# Patients with higher body mass index treated with direct / novel oral anticoagulants (DOAC / NOAC) for atrial fibrillation experience worse clinical outcomes

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**Title:** Patients with higher body mass index treated with direct / non vitamin K dependent anticoagulants (DOAC / NOAC) experience worse clinical outcomes

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## Introduction

Obesity, simply defined as an excess of body weight for height, is a complex multifactorial disease affecting one third of world's population [1]. It can be classified as class I (body mass index (BMI) 30-34.9 kg/m$^2$), class II (BMI 35-39.9 kg/m$^2$) and class III obesity (BMI ≥40 kg/m$^2$). Pharmacokinetic data for majority of drugs are scarce or do not exist in obese patients, and their effects are not well elucidated in this still growing population [2]. Advent of direct/novel oral anticoagulants (DOAC/NOAC) has dramatically changed the practice of anticoagulation [3]. In contrast to warfarin, whose dose is individually titrated based on international normalized ratio, DOACs are administered at fixed doses providing much more convenient experience but without reassurance of a well optimized drug effect. Pharmacokinetic studies of DOACs showed that drug levels depend on weight, renal function, age and concomitant medications [4-6]. Randomized controlled trials of DOACs included limited number of obese patients providing uncertainty about their efficacy in this population [5, 6]. Since DOACs are expected to be increasingly used, more information about efficacy and safety, especially among obese patients which might be exposed to suboptimal drug levels, is urgently needed. Therefore, we aimed to investigate in the real-life setting whether DOAC anticoagulated patients with atrial fibrillation stratified according to the different BMI subgroups experience different risks of unwanted outcomes.

## Patients and methods

We retrospectively analyzed a cohort of 325 patients with atrial fibrillation treated in our institution that received DOACs [179 (55%) dabigatran; 72 (22%) rivaroxaban; 74 (23%) apixaban] as a part of stroke/systemic embolism risk reduction management. Patients were recruited at the start of anticoagulation in the period from 2011 to 2018. Patients were stratified according to the BMI subgroups (non-obese with BMI <30 kg/m$^2$; class I obesity with BMI 30-34.9 kg/m$^2$; class II+ obesity with BMI ≥35 kg/m$^2$). In addition, non-obese patients were evaluated as normal weight (with BMI 18.5-24.9 kg/m$^2$) and overweight (with BMI 25-29.9 kg/m$^2$) in comparison to other subgroups. Clinical data were obtained from the hospital information system, estimated glomerular filtration rate (eGFR) was calculated according to the MDRD formula [7], predetermined stroke risk was

assessed using the $CHA_2DS_2VASC$ score [8], predetermined major bleeding risk was assessed using the HAS-BLED score [9]. The study complies with the Declaration of Helsinki and it was approved by the Institutional Review Board.

Normality of distribution of numerical variables was tested using the Shapiro-Wilk test. Neither of tested numerical variables followed normal distribution and they were presented as median and interquartile range and were compared between the groups of interest using the Kruskal-Wallis one-way analysis of variance with post-hoc test by Conover. Categorical variables were presented as ratios and percentages and were compared between the groups of interest using the $\chi^2$ test. Survival analyses were based on the Kaplan-Meier method [10]. Survival curves were analyzed using the log-rank test [11] / the log-rank test for trend and the Cox regression analysis. Outcomes of interest were time to thrombosis (TTT; defined as time from inclusion to first occurrence of stroke or systemic embolism), time to bleeding [TTB; defined as time from inclusion to first occurrence of major bleeding event defined according to the International Society on Thrombosis and Haemostasis (ISTH) definition [12]], overall survival (OS; defined as time from inclusion to death of any cause) and event free survival (EFS; defined as time from inclusion to occurrence of thrombosis, bleeding or death, whichever occurred first). P values <0.05 were considered statistically significant. Initial associations with survival were screened using the custom-made MS Excel workbook [13]. MedCalc Statistical Software version 18.10.2 (MedCalc Software bvba, Ostend, Belgium) was used for all presented analyses.

## Results

### Patients' characteristics

Among 325 analyzed DOAC anticoagulated patients, there were 172/325 (53%) male patients. Median age was 70 years. A total of 279/325 (85.8%) patients had moderate to high predetermined stroke risk (defined as CHA2DS2-VASC score ≥2) and a total of 80/325 (24.6%) patients had high predetermined major bleeding risk (defined as HAS-BLED score ≥3). Patients' characteristics stratified according to the BMI categories are shown in the Table 1.

Three investigated BMI subgroups did not significantly differ regarding sex (P=0.778), age (P=0.130), estimated glomerular filtration rate (P=0.581), predetermined stroke risk [CHA2DS2-VASC (P=0.964)] or predetermined major bleeding risk [HAS-BLED (P=0.528)]. However, there was statistically significant difference in frequency of diabetes (15%, 25.4% and 33.3% of non-obese, class I and class II+ obesity patients, respectively; P=0.028), smoking (10.7%, 14.1% and 33.3%, respectively;

P=0.012), persistent atrial fibrillation (11.2%, 28.2% and 14.3% of non-obese, class I and class II+ obesity patients, respectively; P=0.002), levels of C reactive protein (median 3.8 mg/L, 5.1 mg/L and 7 mg/L for non-obese, class I and class II+ obesity patients, respectively; P=0.005) and diastolic blood pressure (median 80 mm Hg, 80 mm Hg and 85 mm Hg for non-obese, class I and class II+ obesity patients, respectively; P=0.016) between BMI categories.

**BMI as a modifier of thrombotic and bleeding risks**

Median follow-up of our patients was 33 months. During study period a total of 15 patients died, a total of 12 patients experienced major bleeding, and a total of 12 patients experienced thrombotic incident, and a total of 35 patients experienced composite event. In the whole cohort of DOAC treated patients, those belonging to higher BMI subgroups were significantly more likely to experience shorter **time to thrombosis** (overall P=0.083, P for trend=0.043, with 2-year TTT rates of 98%, 95% and 89% for non-obese, class I and class II+ obesity patients, respectively) as shown in the Figure 1A. This phenomenon was most pronounced among dabigatran treated patients (overall P=0.007, P for trend=0.009, with 2-year TTT rates of 97%, 92% and 79% for non-obese, class I and class II+ obesity patients, respectively; Figure 2A), but not evident in other DOAC subgroups (Figure 2B).

Similarly, considering whole cohort of patients, those belonging to higher BMI subgroups were significantly more likely to experience **major bleeding** sooner (overall P<0.001, P for trend=0.001, with 2-year TTB rates of 99%, 97% and 92% for non-obese, class I and class II+ obesity patients, respectively) as shown in the Figure 1B. Conversely, this phenomenon was most pronounced among patients treated with factor Xa inhibitors (overall P<0.001, P for trend=0.001, with 2-year TTB rates of 96%, 97% and 87% for non-obese, class I and class II+ obesity patients, respectively; Figure 2C), but not evident among dabigatran treated patients (Figure 2D).

**Overall survival** did not differ between three BMI categories, neither in the whole cohort as shown in the Figure 1C, nor in the investigated DOAC subgroups (P>0.05 for all analyses; Figure 2E and Figure 2F). As expected from the **composite endpoint** definition, event free survival significantly differed between BMI categories with patients presenting with higher BMI being more likely to experience an event sooner (overall P<0.001, P for trend<0.001, with 2-year EFS rates of 95%, 89% and 82% for non-obese, class I and class II+ obesity patients, respectively) as shown in the Figure 1D. Shorter EFS associated with higher BMI was evident in both dabigatran and anti-Xa treated patients (Overall P and P for trend <0.05 in both subgroups; Figure 2G and Figure 2H).

Associations of inferior TTT, TTB and EFS with higher BMI remained statistically significant in multivariate Cox regression models additionally adjusted for age, gender, eGFR, $CHA_2DS_2VASC$ and HAS-BLED as shown in the Table 2.

**Additional considerations excluding patients with body weight >120 kg or BMI >40 kg/m$^2$**

There were a total of five patients with either body weight >120 kg (two patients) or BMI >40 kg/m$^2$ (five patients) that received DOACs. Only one patient (BMI >40 kg/m$^2$; body weight <120 kg on rivaroxaban) experienced an event (major bleeding) and separate analyses of this subgroup were uninformative. There were no underweight individuals (BMI <18.5). We further repeated TTT, TTB, EFS and OS analyses with exclusion of these patients from the whole cohort (defining upper limit of class II+ obesity subgroup at BMI of 40 kg/m$^2$ or body weight of 120 kg) and we observed no substantial differences in results.

Regarding **TTT: all DOAC subtypes** overall P=0.020, P for trend=0.023, with 2-year TTT rates of 98%, 95% and 86% for non-obese, class I and class II+ obesity patients, respectively; **dabigatran** overall P<0.001, P for trend=0.004, with 2-year TTT rates of 97%, 92% and 73% for non-obese, class I and class II+ obesity patients, respectively; **factor Xa inhibitors** P>0.05. Regarding **TTB**: **all DOAC subtypes** overall P<0.001, P for trend=0.003, with 2-year TTB rates of 99%, 98% and 89% for non-obese, class I and class II+ obesity patients, respectively; **dabigatran** P>0.05; **factor Xa inhibitors** overall P<0.001, P for trend=0.003, with 2-year TTB rates of 96%, 97% and 80% for non-obese, class I and class II+ obesity patients, respectively. Regarding **OS**, there were no significant associations of BMI subgroups with OS (P>0.05 for all analyses). Regarding **EFS**: **all DOAC subtypes** overall P<0.001, P for trend<0.001, with 2-year EFS rates of 95%, 89% and 75% for non-obese, class I and class II+ obesity patients, respectively; **dabigatran** overall P=0.003, P for trend<0.001, with 2-year EFS rates of 96%, 82% and 73% for non-obese, class I and class II+ obesity patients, respectively; **factor Xa inhibitors** overall P=0.006, P for trend=0.088, with 2-year EFS rates of 92%, 94% and 80% for non-obese, class I and class II+ obesity patients, respectively.

**Analysis of normal weight and overweight patients in comparison to obese patients**

We performed the same analyses after separating a cohort of non-obese patients into normal weight (BMI 18.5-24.9 kg/m$^2$) and overweight patients (BMI 25-29.9 kg/m$^2$), comparing four BMI subgroups (normal weight, overweight, class I obesity, class II+ obesity) with similar conclusions, survival curves are shown in Supplementary Figure S1.

Regarding **TTT** (Figure S1A-C): **all DOAC subtypes** overall P=0.073, P for trend=0.018, with 2-year TTT rates of 100%, 97%, 95% and 89% for normal weight, overweight, class I and class II+ obesity patients, respectively; **dabigatran** overall P=0.009, P for trend=0.006, with 2-year TTT rates of 100%, 96%, 92% and 79% for normal weight, overweight, class I and class II+ obesity patients, respectively; **factor Xa inhibitors** P>0.05. Regarding **TTB** (Figure S1D-F): **all DOAC subtypes** overall P<0.001, P for trend<0.001, with 2-year TTB rates of 100%, 98%, 96% and 92% for normal weight, overweight, class I and class II+ obesity patients, respectively; **dabigatran** P>0.05; **factor Xa inhibitors** overall P<0.001, P for trend=0.002, with 2-year TTB rates of 100%, 96%, 97% and 88% for normal weight, overweight, class I and class II+ obesity patients, respectively. There was no significant association of BMI with **OS** (P>0.05 for all analyses; Figure S1G-I). Regarding **EFS** (Figure S1J-L): **all DOAC subtypes** overall P<0.001, P for trend<0.001, with 2-year EFS rates of 100%, 93%, 89% and 82% for normal weight, overweight, class I and class II+ obesity patients, respectively; **dabigatran** overall P=0.009, P for trend<0.001, with 2-year EFS rates of 100%, 94%, 82% and 79% for normal weight, overweight, class I and class II+ obesity patients, respectively; **factor Xa inhibitors** overall P=0.005, P for trend=0.024, with 2-year EFS rates of 100%, 90%, 94% and 88% for normal weight, overweight, class I and class II+ obesity patients, respectively.

When considering comparison of overweight vs obese patients only, similar findings were observed for TTT (all DOAC subtypes P=0.115; dabigatran P=0.049; factor Xa inhibitors P=0.671), TTB (all DOAC subtypes P=0.033; dabigatran P=0.677; factor Xa inhibitors P=0.048) and EFS (all DOAC subtypes P=0.006; dabigatran P=0.002; factor Xa inhibitors P=0.350). In this context, obese in comparison to overweight dabigatran treated patients experienced inferior OS (P=0.037).

**Discussion**

To the best of our knowledge, our study is first to show statistically significantly increased risks for thrombotic incidents and bleeding in obese patients with atrial fibrillation anticoagulated with DOACs.

DOACs are lipophilic drugs [14]. Pharmacokinetic studies indicate their volumes of distribution are increased [15, 16] and drug concentrations decreased [16-18] with standard fixed dosing in obese/overweight patients. This may lead to suboptimal drug levels and potentially increased risk of thrombosis, but also to currently not well characterized long-term side-effects due to drug accumulation. Evidence exists that the risk for ischemic events is higher with lower drug levels in the case of dabigatran [17], which might be also possible, but unknown at the moment for other drugs in

the DOAC class. Our data based on a real-life cohort of patients with decent follow-up suggest that DOAC anticoagulated patients with higher BMI (especially class II+ obese patients with BMI ≥35 kg/m$^2$) tend to experience worse clinical outcomes (thrombosis and bleeding), a biologically plausible finding considering pharmacokinetic concerns. Interestingly, higher thrombotic risk is especially pronounced among dabigatran treated patients, for whom the most pharmacokinetic concerns exist. On the opposite, patients with higher BMI receiving factor Xa inhibitors seem to be more prone to major bleeding. Although small studies and sub-analyses of larger trials investigating pharmacokinetics and efficacy of DOACs did not identify significantly higher risks for unwanted outcomes among overweight/obese patients, such analyses might be underpowered to assess this issue properly. Recent data from a large registry-based study [19] implied there is no statistically significant difference in clinical outcomes regarding different BMI subgroups in patients treated with DOAC and reported that overweight and obese patients even had lower rates of unwanted outcomes which is in contrast with our findings. It should be noted however that dabigatran was given to only 10.1% of patients in the aforementioned study [19], whereas it was the predominantly used DOAC in our cohort of patients (55% of patients receiving dabigatran). Therefore, observed differences between studies might be DOAC-subtype specific and obesity might differently affect clinical outcomes in patients treated with dabigatran and factor Xa inhibitors.

When interpreting available data, differences between real-life and clinical trial settings must also be considered. In clinical trials issues like non-adherence to therapy, drug-to-drug interactions and inclusion of patients with adverse or characteristics are of much less magnitude. Our study included small proportion of patients that are considered ineligible for DOAC treatment by the guidelines (body weight >120 kg, BMI >40 kg/m$^2$), but with their exclusion no substantial differences in results were observed. By chart review, we did not identify drugs with high degree of interaction with DOACs (verapamil, ticagrelor, macrolides…) however we could not control for this issue during follow-up period. Also, clinical decision making can be guided by alternative approaches in real-life and clinical trials (like MDRD or CKD-EPI as a method for creatinine clearance estimation, rather than Cockcroft-Gault formula that was used in majority of DOAC clinical trials). All of these aforementioned factors are more likely to represent a problem among obese patients and can result in under- or over-dosing of DOACs and consequently higher tendency for worse clinical outcomes.

Limitations of our study are retrospective design, single center experience and inability to properly investigate risks for unwanted outcomes among specific DOAC subtypes (different factor Xa inhibitors) due to statistical power constraints. Also, we could not assess DOAC concentrations and consequently miss pharmacokinetic data regarding the appropriateness of their dosing. Nevertheless, our findings suggest that safety concerns regarding one-size-fits-all approach with

DOAC dosing, especially in patients with BMI ≥35 kg/m$^2$, might be legitimate. Also, our findings imply that detrimental effects of higher BMI regarding higher thrombotic and bleeding risks might be DOAC subtype dependent. Future prospective studies on large cohorts of patients focusing on this issue are needed to provide further insights into possible loss of efficacy and safety of DOACs in obese patients.

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**Table 1:** Patients' characteristics stratified according to the body mass index categories.

| | **BMI** **<30kg/m$^2$** | **BMI** **30-34.9 kg/m$^2$** | **BMI** **≥35 kg/m$^2$** |
|---|---|---|---|
| **Number of pt.** | 233 | 71 | 21 |
| **Dabigatran** | 137 (58.8%) | 32 (45.1%) | 10 (47.6%) |
| **Rivaroxaban** | 46 (19.7%) | 20 (28.2%) | 6 (28.6%) |
| **Apixaban** | 50 (21.5%) | 19 (26.8%) | 5 (23.8%) |
| **Age (years)** | 71 IQR (63-77.3) | 67 IQR (60.3-75) | 69 IQR (63.5-72.8) |
| **Male gender** | 126 (54.1%) | 36 (50.7%) | 10 (47.6%) |
| **Hypertension** | 183 (78.5%) | 56 (78.9%) | 18 (85.7%) |
| **Diabetes mellitus *** | 35 (15%) | 18 (25.4%) | 7 (33.3%) |
| **Prior stroke/TIA** | 23 (9.9%) | 6 (8.5%) | 3 (14.3%) |
| **CAD** | 25 (10.7%) | 10 (14.1%) | 2 (9.5%) |
| **CAD family history** | 66 (28.3%) | 27 (38%) | 5 (23.8%) |
| **PAD** | 14 (6%) | 5 (7%) | 2 (9.5%) |
| **CHF** | 42 (18%) | 20 (28.2%) | 7 (33.3%) |
| **COPD** | 14 (6%) | 5 (7%) | 2 (9.5%) |
| **Smoking *** | 25 (10.7%) | 10 (14.1%) | 7 (33.3%) |
| **Alcohol use** | 21 (9%) | 10 (14.1%) | 3 (14.3%) |
| **Bleeding history** | 10 (4.3%) | 2 (2.8%) | 2 (9.5%) |
| **Concomitant ASA** | 15 (6.4%) | 1 (1.4%) | 2 (9.5%) |
| **BMI (kg/m$^2$)** | 26.4 IQR (25-28) | 31.6 IQR (31.1-23.9) | 36.4 (35.8-39.1) |
| **eGFR (ml/min/1.73m$^2$)** | 66 IQR (54.7-80.7 | 63.3 IQR (57.4-74.2) | 66 IQR (59.2-84.9) |

| | | | |
|---|---|---|---|
| **Hemoglobin (g/L)** | 138 IQR (131-146) | 136 IQR (131-143) | 140 IQR (133.8-151) |
| **Anemia** | 24 (10.3%) | 7 (9.9%) | 1 (4.8%) |
| **CRP (mg/L) *** | 3.8 IQR (1.7-6.9) | 5.1 IQR (3-7.8) | 7 IQR (4.7-10.3) |
| **Platelets x$10^9$/L** | 215 IQR (173-263) | 233 IQR (193-274) | 216 IQR (195-239) |
| **WBC x$10^9$/L** | 7.3 IQR (6.1-9.1) | 7.6 IQR (5.6-9.5) | 8.5 IQR (7.3-11.1) |
| **Systolic BP (mm Hg)** | 130 (120-140) | 135 (125-140) | 130 (120-140) |
| **Diastolic BP (mm Hg) *** | 80 IQR (75-90) | 80 IQR (80-90) | 85 IQR (80-96) |
| **Paroxysmal AF**<br>**Persistent AF ***<br>**Permanent AF** | 139 (59.7%)<br>26 (11.2%)<br>68 (29.2%) | 32 (45.1%)<br>20 (28.2%)<br>19 (26.8%) | 13 (61.9%)<br>3 (14.3%)<br>5 (23.8%) |
| **CHA2DS2VASC** | 3 IQR (2-4) | 3 IQR (2-4) | 3 IQR (2-4) |
| **CHA2DS2VASC ≥2** | 198 (85%) | 63 (88.7%) | 18 (85.7%) |
| **CHA2DS2VASC ≥3** | 158 (67.8%) | 47 (66.2%) | 14 (66.7%) |
| **CHA2DS2VASC ≥4** | 94 (40.3%) | 31 (43.7%) | 8 (38.1%) |
| **HAS-BLED** | 2 IQR (1-2) | 2 IQR (1-2) | 2 (1.75-3) |
| **HAS-BLED ≥3** | 58 (24.9%) | 15 (21.1%) | 7 (33.3%) |

*statistically significant at level $P<0.05$

Numerical variables did not follow normal distribution and are presented as median and interquartile range. They were compared between subgroups using the Kruskal-Wallis one-way ANOVA and post-hoc Conover test. Categorical variables were presented as frequency and percentage and were compared between subgroups using the $\chi^2$ test.

Abbreviations: BMI – body mass index; eGFR – estimated glomerular filtration rate; CAD; PAD – peripheral arterial disease; COPD – chronic obstructive pulmonary disease; CHF – congestive heart failure; ASA – acetylsalicylic acid; WBC – white blood cells; CRP – C reactive protein; BP – blood pressure; FA – atrial fibrillation.

**Table 2:** Overview of multivariate Cox regression models investigating associations of BMI with clinical outcomes in patients receiving direct oral anticoagulants.

| | Model 2 (TTT) | Model 3 (TTB) | Model 1 (OS) | Model 4 (EFS) |
|---|---|---|---|---|
| BMI | **HR=2.19 95%C.I. (1.00-4.76) P=0.048*** | **HR=2.78 95%C.I. (1.31-5.91) P=0.008*** | HR=1.49 95%C.I. (0.69-3.2) P=0.311 | **HR=2.13 95%C.I. (1.36-3.35) P=0.001*** |
| Age | HR=0.36 95%C.I. (0.07-1.92) P=0.232 | **HR=1.1 95%C.I. (1.01-1.21) P=0.039*** | **HR=1.14 95%C.I. (1.05-1.26) P=0.004*** | **HR=1.06 95%C.I. (1.01-1.11) P=0.019*** |
| Male gender | HR=0.97 95%C.I. (0.28-3.32) P=0.962 | HR=1.01 95%C.I. (0.27-3.87) P=0.977 | HR=1.97 95%C.I. (0.66-5.91) P=0.225 | HR=1.21 95%C.I. (0.58-2.5) P=0.607 |
| eGFR | HR=1.00 95%C.I. (0.97-1.04) P=0.887 | HR=0.98 95%C.I. (0.94-1.02) P=0.279 | **HR=0.97 95%C.I. (0.94-0.99) P=0.049*** | HR=0.98 95%C.I. (0.96-1.01) P=0.173 |
| $CHA_2DS_2VASC \geq 2$ | HR=1.14 95%C.I. (0.67-1.96) P=0.957 | HR=0.98 95%C.I. (0.61-1.58) P=0.968 | HR=0.94 95%C.I. (0.62-1.45) P=0.960 | HR=0.94 95%C.I. (0.62-1.45) P=0.957 |
| HAS-BLED ≥3 | **HR=13.9 95%C.I. (3.23-59.88) P<0.001*** | **HR=7.36 95%C.I. (1.49-36.17) P=0.014*** | HR=1.30 95%C.I. (0.42-4.04) P=0.645 | **HR=3.59 95%C.I. (1.74-7.41) P<0.001*** |

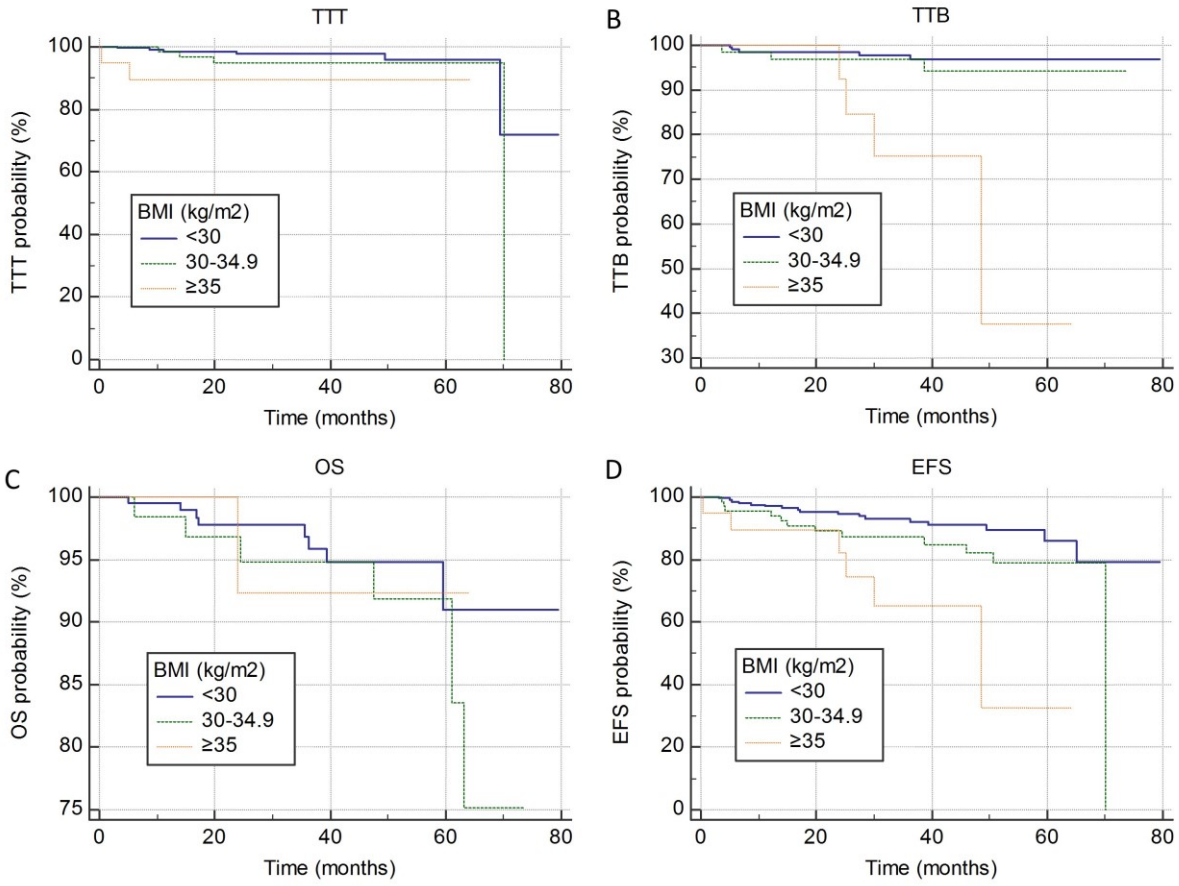
*statistically significant at level P<0.05

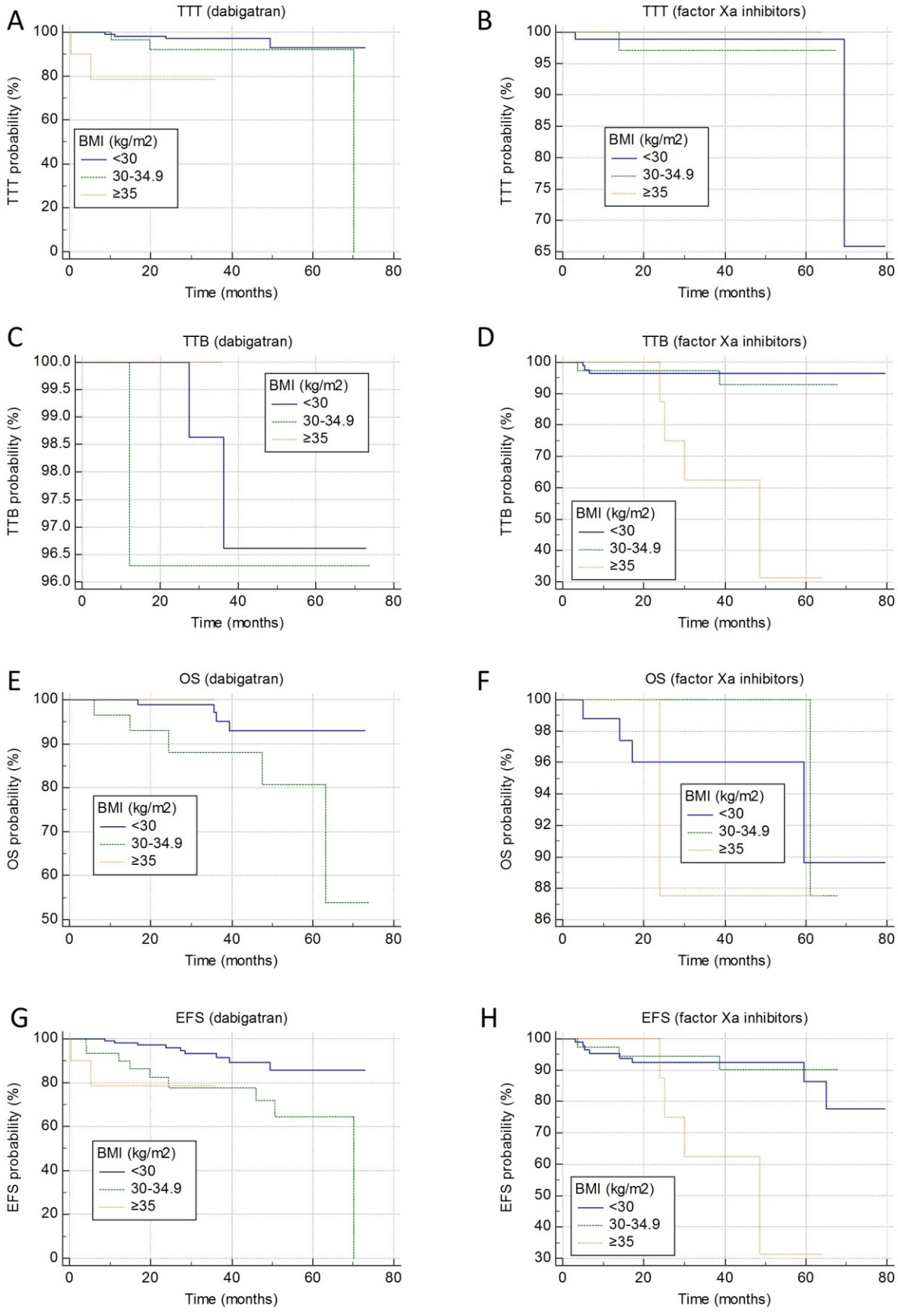
Abbreviations: OS – overall survival; TTT – time to thrombosis; TTB – time to bleeding, EFS – event free survival; BMI – body mass index; eGFR – estimated glomerular filtration rate; HR – hazard ratio; 95% C.I. – 95% confidence interval.

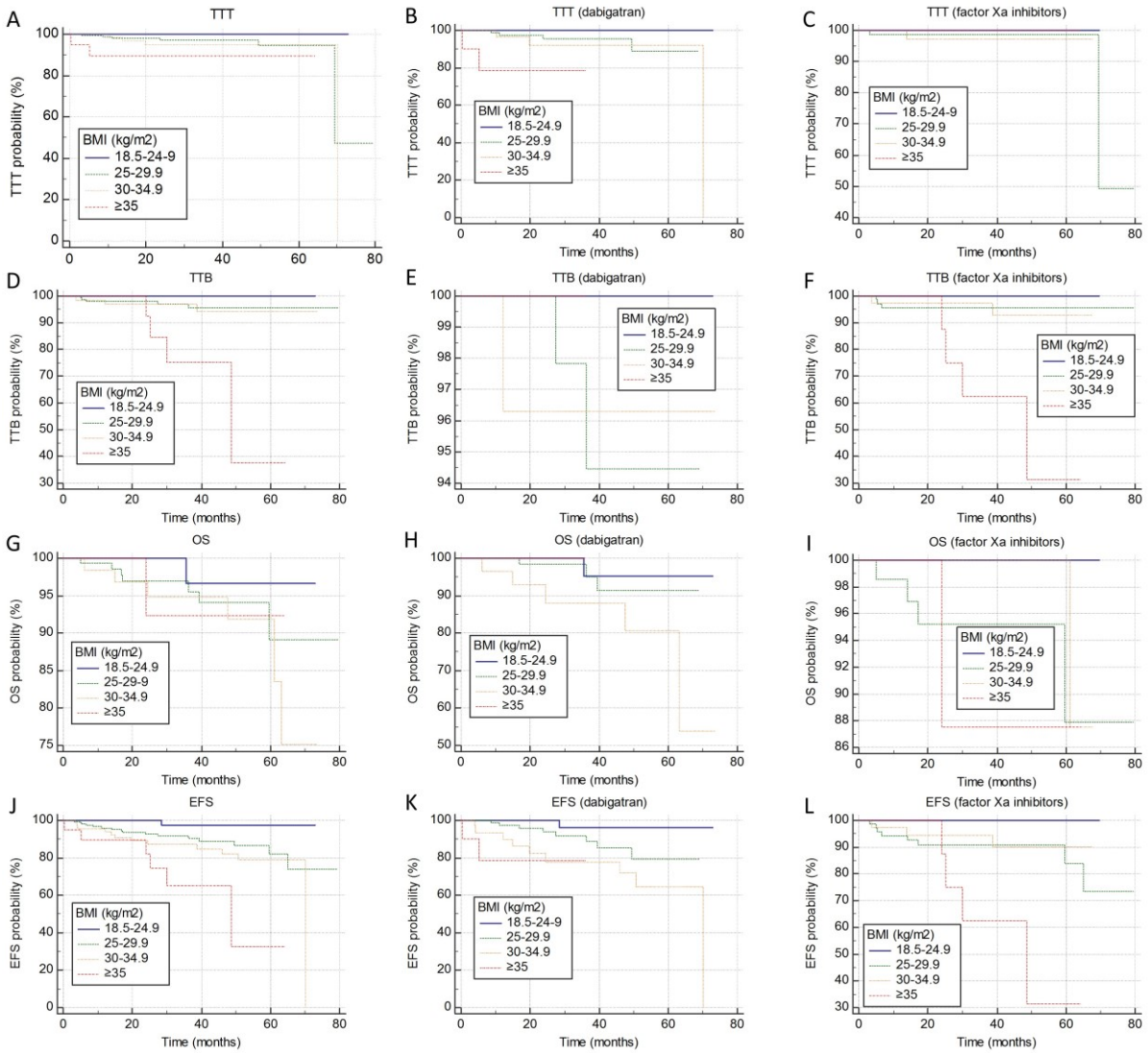
**Figure 1: A)** Time to thrombosis (TTT), **B)** time to bleeding (TTB), **C)** overall survival (OS) and **D)** event free survival (EFS) curves stratified into three subgroups (non-obese, class I and class II+ obesity) according to the body mass index (BMI). Vertical axes were cut above 0% to show separation of curves more clearly.

**Figure 2:** Time to thrombosis (TTT) in **A)** dabigatran and **B)** factor Xa inhibitors treated patients. Time to bleeding (TTB) in **C)** dabigatran and **D)** factor Xa inhibitors treated patients. Overall survival (OS) in **E)** dabigatran and **F)** factor Xa inhibitors treated patients. Event free survival (EFS) curves in **G)** dabigatran and **H)** factor Xa inhibitors treated patients, stratified into three subgroups (non-obese, class I and class II+ obesity) according to the body mass index (BMI). Vertical axes were cut above 0% to show separation of curves more clearly.

**Supplementary Figure S1:** Time to thrombosis (TTT) in **A)** all DOAC, **B)** dabigatran and **C)** factor Xa inhibitors treated patients. Time to bleeding (TTB) in **D)** all DOAC, **E)** dabigatran and **F)** factor Xa inhibitors treated patients. Overall survival (OS) in **G)** all DOAC, **H)** dabigatran and **I)** factor Xa inhibitors treated patients. Event free survival (EFS) curves in **J)** all DOAC, **K)** dabigatran and **L)** factor Xa inhibitors treated patients, stratified into four subgroups (normal weight, overweight, class I and class II+ obesity) according to the body mass index (BMI). Vertical axes were cut above 0% to show separation of curves more clearly.


TTT
TTT probability (%)
Time (months)
BMI (kg/m2)
<30
30-34.9
≥35
B
TTB
TTB probability (%)
Time (months)
BMI (kg/m2)
<30
30-34.9
≥35
C
OS
OS probability (%)
Time (months)
BMI (kg/m2)
<30
30-34.9
≥35
D
EFS
EFS probability (%)
Time (months)
BMI (kg/m2)
<30
30-34.9
≥35


A
TTT (dabigatran)
TTT probability (%)
Time (months)
BMI (kg/m2)
<30
30-34.9
≥35
B
TTT (factor Xa inhibitors)
TTT probability (%)
Time (months)
BMI (kg/m2)
<30
30-34.9
≥35
C
TTB (dabigatran)
TTB probability (%)
Time (months)
BMI (kg/m2)
<30
30-34.9
≥35
D
TTB (factor Xa inhibitors)
TTB probability (%)
Time (months)
BMI (kg/m2)
<30
30-34.9
≥35
E
OS (dabigatran)
OS probability (%)
Time (months)
BMI (kg/m2)
<30
30-34.9
≥35
F
OS (factor Xa inhibitors)
OS probability (%)
Time (months)
BMI (kg/m2)
<30
30-34.9
≥35
G
EFS (dabigatran)
EFS probability (%)
Time (months)
BMI (kg/m2)
<30
30-34.9
≥35
H
EFS (factor Xa inhibitors)
EFS probability (%)
Time (months)
BMI (kg/m2)
<30
30-34.9
≥35


A
TTT
TTT probability (%)
BMI (kg/m2)
18.5-24-9
25-29.9
30-34.9
≥35
B
TTT (dabigatran)
TTT probability (%)
Time (months)
C
TTT (factor Xa inhibitors)
TTT probability (%)
Time (months)
D
TTB
TTB probability (%)
Time (months)
E
TTB (dabigatran)
TTB probability (%)
Time (months)
F
TTB (factor Xa inhibitors)
TTB probability (%)
Time (months)
G
OS
OS probability (%)
Time (months)
H
OS (dabigatran)
OS probability (%)
Time (months)
I
OS (factor Xa inhibitors)
OS probability (%)
Time (months)
J
EFS
EFS probability (%)
Time (months)
K
EFS (dabigatran)
EFS probability (%)
Time (months)
L
EFS (factor Xa inhibitors)
EFS probability (%)
Time (months)