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New anticoagulant therapies in atrial fibrillation: Clinical outcomes

Yosef Houmid Al Shammari
KSA, National Guard Health Affairs
Email: zx5zx6@hotmail.com

Homoud Awade Al Shammari
KSA, National Guard Health Affairs
Email: Abomlk022@gmail.com

Talal Muhammad bin Barak
KSA, National Guard Health Affairs
Email: gdmol2014@gmail.com

Bandar Said Alharbi
KSA, National Guard Health Affairs
Email: aa4605a@gmail.com

Saud Tawfiq Alshammari
KSA, National Guard Health Affairs
Email: Tobksa79@gmail.com

Saleh Abdullah Alnais
KSA, National Guard Health Affairs
Email: Salehalnais22@gmail.com

Saeed Awad Aljohani
KSA, National Guard Health Affairs
Email: 4uvideoclip@gmail.com

Abdulrahman Abdullah Alorf
KSA, National Guard Health Affairs
Email: abdulrahmanab7557@gmail.com

Meshari Abdulmajeed Alnawmasi
KSA, National Guard Health Affairs
Email: Alnomasime@gmail.com

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Mohammed Awad Alshammari
KSA, National Guard Health Affairs
Email: alshammarimo15@ngha.med.sa

Majed Farhan Alharbi
KSA, National Guard Health Affairs
Email: Alharbima2@ngha.med.sa

Abdulrahman Gobile Al Enazi
KSA, National Guard Health Affairs
Email: Alenazia13@ngha.med.sa

Abdulelah Mohammed Mubashir Alamri
KSA, National Guard Health Affairs
Email: Deloo.hellcat@gmail.com

***Abstract*---**Background: Global observational studies are revealing a lack of agreement between recommendations and actual clinical practice when it comes to the dosages of direct oral anticoagulant drugs (DOACs). Aim of Work: This review provides a concise and critical assessment of the use of Direct Oral Anticoagulants (DOACs) in real-world clinical setting. Methods: This study was conducted using the PubMed (MEDLINE) and Medscape databases for the search. Results: Analysis of data from 75 trials revealed that the majority of patients who were administered DOACs for stroke prevention in atrial fibrillation were given dosages that aligned with the recommended recommendations. Nevertheless, a considerable proportion of patients were given dosages that were not approved for their specific condition (ranging from 25% to 50% in the majority of the assessed trials). Overdosing on DOACs was linked to higher rates of death from any cause and more severe bleeding episodes. Underdosing, on the other hand, was connected with higher rates of hospitalization for cardiovascular issues. Specifically, with apixaban, underdosing was linked to a nearly five times higher risk of stroke. Conclusion: Patients who were administered off-label dosages of DOACs did not experience the whole advantages of anticoagulation and had a heightened susceptibility to stroke, bleeding, and/or negative side effects.

***Keywords*---**Adverse Drug Effects, Anticoagulant, Knowledge, Atrial Fibrillation, Clinical Outcomes, Pharmacists, Review.

Introduction

Atrial fibrillation (AF) is the prevailing and enduring irregularity of the heart's rhythm. AF, which has been increasing in frequency in recent decades, is projected to double by 2050 [1,2]. AF is linked to heart failure, hospitalization, and a fivefold increase in the likelihood of stroke. Thus, it is crucial to prioritize stroke prevention in the management of atrial fibrillation (AF), especially in

patients with additional risk factors. Currently, the preferred initial treatments for preventing strokes in nonvalvular AF (NVAF) are the direct oral anticoagulants (DOACs). In Europe, there are currently four DOACs available: dabigatran (a thrombin inhibitor) and rivaroxaban, apixaban, and edoxaban (factor Xa inhibitors). DOACs have been favored over vitamin K antagonists, like warfarin, since clinical studies have shown that they have a more consistent pharmacokinetic profile, a defined dose schedule, and a decreased likelihood of drug–drug interactions [3,4]. Also, unlike to warfarin, therapeutic drug monitoring was not initially demanded for DOACs [5,6]. However, there is concern about the extrapolation of randomized clinical trials to real-life patientssince the reality observed in the idealized clinical trial setting is different from the real clinical practice, where patient characteristics and outcomes differ amongst distinct trials [7,8].

In fact, although fixed doses of DOACs are defined in the guidelines, dose adjustments are currently recommended in the presence of specific clinical conditions, including renal function, age and body weight, increased bleeding risk (e.g. gastritis, oesophagitis, gastroesophageal reflux) and concomitantly administration with other drugs that compromise DOACs systemic exposition and pharmacological effects (e.g. modulators of P-glycoprotein and/or of cytochrome P450 isoenzymes) [9-13,10,14,15,16,17]. Therefore, it is important to guarantee that the doses administered to each patient will attain the therapeutic plasma concentration window and are, consequently, therapeutic and safe [6,15]. Overdosing of DOACs is expected to compromise drug safety, by increasing the risk of major bleeding occurrence, while underdosing is expected to increase the risk of systemic embolism or ischaemic stroke [11,18,19].

Significantly, recent real-life incidents have documented the use of off-label doses of direct oral anticoagulants (DOACs), which raises concerns about the potential effects of administering too little or too much medication on patient outcomes. Remarkably, this issue is still unsolved, which has led to the creation of the current review. This study aims to examine the use of DOACs in real-world settings to evaluate the relationship between off-label dosages of DOACs and their efficacy and safety in therapy.

Aim of Work

In order to precisely detect patients who have been given insufficient or excessive doses, it is necessary to take into account the dosage adjustment criteria outlined in international recommendations. Nevertheless, these recommendations lack consistency on a global scale, making it difficult to determine the most suitable dosage and identify instances of suboptimal use of DOACs. It is worth noting that guidelines highlight certain disparities in comparison to the guidelines set by the EMA and FDA, particularly regarding the smaller physique, distinct pharmacokinetic characteristics, and genetic profiles of Asian populations as opposed to European or American patients. These recommendations were considered to determine whether adjusting the dosage of DOACs was necessary and to evaluate the effect of off-label DOAC doses on the clinical outcomes of patients with AF.

Methods

The current review was carried out in accordance with the principles provided by the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA). A comprehensive literature search was conducted using PubMed (MEDLINE) and Medscape, without any restrictions on the publication dates. The search terms used were "atrial fibrillation" AND "dabigatran" OR "rivaroxaban" OR "apixaban" OR "edoxaban" OR "direct oral anticoagulants" OR "DOACs" OR "NOACs" OR "non-vitamin K antagonist" in combination with "outcomes" OR "stroke" OR "hemorrhage" OR "prognosis" OR "hospitalization" OR "mortality" AND "real-world" OR "humans". Exclusion criteria were used to eliminate papers that did not include the use of DOACs for the prevention of stroke and systemic embolism in patients with NVAF. This includes studies that focused on the use of DOACs for preventing or treating venous thromboembolism and pulmonary embolism, as well as articles that explored off-label applications for DOACs. Additionally, studies that were not based on real-world data, such as those that only relied on randomized controlled trial data, preclinical studies, specialized cost-effectiveness assessments, perioperative usage of DOACs, and reversal procedures or antidotes, were also omitted. The search results were restricted to only include information related to humans.

Dabigatran

The findings of the most significant research on dabigatran dosage modification are summarized in Figure 1A. These studies indicated rates ranging from 8% to 49% of possibly incorrect prescriptions for dabigatran, with underdosing being more prevalent than overdose [20,21,22,23]. In a study conducted by Graham et al. [18], it was shown that some patients were prescribed a dosage of 75 mg of dabigatran twice a day, even though they did not have a significant kidney impairment that would need a lower dose. In cases where patients have moderate, mild, or no renal impairment, the use of the 75 mg dose of dabigatran, which is not officially approved, may lead to patients receiving insufficient dosage [24]. This might explain why no significant changes were seen in the risk of ischemic stroke, major gastrointestinal bleeding, or death between warfarin and the lower dose of dabigatran. A retrospective research done in Japan also observed this phenomenon, where 54 out of 228 patients (23.7%) had incorrect prescriptions for dabigatran.

Similarly, the data from the GLORIA-AF registry indicates that there is a need for improvement in adhering to guidelines for atrial fibrillation (AF) treatment. It was found that almost half of the low-risk patients are receiving excessive treatment, while patients at high risk of stroke are not receiving enough oral anticoagulants [25]. Several studies by Larock et al. [26], McDonald et al. [27], and Chowdry et al. [28] also reported a high percentage of potentially inappropriate prescriptions for dabigatran (ranging from 31.2% to 51.1%). This further highlights the issue of off-label doses with dabigatran. Nevertheless, the research conducted by Olesen et al [29] used comprehensive Danish statewide descriptive data from 2011 to 2013 and reached the conclusion that dabigatran is administered in accordance with established recommendations.

Rivaroxaban

Figure 1B illustrates the findings from empirical investigations about dosage modifications of rivaroxaban in real-life scenarios. Similarly, it seems that underdosing is more prevalent than overdose. Research on rivaroxaban revealed rates of incorrect prescriptions ranging from 13% to 41%. The phenomenon of underdosing was also seen in another Spanish investigation that included 137 individuals. Consequently, all patients with a creatinine clearance (CrCl) less than 50 mL/min were prescribed a dosage of 15 mg of rivaroxaban. Additionally, 38.4% of the patients with a CrCl equal to or greater than 50 mL/min received the same dosage. Furthermore, there was an erroneous prescription of rivaroxaban 15 mg in 60.1% of patients aged over 75 years. This research demonstrated that the prescription of a 15 mg dosage was incorrect, with age being the primary factor responsible for this error (87.8%). However, this was not exclusive to rivaroxaban, but also applied to the other direct oral anticoagulants (DOACs) as will be further upon in later sections. In a research including 140 senior patients who were using direct oral anticoagulants (DOACs), it was found that 21 patients (15%) were prescribed an initial loading dose (ILD) of rivaroxaban. Specifically, 7 patients were given a 10-mg dosage, while 14 patients were given a 15-mg dose [12].

In the EXPAND study, which aimed to assess the effectiveness and safety of Xa inhibitor for preventing stroke and systemic embolism in Japanese patients diagnosed with NVAF, 30.2% (1609 out of 5326) of patients with a CrCl ≥50 mL/min were treated with a once-daily dose of 10 mg of rivaroxaban. This treatment choice may have influenced the outcomes related to efficacy and safety [30]. Additionally, a planned analysis of data from the XANTUS, XANAP, and XANTUS-EL studies was conducted to evaluate the appropriate dosage of rivaroxaban based on the label. The findings indicated that out of the 5798 patients with a confirmed CrCl ≥50 mL/min, 1061 (18.3%) were administered an unsuitable 15-mg dosage of rivaroxaban, while 58 (1.0%) got dosages that were not recommended [31].

Nevertheless, the issue of overdose is a significant concern while using rivaroxaban. The XANTUS study, a Phase IV observational study, included patients with AF who were prescribed rivaroxaban [32,33]. Additionally, Coleman et al. [34] conducted a study on 3319 patients who were treated with rivaroxaban at a dosage of 20 mg. They found that more than 5% of the patients had a history of stage III or lower chronic kidney disease and were not receiving the appropriate dose reduction of 15 mg OD as recommended by the rivaroxaban labeling.

A study conducted in real-world conditions found that out of 1290 patients with non-valvular atrial fibrillation (NVAF) who were treated with rivaroxaban and had a creatinine clearance (CrCl) of 50 mL/min or less (including patients with a CrCl of less than 30 mL/min who were excluded from the ROCKET-AF trial), 35.4% were prescribed the standard dose [35]. A similar issue of potential overdosing was identified in a Spanish study involving 230 patients. Among those who were prescribed a dose of less than 20 mg, 15.3% had a CrCl of less than 50 mL/min and should have been treated with a lower dose of 15 mg of rivaroxaban. In contrast, a considerable proportion (36.4%) of patients who received a 15 mg dose

of rivaroxaban had a creatinine clearance (CrCl) of 50 mL/min or higher, indicating that they should have been treated with a higher dose of 20 mg [36]. This finding highlights the large occurrence of underdosing. Another study conducted in the real world found that 17 patients with a creatinine clearance (CrCl) of 50 mL/min or less were prescribed a daily dose of 20 mg of rivaroxaban, while 33 patients with a CrCl greater than 50 mL/min were prescribed a reduced dose [37]. In a recent study conducted in Asturias, it was found that among patients treated with 20 mg and 15 mg of rivaroxaban, 3.6% and 22.5% respectively, received doses that were not sufficient [38].

Apixaban

Figure 1C provides a concise overview of the findings from the most relevant research on the adjustment of apixaban dosage in real-world settings. Similar to the other two direct oral anticoagulants (DOACs), apixaban had a higher prevalence of underdosing compared to overdosing in all of the aforementioned investigations. The reported frequencies of possibly improper apixaban prescriptions ranged from 12.9% to 87.5% [5]. In the ORBIT-AF registry II, apixaban was found to be the most frequently underdosed direct oral anticoagulant (DOAC). This observation is supported by the Barra et al. study and a smaller Canadian study, which included a total of 47 patients. Among these patients, 25 (53%) were receiving apixaban in a manner inconsistent with the ARISTOTLE trial and the product monograph [39,40].

During a retrospective analysis conducted at three hospitals in the United States, a total of 556 patients were included. The medication apixaban was administered in accordance with the guidelines provided by the FDA in 83.4% (n = 464) of the orders placed by healthcare professionals. Following a thorough evaluation by the pharmacist, it was determined that 87.1% (n = 484) of the orders were administered at the recommended dosage, while 12.2% (n = 68) were administered at a lower dosage, and 0.7% (n = 4) were administered at a higher dosage than recommended. The primary cause of underdosing was those aged 80 years or older, accounting for 56% of cases. Among the participants who were given a lower dosage in this trial, 50% were found to be underdosed based on the dose-reduction criteria allowed by the FDA. This highlights the issue of underdosing with this particular DOAC [41].

Upon analyzing the data from these studies, it becomes apparent that the majority of them had adjustment percentages ranging from 50 to 75% (Figure 1D). This highlights the difference between the recommended dosages and the actual amounts administered in clinical practice. Nevertheless, certain studies reported lower rates of off-label dosing. For instance, a Spanish study conducted at Sant Pau Hospital, which involved 223 patients (137 on dabigatran and 86 on rivaroxaban); found that only 1.5% of dabigatran users and 14% of rivaroxaban users began treatment with incorrect doses [42]. In a research conducted at Marshfield Clinic, it was shown that the primary causes for nonadherence to the prescribed protocol for apixaban and rivaroxaban were off-label indications (11% and 13% respectively) as well as insufficient dosage (11% and 11% respectively). The most prevalent causes for dabigatran prescriptions not adhering to the

protocol were patients aged 75 years or older (35%) and prescriptions for off-label indications (5%) [33].

Influence on Medical Results

The preceding section demonstrated that in clinical practice, dosages of DOACs are often administered in a manner that deviates from the dosage recommendations provided by regulatory bodies such as the FDA, EMA, or other organizations. The purpose of this section is to examine the impact of that particular situation on the safety and effectiveness of DOACs. While many real-world studies may lack sufficient patient enrollment to assess outcomes, they may nonetheless provide valuable insights into the use and repercussions of off-label dosing. Only three research, performed by Yao et al. [11], Steinberg et al. [43], and Shinoda et al. [44], provide precise quantitative data on the relationship between dosage modifications of DOACs (excluding edoxaban) and the resulting outcomes. The summary findings of these studies may be seen in Figure 2.

Discussion

Real-world studies are considered crucial for assessing the long-term safety and efficacy of DOACs in routine clinical practice, especially for patients who may not be included in randomized controlled trials. However, there is a lack of real-world data on edoxaban, the newest approved DOAC in Europe [45]. Therefore, more studies and clinical reports are needed to generate information on its use. Frequent observations were made of patients receiving a decreased dosage of DOAC who had mild to severe renal impairment, advanced age, a history of bleeding episodes, and were concurrently taking drugs that enhance the risk of bleeding. Adjusting the dosage based on renal function has previously been established as a central focus. In a study involving 142 patients, it was found that all 5 major bleeding episodes observed were linked to a decrease in kidney function compared to the initial state [12].

Andreu Cayuelas et al. [9] also propose that enhancing the monitoring of kidney function in patients receiving DOAC therapy would likely decrease the risk of major bleeding and safeguard them from excessive thromboembolism risk. It is essential to frequently evaluate the kidney function of patients using DOACs on a global scale. This evaluation allows for the customization of DOAC dosage or the switch to another oral anticoagulant (OAC) if there is a reduction in renal function. These results suggest that there is a need for continual education about the correct dosage of medications for patients with kidney problems, as well as the necessity for regular monitoring of kidney function. Furthermore, it is important to mention that clinical data indicates that the administration of conventional dosages of DOACs to patients with severe renal impairment (which might result in overdose) increases the risk of bleeding twofold, while not significantly reducing the risk of stroke. This data indicates that the level of protection against stroke reaches a plateau as the amount of medication exposure increases. Nevertheless, the administration of DOACs is intricate, as seen by the fact that even with dosage decreases, over 20% of patients still have bleeding episodes. The incidence of bleeding events in real-world settings was marginally

higher compared to the rates reported in randomized clinical trials of direct oral anticoagulants (DOACs) [11].

There are several potential explanations for the discrepancy between the real-world outcomes and the findings of randomized clinical trials. The regular use of lower dosages of DOACs may have an impact on unfavorable clinical outcomes. While lower dosages of DOACs may have a positive impact on reducing bleeding, they may not provide enough protection against strokes. Using a lower dosage of DOAC for purposes other than its approved use is also linked to a higher likelihood of being hospitalized for cardiovascular issues [46]. In the real-world studies included in this review, the majority of patients with AF who were treated with a DOAC in community settings were prescribed dosages that were in line with authorized labeling. However, it was observed that off-label doses were still prevalent across all types of DOACs and dosage levels. Similarly, in our analysis, the majority of the studies reported dosage adjustment rates ranging from 50% to 75% (Figure 1D), indicating a divergence between the recommended doses outlined in the recommendations and the actual doses administered in clinical settings.

The variations in rules and medicine labeling throughout Europe, USA, Japan, and Canada likely complicate the interpretation of the data and subsequent conclusions offered here. Furthermore, a notable constraint of the aforementioned studies is that most of them did not analyze the outcomes separately for adjusted and non-adjusted dosages. This hinders our comprehension of whether the disparities seen were due to the inefficient use of DOACs or the DOACs themselves. Additionally, several studies had a limited sample size, which hindered their ability to accurately identify outcomes, therefore excluding them from inclusion in our analysis. Currently, there is a severe lack of evidence on the possible impact of underdosing or overdoing regimens on the safety and efficacy of DOACs. Therefore, more research is necessary to gather additional information.

Furthermore, it becomes clear at the conclusion of this research that a crucial issue arises: should the prescribed dosage reduction criteria provided in the package inserts of DOACs be considered the optimal practices, or should they be disregarded? The approval and modification of DOAC doses vary globally, and many real-life DOAC users may not have met the eligibility criteria for the clinical studies that established the recommendations for dosage reduction. Various international and local registries, such as ORBIT-AF I and II, SAKURA AF, and real-world studies like XANTUS, have provided new information and emphasized that the management of thromboembolism is not optimal in certain situations [47]. However, it is important to note that these studies are still selective in terms of patient recruitment, so the actual extent of inappropriate dosing in everyday clinical practice may be underestimated [11]. Another significant finding is that studies have shown that low-dose rivaroxaban may be less effective than the standard dose in preventing adverse bleeding effects [48]. This can be partly attributed to clinicians not always following the guidelines and prescribing the reduced-dose regimen to patients who should be receiving the standard dose [49].

Consequently, these patients are not receiving adequate treatment, which raises their chances of developing blood clot-related complications. It is crucial to note

that administering lower doses of direct oral anticoagulants (DOACs) can have significant consequences, as patients who receive lower doses are more likely to experience systemic embolism, stroke, major bleeding, and even death compared to those who receive higher doses [46]. Nevertheless, certain studies propose that in the future, using suboptimal low-dose DOAC therapy may be a suitable option for certain patients who are at a high risk of stroke and bleeding [40].

Pharmacists, physicians, and other healthcare professionals are responsible for ensuring that patients with AF get the correct dose of DOAC to maximize the balance between risks and benefits of this medication. It is important for them to actively engage in identifying issues such as incorrect medication doses, failure to follow the treatment plan, insufficient patient monitoring, and premature discontinuation of DOAC before a surgical procedure. These problems can contribute to half of the hemorrhagic or thrombotic complications [42]. In a study involving multiple healthcare centers, reviewing medication orders by pharmacists led to a 3.6% overall increase in correctly prescribed apixaban doses [41].

Conclusion

The current research confirms that the majority of patients undergoing treatment with DOACs for stroke prevention in AF are given dosages in accordance with the recommendations followed in their respective countries. Nevertheless, even though medication labeling has been authorized, a significant use of off-label dosages has been detected, indicating inefficient utilization of DOAC in clinical practice. Out of the research mentioned, only 3 explicitly linked the modification of DOAC dosage to their particular result. Furthermore, they proposed that both insufficient and excessive dose of DOACs are linked to a heightened likelihood of experiencing negative outcomes. Moreover, the administration of lower-than-recommended doses of medication seems to be linked to a higher likelihood of cardiovascular hospitalization, particularly in cases when apixaban is used as the treatment. Undoubtedly, the underdosing of the medication, which was not prescribed for its intended use, was associated with an almost five-fold higher likelihood of experiencing a stroke. Overdosing on DOACs was linked to higher rates of death from any cause, especially in individuals with reduced kidney function, who had more severe bleeding complications. Additional empirical investigations and data collections are necessary to comprehensively comprehend the consequences of both suboptimal and excessive administration of Direct Oral Anticoagulants (DOACs) on patient outcomes in real-life scenarios.

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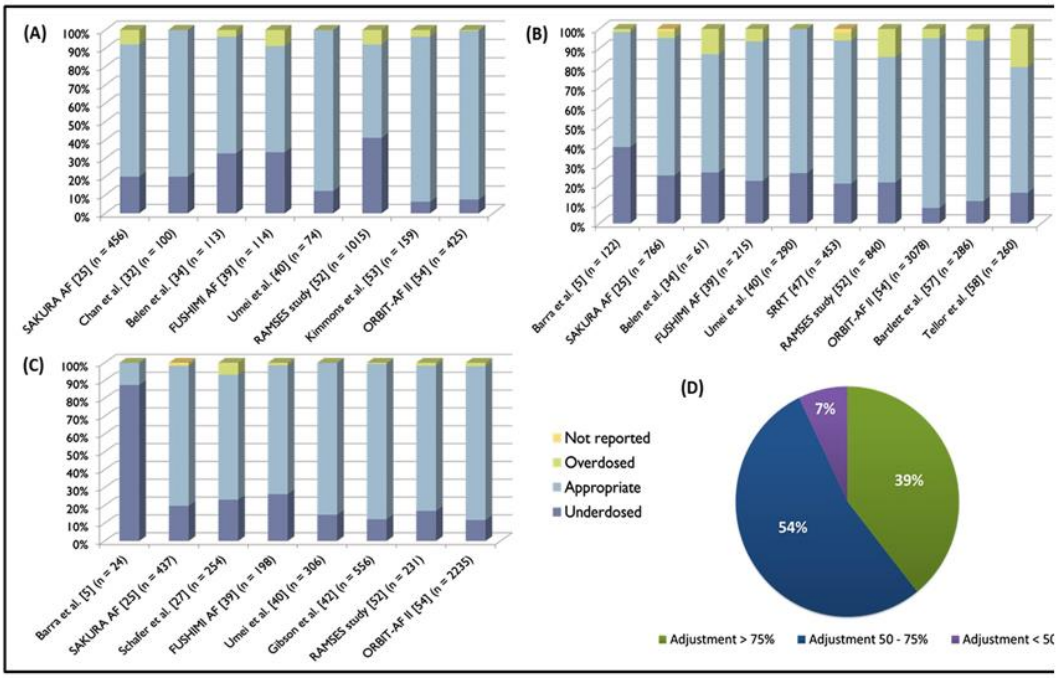

Figure 1. Findings from real-world trials on dosage modifications of direct oral anticoagulants

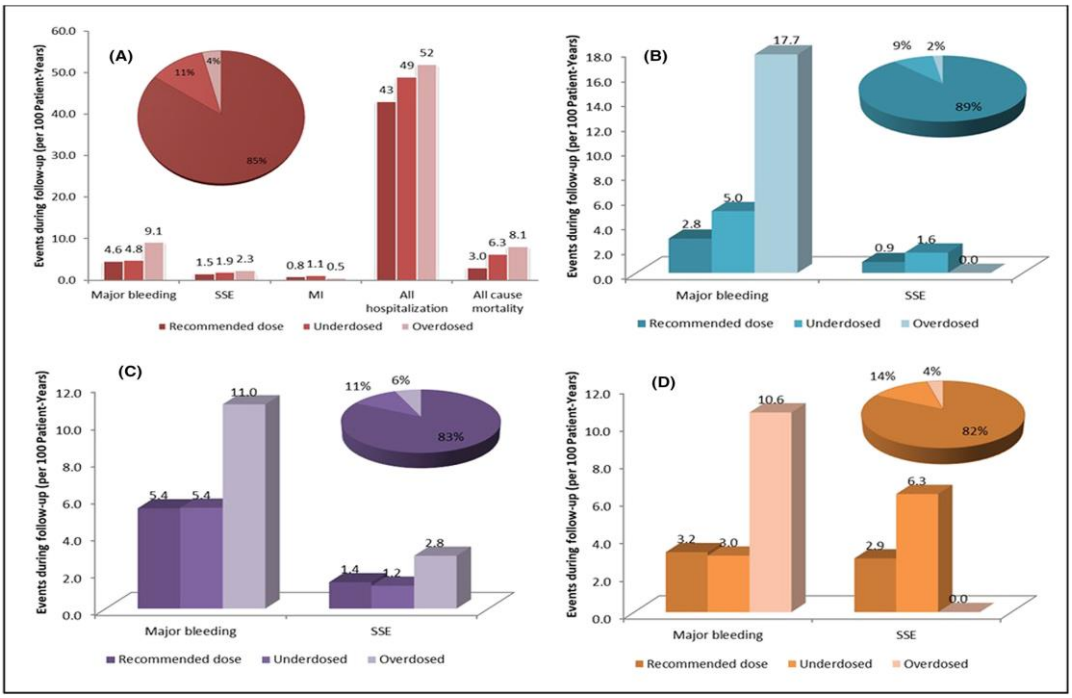

Figure 2. Findings from research that assessed the effects of adjusting the dosage of direct oral anticoagulants on outcomes