Off-label use of reduced dose direct oral factor Xa-inhibitors in subjects with atrial fibrillation: a review of clinical evidence

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ABSTRACT

In real-world clinical practice, underdosing, i.e. off-label use of reduced doses (RD), of oral factor Xa inhibitors (oFXaIs) is quite common in stroke prevention in nonvalvular atrial fibrillation, possibly reflecting the hope to increase safety without reducing efficacy in selected patients. To assess whether this strategy is associated with some clinical benefit, we used a physician-centered approach to evaluate whether current evidence supports the hypothesis that a substantial proportion of underdosing may be voluntary rather than casual, whether and to what extent oFXaIs' dose rather than patients' characteristics are associated with bleeding events, and which are the safety and efficacy clinical implications of oFXaIs' underdosing. Our review found consistent evidence that underdosing is often an intentional strategy; however, available studies do not demonstrate a sizeable net clinical benefit of using off-label RD oFXaIs.

KEYWORDS: nonvalvular atrial fibrillation, direct oral anticoagulants, oral anticoagulant therapy, underdosing, off-label dosing, reduced doses

ONE SENTENCE SUMMARY: Available evidence does not demonstrate a sizeable net clinical benefit of off-label use of oFXaI RDs, rather suggesting an increased risk of adverse events, including hospitalizations for cardiovascular causes and stroke, without a consistent reduction of bleeding events.

INTRODUCTION AND SCOPE OF THE REVIEW

Since the net clinical benefit of direct oral anticoagulants (DOACs) over warfarin has been demonstrated in randomized clinical trials (RCTs)[1–4], DOACs have become the recommended first line therapy for stroke prevention in nonvalvular atrial fibrillation (NVAF). These medications are fixed-dose oral regimens available in two different dose options, which have been variously named (standard, full or higher dose, and reduced or lower dose); anyway, dose prescription should be in keeping with drug- specific dosing guidelines[5–7]. The criteria for posology adjustment and approved doses of oral factor Xa inhibitors (oFXaIs) for stroke prevention in NVAF according to the European Medicines Agency summary of product characteristics (SmPC) are available in Supplementary Data Tables S1 and S2, respectively. Use of reduced dose (RD) DOACs is primarily recommended along the published European guidelines dose reduction criteria[7].

In this regard, however, the differences in the RCTs' design may help to clarify the question of appropriate or inappropriate use of DOAC doses and to uniform the terminology. In the RE-LY trial patients were randomly assigned to receive dabigatran at a dose of 150 mg or 110 mg twice daily (BID), both showing consistent efficacy and safety across a wide range of NVAF patients, with an increasing net clinical benefit when prescribed according to European recommendations[1,7–10]. Being independent from any patient's characteristics, the selection of the lower dabigatran dose is entirely at the physician's discretion, mainly based on patient's age, renal function and concomitant drug therapies, and should not be regarded as inappropriate[7]. On the other hand, in RCTs investigating the non-inferiority of oFXaIs over warfarin, patients received full dose (FD) or reduced dose (RD) of the experimental drug according to predefined criteria[2–4]. In the ENGAGE AF-TIMI 48 study, higher dose (HDE) and lower dose (LDE) once-daily (OD) edoxaban regimens have been evaluated, each including a RD according to pre-specified criteria (60/30 mg OD - HDE and 30/15 mg OD - LDE)[4]. In the LDE group, it has

been observed a 41% higher ischemic stroke risk compared with warfarin, leading to the non-approval of this dosing regimen. Therefore, prospective RCTs data for lower doses only exist for dabigatran (110 mg BID) and edoxaban (30/15mg OD, but not approved)[7]. In contrast, no lower dose group was studied for rivaroxaban in the ROCKET AF trial[2] and for apixaban in the ARISTOTLE trial[3], but eligibility for the RD arm was predefined according to the patient's characteristics; as such, no clinical outcome data on hard end-points are available for the use of these doses outside the tested dose reduction algorithms[7]. Therefore, the issue of inappropriate (or off-label) use of RD DOACs in patients not meeting the criteria for dose reduction (i.e., underdosing) mainly concerns oFXaIs, and is by far more common than inappropriate use of FD in patients who qualify for RD (i.e., overdosing)[11–50]. Undoubtedly, some underdosing may be ascribed to involuntary errors or to physiological fluctuations of creatinine clearance (CrCl) around the dose-reduction level, but a substantial proportion of it might reflect an intentional "cautious" approach to DOAC use in selected patients, implying high hopes that underdosing may lessen the risk of bleeding without reducing the efficacy in stroke prevention. In fact, some uncertainties in dose selection may arise when considering that the latest European recommendations for practical use of DOACs suggest to consider the use of a RD in the presence of two or more factors including, among others, age over 75 years, previous bleeding, frailty and high fall risk[7]. This may appear somehow counterintuitive since the risk of thromboembolic events has been demonstrated to further increase in very advanced age[51] and age over 75 years is the most powerful risk factor for stroke in NVAF patients[52]. Moreover, frail older patients with NVAF are less likely to receive an appropriate oral anticoagulant therapy (OAT) and, at the same time, are at greater risk of embolic stroke and death[53,54]. It has been well demonstrated that patients on OAT at high risk of falls have not a significantly increased risk of major bleeding (MB)[54], and current recommendations do not require fall risk estimation in OAT candidates[7]. The lack of evidence to guide optimal care for older patients

with NVAF and frailty might in part explain the gap between current recommendations not to undertreat frail older patients[55] and the high prevalence of underdosing in real-life patients[53,54]. In order to assess whether there is some evidence of a potential clinical benefit for oFXaIs' underdosing, we will use a physician-centered approach to evaluate current literature for the presence of 1) evidence supporting the hypothesis that a substantial proportion of underdosing may be voluntary rather than casual; 2) a possible association of oFXaIs' dose with bleeding events, and its extent; and 3) data on the safety and efficacy clinical implications of oFXaIs' underdosing. We will not discuss DOAC dose adjustment strategies according to plasma concentration because, despite some potential benefit has been observed in small studies[56–59], there is no evidence from large RCTs that this strategy may be associated with a higher clinical benefit compared with current practice[7].

METHODS

The medical literature was systematically searched through Pubmed (MEDLINE) and Embase using a combination of Medical Subject Heading (MeSH) terms and keywords relevant for the treatment and conditions of interest for primary studies and systematic reviews. Search was limited to studies published in English language, between January 2010 and May 2020. Predefined exclusion criteria included: basic science and animal studies, studies focusing on different drug molecules (e.g., ximelagatran, anticoagulation reversal agents including idarucizumab), on specific non-relevant conditions (e.g., NVAF ablation, periprocedural OAT, end-stage chronic kidney disease – CKD - and hemodialysis), on outcomes not relevant for the purpose of this review (e.g. cost-effectiveness, medication adherence, quality of life), wrong publication types (e.g. case reports, abstracts and oral communications), and studies with unclear underdosing definitions. Additional relevant studies were included from the

bibliographies of existing reviews and meta-analyses. The full search strings are available in Supplementary Data.

RESULTS

Underdosing of oral factor Xa inhibitors in real-life clinical practice

In real-life, patients with NVAF are older, more frequently of female gender, and show a high prevalence of comorbidities, polypharmacy and functional and/or cognitive impairment[54], with a high prevalence of RD use[11–50,54,60], particularly for apixaban. A descriptive summary of the systematically identified studies which investigated the prevalence of and the variables associated with off-label use of oFXaI RDs is available in Supplementary data, Table S3. In the ORBIT-AF II study underdosing was associated with older age, female gender, and higher embolic and bleeding risk scales[13], as well as with non-white ethnicity[61]. DOAC underdosing in 6658 Canadian primary care patients (7.2%) was associated with female gender, presence of multiple comorbidities (particularly heart failure and dementia) and concomitant therapy with aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs)[17]. Among 460 older outpatients, underdosing (18%) was associated with older age, higher embolic risk score, previous MB and history of CKD[18]. In a sample of 772 hospitalized patients, factors associated with inappropriate DOAC prescribing (mainly represented by underdosing, 17.4% in the overall sample) were, among others, age ≥80 years, apixaban prescription, and moderate CKD[24]. In a large sample of 8425 newly prescribed NVAF patients, underdosing (39%) was associated at univariate analysis with several variables, including, among others, female gender, advanced age, lower BMI, history of CKD and lower CrCl, greater comorbidity burden, higher embolic risk score and concomitant use of antiplatelet drugs[30]. Among others, age over 80 years alone, history of bleeding or high perceived bleeding risk have been reported as reasons for persistent apixaban underdosing (16.6%)[15]. In a recent French study on 2027 NVAF patients, apixaban underdosing

(18.1%) was more frequent with advancing age, despite normal renal function and body weight (BW)[32]. Among 30467 outpatients with NVAF from UK primary care, underdosing was observed in 21.6% and 9.1% of patients that initiated treatment with apixaban and rivaroxaban, respectively, with increasing use of RD along with lower CrCl[33]. Of note, 26.9% of apixaban-underdosed patients met none dose reduction criteria[33]. In a recent systematic review, Santos et al reported data from 75 studies and showed that a substantial proportion of patients (25-50%) received off-label DOACs doses[14].

In conclusion, in real-life clinical practice, underdosing is quite common, particularly for apixaban. Several conditions, including advanced age, female gender, higher embolic and bleeding risk scores, history of bleeding and/or perceived high risk of bleeding, history of CKD, concomitant use of antiplatelet drugs or NSAIDs, have been consistently reported to be associated with underdosing, supporting the hypothesis that a substantial proportion of off-label RD oFXaIs' prescriptions may be voluntary rather than casual[11,13–50,62].

Oral factor Xa inhibitors' dose, patients' characteristics and bleeding events

In the ROCKET AF study, patients who experienced a gastrointestinal bleeding (GIB) were older and less often female[2]. GIB occurred in the upper gastrointestinal (GI) tract (48%), lower GI tract (23%), and rectum (29%), without differences between treatment arms[2,63]. Rivaroxaban-treated patients with MB were more likely to be older, have a history of chronic obstructive pulmonary disease or GIB, prior use of aspirin, mild anemia and diastolic blood pressure ≥90 mmHg[64]. Compared with FD-treated patients, those treated with RD rivaroxaban (20.7%) were older, more frequently of female gender, with a greater comorbidity burden and higher stroke risk[2,65]. The primary safety endpoint (MB and clinically relevant non-major bleeding, CRNMB) occurred more frequently in those treated with RD rivaroxaban than in those treated with FD rivaroxaban[65]. Rates per year of stroke and systemic embolism (SE), GIB,

hemorrhagic stroke, intracranial hemorrhage and fatal bleeding were consistently higher among patients eligible for RD, irrespective of treatment allocation[65,66].

In the overall sample of the ARISTOTLE study, the incidence of MB, which was lower in the apixaban group[3], increased with advancing age (75 years or older), this latter being independently associated with an increased risk of bleeding, along with history of hemorrhage, stroke or transient ischemic attack (TIA), concomitant use of antiplatelet drugs or NSAIDs, diabetes, lower CrCl, and anemia prior to treatment[67]. Patients eligible for apixaban RD were older and at increased risk of stroke, MB and all-cause death compared with the subjects on FD[66,67]. However, the effect of properly used RD apixaban versus warfarin in these patients was consistent with that of the FD in reducing stroke, MB and all-cause mortality[68,69]. Patients with only one dose reduction criterion and appropriately treated with FD apixaban did not show differences in the efficacy and safety outcomes compared with FD-treated patients who did not fulfill any dose reduction criteria[70]. In patients with prior GIB (who were at increased risk of recurrent major GIB) treated with an appropriate apixaban dose, efficacy and safety were consistent with the results of the overall trial[71]. The use of NSAIDs was associated with incident MB e CRNMB, but not with GIB[72].

In the AVERROES trial, the rate of bleeding events was 3.8%/year and 4.5%/year with aspirin and apixaban, respectively[73]. The anatomic site of bleeding did not differ between therapies, and higher embolic risk scores were associated with increasing risk of both bleeding and stroke[73]. Rates of MB on apixaban were similar to those of aspirin across all age groups, and increased with age, with absolute rates of 2.6%/year and 2.2%/year, respectively, in patients 75 years and older, compared with 0.8%/year and 0.7%/year, respectively, in patients under 75 years, with no significant treatment-by-age interaction[74]. Moreover, the risk of MB in patients 85 years and older was similar on apixaban and aspirin (4.7%/year and 4.9%/year)[74].

In the ENGAGE AF-TIMI 48 trial, the annualized rate of MB was significantly reduced in patients treated with HDE (2.75%) and with LDE (1.61%) compared with warfarin (3.43%), whereas the risk of major GIB was higher with HDE, but lower with LDE[4]. In the overall sample of patients, several variables were associated with an increased risk of major GIB, including older age, male gender, comorbidities (particularly heart failure, diabetes and CKD), and concomitant use of aspirin or other antiplatelet agents, and of proton pump inhibitors (PPIs) or other gastro-protective agents[75]. Patients who met criteria for dose reduction at randomization had a higher risk of stroke, bleeding and death compared with those who did not fulfill dose-reduction criteria[66,76].

These data from RCTs demonstrate that several patients' characteristics (including older age, greater comorbidity burden, CKD, previous bleeding events, use of NSAIDs and antiplatelet drugs), rather than oFXaIs' dose, are significantly and consistently associated with an increased occurrence of MB in oFXaI-treated patients. Rates of MB were consistently higher among RD-treated than in FD-treated patients[66]. However, appropriately dose-adjusted oFXaIs showed an improved benefit-harm profile compared with warfarin and with aspirin[66,73]. Of note, in elderly patients rates of MB were similar on apixaban and on aspirin in the unique study comparing a DOAC with aspirin[74].

Real-life studies demonstrated that in OAT-treated patients most MBs occur in subjects with underlying gastrointestinal (GI) pathology (colonic diverticula, angiodysplasia, peptic ulcer disease, arteriovenous malformations, inflammatory bowel disease, hemorrhoids and malignancy[77,78]. Older age is associated with an increased prevalence of these underlying conditions, predisposing to bleeding, and this risk is further increased in patients on OAT[2,64,65,67,73–75,79,80] as well as in patients on antiplatelet therapy[73,74,81]. There is scant evidence that OAT intensity is associated with increased bleeding risk, but strong evidence that concomitant drug therapies, including gastrotoxic drugs, single or dual antiplatelet therapy, and

therapies with the potential for drug-drug interactions may substantially increase the risk of bleeding[82–84], whereas the incidence of hospitalization for upper GIB was lower among DOAC-treated patients receiving concomitant PPI therapy[85].

Clinical implications of oral factor Xa inhibitors' underdosing on safety and efficacy outcomes

Since in phase III RCTs patients received oFXaIs at appropriate doses, with a better benefit-harm profile compared with subjects on warfarin, evidence about clinical implications of oFXaIs' underdosing may be inferred only from observational real-life studies. In this context, except minor differences regarding renal function estimation formulas, consideration of potential drug-drug interactions and country-specific rivaroxaban dose differences, underdosing has been almost always defined as the prescription of RD oFXaIs not in keeping with the SmPC–specified dose reduction criteria.

Table 1 summarizes the main efficacy and safety outcome results coming from real-world studies which evaluated the clinical implications of off-label RD use. In the ORBIT-AF II study, underdosing was associated with increased cardiovascular hospitalization, without reduced bleeding events and/or bleeding-related hospitalizations[13]. In the STANDARD study, including 6306 NVAF subjects on apixaban, there was no evidence of increasing safety (MB or any bleeding event) with the use of off-label RD[45]. In a recent retrospective analysis including 1023 patients on DOACs presenting in an emergency department, no significant difference was found with respect to bleeding according to DOAC dosing[50]. In a large sample of 16568 Korean outpatients, compared with warfarin, off-label RD rivaroxaban was associated with a lower risk of thromboembolic events and all-cause mortality, with a similar risk of MB, whereas off-label RD apixaban was associated with similar risks of thromboembolic events, all-cause mortality and MB[20]. Among 8425 NVAF patients, DOAC underdosing was associated with significantly

reduced effectiveness without a significant safety benefit[30]. In a retrospective analysis including 6392 NVAF Asian outpatients, DOAC underdosing was associated with a 2.5-fold increased risk of thromboembolism compared with warfarin, with a comparable risk of MB[47].

Potential underdosing in 14865 NVAF patients who initiated DOAC therapy and did not meet renal criteria for RD use was found to be associated with a higher risk of stroke, particularly in apixaban-treated patients, without a significant difference in MB events; however, lack of data on BW strongly limited the correct assessment of off-label RD use in apixaban-treated patients[22]. Briasoulis et al reported that patients who received off-label RD rivaroxaban (12.9%) had an increased risk of MB, which was not significant after propensity score matching[44]. On the contrary, clinical outcomes were not worse for underdosed rather than correctly dosed subjects enrolled in the prospective multicenter SAKURA AF registry in Japan[40]. In a retrospective Spanish study of 2494 NVAF patients on DOAC, underdosing was associated with a non-significant higher death rate, without differences in MB and stroke[49]. After adjusting for patients' characteristics by propensity scoring and inverse probability of treatment weighting, compared with patients who received the recommended dose, patients enrolled in the XAPASS study who received off-label RD rivaroxaban experienced comparable rates of MB and higher rates of stroke/SE and myocardial infarction[35]. Very similar findings were reported by Cheng et al in 2214 rivaroxaban-treated patients in Taiwan; compared with on-label dosing, off-label RD rivaroxaban was associated with an increased risk of ischemic stroke, and a negative net clinical benefit in different weighted models[31]. In a Korean study, on-label FD rivaroxaban showed better results for the composite clinical outcome (ischemic stroke, intracranial hemorrhage, hospitalization for GIB, all-cause death) compared with off-label RD[38]. Using data from the XANTUS study, Amarenco et al reported that use of off-label RD rivaroxaban was associated with a trend to less favorable outcomes (MB, stroke/SE, and death), association not confirmed when correcting for patients' characteristics at multivariate

analysis[29]. In a small retrospective study including 354 NVAF patients aged 80 years and over with non-severe frailty, 42 of 273 patients on DOAC (15.4%) were underdosed, without differences in the incidence of bleeding and thromboembolic events[86]. Paciaroni et al retrospectively investigated the risk factors for cerebrovascular ischemic events occurring during DOAC therapy for stroke prevention in AF in a sample of 713 cases (641 ischemic strokes and 72 TIAs) and 700 controls: on multivariate analysis, use of off-label RD was associated with a 3-fold increased risk of ischemic events[87]. In a prospective cohort study on 1124 AF patients aged 85 years and older treated with VKAs (58.7%) or DOACs (41.3%), no thrombotic events occurred in the small group of underdosed DOAC patients[88]. Recent studies demonstrated that oFXaIs' underdosing was associated with a higher stroke severity in patients admitted with ischemic stroke[89], and with a higher rate of major vascular occlusion in patients admitted with suspected ischemic stroke[90].

In conclusion, despite inherent limitations of observational studies, and with few exceptions[40,86,88], there is consistent evidence that underdosing of oFXaIs is not associated with a significant reduction of bleeding events and is possibly associated with an increased risk of thromboembolic events.

CONCLUSIONS

Despite the well demonstrated greater net clinical benefit of DOACs compared with warfarin in the general population and in older patients[91,92], there is still a persistent underuse of OAT[53,93] and an increasing use of off-label RD of oFXaIs[14]. Our literature review, summarized in the Central Illustration, demonstrated that a substantial proportion of oFXaIs' underdosing may be voluntary, suggesting a cautious approach to patients perceived to be at high risk of bleeding. However, available evidence suggests that patients' characteristics (e.g., advanced age, comorbidity, anemia, previous bleedings, concomitant therapy with antiplatelet drugs or

NSAIDs) and underlying GI pathology, rather than with OAT intensity, are associated with the risk of bleeding events. Indeed, in oFXaIs' RCTs, the rates of MB were consistently higher among patients treated with RD rather than in those treated with FD. Moreover, correct use of RD had reassuringly the same efficacy and safety as FD oFXaIs compared with warfarin[66]. Real-life studies do not provide evidence of a sizeable net clinical benefit by using off-label RD oFXaIs, but rather suggest an increased risk of adverse events, including hospitalizations for cardiovascular causes and stroke, without a significant reduction of bleeding events.

All three oFXaIs show a first-order kinetic, which means that, at the dosage range tested, they show a linear correlation between their drug plasma concentrations (DPCs) and the pharmacodynamic (PD) inhibition of clotting factor X activated (FXa), without any tendency to reach a plateau. Such linearity is consistent and independent of age and sex[94]. On these bases, an inverse and a direct relationship of DPC with the probability of stroke/SE and MB, respectively, have been observed, although within-patient clinical variability complicates the interpretation of these results[95].

Indeed, it has been reported that treatment with off-label RD DOACs compared with on-label dose was associated with lower DPCs[96], and that C-trough levels in the lowest level class were associated with a significantly increased incidence of thromboembolic events[97]. Use of a RD implicates halving the dose of apixaban (from 5 mg to 2.5 mg) and edoxaban (from 60 mg to 30 mg) while reducing of only 25% the dose of rivaroxaban (from 20 mg to 15 mg) and of 33% (from 15 mg to 10 mg) in Japanese patients. Halving the dose of apixaban or edoxaban is associated to an approximate 50% proportional reduction of their maximum DPCs[76,98]. However, it must be taken into consideration that in the ENGAGE AF-TIMI 48 trial, the predefined halving of edoxaban dose was associated to only an approximate 25% reduction of DPC and anti-FXa activity[76]. Moreover, the investigation of the effects of low BW (≤50 kg) on pharmacokinetics and PD showed approximately 27% higher apixaban Cmax and AUC[99], and

a 24% higher rivaroxaban Cmax resulting in a 15% increase in prolongation of prothrombin time[100]. Thus, by considering the criteria for edoxaban dose reduction, such as BW ≤60 kg, estimated CrCl 30 to 50 ml/min, or concomitant use of verapamil or quinidine, DPCs of the 30 mg dose were similar to those reached with 60 mg[76]. Very similar results were obtained for apixaban where a 25% reduction of DPC was observed in patients treated with 2.5 mg vs 5 mg when 2 of 3 dose reduction criteria of the ARISTOTLE study were met[101]. Finally, the DPCs of on-label rivaroxaban FD and RD were also superimposable[102]. These results suggest that DPCs, and thus activities, of all oFXaIs in patients prescribed on-label RDs are similar to those observed with on-label FD, thereby reinforcing prescription according to recommended dose.

In our view, the main strength of the present study is the physician-centered approach we used to assess the reasons underlying the decision to underdose oFXaIs in selected patients, the inconsistent and frail pharmacologic and clinical background supporting this strategy, and the clinical safety and efficacy implications of underdosing in real-life studies. The major limitation of the present study is that the evidence about the clinical implications of underdosing derives from observational studies, which have inherent weaknesses. Most of these studies are registry-based, mainly retrospective, with potential for residual confounding from unmeasured variables, such as over-the-counter use of aspirin, polypharmacy, drug-drug interactions, body size and general health status. Moreover, these studies are heterogeneous, differing for clinical setting, country and ethnic groups, definition of potential underdosing and clinical outcomes considered. Eventually, most patients were treated with apixaban and rivaroxaban, with a small proportion of patients on edoxaban. Notwithstanding these limitations, the available evidence is quite consistent, and does not suggest a potential benefit from oFXaIs' underdosing. At the same time, even if current evidence is not sufficient to allow any speculation about possible safety or efficacy differences among different oFXaIs used at inappropriate RDs, there are quite consistent data that underdosing is more frequent, and has the potential to be particularly

detrimental, in apixaban-treated patients. Being hard to imagine the ethical and practical feasibility of a RCT assessing the potential clinical benefit of off-label oFXaI RDs in selected patients, only prospective, dedicated, observational real-life studies involving subjects at high risk of underdosing (older polypathologic NVAF patients) might further shed some light on this topic. In these patients, OAT prescription is often a troublesome decision, involving a global evaluation of health, residual life-expectancy, functional and cognitive status, rather than a simple addition of variables within cardio-embolic and bleeding risk scales[53,54]. In keeping with current recommendations not to undertreat older frail patients[55], our review demonstrates that oFXaIs' underdosing may be associated with a reduced efficacy without greater safety, thereby implying a poor benefit and possible harm from this strategy. At the moment, less is not more, in this case.

AUTHOR CONTRIBUTIONS

All the authors listed in the contributors' affiliations meet the ICMJE Authorship Criteria; that is, they substantially contributed to conception and design, acquisition of data, drafting of the article, critical revision, and final approval of the manuscript.

CONFLICT OF INTEREST

M.B. reports receiving consulting fees from Bayer, Boehringer, BMS-Pfizer and Daiichi-Sankyo. A.C. reports receiving consulting fees from Bristol-Myers, Daiichi-Sankyo, Mylan, AstraZeneca, Sanofi, Recordati, Novartis, MSD, Mediolanum DOC, Pfizer. N.F. reports receiving consulting fees Bristol-Myers, Daiichi-Sankyo, Mylan. E.B., G.I., M.G., D.P., N.M. and G.M.D.F. have nothing to disclose.

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Table 1. Clinical outcomes associated with off-label reduced dose oral factor Xa inhibitors in relevant clinical studies

Study	Setting, population and definition of off-label RD oFXaIs' use	Incidence rate/proportion (absolute number) of selected clinical outcomes (unadjusted)	Clinical outcomes associated with off-label RD oFXaIs use
Steinberg BA et al, 2016[13]	U.S.A.: 5738 NVAF outpatients on DOAC (median age 71 ys, 41.8% female), 9.4% underdosed (RD use not consistent with FDA-SmPC) 3078 RI, 2235 AP, 425 DA Median follow-up: 0.99 ys	Ischemic stroke/SE/TIA: 1.32% (n=70) on-label dose DOACs, 1.95% (n=11) off-label RD DOACs MB: 3.59% (n=187) on-label dose DOACs, 4.12% (n=23) off-label RD DOACs MI: 0.77% (n=41) on-label dose DOACs, 1.06% (n=6) off-label RD DOACs All hospitalization: 42.77% (n=1727) on-label dose DOACs, 48.56% (n=212) off-label RD DOACs CV hospitalization: 24.16% (n=1093) on-label dose DOACs, 26.11% (n=129) off-label RD DOACs Bleeding hospitalization: 2.91% (n=152) on-label dose DOACs, 4.12% (n=23) off-label RD DOACs	Increased CV hospitalization (aHR 1.26; 95% CI 1.07-1.50). Non-significant differences in ischemic stroke/SE/TIA, MI, MB.

		All-cause mortality: 2.95% (n=158) on-label dose DOACs, 6.30% (n=36) off-label RD DOACs	
Yao X et al, 2017[22]	U.S.A.: 13392 NVAF patients on DOAC with no renal indication for RD (median age 70 ys, 41.8% female). 3340 AP, 5399 RI, 4653 DA Off-label RD (RD use in the absence of a renal indication): 13.3% (AP 16.5%, RI 15.1%, DA 8.9%) Median follow-up: 4.0 mo	Ischemic stroke/SE: 1.43%/y (n=14) on-label FD DOACs, 1.70%/y (n=16) off-label RD DOACs MB: 5.03%/y (n=49) on-label FD DOACs / 5.43%/y (n=51) off-label RD DOACs	Off-label RD vs on-label FD AP associated with higher stroke risk (HR 4.87; 95% CI 1.30-18.26), but similar MB risk (HR 1.29; 95% CI 0.48-3.42). No differences in stroke or MB risk between off-label RD and on-label FD RI.
Sato T et al, 2018[25]	Japan: 2272 NVAF patients on DOAC (mean age 72 ys, 37% female), 498 RI†, 1014 AP, 267 ED, 493 DA Off-label RD (RD use not consistent with Japan SmPC†): 21.6% (490); RI 23.9%, AP 22.5%, ED 12.4%, A 20.7% Follow-up: up to 2 ys	Stroke/SE: 2.2%/y on-label dose DOACs, 2.4%/y off-label RD DOACs MB: 2.0%/y on-label dose DOACs, 2.4%/y off-label RD DOACs GIB: 1.1%/y on-label dose DOACs, 1.0%/y off-label RD DOACs	No significant differences in stroke/SE and MB between on-label dose DOACs and off-label RD DOACs

		ICH: 0.3%/y on-label dose DOACs, 1.2%/y off-label RD DOACs All-cause mortality: 2.3%/y on-label dose DOACs, 2.6%/y off-label RD DOACs	
Steinberg BA et al, 2018[26]	U.S.A.: 7925 NVAF outpatients on DOAC (mean age 71.0 ys, 41.3% female) 3833 RI, 3528 AP, 70 ED, 494 DA Off-label RD (RD use not consistent with FDA SmPC): 9.3% (734) Median follow-up: 1.0 ys	Stroke/SE/TIA: 1.35%/y (n=91) on-label FD RI or AP, 2.11%/y (n=16) off-label RD RI or AP MB: 2.84%/y (n=189) on-label FD RI or AP, 4.28%/y (n=32) off-label RD RI or AP MI: 0.60%/y (n=41) on-label FD RI or AP, 0.78%/y (n=6) off-label RD RI or AP Bleeding hospitalization: 2.38%/y (n=159) on-label FD RI or AP, 3.60%/y (n=27) off-label RD RI or AP All-cause mortality: 2.60%/y (n=177) on-label FD RI or AP, 6.77%/y (n=52) off-label RD RI or AP	Off-label RD vs on-label FD in patients receiving either RI or AP showed higher unadjusted rates of stroke/SE/TIA (HR 1.56, 95% CI 0.92- 2.67), MB (HR 1.49, 95% CI 1.02- 2.18), and overall mortality (HR 2.61, 95% CI 1.86- 3.67), with borderline non-significant values after multivariate adjustment,
Amarenco P et al, 2019[29]	Europe, Canada, Israel: subanalysis on 4464 NVAF patients on RI.	MB/stroke/SE/all-cause mortality: 4.8%/y (n=157, 4.4%) on-label dose RI, 7.6%/y (n=39, 6.7%) off-label RD RI	Off-label RD RI vs on-label dose RI was associated with a higher risk of the composite of MB/stroke/SE/all-cause

	Off-label RD RI (RD use not consistent with SmPC) 13.1% (583) Follow-up: 1 ys	Stroke/SE/MI: 1.9%/y (n=62, 1.7%) on-label dose RI, 2.7%/y (n=14, 2.4%) off-label RD RI MB: 2.6%/y (n=86, 2.4%) on-label dose RI, 3.9%/y (n=20, 3.4%) off-label RD RI ICH: 0.5%/y (n=15, 0.4%) on-label dose RI, 1.0%/y (n=5, 0.9%) off-label RD RI Fatal bleeding: 0.2%/y (n=7, 0.2%) on-label dose RI, 0.4%/y (n=2, 0.3%) off-label RD RI All-cause mortality: 1.9%/y (n=62, 1.7%) in-label dose RI, 3.1%/y (n=16, 2.7%) off-label RD RI	death (HR 1.57, 95% CI 1.10-2.22), but not after multivariate adjustment
Arbel R et al, 2019[30]	Israel: 8425 NVAF outpatients on on-label FD or off-label RD DOAC (56.4% >75 ys, 51.9% female) Off-label RD (RD use non consistent with drug label): 3285 (39%)	Overall mortality/stroke/MI:8.7% (n=447) on-label dose DOACs, 22.8% (n=749) off-label RD DOACs Stroke:1.6% (n=84) on-label dose DOACs, 2.6% (n=86) off-label RD DOACs MI:0.93% (n=48) on-label dose DOACs, 1.3% (n=44) off-label RD DOACs	Off-label RD use compared with on label FD was associated with a higher rate of the composite of overall mortality/stroke/MI (aHR 1.57, 95% CI 1.34-1.83) and a higher rate of bleeding events requiring hospitalization (aHR 1.63, 95% CI, 1.14-2.34).

		Bleeding hospitalization: 1.6% (n=80) on-label dose DOACs, 3.1% (n=101) off-label RD DOACs All-cause mortality: 6.9% (n=354) on-label dose DOACs, 20.9% (n=686) off-label RD DOACs	
Cheng W-H et al, 2019[31]	Taiwan: 2214 NVAF patients on RI‡ (mean age 75.7 ys, 36% female) Off-label RD (RD use non consistent with J-ROCKET study‡): 26.4% (584) Mean follow-up: 2.10 ys	Ischemic stroke: 0.86%/y (n=32) on-label dose RI, 2.82%/y (n=29) off-label RD RI ICH: 1.14%/y (n=42) on-label dose RI, 1.16%/y (n=12) off-label RD RI	Compared with the on-label dose group, off-label RD RI was associated with an increased risk of ischemic stroke (aHR 2.75, 95% CI 1.62-4.69), and with a negative net clinical benefit (aHR 1.54, 95% CI 1.02-2.31) in different weighted models, no significant differences in ICH
Ikeda T et al, 2019[35]	Japan: 6521 NVAF patients on RI† and CrCl ≥50 ml/min. Off-label RD (RD use not consistent with Japan SmPC†): 35.8% Mean follow-up 305 days	Stroke/SE/MI: 1.48%/y on-label FD RI, 2.15%/y off-label RD RI Any bleeding: 8.05%/y on-label FD RI, 5.29%/y off-label RD RI MB: 1.63%/y on-label FD RI, 1.34%/y off-label RD RI	Off-label RD RI resulted in a lower incidence of the primary safety outcome (any bleeding; HR 0.66, 95% CI 0.57–0.76), without a significant difference in MB, and a higher incidence of the primary

		ICH: 0.64%/y on-label FD RI, 0.75%/y off-label RD RI Fatal bleeding: 0.14%/y on-label FD RI, 0.06%/y off-label RD RI Ischemic stroke: 1.09%/y on-label FD RI, 1.26%/y off-label RD RI MI: 0.05%/y on-label FD RI, 0.09 per 100 person/ys off-label RD RI	effectiveness outcome (stroke/SE/MI; HR 1.45, 95% CI 1.10–1.91)
Lee S-R, Stroke 2019[38]	Korea: 33980 NVAF patients with CrCl >50 ml/min, no previous ischemic stroke/ICH/GIB (mean age 66.9 ys, 37.8% female), 20431 on VKA, 13549 on RI Off-label RD RI (RD RI use in the absence of a renal indication): 42.8% Median follow-up 1.4 ys	Ischemic stroke/ICH/hospitalization due to GIB or ICH/all-cause mortality*: 7.07%/y (n=349/5196) on-label FD RI, 8.47%/y (n=361/5196) off-label RD RI Ischemic stroke*: 2.16%/y (n=108/5196) on-label FD RI, 2.55%/y (n=110/5196) off-label RD RI MB (ICH/GIB) hospitalization*: 2.28%/y (n=114/5196) on-label FD RI, 2.71%/y (n=117/5196) off-label RD RI	On-label FD RI vs off-label RD RI showed a significantly lower incidence of the composite of ischemic stroke/ICH/hospitalization due to GIB or ICH/all-cause death (HR 0.85, 95% CI 0.74-0.99), but no significant difference for any of the single outcomes*.

		ICH*: 0.89%/y (n=45/5196) on-label FD RI, 0.83%/y (n=36/5196) off-label RD RI GIB hospitalization*: 1.41%/y (n=71/5196) on-label FD RI, 1.89%/y (n=82/5196) off-label RD RI All-cause mortality*: 3.60%/y (n=182/5196) on-label FD RI, 4.32%/y (n=189/5196) off-label RD RI	
Murata N et al, 2019[40]	Japan: 1676 NVAF outpatients on DOAC (mean age 71.7 ys, 28.5% females), RI† 45.5%, AP 25.6%, ED 1.9%, DA 27.1% Off-label RD (RD use not consistent with Japan SmPC†): 22.2%. Median follow-up: 39.3 mo	Ischemic stroke/TIA/SE: 1.17%/y (n=25, 3.3%) on-label FD DOACs, 2.07%/y (n=27, 5.6%) on-label RD DOACs, 1.02%/y (n=11, 2.9%) off-label RD DOACs MB: 1.21%/y (n=26, 3.5%) on-label FD DOACs, 1.45%/y (n=19, 4.0%) on-label RD DOACs, 0.64%/y (n=7, 1.9%) off-label RD DOACs ICH: 0.46%/y (n=10, 1.3%) on-label FD DOACs, 0.53%/y (n=7, 1.5%) on-label RD DOACs, 0.37%/y (n=4, 1.1%) off-label RD DOACs	Ischemic stroke/TIA/SE, mortality and MB did not significantly differ between the on-label FD, and off-label RD groups, before and after propensity score matching

		All-cause mortality: 0.64%/y (n=14, 1.9%) on-label FD DOACs, 4.07%/y (n=54, 11.3%) on-label RD DOACs, 1.28%/y (n=14, 3.8%) off-label RD DOACs	
Navarro-Almenzar B et al, 2019[49]	Spain: 2494 NVAF patients on DOAC (mean age 76 ys, 52.9% female), RI 41.1%, AP 38.5%, ED 2.8%, DA 17.6% Off-label DOAC dose in 517 patients (23.5%), FXaI mainly underdosed (dose not consistent with SmPC); RI 26.1%, AP 21.2%, ED 23.9%, DA 22.8% Mean follow-up 20.2 mo	Ischemic stroke: 1.8%/y (n= 52/1682, 3.1%) on-label dose DOACs, 2.0%/y (n= 15/441, 3.4%) off-label RD DOACs. MB: 3.0%/y (n= 87/1682, 5.2%) on-label dose DOACs, 3.3%/y (n= 25/441, 5.7%) off-label RD DOACs. ICH: 0.3%/y (n= 10/1682, 0.6%) on-label dose DOACs, 0.4%/y (n= 3/441, 0.7%) off-label RD DOACs. All-cause mortality: 5.1%/y (n= 142/1682, 8.4%) on-label dose DOACs, 9.3%/y (n= 69/441, 15.6%) off-label RD DOACs.	Off-label RD patients showed a non-significant higher overall mortality, and no differences in stroke/TIA and MB

Briasoulis A et al, 2020[44]	U.S.A.: 27747 Medicare beneficiaries with AF, 19712 on RI, 8035 on DA Off-label RD RI (RD use without eGFR <50 ml/min or drug-drug interactions): 12.9% (2551) Mean follow up: 13 mo	Ischemic stroke: 0.026/ys (n=256) on-label FD RI, 0.057/ys (n=176) on-label RD RI, 0.040/ys (n=89) off-label RD RI MB: 0.043/ys (n=426) on-label FD RI, 0.099/ys (n=307) on-label RD RI, 0.067/ys (n=147) off-label RD RI ICH: 0.004/ys (n=38) on-label FD RI, 0.008/ys (n=25) on-label RD RI, 0.006/ys (n=13) off-label RD RI GIB: 0.034/ys (n=341) on-label FD RI, 0.078/ys (n=243) on-label RD RI, 0.050/ys (n=111) off-label RD RI	Compared with the on-label FD RI dose group, the off-label RD RI group showed similar rates of stroke, ICH and GIB, and a higher rate of MB (HR 1.35, 95% CI 1.12-1.6), that was not confirmed after controlling for several patients' characteristics in propensity-matched samples
Cho MS et al, 2020[20]	Korea: 16568 NVAF outpatients on OAT and no indication to RD use (56.1% female) Off-label RD (RD use inconsistent with SmPC): 51.6% (8549/16568 patients on	Ischemic stroke/SE: 2.30%/y (n=197, 2.5%) on-label FD DOACs, 2.38%/y (n=226, 2.6%) off-label RD DOACs; 2.47%/y (n=128, 2.7%) on-label FD RI, 2.02%/y (n=106, 2.2%) off-label RD RI; 2.04%/y	Off-label RD RI vs on-label FD RI: no significant differences in ischemic stroke/SE, overall mortality and MB. Off-label RD AP vs in-label AP: non-significant increase on ischemic stroke/SE

	DOAC); RI 50.6% (mean age 71.4 ys), AP 53.0% (mean age 73.0 ys) Median follow up: 15 mo	(n=69, 2.1%) on-label FD AP, 2.88%/y (n=120, 3.3%) off-label RD AP MB: 1.51%/y (n=151, 1.9%) on-label FD DOACs, 1.99%/y (n=187, 2.2%) off-label RD DOACs; 1.69%/y (n=99, 2.1%) on-label FD RI, 2.20%/y (n=119, 2.4%) off-label RD RI; 1.24%/y (n=52, 1.6%) on-label FD AP, 1.72%/y (n=68, 1.9%) off-label RD AP All-cause mortality: 1.59%/y (n=135, 1.7%) on-label FD DOACs, 2.38%/y (n=205, 2.4%) off-label RD DOACs; 1.70%/y (n=86, 1.8%) on-label FD RI, 1.89%/y (n=95, 2.0%) off-label RD RI; 1.42%/y (n=49, 1.5%) on-label FD AP, 3.04%/y (n=110, 3.0%) off-label RD DOACs	(aHR 1.27, 95% CI 1.00-1.63), higher overall mortality (aHR 1.49, 95% CI 1.12-1.97), no significant differences in MB.
Eschler CM et al, 2020[50]	Switzerland: 19662 consecutive emergency department admissions, 1721 (9%) on OAT (mean age 77 ys,	Bleeding presentation in the emergency department: 9.6% of patients on OAT (n=166)	Only use of ASA (OR 1.7, 95% CI 1.0-2.8) was associated with bleeding presentation in the emergency department and a higher

	47% female, 63.2% for NVAF): VKAs (40.7%), RI (35.8%), AP (18.7%), ED (4.4%), DA (0.5%) 175 (17.1%) of DOACs off-label RD (RD use not consistent with SmPC, according to diagnosis); 345 (20%) of the overall sample was underdosed (including subtherapeutic AVKs) 166 cases (9.6%) presented to the ED with bleeding		likelihood of severe bleeding ($p = 0.042$). No significant association among anticoagulant molecules and bleeding or in-hospital mortality.
Inoue H et al, 2020[45]	Japan: 6306 NVAF on AP (72.8% ≥70 ys, 41.1% female), 15% underdosed (RD use not consistent with Japan SmPC) Mean follow-up: 17.4 mo.	Ischemic stroke/SE/TIA: 0.70%/y (n=33) on-label FD AP, 1.69%/y (n=37) on-label RD AP, 0.95%/y (n=13) off-label RD AP MB: 2.00%/y (n=94) on-label FD AP, 3.30%/y (n=72) on-label RD AP, 2.50%/y (n=34) off-label RD AP	AP dosing not associated with MB or ischemic stroke/SE/TIA.

		ICH: 0.57%/y (n=27) on-label FD AP, 1.14%/y (n=25) on-label RD AP, 0.88%/y (n=12) off-label RD AP Major GIB: 0.89%/y (n=42) on-label FD AP, 1.60%/y (n=35) on-label RD AP, 0.80%/y (n=11) off-label RD AP Any bleeding: 4.80%/y (n=221) on-label FD AP, 7.01%/y (n=150) on-label RD AP, 5.53%/y (n=74) off-label RD AP	
Lee K-N et al, 2020[47]	Korea: 3733 NVAF outpatients on DOAC (mean age 68.0 ys, 37.6% female), 2659 on warfarin Off-label RD DOAC (RD use not consistent with Korea SmPC) 20.3% Mean follow-up: 6.3 months (DOAC group) vs 9.9 months (warfarin group)	Ischemic stroke/SE/MI/intracavitary thrombus: 1.35%/y warfarin, 1.05%/y on-label FD DOACs, 1.94%/y on-label RD DOACs, 2.73%/y off-label RD DOACs MB: 2.14%/y warfarin, 0.89%/y on-label FD DOACs, 1.23%/y on-label RD DOACs, 1.46%/y off-label RD DOACs	Compared with warfarin, off-label RD group had an increased risk of ischemic stroke/SE/MI/intracavitary thrombus (aHR 2.51, 95% CI 1.28–4.93) in several adjusted models, and a higher risk of MB in the unadjusted model (HR 6.16; 95% CI 1.60–23.62), but not in the adjusted model

† = in Japan, approved doses of RI are 15 mg once daily FD and 10 mg once daily for RD, with the same criteria for RD use as European-approved doses; ‡including patients both in Japan-approved (i.e. 15 mg/10 mg once daily) and in European-approved doses (i.e. 20mg/15 mg once daily), considering only 10 mg once daily as underdosed in absence of criteria for RD use; *in propensity score-matched cohorts

Abbreviations: AF = atrial fibrillation; aHR = adjusted hazard ratio; AP = apixaban; ASA = acetylsalycilic acid, CI = confidence interval, CRNMB = clinically relevant non major bleeding, CV = cardiovascular, DA = dabigatran; DOAC = direct oral anticoagulant, ED = edoxaban, eGFR = estimated glomerular filtration rate, FD = full dose, FDA = Food and Drug Administration, FXaI = factor Xa inhibitor, GIB = gastro-intestinal bleeding, HR = hazard ratio, ICH = intracranial hemorrhage, MB = major bleeding, MI = myocardial infarction, mo = months, NVAF = nonvalvular atrial fibrillation, OAT = oral anticoagulant therapy, OR = odds ratio, RD = reduced dose, RI = rivaroxaban, SE = systemic embolism, SmPC = summary of product characteristics, TIA = transient ischemic attack, U.S.A. = United States of America, VKA = vitamin K antagonist, ys = years

Central illustration