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Dosing According to Different Prescription Guides Used in Belgian
Ambulatory Care

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Appropriateness of non-vitamin K antagonist oral anticoagulants dosing according to different prescription guides used in Belgian ambulatory care

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Short title: Appropriateness of NOAC dosing according to different prescription guides in ambulatory care.

1 **Abstract**

2 **Background:**

3 Non-vitamin K antagonist oral anticoagulants (NOACs) are the preferred choice of anticoagulants to
4 prevent stroke in most patients with atrial fibrillation (AF). NOAC dosing algorithms are defined in the
5 respective Summary of Product Characteristics (SmPC) but the European Heart Rhythm Association
6 (EHRA) Practical Guide can also be used as it takes more complex clinical scenarios into account.
7 Nevertheless, suboptimal dosing of NOACs compromises the efficacy and safety of this commonly
8 prescribed therapy in the AF population. Clearer objectification of inappropriate dosing and its
9 influencing factors is needed to optimize management of AF patients.

10 **Aim:**

11 The primary aim is to provide insights into the dosing appropriateness of NOACs conform the SmPC and
12 the 2018 EHRA criteria and influencing factors. The secondary aim was to explore if there were
13 differences in appropriateness of NOAC dosing between primary care and specialist care, and when
14 using different renal function formulas.

15 **Methods:**

16 This retrospective study included AF patients treated with a NOAC in primary- or in ambulatory specialist
17 care in Antwerp (Belgium). Appropriateness of the NOAC dose was assessed according to the SmPC and
18 2018 EHRA recommendations. Univariate/multivariate analysis were performed to explore influencing
19 factors for under- and overdosing of NOACs.

20 **Results:**

21 Of the included 294 AF patients, 19.4% and 15.6% received an inappropriate dose according to the SmPC
22 and the 2018 EHRA Practical Guide respectively ($p=0.003$). Perceived frailty and higher weight were
23 associated with underdosing relative to the SmPC, while a higher body mass index and the use of

24 drugs/alcohol were associated with underdosing relative to the EHRA 2018 recommendations. Lower
25 renal function and treatment with other NOACs than apixaban were associated with relative overdosing
26 compared to both standards.

27 **Conclusions:**

28 Inappropriate NOAC dosing is present in almost twenty percent of AF patients according to the SmPC
29 and requires further education of health care professionals and frequent reassessment of NOAC dosing.
30 However, a significant lower prevalence of underdosing was present when judged by the 2018 EHRA
31 criteria, likely reflecting decision making in complex AF patients. Perceived frailty, weight, renal function
32 and type of NOAC are the main determinants of deviated dosing.

33 **Key Points**

- 34 • A significant proportion of non-vitamin K antagonist oral anticoagulants are inappropriately
35 dosed compromising its efficacy in stroke prevention in patients with atrial fibrillation
- 36 • Dosing of these oral anticoagulants can be based on different dosing recommendations
- 37 • Insights in deviating dosing decisions can improve real-life stroke prevention, a cornerstone of
38 atrial fibrillation management

39 **1. Introduction**

40 Non-vitamin K antagonist oral anticoagulants (NOACs) are now the standard of care for stroke
41 prevention worldwide in patients with atrial fibrillation (AF) with high thrombo-embolic risk and in the
42 absence of mechanical prosthetic heart valves or moderate/severe mitral stenosis, or severely
43 depressed renal function.^[1,2] Currently, four NOACs are available in Europe, each with specific dose
44 reduction criteria defined in their respective ‘Summary of Product Characteristics (SmPC) documents’.
45 These criteria include age, renal function, weight and specific concomitant intake of medication.
46 However, in daily practice, several less well researched relevant aspects can influence the decision of
47 clinicians to prescribe a different dose than recommended by the SmPC. This is why the European Heart
48 Rhythm Association (EHRA) has developed sequentially updated practical guides for healthcare
49 professionals concerning the use of NOACs in AF patients incorporating the SmPC criteria and important
50 patient characteristics (e.g. frailty, concomitant use of antiplatelets) to provide support and scientific
51 evidence concerning the dosing and use of NOACs.^[3-6] Nevertheless, real-world studies have shown that
52 a significant portion of AF patients treated with a NOAC receive inappropriate NOAC doses for which
53 underdosing can lead to a higher risk of stroke, and overdosing can impair safety outcomes of these oral
54 anticoagulants.^[7]

55 **2. Aims**

56 The **primary aim** of this retrospective study was to investigate whether there is a difference in the
57 perceived appropriateness of NOAC dosing with respect to the SmPC or the 2018 EHRA Practical Guide
58 in AF patients presenting for an outpatient visit at the Cardiology department of the Antwerp University
59 Hospital or at six primary care centers (all located in the Antwerp region).

60 The **secondary aims** were (i) to explore if there was a significant difference in appropriateness of NOAC
61 dosing between primary care and specialist care, and (ii) when renal function was calculated according
62 to different formulas.

63 **3. Ethics approval**

64 The research protocol was approved by the Ethics Committees of the Antwerp University
65 Hospital/University of Antwerp on the 12th of August 2019 and the study was conducted in compliance
66 with the Declaration of Helsinki (local project reference 19/27/331).

67 **4. Methods**

68 **4.1. Study population and enrolment procedure**

69 Patients were eligible for this study if they were (I) ≥ 18 years old, (II) diagnosed with AF or atrial flutter
70 on an electrocardiogram and (III) chronically treated with one of the four NOACs, namely apixaban,
71 rivaroxaban, edoxaban or dabigatran. The indication if a patient should be treated with a NOAC was
72 checked based on his/her CHA₂DS₂-VASc score. For the eligible patients of the Antwerp University
73 Hospital no explicit informed consent (IC) was needed as data was internally available and
74 retrospectively retrieved by the study investigators; all patients of the hospital have consented with
75 inclusion in retrospective analysis. Enrolment of AF patients at the primary care centers was done
76 consecutively by the general practitioner (GP), who explained the study to the patient and obtained the
77 IC. AF patients already enrolled in an interventional NOAC study or patients unable to sign the IC (i.e.
78 language barrier) were excluded.

79 **4.2. Data collection**

80 After approval of the research protocol, patients who had presented to any of the outpatient clinics
81 after April 2018 (the date of publication of the EHRA 2018 Practical Guide) were retrospectively
82 screened for inclusion. The inclusions were performed consecutively and equally spread over four
83 cardiology subspecialty clinics (Interventional, Electrophysiology, Heart Failure and General
84 Cardiology/Cardiac Imaging) to ensure a homogeneous AF cohort in follow-up by cardiologists. If a
85 patient was found to have multiple visits, only the first clinic visit was assessed.

86 As mentioned before, primary care patients were only enrolled after consent was given. Recruitment
87 was performed in AF patients presenting after approval of the research protocol (August 2019). Then,
88 the medical file was reviewed retrospectively and the patients' first GP visit after April 2018 was
89 assessed for data extraction in order to have similar time periods evaluated in cardiology and GP
90 patients.

91 The patients' medical data were retrieved from the electronic patient record and included age, sex,
92 actual body weight, height, body mass index (BMI), blood pressure, type of AF, prescribed NOAC and
93 dose, concomitant medication and serum creatinine closest to the index consultation. The patients'
94 medical history was checked for components of the CHA₂DS₂-VASc and HAS-BLED scores. Moreover, a
95 history of gastrointestinal bleeding, bleeding predisposition, recent surgery on a critical organ and
96 available data to estimate frailty, based on the parameters used in the ENGAGE-AF TIMI 48 trial, were
97 recorded as these factors also play a role in the 2018 EHRA Practical Guide.^[8]

98 Based on the collected data, calculation of renal function was estimated using the Cockcroft and Gault-
99 (CG), the Modification of Diet in Renal Disease- (MDRD) and the Chronic Kidney Disease Epidemiology
100 Collaboration- (CKD-EPI) equations.^[9-11]

101 NOAC dosing was evaluated by comparing the actual prescribed dose with the recommendations from
102 the SmPC (**Supplementary Table 1**) and EHRA 2018 Practical Guide.^[12-15] Classification was either
103 appropriate or inappropriate in case of underdosing or overdosing. The EHRA 2018 Practical Guide
104 incorporates additional clinical parameters that may justify dose adjustments and also includes an
105 extensive list of interacting drugs that are not all included in the SmPCs (e.g. extended list of interactions
106 with anticancer and antiepileptic drugs).^[5] This guide also uses a colour code with one important guide
107 rule that recommends consideration of dose adjustment or the use of a different NOAC with less
108 interactions (if available) in the presence of ≥ 2 'yellow' criteria. Consequently, the EHRA 2018 guide is
109 less stringent in case of a combination of 'yellow' criteria, which the SmPC dose adjustment criteria do

110 not take into account. For example, a 77-year-old patient with concomitant use of antiplatelets and a
111 standard dose NOAC was classified as 'appropriate' for both classification systems ('75+' and
112 'concomitant antiplatelet drugs' are both yellow factors). The same patient on a reduced NOAC dose
113 would be classified as 'inappropriate' according to the SmPC, but potentially 'appropriate' according to
114 the EHRA 2018 Practical Guide.

115 Other principal colour codes include: 'Orange'= consider dose adjustment or different NOAC; 'Red'=
116 contraindicated/not recommended; 'Brown (dark)'= contraindicated due to reduced NOAC plasma
117 levels.

118 **4.3. Sample size**

119 For the primary objective, a sample size of 152 AF patients in each arm was calculated using an alpha of
120 0.05 and a power of 0.80. This was based on a 10.4% difference in NOAC dosing appropriateness derived
121 from a retrospective cohort study that investigated the correct prescription of NOACs in hospitalized
122 patients comparing the SmPC prescription rules and the 2015 EHRA guide.^[16] For the second objective
123 of specialist care vs primary care, a sample size of 171 AF patients in each arm was calculated
124 (alpha=0.05 and power=0.80), based on a substudy of the ORBIT AF-II registry which reported data of
125 incorrect NOAC dosing by different medical specialities (based on United States approved package
126 inserts).^[17] Combining these two sample size calculations, and anticipating 15% of incomplete patient
127 files, an inclusion target of 197 AF patients, for both specialist- and primary care was set forward (in
128 total 394 patients). Due to the COVID-19 pandemic, we did however not reach the target inclusion rate
129 in the GP cohort due to the severe impact on consenting procedures.

130 **4.4. Statistics**

131 Data were analyzed using IBM SPSS version 27.0. Variables were described as numbers and percentages
132 or as mean \pm standard deviation, as appropriate. For continuous variables, differences between two
133 (un)paired groups were compared using the paired-samples T-test or independent-samples T-test. The
134 chi-squared test, the McNemar test and Fisher's exact test were used for categorical variables, as

135 appropriate. All comparisons were tested two-sided. P-values <0.05 were considered statistically
136 significant.

137 The relative risks (RRs) and odds ratios (ORs) were calculated and reported with their 95% confidence
138 intervals (CIs) for significant categorical predictors for inappropriate dosing of NOACs (i.e. under- and
139 overdosing). For continuous variables, univariate logistic regression models were used to calculate the
140 ORs (with their 95% CI), and p-values were derived from the likelihood-ratio test. Candidate variables,
141 categorical as well as continuous, with a p-value <0.10 were considered for multivariate regression
142 analysis and the optimal regression model was composed using a backward elimination strategy.

143 **5. Results**

144 **5.1. Patient characteristics**

145 A total of 294 AF patients were included for this study, of which 200 (68.0%) patients were recruited at
146 the cardiology outpatient clinic and only 94 patients (32.0%) at the GPs' office (between September
147 2019 and February 2020) (**Figure 1**).

148 **Table 1** presents the baseline characteristics of the included AF population. Mean serum creatinine was
149 1.09 ± 0.39 mg/dL for which the estimated renal functions calculated by the CG, MDRD and CKD-EPI
150 formulae were 70.3 ± 28.8 mL/min, 71.2 ± 23.4 mL/min/1.73m² and 65.5 ± 20.3 mL/min/1.73m²
151 respectively. Apixaban was the most commonly prescribed NOAC (41.5%) followed by rivaroxaban
152 (34.4%), edoxaban (13.6%) and dabigatran (10.5%) with a reduced dose in 26.2%, 21.8%, 15.0% and
153 41.9% for each NOAC respectively (p=0.066; **table 2**).

154 When comparing the patients included in primary care versus specialist care, AF patients followed by
155 GPs were older (78.6 ± 7.3 years). Consequently, they had a lower renal function calculated by the CG
156 formula (65.1 ± 26.1 mL/min). These patients were also less known with congestive heart failure (24.5%
157 vs. 37.5%) and took less antiplatelet drugs (3.2% vs. 15.5%) (Table 1).

158 **5.2. Appropriateness of NOAC dosing**

159 In general, according to the SmPC and EHRA 2018 guide, a rather high proportion of patients received
160 an inappropriately dosed NOAC, in 19.4% and 15.6% of patients (p=0.003), respectively (table 2). The
161 significant difference was driven by a more lenient interpretation of potentially correctly underdosed
162 NOACs by the EHRA 2018 (4.0%, p=0.003). Translated in absolute numbers, of the 31 underdosed SmPC
163 patients, 12 patients (38.7%) received a potentially correct NOAC dose according to the EHRA 2018
164 guide. These patients were more often classified as frail (RR= 5.46; 95% CI 1.85-16.06; p<0.001) and
165 used more often amiodarone (RR= 2.98; 95% CI 1.44-6.14; p=0.022). Overdosed patients were the same
166 when classified according to SmPC or EHRA 2018 (8.8%; n=26).

167 **Figure 2** shows dosing appropriateness per NOAC according to the SmPC guidelines and the 2018 EHRA
168 Practical Guide.

169 **5.3. Influencing factors for under- and overdosing of NOACs**

170 Inappropriate NOAC underdosing according to the SmPCs was univariately significantly related to the
171 use of diuretics and to weight (or BMI) (all p<0.05; Table 3), with borderline relations with perceived
172 frailty and drug or alcohol use. In multivariate analysis, frailty and higher body weight were the only
173 significant factors. Based on the EHRA 2018 Practical Guide only the use of drugs/alcohol and a higher
174 BMI were correlated with an inappropriate reduced dose in both univariate and multivariate analysis
175 (**Table 3**).

176 For the overdosed NOAC patients (both according to the SmPC and EHRA 2018 guide as identified
177 patients were identical), primary care, permanent AF, older patients, not taking apixaban, lower weight
178 (or lower BMI) and lower renal function were factors significantly correlated with a higher risk for
179 overdosing (univariate analysis). In multivariate analysis, patients not on apixaban and with lower renal
180 function were associated with inappropriate overdosing of their NOAC (**Table 4**).

181 **5.4. Primary care versus specialist care**

182 Although the number of recruited patients in GP care was too low due to the COVID-19 circumstances
183 (see above), GP care vs. cardiologist care was not retained in any multivariate analysis of factors related
184 to underdosing or overdosing (Table 3 and Table 4). Nevertheless, patients in GP care showed a higher
185 rate of inappropriate dosing compared to cardiologists, which was non-significant based on the SmPCs
186 (24.5% vs 17.0%; p=0.131) but significant based on the EHRA 2018 guide (22.3% vs 12.5%; p=0.03). This
187 seems mainly the result of inappropriate overdosing (Table 4; p=0.039 univariate p-value), which could
188 be an indication that cardiologists take more factors into account to reduce dose.

189 **5.5. Influence of different renal function estimation formulae**

190 When comparing appropriateness of dosing based on renal function calculated by CG-, MDRD-, or CKD-
191 EPI formulae, no significant differences were seen between these formulas, neither for the SmPC nor
192 for the EHRA 2018 based evaluation (**Supplementary table 2**). On the other hand, the significant
193 difference between the SmPC and EHRA 2018 Practical Guide as described with the CG formula in
194 section 5.2 (p=0.003) remained significant when reclassifying appropriateness using the MDRD and CKD-
195 EPI formulae (with p-values of <0.001 and 0.002, respectively) (**Supplementary table 3**).

196 **6. Discussion**

197 This study in ambulatory AF patients found a high prevalence of inappropriate NOAC dosing (19.4%)
198 according to the SmPC. When based on the EHRA 2018 Practical Guide, the proportion is significantly
199 lower (15.6%) but still, 1 out of 7 AF patients, seem to be receiving an inappropriate dose of NOAC. The
200 explanation, i.e. whether prescribers are incorrect, or whether prescribers have good reasons beyond
201 the guidance to adapt the dose, remains a topic of study. We identified several factors associated with
202 inappropriate NOAC dosing. Of note, reclassification of NOAC appropriateness based on the MDRD and
203 CKD-EPI renal function estimation formulae (which are more readily available to clinicians than the CG
204 calculation) did not explain the difference in classification of dosing.

205 **6.1. Prevalence of NOAC misdosing**

206 As AF prevalence is expected to increase in the upcoming decades, optimal treatment of these patients
207 is necessary to minimize AF complications and reduce the health burden, both for patients and for
208 healthcare systems. A cornerstone of AF management is the prevention of stroke, for which NOAC
209 treatment is the first choice therapy.^[18-21] Besides identifying and treating AF patients with high risk of
210 stroke, correct NOAC dosing is also of primordial importance to ensure efficacy and safety.

211 The range of ambulatory AF patients treated with inappropriately dosed NOACs in our study is in line
212 with other large international investigations ranging between 12.8-31.1%.^[17,22-24] Two smaller Belgian
213 studies by other centers in our country reported off-label dosing in 25.0% and 18.3%.^[16,25] Remarkably,
214 in the aforementioned studies overdosing ranged between 3.4-7.8% whereas in our study overdosing
215 was slightly more prevalent in 8.8% of patients.

216 When applying the EHRA 2018 Practical Guide, an expected (but significant) decline of inappropriate
217 dosing was found (-3.8%) compared with the SmPC. This was driven by more lenient acceptance of
218 reduced NOAC doses as potentially appropriate (from 10.5% to 6.8%). Moudallel et al. reported NOAC
219 underdosing in 17.4 vs. 7.0 % according to the SmPC and EHRA 2015 Practical Guide respectively and is
220 in line with our results regarding NOAC underdosing (6.1% was overdosed according to the SmPC but
221 no data was reported concerning overdosing according to the EHRA 2015 guide).^[16] Two other European
222 studies also evaluated NOAC dosing appropriateness according to the EHRA 2015 guide, but interpreted
223 the presence of ≥ 2 'yellow' interactions as an indication for a reduced dose. A retrospective subanalysis
224 of the FANTASIA Registry (a Spanish prospective, observational, multicenter study including adults with
225 AF on anticoagulant evaluating the incidence of thrombo-embolic and bleeding events) found
226 inappropriate doses in 32% of AF patients. More specifically, 15% was inappropriately overdosed and
227 17% was inappropriately underdosed (off-label dosing according to SmPC criteria was not reported).^[26]
228 Capiou et al. found an increase of inappropriate dosing from 18.3% to 23.4% according to the SmPC and
229 EHRA 2015 guide, respectively (for both systems 0.8% of NOACs were contra-indicated).^[25] Of the SmPC

230 underdosed patients (9.8%), 21.9% were correctly dosed when classified by the 2015 EHRA guide,
231 resulting in 7.6% underdosed patients. Therefore, the global increase of dose inappropriateness was
232 related to the increase of overdosed patients according to the EHRA 2015 guide (from 7.8% to 15.0%).
233 Of note, since this interpretation of “≥2 yellow factors” is suggested as a possibility in the EHRA Practical
234 Guide, we considered both a standard dose as a reduced dose ‘appropriate’ in such cases, which
235 explains the overall lower prevalence of inappropriateness in our study.

236 Since the EHRA Practical Guide takes more factors with relevance for dosing into account, we
237 anticipated that incorrect dosing would be less when judged by the Practical Guide than by the SmPC.
238 It shows that in daily life a large proportion of AF patients have a complex presentation. Nevertheless,
239 even when evaluated by the EHRA Practical Guide standard inappropriate dosing is prevalent. This could
240 be explained in two ways. One is that physicians correctly take more clinical factors into consideration
241 and hence, both the SmPC and EHRA PG still fall short to guide clinical practice. However, prior
242 retrospective and observational data have clearly shown that dosing that deviates from
243 recommendations is associated with increased risk of adverse events and even mortality.^[7,27] Therefore,
244 the second explanation is that physicians still are falling short on making correct dosing decisions, which
245 calls for more physician education to improve patient outcomes. This education could focus more
246 specifically on some of the factors that our research has shown to be related with prescription errors. It
247 also calls for better patient tailored (transmural) follow-up with frequent reassessment of NOAC dose
248 to improve results.

249 **6.2. Contributing factors for under-and overdosing of NOACs**

250 Prior studies have identified various univariate factors related to inappropriately reduced dosing, such
251 as age, CHA₂DS₂-VASc score <4, sex (female), ethnicity (non-Caucasian), acute coronary syndrome,
252 vascular disease, prior stroke, diabetes and concomitant antiplatelet therapy.^[23,24] The FANTASIIA
253 Registry found that the factors ‘younger age’ and ‘dabigatran use’ were also associated with
254 inappropriately low NOAC dosing.^[26] Our study, also retained the (univariate) association of drugs (i.e.

255 antiplatelets or NSAID) and alcohol with underdosing. Of note, alcohol is a factor in the HAS-BLED score
256 and not in the SmPC or EHRA Guide, and is a modifiable bleeding risk factor that should be addressed
257 rather than leading to an adaption of the NOAC dose.

258 Based on the SmPC multivariate analysis, the factors 'higher body weight' and 'frailty' were associated
259 with off-label underdosing.

260 For overweight or obese patients, this is a paradoxical finding: although higher weight is associated with
261 both a higher volume of distribution and higher renal clearance, no specific (i.e. increased) NOAC dosing
262 algorithm currently exists. At least the standard NOAC dose would be expected. This suggests that other
263 factors that are not even part of the SmPC or EHRA Guide led physicians to paradoxically reduce the
264 dose. One could postulate that some conditions for dose reduction are more prevalent in overweight
265 patients (e.g. vascular disease for which antiplatelets are indicated), but our analysis could not identify
266 such explanation. This paradoxical finding certainly requires confirmation and further study.

267 Frailty is included as a 'yellow' parameters in the EHRA 2018 Practical Guide, and hence, in combination
268 with other yellow factors, can justify an appropriately reduced dose according to this system.

269 Regarding factors related to NOAC overdosing, our study identified lower renal function and AF patients
270 not treated with apixaban. This can be explained by the fact that prescription of a reduced dose of
271 apixaban depends on the presence of a minimum of two out of three criteria (see Supplementary Table
272 1) which decreases the probability for an overdose. Renal function is a well-known risk factor as all
273 NOACs are renally excreted and three of the four NOACs have absolute SmPC dosing reduction criteria
274 depending on renal function. ^[22]

275 Noteworthy, when reviewing the patients taking a NOAC concomitant with antiepileptic drugs (which
276 can *lower* NOAC plasma concentrations), three patients (75.0%) were inappropriately dosed as classified
277 by the two systems and one patient was appropriately dosed according to the SmPC but potentially

278 underdosed according to the EHRA 2018 guide (apixaban 5 mg plus valproic acid, 'dark brown'). This
279 reflects the unawareness of the interaction of antiepileptics with NOACs among clinicians, and the
280 almost full absence of data on the clinical effect of plasma lowering medication on the efficacy of NOACs.
281 Further phase-1 studies are needed in which NOAC plasma concentrations may be better defined under
282 these combinations.

283 **6.3. Primary care versus specialist care**

284 Although one of the initial objectives of this study was to investigate the prescription patterns in primary
285 care versus cardiologist care, well-founded conclusions cannot be made due to the underpowerment
286 as the result of the cessation of inclusions by the COVID-19 pandemic. Moreover, the data would need
287 interpretation in the light of the different patient demographics, like age and renal function (Table 1).
288 These two parameters are critical factors in the dosing criteria of both SmPC and EHRA 2018 guides.
289 Nevertheless, there is a higher rate of inappropriate dosing in GP care compared to cardiologists, which
290 seems mainly the result of inappropriate overdosing. Overall, inappropriate NOAC dosing in primary
291 care in Portugal, Belgium and the UK has been reported by other investigators in a range between 18.3-
292 30.3%.^[25,28,29] So far, a proven difference with specialist care is lacking from the literature although such
293 findings might be important to tailor and focus educational initiatives.

294 **6.4. Influence of different renal function formulae**

295 Although the Cockcroft-Gault renal formula was used in all the landmark NOAC trials, and hence
296 adopted in the SmPC guidelines and EHRA guide, laboratories cannot routinely report this value since
297 they miss information like patient weight, and rather report estimated glomerular filtration rate (eGFR)
298 based on the MDRD or CKD-EPI formulae. A post-hoc analysis using these two eGFR formulae showed
299 no significant impact on the classification of appropriateness according to the SmPC and EHRA 2018
300 Practical Guide, although a slightly higher proportion of patients received a non-significantly
301 inappropriate NOAC dose when MDRD or CKD-EPI were used. Hence, recalculating renal function using
302 the CG formula, especially in AF patients with borderline eGFR, could be helpful to improve prescription

303 correctness among clinicians. Other studies in larger AF cohorts also investigated the influence of eGFR
304 formulae on dosing appropriateness and recommended using the CG formula in patients with a
305 GFR<70mL/min and/or elderly ≥ 75 years.^[30,31]

306 **6.5. Limitations**

307 Several limitations have to be acknowledged. An important limitation was the underrepresentation of
308 primary care patients, as already mentioned. AF patients included at the cardiology outpatient clinic
309 originated from one center, which limits generalizability, although they were recruited from the
310 different Cardiology subspecialty clinics. Some primary care patients could be in regular follow-up by
311 other cardiologists than those of the Antwerp University Hospital. The size of our cohort did not allow
312 for analyses of each NOAC separately. The same applies to the multivariate results, which need to be
313 interpreted with caution. Furthermore, as this was a retrospective quantitative study, based on the
314 factors for NOAC dose adaptation included in the SmPC and 2018 EHRA Practical Guide, other possible
315 influencing factors could not be objectified. Additional prospective (qualitative) research in specialist-
316 and primary care can aid in gaining more insights into dosing decisions and improving AF care. Finally,
317 the EHRA Practical Guide and its dose adjustment chart has to be regarded as a guidance tool to support
318 clinicians in rational decisions, although definitive evidence on outcomes is often not yet available and
319 further studies are needed.

320 **7. Conclusion**

321 Inappropriate NOAC dosing in AF patients in follow-up by cardiologists and primary care physicians still
322 occurs regularly, i.e. in about one in five patients (19.4%), according to the SmPC. Based on the 2018
323 EHRA Practical Guide, this proportion is significantly lower (15.6%), likely because more complex
324 patients can be accounted for, but it is still very high. This calls for further physician education, a
325 structured and frequent reassessment of NOAC dosing in complex AF patients and further investigation
326 on what might be appropriate dosing in very specific patient situations.

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468

469 **Statements and declarations**

470 **Ethics Approval**

471 All procedures in this study were in accordance with the 1964 Helsinki declaration (and its
472 amendments). The research protocol was approved by the Ethics Committees of the Antwerp University
473 Hospital/University of Antwerp on the 12th of August 2019 (local project reference 19/27/331).

474 **Availability of data and material**

475 The datasets generated during and/or analysed during the current study are available from the
476 corresponding author on reasonable request.

477 **Consent to participate**

478 All patients of the Antwerp University Hospital have consented with inclusion in retrospective analysis.
479 All patients included at the primary care centers provided written informed consent.

480 **Consent for publication**

481 Not applicable.

482 **Code availability**

483 Not applicable.

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489 **Competing interests**

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493 Medical. None of the other authors has any personal conflicts of interest.

494 **Author contributions**

495 All authors contributed to the study conception and design. Material preparation, data collection and
496 analysis were performed by Arne Ballet, Cedric Hillegeer and Michiel Delesie. The first draft of the
497 manuscript was written by Michiel Delesie and all authors commented on previous versions of the
498 manuscript. All authors read and approved the final manuscript.

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Table 1: Baseline characteristics of the study population

Characteristic	Total study population (n=294)	Specialist care (n=200)	Primary care (n=94)	P-value
Age (years), mean ± SD	74.5 ± 10.0	72.6 ± 10.5	78.6 ± 7.3	<0.001
Male, n (%)	185 (62.9)	131 (65.5)	54 (57.4)	0.182
BMI (kg/m²), mean ± SD	27.7 ± 5.4	27.5 ± 5.5	28.1 ± 5.2	0.363
Weight (kg), mean ± SD	80.3 ± 16.5	80.7 ± 17.3	79.4 ± 14.7	0.499
<60kg, n (%)	26 (8.8)	19 (9.5)	7 (7.4)	0.563
≥60kg, n (%)	268 (91.2)	181 (90.5)	87 (92.6)	
Type of AF, n (%)				0.616
Permanent	68 (23.1)	48 (24.0)	20 (21.3)	
Non-permanent	212 (72.1)	144 (72.0)	68 (72.3)	
CHA₂DS₂-VASc score, mean ± SD	3.9 ± 1.6	3.9 ± 1.7	4.1 ± 1.5	0.270
HAS-BLED score, mean ± SD	1.4 ± 0.7	1.4 ± 0.8	1.3 ± 0.6	0.814
NOAC therapy, n (%)				0.105
Apixaban	122 (41.5)	90 (45.0)	32 (34.0)	
Rivaroxaban	101 (34.4)	65 (32.5)	36 (38.3)	
Edoxaban	40 (13.6)	22 (11.0)	18 (19.1)	
Dabigatran	31 (10.5)	23 (11.5)	8 (8.5)	
Serum creatinine, mg/dL	1.09 ± 0.39	1.09 ± 0.40	1.08 ± 0.38	0.768
Renal function, CG formula (ml/min), mean ± SD	70.3 ± 28.8	72.7 ± 29.7	65.1 ± 26.1	0.033
<30, n (%)	10 (3.4)	5 (2.5)	5 (5.3)	0.387
30-49, n (%)	64 (21.8)	42 (21.0)	22 (23.4)	
>50, n (%)	220 (74.8)	153 (76.5)	67 (71.3)	
Concomitant disease, n (%)				
Congestive Heart failure	98 (33.3)	75 (37.5)	23 (24.5)	0.027
Hypertension	224 (76.2)	146 (73.0)	78 (83.0)	0.061
Diabetes mellitus	57 (19.4)	43 (21.5)	14 (14.9)	0.181
Stroke/TIA/trombo-embolism	53 (18.0)	37 (18.5)	16 (17.0)	0.758
(Coronary) artery disease	149 (50.7)	105 (52.5)	44 (46.8)	0.363
Other medication of interest, n (%)				
Antiplatelet drugs	34 (12.6)	31 (15.5)	3 (3.2)	0.002
NSAIDs/systemic steroids	13 (4.4)	11 (5.5)	2 (2.1)	0.237
Amiodarone	38 (12.9)	29 (14.5)	9 (9.6)	0.240
Anti-epileptic drugs	4 (1.4)	3 (1.5)	1 (1.1)	0.763

AF: Atrial Fibrillation; BMI: Body Mass Index; NOAC: Non-vitamin K antagonist Oral AntiCoagulant; SD: Standard Deviation; CHA₂DS₂-VASc: Congestive heart failure(1), Hypertension (1), Age ≥75 years (2), Diabetes mellitus (1), Stroke (2), Vascular disease (1), Age 65-74 years (1), Sex category (female=1); HAS-BLED: Systolic blood pressure >160mmHg (1), Abnormal renal and/or hepatic function (1 point each), Stroke (1), Bleeding history or predisposition (1), Labile INR (1), Age >65 years (1), Drugs or excessive alcohol drinking (1 point each); SmPC: Summary of Product Characteristics documents; EHRA: European Heart Rhythm Association; CG: Cockcroft and Gault; TIA: Transient Ischemic Attack; NSAID: Non-Steroidal Anti-Inflammatory Drugs. Bold indicates significant p-values < 0.05.

Table 2: Appropriateness of NOAC dosing

Parameter	Total study population (n=294)	Apixaban (n=122)	Rivaroxaban (n=101)	Edoxaban (n=40)	Dabigatran (n=31)	P-value
Dosage, n (%)						0.066
Standard Dose	221 (75.2)	90 (73.8)	79 (78.2)	34 (85.0)	18 (58.1)	
Reduced Dose	73 (24.8)	32 (26.2)	22 (21.8)	6 (15.0)	13 (41.9)	
Appropriate dose SmPC, n (%)						0.713
Appropriate	237 (80.6)	102 (83.6)	79 (78.2)	32 (80.0)	24 (77.4)	
Inappropriate	57 (19.4)	20 (16.4)	22 (21.8)	8 (20.0)	7 (22.6)	
Overdosed	26 (8.8)	6 (4.9)	12 (11.9)	5 (12.5)	3 (9.7)	
Underdosed	31 (10.5)	14 (11.5)	10 (9.9)	3 (7.5)	4 (12.9)	
Appropriate dose EHRA 2018, n (%)						0.282
Appropriate	248 (84.4)	108 (88.5)	84 (83.2)	32 (80.0)	24 (77.4)	
Inappropriate	46 (15.6)	14 (11.5)	17 (16.8)	8 (20.0)	7 (22.6)	
Overdosed	26 (8.8)	6 (4.9)	12 (11.9)	5 (12.5)	3 (9.7)	
Underdosed	20 (6.8)	8 (6.6)	5 (5.0)	3 (7.5)	4 (12.9)	

NOAC: Non-vitamin K antagonist; SmPC: Summary of Product Characteristics documents; EHRA: European Heart Rhythm Association. The Cockcroft-Gault renal formula was used for estimation of renal function.

Table 3: Factors related to underdosing of NOACs

Factor	RR (95% CI)	OR (95% CI)	P-value
Univariate factors correlated to underdosing of NOACs (SmPC)			
Frailty	1.86 (0.94-3.69)	2.03 (0.92-4.49)	0.075
Diuretics	2.08 (1.04-4.19)	2.27 (1.05-4.92)	0.034
Drugs or alcohol usage	2.11 (0.94-4.73)	2.39 (0.89-6.40)	0.075
BMI	/	1.09 (1.02-1.15)	0.008
Weight	/	1.02 (1.00-1.04)	0.047
Univariate factors correlated to underdosing of NOACs (EHRA 2018)			
Sex (male)	0.48 (0.21-1.12)	0.46 (0.18-1.14)	0.086
Drugs or alcohol usage	2.93 (1.15-7.50)	3.32 (1.11-9.90)	0.024
BMI	/	1.09 (1.02-1.17)	0.022
	Coefficient (SE)	OR (95% CI)	P-value
Multiple regression model for underdosing of NOACs (SmPC)			
Frailty	0.81 (0.412)	2.25 (1.00-5.04)	0.050
Weight	0.024 (0.011)	1.02 (1.00-1.05)	0.028
Multiple regression model for underdosing of NOACs (EHRA 2018)			
Drugs or alcohol usage	1.04 (0.57)	2.82 (0.92-8.63)	0.069
BMI	0.076 (0.04)	1.08 (1.01-1.16)	0.031

BMI: body mass index, SE: Standard Error, OR: Odds Ratio, CI: Confidence Interval, RR: Relative Risk, / : not available for continuous variables – factors with a p-value < 0.10 are mentioned as they were considered in multivariate regression models

Table 4: Factors related to overdosing of NOACs

Factor	RR (95% CI)	OR (95% CI)	P-value
Univariate factors correlated to overdosing of NOACs (SmPC and EHRA 2018)			
Primary care	2.13 (1.03-4.41)	2.31 (1.03-5.20)	0.039
Permanent AF	2.54 (1.10-5.82)	2.29 (1.10-4.73)	0.024
Apixaban	0.42 (0.18-1.02)	0.39 (0.15-1.01)	0.046
BMI	/	0.90 (0.82-0.99)	0.016
Weight	/	0.97 (0.94-1.00)	0.018
Age	/	1.10 (1.04-1.17)	<0.001
CHA ₂ DS ₂ -VASc	/	1.25 (0.97-1.61)	0.083
Renal function (CG)	/	0.96 (0.93-0.97)	<0.001
	Coefficient (SE)	OR (95% CI)	P-value
Multiple regression model for overdosing of NOACs (SmPC and EHRA 2018)			
Apixaban	-1.27 (0.509)	0.282 (0.10-0.77)	0.013
Renal function (CG)	-0.05 (0.013)	0.950 (0.93-0.97)	<0.001

BMI: body mass index, CG: Cockcroft and Gault, RR: Relative Risk, SE: Standard Error, OR: Odds Ratio, CI: Confidence Interval, RR: Relative Risk, / : not available for continuous variables – factors with a p-value < 0.10 are mentioned as they were considered in multivariate regression models

Figure 1: Enrolment procedure

See separate file

Legend

UZA: Antwerp University Hospital, PC: Primary Care, AF: Atrial Fibrillation, NOAC: Non-vitamin K antagonist Oral AntiCoagulant

Figure 2: Appropriateness of NOAC dosing according to the SmPC and EHRA 2018 guide

See separate file

Legend

SmPC: Summary of Product Characteristics documents, EHRA 2018: European Heart Rhythm Association 2018 Practical Guide

