improved stroke risk reduction strategies among patients taking DAPT and the opportunities of using OAC in high risk groups to prevent more events.

Keywords: non-vitamin K antagonist oral anticoagulants; aspirin; clopidogrel; atrial fibrillation; stroke; bleeding

Abstract word count: 250

Introduction

Atrial Fibrillation (AF) is the most common sustained cardiac arrhythmia that increases the risk of stroke. For many decades, warfarin and other vitamin K antagonists have been the only class of oral anticoagulation therapy (OAC) available for the prevention of stroke. When patients refused or are deemed potentially unsuitable for warfarin, dual antiplatelet therapy (DAPT) with aspirin and clopidogrel may be considered.[1, 2] Current understanding of the effectiveness of DAPT among patients potentially eligible to receive OAC is primarily derived from a single clinical trial published in 2006.[3] The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) trial suggested that DAPT was inferior to warfarin for the prevention of stroke, with no difference in bleeding events.[3] However, the majority of included patients (77%) were prior users of warfarin,[3] who were likely to tolerate warfarin better. It is also unclear how evidence from a restrictive trial setting translates to every-day clinical practice.

Dabigatran is the first non-vitamin K antagonist oral anticoagulant (NOAC) approved for use as an alternative to warfarin in patients with nonvalvular atrial fibrillation (NVAF, i.e. AF in the absence of mitral stenosis or mechanical valves).[4] Although DAPT might also be considered in patients who refuse dabigatran or any form of OAC,[1, 2] existing evidence was only based on warfarin (ACTIVE-W) and we are not aware of any studies that simultaneously described the outcomes among users of DAPT, dabigatran, and warfarin in the same setting.

In a population-based healthcare setting, first we assessed a range of effectiveness and safety outcomes in patients with NVAF treated with DAPT. Second, we examined the factors associated with prescribing DAPT over OAC. Third, we described the outcomes among

DAPT users who were potentially eligible to prescribe OAC, and compared them with the outcomes among warfarin and dabigatran users.

Methods

Data source

This study utilised the electronic medical records of the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority (HA), a statutory body that manages all public hospitals and their ambulatory clinics in Hong Kong.[5] HA is currently serving a population of over 7 million through 42 hospitals and institutions, 47 specialist outpatient clinics, and 73 general outpatient clinics.[5] Computerized patient records, including demographics, date of registered death, date of hospital admission and discharge, date of outpatient visits, drug dispensing records, diagnoses, procedures, and laboratory tests are centralized in CDARS for practice, research, and audit purposes. Patient records are anonymized to protect patient identity. CDARS had been extensively used for conducting large population-based studies.[6-12] Data validity has been shown to be high for a variety of diagnoses, including AF (positive predictive value [PPV]=95%), ischemic stroke (PPV=90%), intracranial hemorrhage (ICH) (PPV=95%), and gastrointestinal bleeding (GIB) (PPV=100%).[8-10] Detailed descriptions of CDARS were published previously.[9, 11, 12]

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW13-468). Informed patient consent was not required as the data used in this study were anonymized.

Study design and selection of patients

This was a retrospective cohort study. We selected new patients who received their first AF diagnosis (International Classification of Disease, Ninth Revision, Clinical Modification

[ICD-9-CM]=427.3) between January 1, 2010 and December 31, 2014 from CDARS. Possible cases of transient AF, including those who had cardiac surgery, myocarditis, pericarditis, or pulmonary embolism within 3 months before their first AF occurrence were excluded. Patients who were diagnosed with mitral stenosis, hyperthyroidism, or underwent valve replacement at or prior to their first AF occurrence were excluded (ICD-9-CM; Supplemental Table 1), as were patients with missing date of birth or sex information, aged<18 years, or died at first AF occurrence.

Patients were classified into respective treatment group based on their first prescription of DAPT (aspirin in combination with clopidogrel), warfarin, or dabigatran following AF diagnosis. Index date was defined as the date of the first prescription following AF. To select new users only, patients who were exposed to either therapy within 180 days prior to index date were excluded. Compared to OACs, DAPT is more commonly indicated for ischemic heart disease such as myocardial infarction instead of AF.[1] To minimize this potential systematic differences between OACs and DAPT groups, we excluded patients with ischemic heart disease (ICD-9-CM=410-414) to include only those who were likely to receive treatment because of AF. Sensitivity analyses were conducted by repeating the main analyses without exclusion of patients with ischemic heart disease. Patients who died within 7 days of index date were excluded as any deaths occurred on the first few days after treatment commencement is likely related to the condition that led to the initiation of treatment (e.g. AF and ischemic stroke) rather than the treatment itself. Post-hoc analyses were conducted with inclusion of patients who died within 7 days of index date.

Outcomes

The primary effectiveness outcome was a composite of ischemic stroke, systemic embolism, and death from any cause. The secondary safety outcome was bleeding events, including ICH

and GIB. Net benefit was assessed by a composite of all effectiveness and safety endpoints.[13] Outcome events were identified from diagnosis records using physician-assigned ICD-9-CM codes (Supplemental Table 1). Stratified analyses were conducted for each individual component in the composite outcomes. Deaths were further stratified into vascular and non-vascular deaths (Supplemental Table 1). In this stratified analysis patients with unknown cause of death were censored and not classified as having an outcome.

Follow-up

The follow-up for each patient commenced from the index date until occurrence of outcome, end of study period (July 31, 2016), discontinuation of treatment, switching to other therapy (between apixaban, dabigatran, rivaroxaban, warfarin, and DAPT), or death, whichever came first. Discontinuation of DAPT was determined by either stopping aspirin or clopidogrel. Treatment was assumed to be continuous unless a bleeding event was recorded (GIB or ICH).[3, 14] In Hong Kong, aspirin can also be obtained over-the-counter whereas dabigatran, warfarin, and clopidogrel are available only by prescription.[15] For the drugs that require a prescription (dabigatran, warfarin, and clopidogrel), we additionally assessed the time gap between consecutive prescription refills in CDARS after index date, where treatments were assumed to be continuous when any apparent treatment break was within 5 days.

Statistical analysis

Propensity score (PS) was calculated for each patient to estimate their likelihood to receive DAPT over warfarin and dabigatran.[16] It was estimated using logistic regression based on age, sex, index year, number of hospitalizations within one year prior to index date, medical history (recorded any time on or before index date, Supplemental Table 1) of congestive heart failure, hypertension, diabetes mellitus, ischemic stroke/transient ischemic attack (TIA)/systemic embolism, vascular disease, renal disease, ICH, GIB, other bleeding (a

composite of epistaxis, hematuria, hemarthrosis, hemopericardium, hemoptysis, and hemorrhage from kidney, throat, and vagina);[10] Charlson Comorbidities Index (CCI); recent use (≤90 days on or prior to index date) of angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), beta-blocker, amiodarone, dronedarone, nonsteroidal anti-inflammatory drugs (NSAIDs), histamine type-2-receptor antagonists (H2RAs), proton pump inhibitors (PPIs), statins, and selective serotonin reuptake inhibitors. The resulting odds ratios of the PS were reported to examine the factors associated with prescribing DAPT over OAC.

Each DAPT user was intended to be matched with up to two dabigatran users and two warfarin users by PS using the greedy matching algorithm, which has been demonstrated to perform well in both actual and simulation studies.[17] Patients were eligible for inclusion in every cohort where that treatment was being assessed. Standardized differences were calculated to assess the similarity of baseline characteristics between treatment groups, with difference <0.1 considered negligible.[16] Sensitivity analyses were conducted with exclusion of patients with PS in extreme values (lower and upper 1% of the distribution in the exposed and unexposed group respectively) to reduce any residual patient differences arising from unmeasured confounding factors.[16]

The risks of outcome events were compared using Poisson regression stratified on matched groups. The scale parameters were held fixed and the offset variable was the natural logarithm of the days of follow-up measured from the index date through the date of the outcome/the first censoring event. Result estimates were expressed in terms of incidence rate ratio (IRR) with 95% confidence interval (CI). Post-hoc analyses were conducted using Cox regression model. A two-sided p-value <0.05 was considered as statistically significant. SAS (version 9.3; SAS Institute, Inc, Cary, NC) and R (version: 3.1.1) were used for statistical analyses.

Results

Baseline characteristics

There were 51,946 new patients with AF identified in CDARS between January 1, 2010 and December 31, 2014. Following patient exclusion, a total of 8,520 new users of dabigatran, warfarin, and DAPT remained (Figure 1). The most common dosage of dabigatran was 110 mg bid (n=1,955; 75%), followed by 150 mg bid (n=345; 13%), and 75 mg bid (n=222; 9%).

Factors associated with prescribing DAPT over OAC

Male gender, vascular disease, baseline use of statins, H2RAs, and PPIs were associated with an increased likelihood to prescribe DAPT over both warfarin and dabigatran. Older age was associated with a higher likelihood to prescribe DAPT over warfarin only; whereas higher CCI, congestive heart failure, ICH, and renal disease, and baseline use of amiodarone was associated with a higher likelihood of prescribing DAPT over dabigatran only (Supplemental Table 2).

In contrast, those with prior ischemic stroke/TIA/systemic embolism or baseline NSAIDs use were associated with a lower likelihood to receive DAPT over both warfarin and dabigatran. Patients with baseline use of ACE inhibitors and/or ARBs were less likely to receive DAPT over dabigatran only.

Propensity-score matching

669 DAPT users were successfully matched to 1,241 warfarin users; and 560 DAPT users were successfully matched to 964 dabigatran users. All observed baseline characteristics had standardized differences <0.1 after matching (Supplemental Tables 3 and 4, Supplemental Figures 1 and 2). In the sensitivity analyses without exclusion of patients with ischemic heart

disease, 1,837 DAPT users were matched to 2,511 warfarin users; and 1,049 DAPT users were matched to 1,480 dabigatran users.

Effectiveness outcomes

The crude incidence of ischemic stroke/systemic embolism and death per 100 patient-years were 15.8 and 17.6 respectively among DAPT users; 5.4 and 3.1 respectively among warfarin users; and 4.6 and 2.5 respectively among dabigatran users (Supplemental Table 5).

Within the PS-matched cohort, both warfarin and dabigatran use was associated with a lower risk of ischemic stroke/systemic embolism and/or death when compared to DAPT use (IRR=0.58, 95%CI=0.36-0.95 and IRR=0.32, 95%CI=0.19-0.55, respectively). Results of stratified analyses indicated that warfarin and dabigatran use was associated with fewer deaths from all causes and vascular deaths when compared to DAPT (Table 1, Figure 2).

An association with lower risk of non-vascular death was observed in dabigatran users compared with DAPT (IRR=0.16, 95%CI=0.05-0.54). Although numerically fewer non-vascular deaths were seen with warfarin users than DAPT users, the confidence intervals were wide and include 1.0 (IRR=0.48, 95%CI=0.21-1.19). No significant association between the ischemic stroke/systemic embolism and DAPT users versus dabigatran/warfarin users were found (Table 1). The results were similar in the analyses that did not exclude patients with ischemic heart disease (Table 2, Figure 2).

Safety outcomes

The crude incidence of overall bleeding per 100 patient-years among users of DAPT, warfarin, and dabigatran were 5.1, 3.4, and 3.3 respectively (Supplemental Table 5). Among the PS-matched cohorts, overall bleeding events were numerically more common in patients receiving dabigatran than DAPT, but no significant association in overall bleeding risk for all

head-to-head comparisons were found (Table 1, Figure 2). In the analyses that did not exclude patients with ischemic heart disease, dabigatran was associated with a lower risk of ICH (IRR=0.14, 95%CI=0.03-0.59) but a higher risk of GIB when compared to DAPT (IRR=4.54, 95%CI=1.48-16.1). The resulting overall bleeding risk was not significantly different between dabigatran and DAPT groups (Table 2, Figure 2).

Net benefit

Dabigatran use was associated with a more favorable outcome of net benefit compared to DAPT users (IRR=0.47, 95%CI=0.29-0.79). The risk estimate also pointed towards a trend for a beneficial outcome among warfarin users over DAPT users (IRR=0.70, 95%CI=0.45-1.11) (Table 1, Figure 2). Sensitivity and post-hoc analyses all yielded similar results (Table 2 and Supplemental Tables 6-8).

Discussion

This study showed that among patients with NVAF, the likelihood of prescribing DAPT over OAC increased with bleeding risk factors including older age and previous ICH. However, DAPT use was associated with a moderate risk of bleeding but a remarkably high risk of thromboembolism. Among the DAPT patients who were potentially eligible for OAC (i.e. had similar baseline characteristics with OAC group), we found a higher risk of ischemic stroke/systemic embolism and/or death than seen in those prescribed OAC, with no significant differences in bleeding risk. The results were robust to all sensitivity analyses that reduced any residual patient differences arising from unmeasured confounding factors.

Risk-benefit of using DAPT

Among DAPT users, the risk of ischemic stroke/systemic embolism and overall bleeding was 15.8 vs. 5.1 per 100 patient-years, suggesting that the risk of thromboembolism, which can be

effectively reduced by OAC, was about 3 times higher than that of bleeding. The thromboembolism-bleeding ratio remained high among DAPT users who were estimated to have had similar baseline characteristics to those who received warfarin (15.8 vs. 5.2) or dabigatran (16.9 vs. 3.5). This underscores the potential for improved thromboembolism risk reduction strategies among any patients receiving DAPT. Our results showed that patients prescribed DAPT generally had more risk factors for bleeding, such as prior ICH or older age, than those prescribed OAC. This suggests that patients at high risk of bleeding were likely channeled to DAPT; however, it turned out DAPT users had a moderate risk of bleeding but a remarkably high risk of thromboembolism. Although this strategy might have reduced the risk of bleeding, it probably did not translate into a net benefit in clinical practice. On the whole, our findings indicate the need for a refinement of current strategy on weighing the risks and benefits of using DAPT and OAC, and suggest that greater use of OACs among high risk groups may be warranted.

Comparison with other studies

Current understanding of the effectiveness of OAC vs DAPT is only based on the ACTIVE-W trial.[3] This trial reported a lower rate of vascular events with warfarin against DAPT, but the authors highlight the limitation that most subjects (77%) had been on warfarin at study entry.[3] Patients who had been on warfarin were more likely to tolerate it better than other alternatives, and therefore the study results were largely driven by a group of patients who were already benefiting from warfarin use. Consistently, in patients who were randomised to receive OAC, those who had already been on OAC at study entry had less major bleeding events compared to those who had not been on OAC previously. Conversely, in patients who were randomised to receive DAPT, those who had already been on OAC at study entry had more major bleeding events compared to those who had not been (p-value for interaction=0.028).[3] The trial also excluded high-risk patients likely to be encountered in

clinical practice, such as those with a history of peptic ulcer disease and ICH.[3] Addressing the limitations of ACTIVE-W, our study was based on the usage of antithrombotic therapy in AF patients outside restrictive trial settings. We used a new user design to minimise survival bias, where patients who were previously on either treatment were excluded.

Comparing our results with ACTIVE-W, both studies support that warfarin is more effective in preventing stroke and/or death than DAPT. In ACTIVE-W, results were consistent with a smaller reduction in vascular death, but the difference did not reach statistical significance (risk ratio=0.88, 95%CI=0.68-1.14).[3] Although there was a reduction in vascular events in ACTIVE-W (risk ratio=0.69, 95%CI=0.57-0.85), most vascular events such as strokes occurring in ACTIVE-W were non-fatal,[3] and thus a reduction of which did not lead to a reduction in vascular death. Regarding bleeding risk, our results are consistent with ACTIVE-W, where the major bleeding risk is comparable between warfarin and DAPT groups, suggesting that bleeding risk should not be the only factor for choosing between DAPT and warfarin.[1]

Clinical implications

Current guidelines on the use of DAPT in AF are inconsistent. The 2012 European Society of Cardiology (ESC) guideline recommends the use of DAPT in patients who refuse or cannot tolerate any OAC[1] and discourage its use for this indication in the latest guideline in 2016.[18] However, both the most recent 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guideline in the United States and the 2014 National Institute for Health and Care Excellence (NICE) guideline in the United Kingdom does not make a specific recommendation regarding the use of DAPT.[4, 19] Despite this, a considerable volume of antiplatelet medication (alone or in combination) is prescribed as a “softer” option over OAC, even after the introduction of NOACs – particularly in Asia.[10]

Our findings contradict this perception, based on current limited evidence, dabigatran or warfarin should be considered for stroke prevention instead of DAPT, with DAPT is an inferior treatment strategy that is not perhaps safer than OAC.

Strengths and limitations

To our knowledge, this is the first study that examined the effect of DAPT among patients with NVAF in real-life practice. Our study was based on the large electronic patient records in CDARS, which covers 80% of all hospital admissions in Hong Kong.[20] The validity of coding in CDARS has been shown to be high, where the PPVs of the outcome events in this study are ranged from 90-100%.[8-10] We applied a new user design to eliminate the residual effect of previous exposure on the study outcomes. Our study cohort was well-matched by PS with respect to important comorbidities and concurrent medications, and all measurable patient characteristics were comparable between groups after matching.

This study has limitations. The number of bleeding cases was relatively small, which limits the power to detect a statistical association and affects the precision of the result estimates. Nonetheless, our results suggest that the high incidence of thromboembolism and mortality with DAPT users seems more concerning than any difference in bleeding risk when compared to OAC users.

We have identified some very strong protective associations between dabigatran and warfarin when compared with DAPT. What matters is whether and to what extent these associations are causal. For example, dabigatran would not be expected to reduce the risk of non-vascular events, and so the observation that dabigatran was associated with a lower risk of non-vascular death compared to DAPT and warfarin warrants further investigations. This could be explained by (i) an effect of dabigatran that indirectly reduces the likelihood of non-vascular deaths, (ii) misclassification of cause of death, with some of those classified as non-vascular

actually being vascular or (iii) confounding whereby people receiving DAPT are generally sicker and at risk of adverse outcome, independent of AF treatment choice. At baseline, patients prescribed DAPT generally possessed more comorbidities than those prescribed dabigatran and warfarin. In addition, a higher proportion of DAPT users died within the first 7 days of treatment than in the other treatment groups, again suggesting a sicker population was given DAPT. Although patients were well-matched on many comorbidities using propensity score matching, an overestimation of any association with lower risk of adverse outcomes with dabigatran and warfarin vs DAPT is possible if the observed comorbidities were unable to account for the underlying differences between patients. To reduce residual confounding, we excluded patients who previously exposed to the treatment of interest or had ischemic heart disease to assemble comparable study groups. We also conducted sensitivity analyses, and the results were found to be robust.

Conclusions

This study showed that DAPT users were at markedly increased risk of thromboembolism and death compared to OAC users. Much of these increased risks were likely to be attributable to patient characteristics. These findings indicate the need for improved risk reduction strategies among patients who refuse or are deemed unsuitable for OAC, and suggest wider use of OACs among higher risk groups may be beneficial because the higher absolute risk provides opportunities to prevent more events.

Acknowledgements

We thank Dr. Anthony Wai Yee Tam, former colleague from the Department of Pharmacology and Pharmacy of the University of Hong Kong, for his help with the cross-checking of statistical analyses.

Funding

This work was supported by the Hong Kong Research Grants Council, General Research Fund received by EWC [17102314]. The funders of the study had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review, or approval of the manuscript.

References

1. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012;33(21):2719-47.
2. National Institute for Health and Care Excellence. Atrial fibrillation: the management of atrial fibrillation: NICE guideline. Draft for consultation 2014 [updated January 2014. Available from: https://www.nice.org.uk/guidance/cg180/documents/atrial-fibrillation-update-nice-version2].
3. The ACTIVE Writing Group of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006;367(9526):1903-12.
4. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2014;130(23):e199-267.
5. Hospital Authority. Introduction. [Available from: http://www.ha.org.hk/visitor/ha_visitor_index.asp?Content_ID=10008&Lang=ENG&Dimension=100&Parent_ID=10004].
6. Lau WC, Chan EW, Cheung CL, et al. Association between dabigatran vs warfarin and risk of osteoporotic fractures among patients with nonvalvular atrial fibrillation. JAMA. 2017;317(11):1151-8.
7. Man KKC, Chan EW, Ip P, et al. Prenatal antidepressant use and risk of attention-deficit/hyperactivity disorder in offspring: population based cohort study. BMJ. 2017;357.

8. Wong AYS, Root A, Douglas IJ, et al. Cardiovascular outcomes associated with use of clarithromycin: population based study. BMJ. 2016;352:h6926.

9. Chan EW, Lau WC, Leung WK, et al. Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study. Gastroenterology. 2015;149(3):586-95.e3.

10. Chan EW, Lau WC, Siu CW, et al. Effect of suboptimal anticoagulation treatment with antiplatelet therapy and warfarin on clinical outcomes in patients with nonvalvular atrial fibrillation: A population-wide cohort study. Heart Rhythm. 2016;13(8):1581-8.

11. Man KK, Chan EW, Coghill D, et al. Methylphenidate and the risk of trauma. Pediatrics. 2015;135(1):40-8.

12. Man KKC, Coghill D, Chan EW, et al. Association of Risk of Suicide Attempts With Methylphenidate Treatment. JAMA Psychiatry. 2017;74(10):1048-55.

13. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2013;369(22):2093-104.

14. Douglas IJ, Evans SJ, Hingorani AD, et al. Clopidogrel and interaction with proton pump inhibitors: comparison between cohort and within person study designs. BMJ. 2012;345:e4388.

15. Drug Office, Department of Health, The Government of the Hong Kong Special Administrative Region. Registered Pharmaceutical Products 2016 [updated 2 Dec 2016. Available from: https://www.drugoffice.gov.hk/eps/do/en/consumer/reg_pharm_products/index.html].

16. Sturmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. J Intern Med. 2014;275(6):570-80.

17. Austin PC. Some Methods of Propensity-Score Matching had Superior Performance to Others: Results of an Empirical Investigation and Monte Carlo simulations. Biometrical Journal. 2009;51(1):171-84.

18. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESCEndorsed by the European Stroke Organisation (ESO). Eur Heart J. 2016;37:2893-962.

19. National Institute for Health and Care Excellence. Atrial fibrillation: management 2016 [Available from: https://www.nice.org.uk/guidance/cg180].

20. Hospital Authority. Hospital Authority Statistical Report 2014-2015 [Available from: http://www.ha.org.hk/haho/ho/stat/HASR1415_2.pdf].

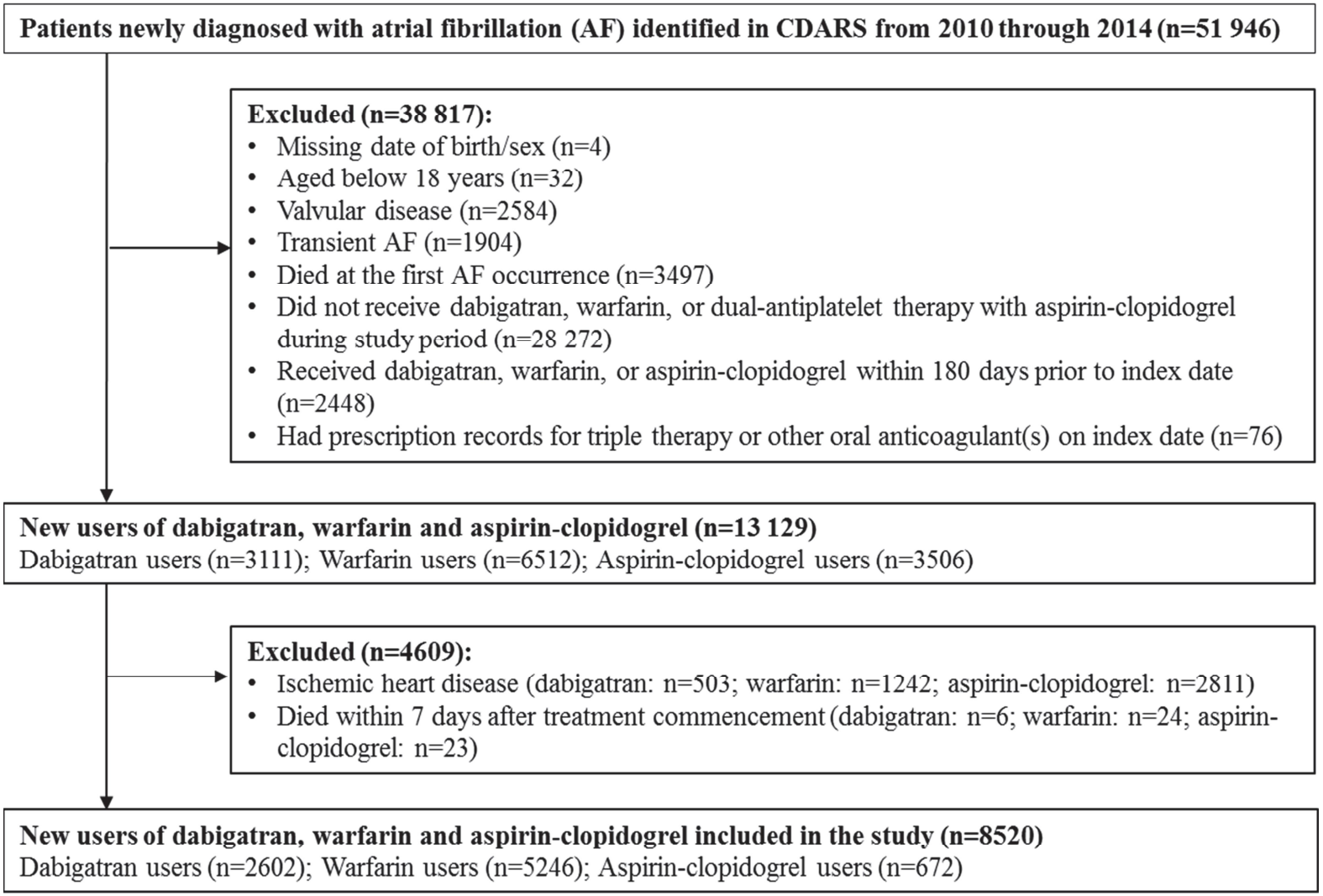


Figure 1. Selection of patients

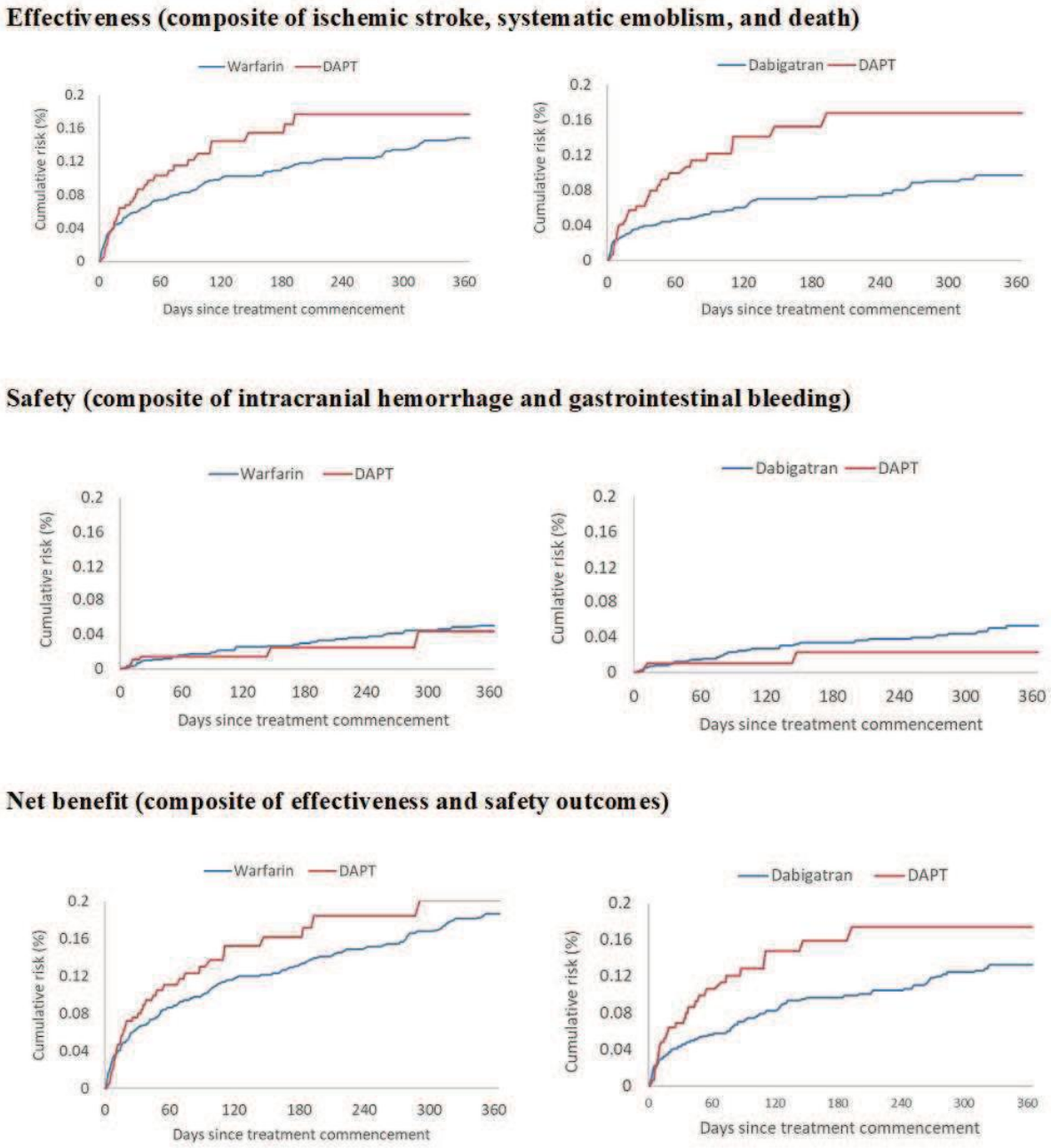


Figure 2. Cumulative risks of the outcomes (DAPT: dual antiplatelet therapy with aspirin plus clopidogrel)

Table 1. Effectiveness and safety outcomes after propensity score matching

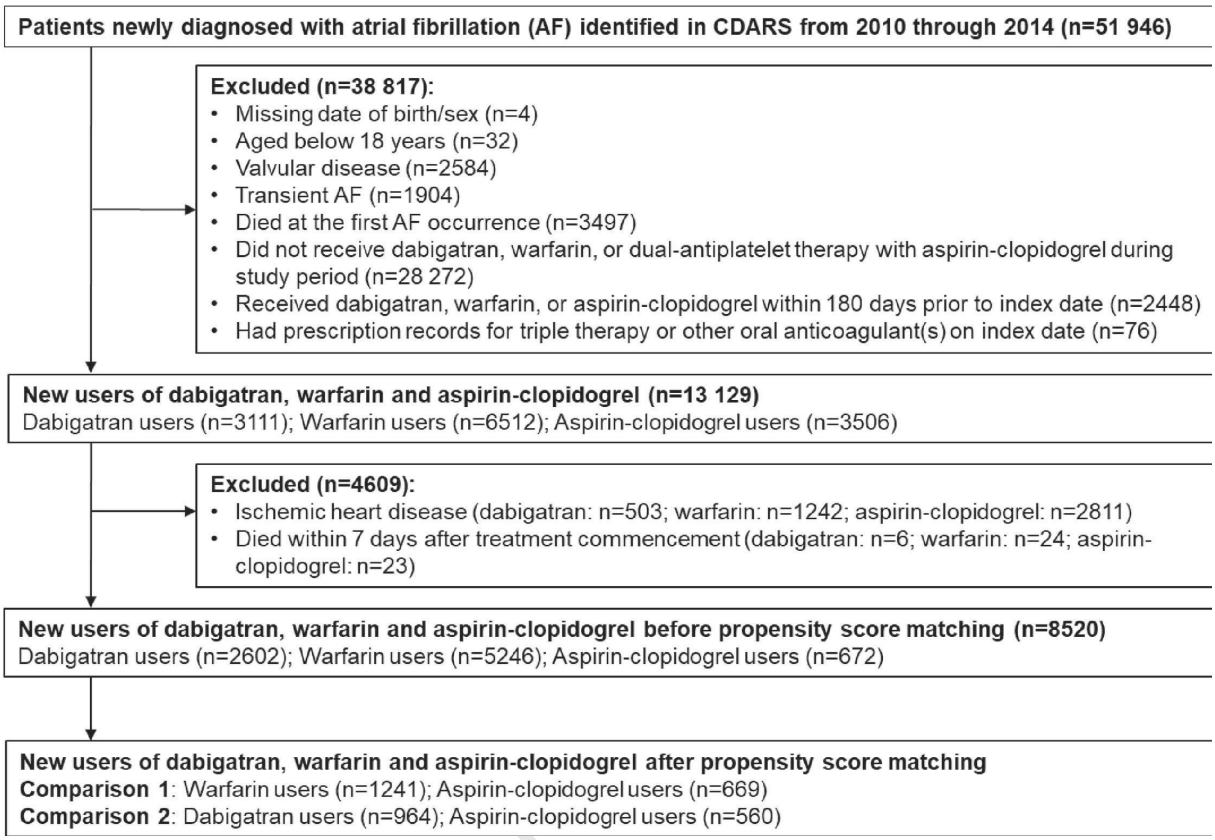
	Warfarin vs DAPT			Dabigatran vs DAPT		
	Warfarin (N=1,241)	DAPT (N=669)	IRR[a] (95% CI)	Dabigatran (N=964)	DAPT (N=560)	IRR[a] (95% CI)
Composite of ischemic stroke, systemic embolism, and death	171 (11.9)	44 (33.2)	0.58 (0.36-0.95)*	97 (8.5)	35 (31.1)	0.32 (0.19-0.55)*
Ischemic stroke and/or systemic embolism	97 (6.7)	21(15.8)	0.75 (0.37-1.59)	63 (5.5)	19 (16.9)	0.59 (0.28-1.30)
Death	85 (5.5)	24 (17.7)	0.43 (0.23-0.81)*	41 (3.4)	17 (14.7)	0.18 (0.09-0.39)*
Vascular death	22 (1.4)	10 (7.4)	0.26 (0.08-0.91)*	10 (0.8)	7 (6.1)	0.09 (0.02-0.34)*
Non-vascular death	49 (3.1)	11 (8.1)	0.48 (0.21-1.19)	21 (1.7)	8 (6.9)	0.16 (0.05-0.54)*
Composite of intracranial hemorrhage and gastrointestinal bleeding	75 (4.8)	7 (5.2)	1.09 (0.39-3.64)	44 (3.6)	4 (3.5)	2.71 (0.77-13.5)
Intracranial hemorrhage	33 (2.1)	4 (2.9)	0.88 (0.22-5.04)	8 (0.7)	2 (1.7)	1.96 (0.18-41.6)
Gastrointestinal bleeding	42 (2.7)	3 (2.2)	1.38 (0.30-9.97)	36 (3.0)	2 (1.7)	3.15 (0.67-30.4)
Net benefit Composite of ischemic stroke, systemic embolism, death, intracranial hemorrhage, and gastrointestinal bleeding	232 (16.1)	48 (36.2)	0.70 (0.45-1.11)	132 (11.6)	37 (32.9)	0.47 (0.29-0.79)*

Values are expressed as number of cases (incidence per 100 patient-years). Abbreviations: DAPT, dual antiplatelet therapy; IRR, incidence rate ratio; CI, confidence interval.
*$p<0.05$.
[a] The incidence rate ratios were obtained by Poisson regression stratified by propensity score matching id.

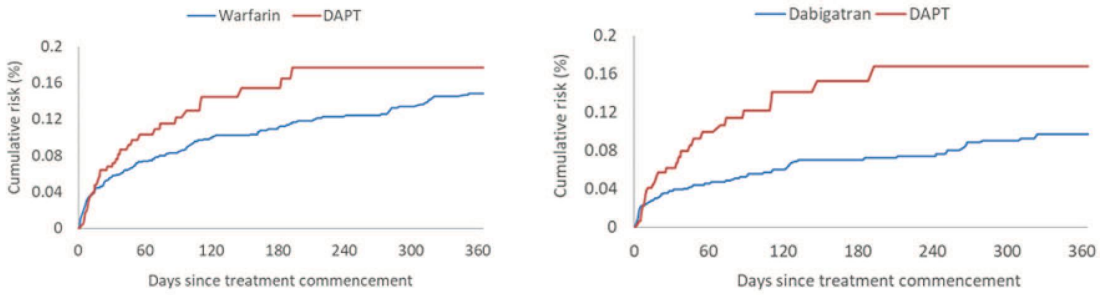
Table 2. Sensitivity analyses without exclusion of patients with ischemic heart disease

	Warfarin vs DAPT			Dabigatran vs DAPT		
	Warfarin (N=2,511)	DAPT (N=1,837)	IRR[a] (95% CI)	Dabigatran (N=1,480)	DAPT (N=1,049)	IRR[a] (95% CI)
Composite of ischemic stroke, systemic embolism, and death	341 (11.8)	129 (29.6)	0.64 (0.48-0.86)*	156 (8.6)	72 (29.7)	0.40 (0.27-0.61)*
Ischemic stroke and/or systemic embolism	165 (5.7)	52 (11.9)	1.14 (0.71-1.86)	99 (5.4)	34 (14.0)	0.89 (0.49-1.68)
Death	202 (6.6)	79 (17.7)	0.53 (0.37-0.76)*	65 (3.4)	40 (16.2)	0.21 (0.12-0.36)*
Vascular death	55 (1.8)	35 (7.9)	0.29 (0.16-0.56)*	13 (0.7)	16 (6.5)	0.10 (0.03-0.27)*
Non-vascular death	103 (3.4)	29 (6.5)	0.58 (0.34-1.03)	39 (2.0)	16 (6.5)	0.42 (0.18-0.98)*
Composite of intracranial hemorrhage and gastrointestinal bleeding	151 (4.9)	40 (9.0)	0.86 (0.53-1.41)	69 (3.6)	14 (5.7)	1.48 (0.65-3.58)
Intracranial hemorrhage	48 (1.6)	12 (2.7)	0.88 (0.34-2.37)	11 (0.6)	7 (2.8)	0.14 (0.03-0.59)*
Gastrointestinal bleeding	104 (3.4)	28 (6.3)	0.91 (0.52-1.67)	58 (3.0)	7 (2.8)	4.54 (1.48-16.1)*
Net benefit						
Composite of ischemic stroke, systemic embolism, death, intracranial hemorrhage, and gastrointestinal bleeding	470 (16.3)	160 (36.7)	0.72 (0.56-0.94)*	215 (11.8)	81 (33.5)	0.59 (0.41-0.86)*

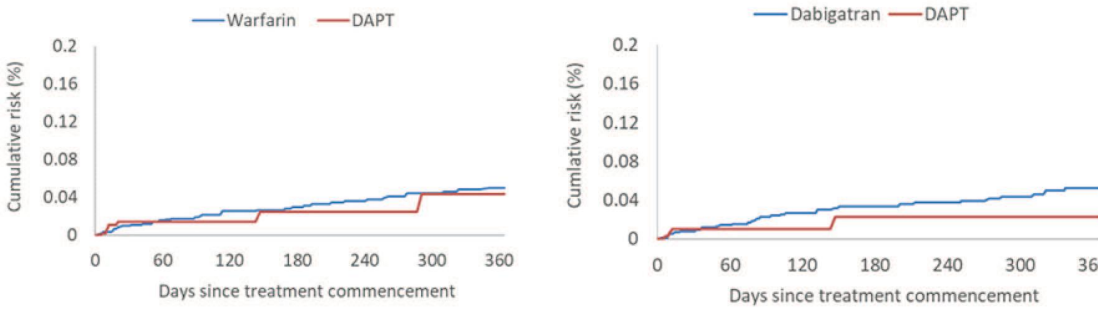
Values are expressed as number of cases (incidence per 100 patient-years). Abbreviations: DAPT, dual antiplatelet therapy; IRR, incidence rate ratio; CI, confidence interval.
*$p<0.05$.
[a] The incidence rate ratios were obtained by Poisson regression stratified by propensity score matching id.


Patients newly diagnosed with atrial fibrillation (AF) identified in CDARS from 2010 through 2014 (n=51 946)
Excluded (n=38 817):
• Missing date of birth/sex (n=4)
• Aged below 18 years (n=32)
• Valvular disease (n=2584)
• Transient AF (n=1904)
• Died at the first AF occurrence (n=3497)
• Did not receive dabigatran, warfarin, or dual-antiplatelet therapy with aspirin-clopidogrel during study period (n=28 272)
• Received dabigatran, warfarin, or aspirin-clopidogrel within 180 days prior to index date (n=2448)
• Had prescription records for triple therapy or other oral anticoagulant(s) on index date (n=76)
New users of dabigatran, warfarin and aspirin-clopidogrel (n=13 129)
Dabigatran users (n=3111); Warfarin users (n=6512); Aspirin-clopidogrel users (n=3506)
Excluded (n=4609):
• Ischemic heart disease (dabigatran: n=503; warfarin: n=1242; aspirin-clopidogrel: n=2811)
• Died within 7 days after treatment commencement (dabigatran: n=6; warfarin: n=24; aspirin-clopidogrel: n=23)
New users of dabigatran, warfarin and aspirin-clopidogrel before propensity score matching (n=8520)
Dabigatran users (n=2602); Warfarin users (n=5246); Aspirin-clopidogrel users (n=672)
New users of dabigatran, warfarin and aspirin-clopidogrel after propensity score matching
Comparison 1: Warfarin users (n=1241); Aspirin-clopidogrel users (n=669)
Comparison 2: Dabigatran users (n=964); Aspirin-clopidogrel users (n=560)

Effectiveness (composite of ischemic stroke, systematic emoblism, and death)



Safety (composite of intracranial hemorrhage and gastrointestinal bleeding)



Net benefit (composite of effectiveness and safety outcomes)