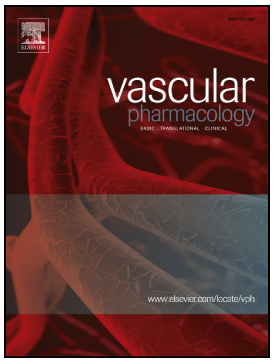

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Prevalence and risk of inappropriate dosing of direct oral anticoagulants in two Swiss atrial fibrillation registries

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Abstract

Background: Direct oral anticoagulants (DOACs) have a favourable risk-benefit profile compared to vitamin K-antagonists (VKAs) in atrial fibrillation (AF). Dosing is based on age, weight and renal function, without need of routine monitoring.

Methods and Results: In two prospective, multicentre AF cohorts (Swiss-AF, BEAT-AF) patients were stratified as receiving VKAs or adequately-, under- or overdosed DOACs, according to label. Primary outcome was a composite of major adverse clinical events (MACE), defined as cardiovascular death, myocardial infarction (MI), ischaemic stroke and systemic embolism. Secondary outcomes included major bleeding. Adjustment for confounding was performed. Median follow-up was 4 years.

Of 3236 patients, 1875 (58%) were on VKAs and 1361 (42%) were on DOACs, of which 1137 (83%) were adequately-, 134 (10%) over- and 90 (7%) under-dosed. Compared to adequately dosed individuals, overdosed patients were more likely to be older and female. Underdosing correlated with concomitant aspirin therapy and coronary artery disease. Both groups had higher CHA_2DS_2-VASc scores. Patients on overdosed DOACs had higher incidence of MACE (HR 1.75; CI 1.10-2.79; adjusted-HR: 1.22) and major bleeding (HR 1.99; CI 1.14-3.48; adjusted-HR: 1.51). Underdosing was not associated with a higher incidence of MACE (HR 0.94; CI 0.46-1.92; adjusted-HR 0.61) or major bleeding (HR 1.07; CI 0.46-2.46; adjusted-HR 0.82). After adjustment, all CIs crossed 1.0.

Conclusion: Inappropriate DOAC-dosing was more prevalent in multimorbid patients, but did not correlate with higher risks of adverse events after adjusting for confounders. DOAC prescription should follow label.

Keywords: atrial fibrillation, direct oral anticoagulants, overdosing, underdosing, adverse cardiovascular events.

Introduction

Four available direct oral anticoagulants (DOACs) (dabigatran, rivaroxaban, apixaban and edoxaban) are approved in many countries worldwide and their use has grown tremendously in recent years. In four pivotal randomized controlled trials (RCTs) (RE-LY, ROCKET AF, ARISTOTLE and ENGAGE AF-TIMI 48[1]), DOACs have proved to have a favourable risk–benefit profile as compared to vitamin K antagonists (VKAs) in patients with non-valvular atrial fibrillation (AF), with at least similar efficacy in terms of stroke reduction, but improved safety regarding intracranial haemorrhage[1]. Furthermore, DOACs overcome the need for regular therapeutic monitoring as well as a major part of the drug and food interactions of VKAs. DOAC dosage needs to be adjusted to patient's kidney function, age, body weight and concomitant medication[2]. Not following these dosing guidelines leads to inappropriate treatment (under- or overdosing), which has been reported in up to 50% of patients (on average: 20-30%) in previous real-world AF registries[3-5]. Inadequate DOAC regimens have been especially recorded in older and multimorbid patients (e.g., patients with renal dysfunction, high bleeding risk or receiving interacting poly-medications[2]). Inappropriate DOAC dosing is a relevant issue, as there is still conflicting evidence regarding its association with adverse outcomes. In large US cohorts, inappropriate DOAC dosing correlated with a higher risk of all-cause mortality[4], whereas other studies showed an association between underdosing and a trend towards more ischaemic strokes and recurrent systemic embolism (SE) compared with VKAs[5,6]. On the other hand, more recent studies, mostly in Asian patients, have found that off-licence reduced DOAC doses may be safe and effective compared to appropriately dosed DOACs[5,6].

To address this issue, we conducted an analysis within two large prospective AF cohorts in Switzerland (Swiss-AF and BEAT-AF) aiming to: 1) investigate the patterns of DOAC prescription for stroke prevention in AF in Switzerland, especially with regards to prevalence of non-recommended dosages; 2) identify patients' characteristics that are associated with DOAC under- and overdosing; 3) analyse the effectiveness and safety of off-license DOAC dosages in terms of bleeding and ischaemic events as compared to recommended treatment, during a long-term follow-up. In order to provide a comprehensive picture of our real-world population, we also included data on VKAs.

Methods

Study population

We combined data from two ongoing prospective, observational, multicentre cohort studies of AF patients in Switzerland. Both cohorts used similar eligibility criteria, outcome definitions and follow-up regime. The detailed study designs of the Swiss-AF and BEAT-AF cohorts have been reported previously[10,11]. In summary, patients were eligible to participate if they had a history of electrocardiographic documented AF. To be eligible for Swiss AF patients must have been 65 years of age or older. Main exclusion criteria for both cohorts were the inability to provide informed consent, any acute illness and the presence of potentially reversible forms of AF (e.g., after cardiac surgery). Patients could not be enrolled in both registries. Patient inclusion started in 2010. Eligible candidates were obtained by screening of in- and outpatients in participating hospitals and by contacting general practitioners in the area. The two studies comply with the Declaration of Helsinki and both study protocols have been approved by the local ethics committees. Informed written consent was obtained from each participant.

Extensive information about patient demographic characteristics, comorbidities and current medications (Table 1 and Table 2 in the Supplementary Appendix) was obtained from medical records and collected by standardized report forms at baseline and at yearly follow-up examinations[10,11]. Type and dosage of anticoagulants were obtained from prescription records of healthcare providers. Body height and weight were directly measured using standardized devices and body mass index was calculated. Non-fasting venous blood samples were collected from each patient at baseline, to measure creatinine levels. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI). The CKD-EPI formula was deliberately chosen to estimate GFR, as this is the most widely available in Swiss clinical laboratories. Chronic kidney failure was defined as an eGFR $\leq$ 60 ml/min.

Dosing of anticoagulants

We distinguished four groups of patients according to type of anticoagulant received at baseline and appropriateness of dosing. Therefore, patients were stratified as receiving VKAs, adequately dosed DOACs, underdosed DOACs or overdosed DOACs. Two VKAs (acenocoumarol and phenprocoumon) were included, as well as all four DOACs. A standard DOAC dose, prescribed when the indication for dose reduction was present, was defined as overdosing. On the other hand, a reduced dose prescribed when the indication for a standard dose existed represented underdosing (Figure 1). Indication for dose reduction was assessed based on age, weight and renal function at baseline, according to the Swiss authorisation and supervisory authority for drugs and medical products (Swissmedic), which is largely similar to European label (Supplemental Table 1S). For VKAs, international normalized ratios (INRs) were systematically collected. The time in therapeutic range (TTR) (defined as percentage of INR measures included in the desirable range [≥ 2, ≤ 3]) was calculated as the fraction of the number of INR measurements in range divided by the total number of INR measurements within the six months before baseline. Anticoagulation regimens with a TTR ≥ 0.7 (meaning that ≥ 70% of the routine INR measures were ≥ 2 and ≤ 3) were considered as optimal[12].

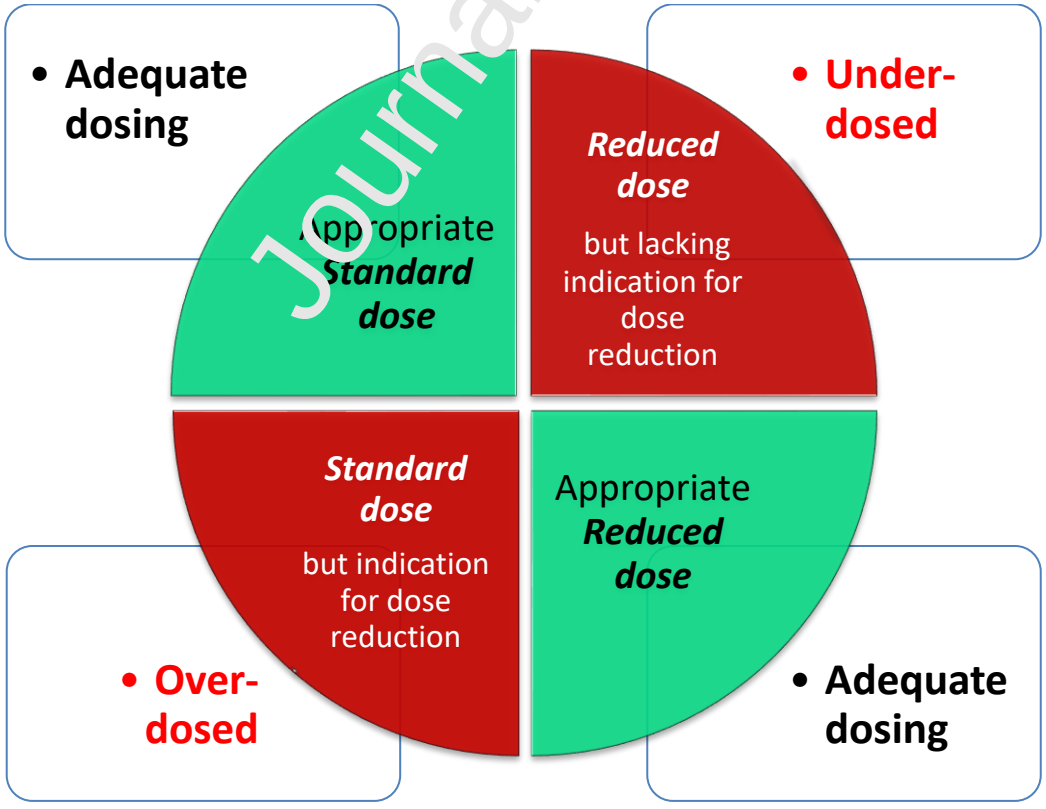


Figure 1. Definitions of adequate, underdosed and overdosed DOACs, as based on age, weight, renal function at baseline.

Outcomes

The primary outcome was a predefined composite of first major adverse clinical events (MACE), a composite of myocardial infarction (MI), cardiovascular death, ischaemic stroke and systemic embolism (ISSE). Secondary outcomes included major bleeding, all-cause mortality, a composite net clinical outcome (combining major bleeding, all-cause mortality and ISSE) as well as the individual endpoints of MACE (MI, cardiovascular death and ISSE). Detailed definitions of outcomes are provided in the Supplemental Table 3S. Information about adverse events was reported by patients and collected through available medical records at each annual follow-up visit. If information was missing, general practitioners were contacted to obtain complete medical reports. All outcomes were independently evaluated by two physicians, using standardized report forms.

Statistical analysis

Data on the analysed outcomes were summarised using incidence rates (as events per 100 patient-years) and corresponding Kaplan-Meier cumulative incidence curves. Cox proportional hazards models were used to analyse the associations between type and dosage of oral anticoagulant at baseline and the clinical outcomes. For each outcome event, we estimated a Cox proportional hazards model with medication status at baseline as factor of interest. First, we calculated crude hazard ratios (HRs), and second we adjusted for potential confounding factors (Table 1), that could affect the individual risk for ischaemic and bleeding events. HRs were estimated with respect to the reference group of patients on DOACs at an adequate dose and were adjusted for the following confounders: age, weight, smoking status, concomitant aspirin therapy, history of chronic kidney failure, hypertension, diabetes, coronary artery disease, heart failure, previous stroke or TIA and previous bleeding. Results are reported as crude and adjusted HRs with 95% confidence intervals [CIs].

Results

Study population

The combined datasets of the Swiss-AF and BEAT-AF registries involved 3894 patients. All patients who were not receiving any oral anticoagulants (N = 616) or who had missing information regarding anticoagulant treatment, kidney function or weight at baseline (N = 42) were excluded, leaving a total of 3236 patients for the analysis. Baseline characteristics of enrolled patients are summarised in Table 1. 1875 patients (58%) received VKAs at baseline (1612 [86%] phenprocoumon, 263 [14%] acenocoumarol). The remaining 1361 subjects (42%) were on DOACs; thereof 1019 patients (75%) received rivaroxaban, 205 (15%) apixaban, 96 (7%) dabigatran, and 41 (3%) edoxaban. The majority of patients on DOACs received a dose consistent with drug labelling (1137 patients [83%]), whereas 134 patients (10%) received an inappropriately high dose and 90 patients (7%) were underdosed (Table 1). Appropriateness of dosage was similar across the four different DOACs and was 88% for apixaban (N = 181), 83% for rivaroxaban (N = 848), 80% for edoxaban (N = 33) and 78% for dabigatran (N = 75).

Compared with patients on adequately dosed DOACs, overdosed patients were older, had a lower BMI and were less likely to be male (43% vs. 73% in the adequately dosed DOAC group). Underdosed patients were more likely to receive concomitant antiplatelet therapy and to have a previous history of bleeding or coronary artery disease. Both off-licence groups tended to have a higher CHA2DS2-VASc score and were more likely to have a history of heart failure and chronic kidney disease (Table 1). The stratification of patients with chronic kidney disease at baseline, according to KDIGO (Kidney Disease: Improving Global Outcomes) classification, is reported in Supplemental Table 4S.

In the VKA group, information regarding INR measurements and consequently TTR was missing for 206 patients. Of the remaining 1669 VKA patients, 43% had a TTR ≥ 0.7 and 57% had a TTR < 0.7. Mean TTR was 0.64, median TTR 0.67 (interquartile range [0.46, 0.83]).

Outcomes

The median follow-up was 4.0 years. Incidence rates for adverse events over the follow-up are presented in Table 2. Corresponding Kaplan-Meier cumulative incidence curves for the primary and main secondary outcomes are provided in Figure 2.

Among patients on DOACs, overdosed individuals had a higher incidence of MACE compared to adequately dosed ones (4.6 vs. 2.6 events/100 patient-years), whereas the incidence of MACE in underdosed patients was not dissimilar to that of appropriately treated individuals (2.5 vs. 2.6/100 patient-years). Additionally, overdosing showed higher rates of all-cause mortality as compared to appropriate DOAC doses (3.5 vs. 2.2/100 patient-years), which was mainly driven by cardiovascular death (13 [76%] of all 17 deaths in the overdosed group). The same was not shown for underdosed patients compared to appropriate DOAC treatment (all-cause mortality rates of 2.0 vs 2.2/100 patient-years). The rate of major bleeding was almost two-fold higher in overdosed as compared to adequately dosed patients (3.3 vs. 1.7/100 patient-years), while underdosage showed a similar incidence rate as appropriate treatment (1.8 vs. 1.7/100 patient-years). Finally, overdosed patients had overall higher incidence rates of net clinical outcome compared to patients on appropriate DOAC treatment (6.5 vs. 4.0/100 patient-years). Once again, this was not true for underdosed patients (3.6 vs. 4.0/100 patient-years).

Similarly to overdosed DOAC patients, those on VKAs had higher rates of MACE (3.5 vs. 2.6/100 patient-years) and all-cause mortality (3.7 vs. 2.2/100 patient-years) as well as more major bleedings (2.2 vs. 1.7/100 patient-years) as compared to adequate DOAC treatment.

Overall, the incidence rates of MI and ISSE did not differ substantially between the four analysed groups, although underdosed and overdosed DOACs had a slightly higher rate of MI (1.5 and 1.3 respectively vs. 0.6/100 patient-years), compared to appropriate DOAC treatment. Similarly, DOAC overdosing showed a slightly higher rate of ISSE (1.3 vs. 0.9/100 patient-years). Major bleeding and

MACE rates in overdosed DOAC patients were also higher as compared to VKAs (3.3 vs. 2.2, respectively 4.6 vs. 3.5/100 patient-years).

Crude and adjusted HRs for all comparisons are listed in Supplemental Table 5S. After adjustment, all CIs crossed 1.0.

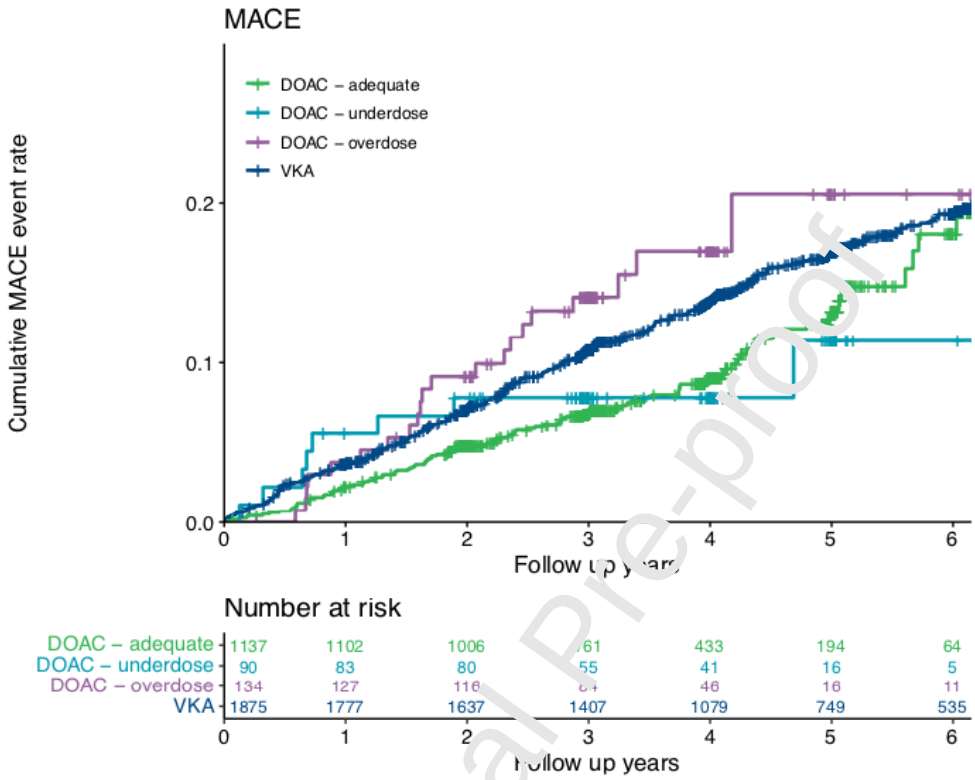
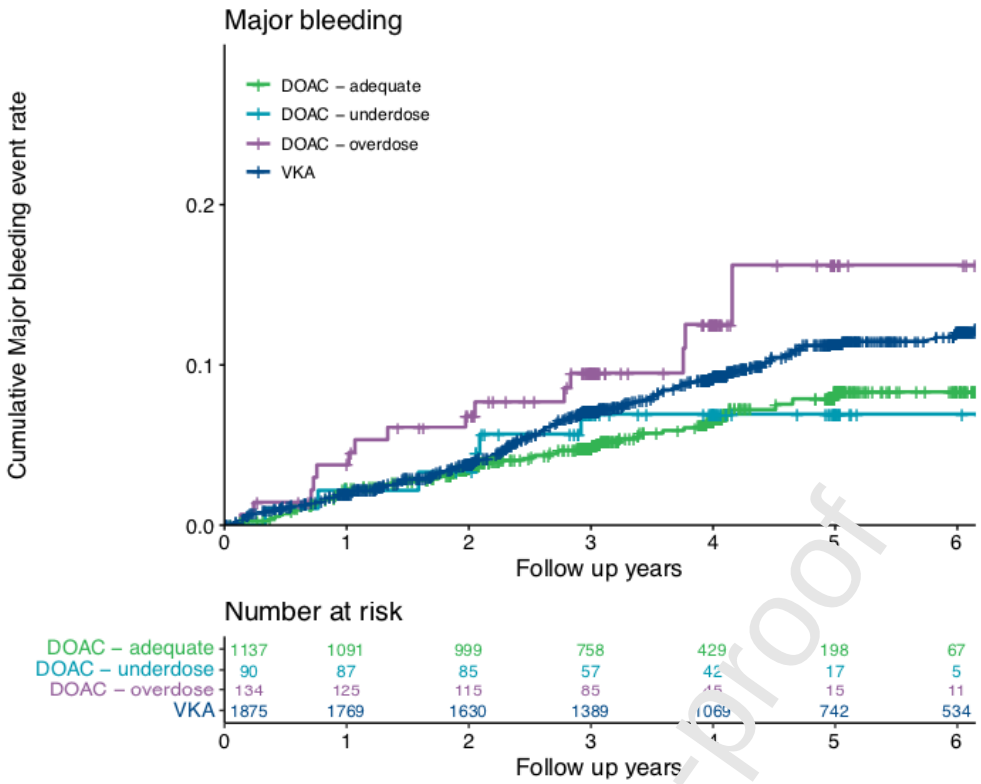


Figure 2a.



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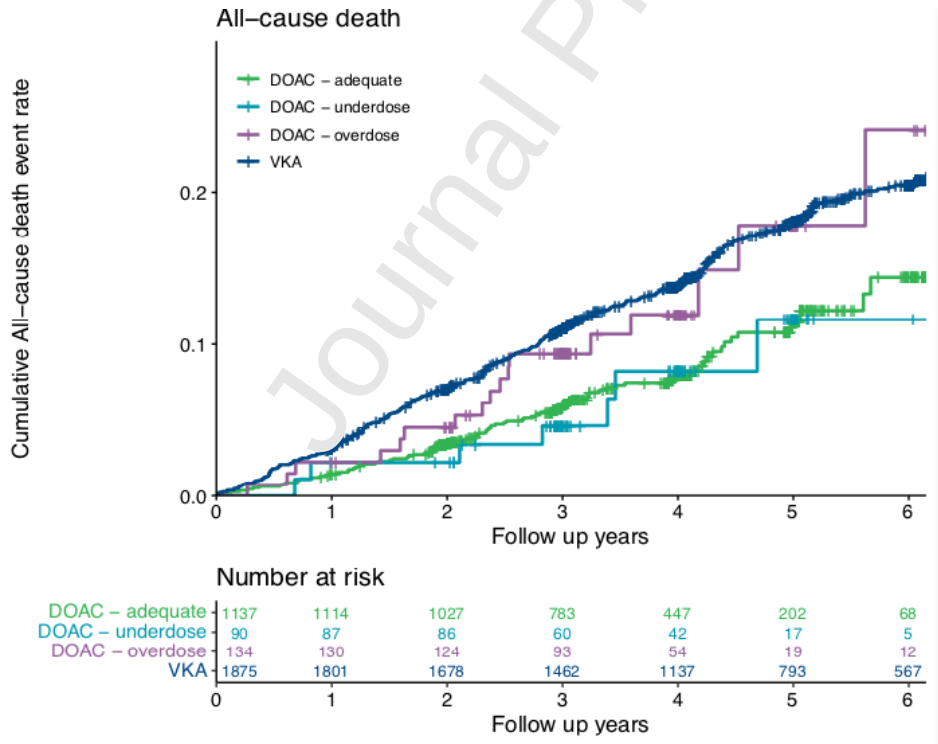

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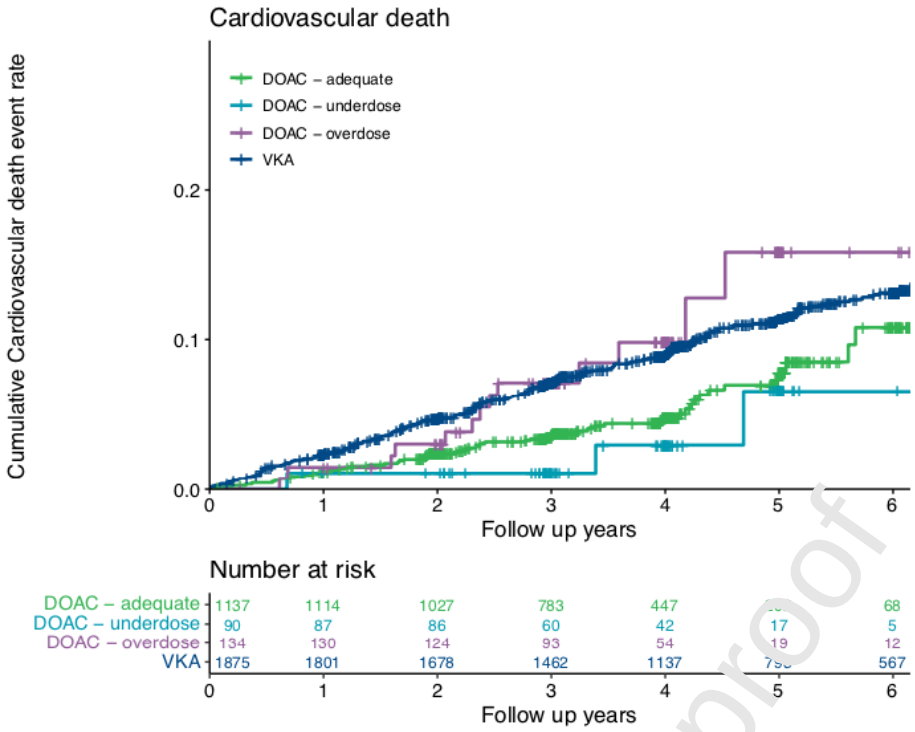

Figure 2d.

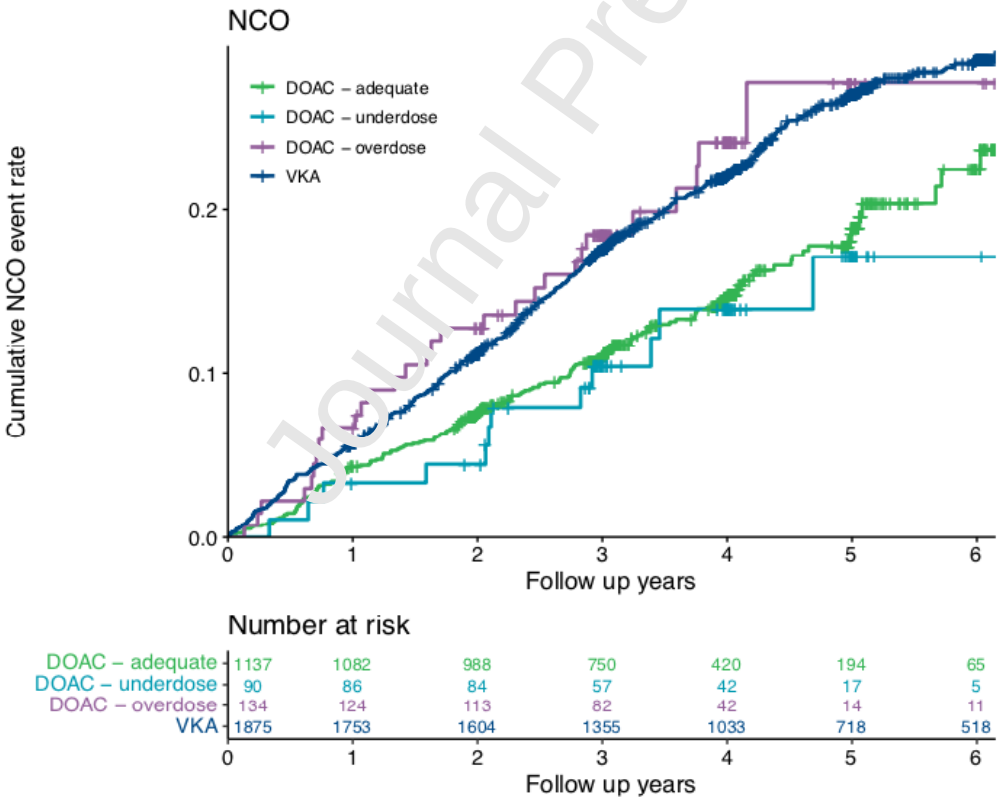

Figure 2e.

Figure 2. Kaplan-Meier cumulative incidence curves for the first occurrence of adverse events. 3a.) MACE (= composite of myocardial infarction, cardiovascular death, ischemic stroke, systemic

embolism). 3b) Major bleeding. 3c) All-cause death. 3d): Cardiovascular death. 3e) NCO = net clinical outcome.

Discussion

The main findings of the study are the following. First, the overall prescription of inappropriate DOAC dosages in our population was 16%, and thus 5-15% lower than that reported in previous AF registries worldwide[3-6]. Second, inappropriate doses of DOACs were more prevalent in older, multimorbid patients. Third, after adjusting for several confounders, we found no compelling evidence for a higher incidence of adverse events in overdosed nor in underdosed patients. Fourth, the crude incidence rate of adverse events in overdosed DOACs was higher compared to those on appropriate DOAC treatment. Lastly, patients on VKAs showed a tendency towards more MACE, major bleedings and all-cause deaths compared to patients on adequate DOACs, in line with the results of the four pivotal RCTs[1]. However, the overall event rate in the study was low, and data were underpowered to make any conclusion about outcomes. Thus, this analysis should be considered as exploratory.

In our study inadequate dosing occurred in 1 out of every 6 patients. This is less frequent than reported in previous literature, where the frequency of inappropriate DOAC dosages in real-world data was up to 50%[8, 13, 14]. This difference might be ascribed to the fact that, despite being a real-world registry, our cohorts were closely followed up and underwent a multitude of tests (MRI, cognitive testing, blood tests), potentially increasing attention of patients and physicians to appropriateness of anticoagulant dosing. In line with other real-world VKA registries[15], only a minority of our VKA population had a TTR ≥ 0.7, reflecting a lower quality of anticoagulation compared to that seen in RCTs. Therefore, the results of the comparisons between VKAs and DOACs in this study might have been influenced by the quality of VKA regimes measured by TTR.

Both over- and underdosed DOAC patients appeared more vulnerable; they had higher CHA_2DS_2-VASc scores and were more likely to have a history of heart failure and chronic kidney disease, indicating that the highest-risk patients were prone to receive inappropriate doses of DOACs.

Overdosing was associated with female sex, lower body weight and older age, suggesting that clinicians did not always consider the latter to reduce dosage in a precautionary way. On the contrary, since female sex and older age are also associated with a higher thromboembolic risk, physicians may have intentionally disregarded a formally recommended dose reduction. This may also be true for subjects with concomitant aspirin therapy. Prescribing rules may have been disregarded unintentionally in patients with other comorbidities: in fact, almost 1 in 5 patients with kidney failure was overdosed (Table 1).

DOAC overdosing was associated with higher crude risks of ischaemic and bleeding events. The excess of MACE in this group was mainly driven by numerically higher rates of cardiovascular deaths. The low event rate in our study, especially for ISSE, prevents any definitive explanation of this seemingly counterintuitive observation. However, this is likely related to selection bias, due to a higher baseline cardiovascular risk of overdosed patients, which may have not been fully captured by adjustment for confounders. DOAC overdosing has been reported to double the risk of bleeding without decreasing stroke and ischaemic risk in general, which indicates that the protection against ischaemic events may reach a plateau with increasing drug exposure[16]. The practice to withhold or withdraw anticoagulation after a bleeding event should also be taken into account. is the need to sMoreover, the exceeding ischaemic risk observed might be attributable to atherosclerotic disease or other non cardio-embolic stroke sources, that are not addressed with higher dosed systemic anticoagulation therapy, albeit very low dose DOACs (e.g. 2x 2.5mg rivaroxaban) in combination with aspirin have been shown to be effective[17]. Furthermore, intra-plaque haemorrhage and intra-plaque micro-bleeds, which might be promoted by a more intense anticoagulation regimen, have been proposed as potential factors that can influence plaque instability in atherosclerosis[18].

Overall, our data on the effect of DOAC overdosing on adverse events are concordant with other large international AF registries[4,19], which reported increased risks of major bleeding and all-cause mortality in this population.

In contrast to overdosing, underdosed DOAC patients not only did not show a higher crude risk of major bleeds, but also a consistent risk of MACE compared to appropriate DOAC treatment. These findings may seem conflicting compared to those from previous US AF registries, where DOAC

underdosing was associated with increased cardiovascular hospitalization and all-cause mortality[4,19]. These diverging results may be due to the low number of adverse events in our cohort, but might also be related to different characteristics of our Swiss population compared to US patients. In our population, female patients were less represented, similarly to the Japanese registries[8], whereas comorbidities, such as chronic kidney disease and history of stroke or TIA, often underrepresented in RCTs[1], where more prevalent. Therefore, a reduced dose of DOACs might be sufficient for the prevention of ischaemic events among our more morbid population, as recently demonstrated in a Japanese population of frail octogenarians[20], alongside with previous evidence that in some rare exceptions off-license low-dosed DOACs might be considered for elderly patients with a high ischaemic and bleeding risk[8,9,16,20]. Of note, underdosed patients in our cohort were more prone to having concomitant antiplatelet therapy, which might mirror the greater net clinical benefit of a lower (versus a higher) dose of DOAC on top of aspirin, as previously demonstrated in patients with chronic coronary or peripheral vascular disease in the COMPASS trial[17].

Overall, our data support the importance of following drug label, as there is no clear benefit anticipated by diverging from it.

Our study has some major strengths. We were able to include a large real-world population of 3236 patients from two considerable prospective cohort studies. Dosage selection was carefully assessed for each DOAC and stratified by numerous demographic and clinical characteristics. The length of follow-up was longer than that of other similar registries in the literature. Missing values were rare, suggesting proper data implementation and management, allowing meaningful statistical analyses. Lastly, by also including a large patient cohort treated with VKAs, we were able to compare the adverse events related to inappropriate DOAC dosing to those of VKA treatment.

Nevertheless, our study has some limitations. First, the observational nature of the study and the low number of adverse events do not allow confirmatory conclusions and the study should be intended as hypothesis generating. Cohort studies are prone to selection bias; participating patients and their physicians are more likely to be motivated to regular follow-up visits and more knowledgeable

regarding appropriate treatment recommendations. Second, this analysis uses baseline information as predictors of events. Crossing over among different DOAC dosing groups during follow-up (due to change in weight, renal function or ageing) may have occurred, and its effects on the results could not be assessed. However, many patients joined the study in their eighties and were considerably heavier than 60 kg, so that these dose reduction criteria were unlikely to significantly change over time. Third, to estimate GFR we deliberately used the CKD-EPI formula instead of the Cockcroft-Gault formula, which was used in the four pivotal RCTs. This may have led to slightly different patient selection and outcomes as those in the RCTs. However, this choice was prompted by the wider availability of the CKD-EPI method in most Swiss clinical laboratories and hospitals. Fourth, information regarding some co-medications which could possibly have influenced the pharmacokinetics of DOACs, such as P-glycoprotein inhibitors, were collected but not considered for the present analysis, since they were used only very infrequently in our registries (81 patients, 2.5% of the study population). Furthermore, even though we adjusted our analysis for a large number of confounders, there is always a possibility of residual confounding. Lastly, our study was performed in Switzerland and is therefore valid for rather high-income Caucasians; generalization to other populations should be performed cautiously.

Conclusions

Our study found that older patients and those with a higher burden of comorbidities were more likely to receive inadequate dosages of DOACs. We did not detect any correlation between inappropriate DOAC dosing and adverse outcomes, however we found a signal towards higher crude incidence rates of MACE and major bleeding for patients on overdosed DOACs, compared to appropriate DOAC treatment. These results should be interpreted cautiously and further studies with frail and elderly AF populations should be promoted to further explore our findings. For the time being, DOAC doses should follow label.

Tables

Table 1. Baseline patients' characteristics across type of anticoagulant and appropriateness of dosing. All variables (except for CHA2DS2-VASc score and DAPT) are controlled for in the adjusted analyses.

	DOACs			**VKAs**	
	Appropriately dosed	Underdosed	Overdosed		SMD
Number	1137	90	134	1875	
Age (years) (mean, (SD))	71 (± 9)	74 (± 7)	77 (± 7)	73 (± 9)	0.400
Weight (kg) (mean, (SD))	84 (± 16)	84 (± 13)	70 (± 14)	82 (± 17)	0.498
Sex (No. male, (%))	829 (73)	71 (79)	65 (49)	1352 (72)	0.333
CHA2DS2-VASc (No., (%))					
• Low (0, 1)	199 (17)	6 (7)	5 (4)	219 (12)	0.328
• Intermediate (2, 3)	507 (45)	32 (35)	47 (35)	718 (38)	
• High (≥ 4)	431 (38)	52 (58)	82 (61)	938 (50)	
Aspirin therapy (No., (%))	110 (10)	17 (19)	10 (7)	260 (14)	0.194
DAPT (No., (%))	13 (1)	2 (2)	0 (0)	37 (2)	0.122
Chronic kidney failure (No., (%))	150 (13)	22 (24)	25 (19)	445 (24)	0.166
Hypertension (No., (%))	776 (68)	73 (81)	98 (73)	1394 (74)	0.154

Diabetes (No., (%))	162 (14)	16 (18)	20 (15)	350 (19)	0.073
Previous stroke/TIA (No., (%))	233 (21)	20 (22)	35 (26)	319 (17)	0.118
Previous bleeding (No., (%))	138 (12)	19 (21)	17 (13)	252 (13)	0.125
CAD (No., (%))	246 (22)	37 (41)	32 (24)	594 (32)	0.243
History of heart failure (No., (%))	196 (17)	36 (40)	38 (28)	571 (31)	0.266
BMI > 30 kg/m^2 (No., (%))	322 (28)	26 (29)	2((15)	488 (26)	0.180
Active smoking (No., (%))	85 (8)	9 (10)	9 (7)	131 (7)	0.063

Numbers refer to N. (%), unless indicated otherwise. DOACs = direct oral anticoagulants. VKAs = vitamin K antagonists. SD = standard deviation. SMD = standardized mean differences. DAPT = dual antiplatelet therapy (Aspirin, Clopidogrel). TIA = transient ischemic attack. CAD = coronary artery disease. BMI = body mass index.

Table 2. Incidence rates for adverse events.

	Outcome	**OAC status**	**Person years**	**Events**	**Incidence rate per 100 person years**
Primary Endpoint	**MACE**	Appropriate DOACs	**4117.2**	**108**	**2.6**
		Underdosed DOACs	**325.6**	**8**	**2.5**
		Overdosed DOACs	**458.4**	**21**	**4.6**

		VKAs	**8495.4**	**299**	**3.5**
Secondary Endpoints	**Cardiovascular death** (MACE component)	Appropriate DOACs	**4201.8**	**58**	**1.4**
		Underdosed DOACs	**342.2**	**3**	**0.9**
		Overdosed DOACs	**490.7**	**13**	**2.6**
		VKAs	**8765.8**	**203**	**2.3**
	Myocardial infarction (MACE component)	Appropriate DOACs	**4157.1**	**24**	**0.6**
		Underdosed DOACs	**327.0**	**5**	**1.5**
		Overdosed DOACs	**477.8**	**6**	**1.3**
		VKAs	**8656.1**	**62**	**0.7**
	Ischemic stroke and systemic embolism (MACE component)	Appropriate DOACs	**4151.0**	**36**	**0.9**
		Underdosed DOACs	**340.7**	**1**	**0.3**
		Overdosed DOACs	**471.4**	**6**	**1.3**
		VKAs	**8603.6**	**70**	**0.8**

	Major bleeding	Appropriate DOACs	**4100.3**	**68**	**1.7**
		Underdosed DOACs	**336.4**	**6**	**1.8**
		Overdosed DOACs	**455.3**	**15**	**3.3**
		VKAs	**8433.1**	**184**	**2.2**
	All-cause death	Appropriate DOACs	**421.8**	**91**	**2.2**
		Underdosed DOACs	**342.2**	**7**	**2.0**
		Overdosed DOACs	**490.7**	**17**	**3.5**
		VKAs	**8765.8**	**323**	**3.7**
	Net clinical outcome	Appropriate DOACs	**4054.3**	**163**	**4.0**
		Underdosed DOACs	**335.0**	**12**	**3.6**
		Overdosed DOACs	**445.2**	**29**	**6.5**
		VKAs	**8279.9**	**474**	**5.7**

MACE = major adverse cardiovascular events (= composite of cardiovascular death, myocardial infarction, ischaemic stroke and systemic embolism). DOACs = Direct oral anticoagulants. VKAs =

Vitamin K antagonists. Net clinical outcome = composite of major bleeding, all-cause mortality, ischaemic stroke and systemic embolism.

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