Table S1. Quality criteria for rating of POPPK models used for the simulation.

| Criteria                        | Rating of quality assessment                                                                 |
|---------------------------------|-----------------------------------------------------------------------------------------------|
| Phases of clinical trials       | High rating for post-marketing studies; medium rating for phase III trials and low rating for phase I-II trials |
| Population size                 | High rating if more than 100 patients included, medium rating if >100 and >50 patients, low rating if fewer than 50 patients included |
| Blood sample/patient            | High rating if more than 4 samples per patient. Medium rating if 2 or 3 samples per patient; Low rating if fewer than 2 samples per patient |
| PopPK results                   | Are the results clearly presented? In particular, is the relationship between drug clearance and the identified covariates together with clearance inter-individual variability explicitly and correctly given? Consensual rating |
| Relevant covariates tested      | Have the known and the relevant covariates for influencing PK of the DOACs been tested in the model? Creatinine clearance, age and weight being the minimum to get medium rate and adding of other parameters such as drug-drug interaction or hepatic enzymes are being scored as high quality |
| Internal validation             | Goodness-of-fit plots, visual predictive check, bootstrap been correctly performed? high rating if all three criteria present, medium rating if two were present and low rating of fewer than two criteria are present |
| External validation             | Has the model been validated on an external population? Yes or no |

These criteria and classification have been previously applied to models used in the TUCUXI tool (http://www.tucuxi.ch/) (unpublished).
Table S2. Dabigatran: summary of studies

| Study                  | PMID       | Formulation | Aim of study | Model type | No of subjects | Validation | Origin of the data set | Type of subjects                          |
|------------------------|------------|-------------|--------------|------------|----------------|------------|------------------------|--------------------------------------------|
| Trocóniz IF et al (2007) | 17322149   | po          | Descriptive  | POPPK      | 287            | Internal   | Phase II study         | Thromboprophylaxis                        |
| Liesenfeld KH et al (2011) | 21972820   | po          | Descriptive  | POPPK      | 9522           | Internal   | Phase III study        | AF                                         |
| Dansirikul et al (2012)  | 22398858   | po          | Descriptive  | POPPK      | 2045           | Internal and external | Phase I study  Phase II study | Healthy volunteers, AF and thromboprophylaxis |
| Delavenne X et al (2013) | 23210726   | po          | Drug-drug interaction | POPPK /PD | 10             | Internal   | Outpatients (post marketing studies) | Healthy volunteers |
| Liesenfeld KH et al (2013) | 23529813   | po          | Descriptive  | POPPK      | 7              | Internal and external | Phase I dialysis study | End-stage renal disease patients (hemodialysis) |
| Ollier E et al (2015)    | 26392328   | po          | Drug-drug interaction | POPPK /PD | 9              | Internal   | Outpatients (post marketing studies) | Healthy volunteers |

AF: atrial fibrillation
Table S3. Rivaroxaban: Summary of studies

| Study | PMID       | Formulation | Aim of study | Model type | No of patients | Validation | Origin of patients                                      | Type of patients                                      |
|-------|------------|--------------|--------------|------------|----------------|------------|--------------------------------------------------------|--------------------------------------------------------|
| Mueck et al (2007) | 17595891 | po           | Descriptive  | POPPK/PD   | 43             | Internal   | Phase I study                                          | Healthy                                               |
| Mueck W et al (2008) | 18766262 | po           | Dose selection | POPPK/PD   | 758            | Internal   | Phase II studies                                       | Thromboprophylaxis                                   |
| Mueck W et al (2008) | 18307374 | po           | Descriptive  | POPPK/PD   | 1009           | Internal   | Phase II studies                                       | Thromboprophylaxis                                   |
| Mueck W et al (2011) | 21895039 | po           | Descriptive  | POPPK      | 870            | Internal   | Outpatients (post marketing studies)                  | VTE                                                   |
| Tanigawa T et al (2012) | 22813718 | po           | Dose selection | POPPK/PD   | 182            | Internal   | Phase II studies                                       | AF                                                    |
| Xu XS et al (2012) | 22242932 | po           | Descriptive  | POPPK/PD   | 2290           | Internal   | Phase III study                                        | ACS                                                   |
| Kaneko M et al (2013) | 23337693 | po           | Dose selection | POPPK/PD   | 597            | Internal   | Phase III study                                        | AF                                                    |
| Girgis IG et al (2014) | 24688660 | po           | Descriptive  | POPPK/PD   | 161            | Internal   | Phase III study                                        | AF                                                    |
| Barsam SJ et al (2017) | 30046886 | po           | Effect of body weight | POPPK    | 101            | Internal   | In and outpatients (post marketing studies)          | Thromboprophylaxis + VTE                             |
| Zhang et al (2017) | 28879020 | po           | Effect of food | POPPK      | 285            | Internal   | Phase II-III studies                                   | VTE + AF                                              |
| Suzuki S et al (2017) | 29773500 | po           | Descriptive  | POPPK/PD   | 96             | Internal   | Outpatients (post marketing studies)                  | AF                                                   |
| Willmann S et al (2018) | 29660785 | po           | Descriptive  | POPPK      | 4918           | Internal   | Phase II-III studies                                   | VTE + ACS + AF                                       |
| Willmann S et al (2018) | 30534008 | po           | Descriptive  | POPPK      | 59             | Internal   | Phase I study                                          | VTE                                                   |
| Wiesen MHJ et al (2018) | 29376194 | po           | Residual rivaroxaban exposure after discontinuation of anticoagulant therapy in patients undergoing cardiac catheterization | POPPK | 56             | Internal   | Inpatients (post marketing studies)                  | VTE + AF                                              |
| Zdovc J et al (2019) | 30725221 | po           | Pharmacogenomics | POPPK/PD   | 17             | Internal   | Inpatients (post marketing studies)                  | Thromboprophylaxis                                   |
| Speed V et al (2020) | 32511863 | po           | Effect of body weight | POPPK      | 913            | Internal   | Outpatients (post marketing studies)                  | AF + VTE                                              |

AF: atrial fibrillation, VTE: venous thrombo-embolism, ACS: acute coronary syndrome
Table S4. Apixaban: Summary of studies

| Study                  | PMID       | Formulation | Aim of study          | Model type | No of patients | Validation | Origin of patients               | Type of patients               |
|------------------------|------------|-------------|-----------------------|------------|---------------|------------|----------------------------------|-------------------------------|
| Leil TA et al (2014)   | 25229619   | po          | Exposure-response analysis | POPPK      | 5510          | Internal  | Phase I-II studies              | Thromboprophylaxis             |
| Byon W et al (2017)    | 28547774   | po          | Descriptive           | POPPK/PD   | 970           | Internal  | Phase I-II-III studies          | Healthy volunteers +VTE        |
| Ueshima S et al (2018) | 29457840   | po          | Pharmacogenomics      | POPPK      | 81            | Internal  | In and outpatients (post marketing studies) | AF                            |
| Cirincione B et al (2018) | 30259707 | po          | Descriptive           | POPPK      | 4385          | Internal  | Phase I-II-III studies          | Healthy volunteers +AF          |

AF: atrial fibrillation VTE: venous thrombo-embolism
Table S5. Edoxaban: Summary of studies

| Study            | PMID        | Formulation | Aim of study         | Model type | No of patients | Validation | Origin of patients                  | Type of patients |
|------------------|-------------|-------------|----------------------|------------|----------------|------------|-------------------------------------|-----------------|
| Salazar DE et al (2012) | 22398655    | po          | Exposure-response analysis | POPPK      | 1281           | Internal   | Phase I-II studies                   | Healthy volunteers +AF |
| Rohatagi S et al (2012) | 23014669    | po          | Exposure-response analysis | POPPK/PD    | 1753           | Internal   | Phase I-II studies                   | Healthy volunteers +AF + thrombophylaxis |
| Yin O et al (2014) | 25186833    | po or IV    | Descriptive          | POPPK      | 278            | Internal   | Phase I studies                      | Healthy volunteers |
| Yin O et al (2014) | 25168620    | po or IV    | Descriptive          | POPPK      | 1134           | Internal   | Phase I-II-III studies                | Healthy volunteers +AF |
| Song SH et al (2014) | 24706516    | po          | Exposure-response analysis | POPPK/PD    | 1624           | Internal   | Phase I-II studies                   | Healthy volunteers +AF |
| Niebecker R et al (2015) | 26218447    | po          | Descriptive          | POPPK      | 3707           | Internal   | Phase I-III studies                   | Healthy volunteers +VTE |
| Jönnson S et al (2015) | 25966665    | po          | Descriptive          | POPPK      | 32             | Internal   | Outpatients                          | Patients with varying degrees of kidney function |
| Krekels EH et al (2016) | 26951208    | po          | Descriptive          | POPPK      | 10432          | Internal   | Phase I-III studies                   | Healthy volunteers +AF |
| Shimizu T et al (2017) | 28032482    | po          | Descriptive          | POPPK      | 10522          | Internal and external | Phase I-III studies             | Healthy volunteers +AF |

VPE: venous pulmonary embolism, VTE: Venous thromboembolism, ACS: acute coronary syndrome, AF: Atrial fibrillation
Table S6. Dabigatran: demographic data

| Study                  | Sample/patient | Age (years) (mean±SD or median (range)) | Weight (kg) (mean±SD or median (range)) | Ethnicity (%) | Hepatic enzymes of function (mean±SD or median (range)) | Clearance Creatinine (ml/min) (Cockroft) (mean±SD or median (range)) | % Female |
|------------------------|----------------|----------------------------------------|----------------------------------------|---------------|----------------------------------------------------------|-------------------------------------------------------------------|----------|
| Trocóniz IF et al (2007) | 16.04          | 66.97 (35-88)                          | 78.21 (49-130)                         | -             | -                                                        | 76.16 (29.35-161.1)                                                | 53       |
| Liesenfeld KH et al (2011) | 2.91          | 72 (22-97)                             | 80.3 (32.7-222.3)                      | Diverse       | -                                                        | 68.6 (16.1-361.4)                                                  | 35       |
| Dansirikul et al (2012)  | 4.38           | 46 (18-69) (healthy) 68 (21-93) (AF+OS) | 60 (48-116) 80 (43-155)                | Predominantly Caucasian | -                                                        | 82.4 (16.0-132.4) (healthy) 87.1 (20.5-321.1) (AF + OS) | 52.5 (healthy) 49.9 (AF + OS) |
| Delavenne X et al (2013) | 11             | 22 (18-33)                             | 75 (64-82)                             | -             | -                                                        | -                                                                | -        |
| Liesenfeld KH et al (2013) | 44             | 38.3 (27-53)                           | 74.0 (60-87)                           | -             | -                                                        | -                                                                | -        |
| Ollier E et al (2015)     | 11             | 18-35                                  | 73.0 (60-83)                           | -             | -                                                        | -                                                                | -        |

AF=atrial fibrillation, OS=orthopedic surgery
Table S7. Rivaroxaban: demographic data

| Study                        | Sample/patient | Age (mean±SD or median (range)) | Weight (mean±SD or median (range)) | Ethnicity                  | Hepatic (mean±SD or median (range)) | Clearance Creatinine (ml/min) (Cockroft) (mean±SD or median (range)) | % Female |
|-----------------------------|----------------|-------------------------------|-----------------------------------|-----------------------------|-------------------------------------|----------------------------------------------------------------------|----------|
| Mueck et al (2007)          | 42.07          | 32.5 (20-45)                  | -                                 | Predominantly caucasian     | -                                   | -                                                                   | -        |
| Mueck W et al (2008)        | 7.58           | 66 (26–93)                    | 75 (45–120)                       | Predominantly caucasian     | -                                   | 88.1 (18.8–208)                                                      | -        |
| Mueck W et al (2008)        | 7.53           | 65 (25–87) (hip study) and 67 (39–92) (knee study) | 76 (45–125) (hip study) and 86 (50–173) (knee study) | Predominantly caucasian     | -                                   | 96 (33–218) (hip study) and 104 (35–259) (knee study)                            | -        |
| Mueck et al (2011)          | 5.33           | 61 (18–94)                    | 85 ± 17 (male) 73 ± 16 (female)    | -                           | -                                   | 87.4 ± 1.5                                                           | 44       |
| Tanigawa T et al (2012)     | 4.63           | 65.6 ± 10.0                   | 67.2 ± 10.4                       | Asian (Japanese)            | AST (IU/L): 28.6 ±10.7; ALT (IU/L): 26.2 ± 13.4 | 79.7 ± 25.2                                                           | 18.7     |
| Xu XS et al (2012)          | 4.93           | 57 (24–87)                    | 84 (36–181)                       | Predominantly caucasian     | -                                   | 96.6 (22.4–298)                                                      | 22       |
| Kaneko M et al (2013)       | 3.07           | 70.98 ± 8.31                  | 64.45 ± 10.65                     | Asian (Japanese)            | AST (IU/L): 27.26 ± 11.37; ALT (IU/L): 23.82 ± 12.85 | 67.41 ± 22.89                                                      | -        |
| Girgis IG et al (2014)      | 4.98           | 65 ± 9.5                      | 57.5 ± 9.9 (lean body weight)     | Predominantly caucasian     | -                                   | Creatinine = 1.09 ± 0.29 (mg/dl)                                      | -        |
| Barsam SJ et al (2017)      | 1.91           | 52 (20-86)                    | 88.0 ± 23.4                       | Diverse                    | -                                   | >80 mL/min 67%, 50-79 mL/min 25%, 30-49 mL/min 7.8%, <30 mL/min 0.2% | 42       |
| Zhang et al (2017)          | 5-8            | 59 (31, 83) (DVT data); 65 (51, 81) (AF data (5th and 95th percentiles) | Lean body weight : 54.1 (40.1, 72.7) (DVT data); 56.6 (42.5, 73.6) (AF data (5th and 95th percentiles) | Predominately caucasian     | -                                   | Baseline SCr (mg/dL) 0.94 (0.64, 1.28) (DVT data); 1.05 (0.74, 1.65) (AF data) (5th and 95th percentiles) | -        |
| Suzuki S et al (2017)       | 2              | 68.0 ± 9.5                    | 69.1±11.4                         | Asian (Japanese)            | AST (IU/L) 26.0±9.7; ALT, (IU/L) 21.7±9.8 | 76.2±21.3                                                            | 15.6     |
| Willmann S et al (2018)     | 4.64           | 60.53 (11.82)                 | 82.48 (16.87)                     | Predominately caucasian     | -                                   | 97.74 (33.97)                                                        | 39.3     |
| Willmann S et al (2018)     | 3.49           | 6.8 ± 4.9, 6.0 (0.5–17.0)     | 29.5 ± 18.3, 27.7 (6.2–77.8)      | Predominately caucasian     | -                                   | -                                                                   | 44       |
| Wiesen MHJ et al (2018)      | 1.70           | 66.8 ± 12.9                   | 81.7 ± 16.5                       | -                           | -                                   | 78.7 ± 29.0                                                          | 41.1     |
| Zdovc J et al (2019)        | 5              | 64 (49–82)                    | 84 (54–125)                       | Predominately caucasian     | -                                   | 82 (57–150) (ml/min/1.73 m2) (Calculated according to the MDRD-4 equation) | 52.94    |
| Speed V et al (2020)        | 1.21           | 67.03 ± 15                    | 87.75 ± 23.07                     | Diverse                    | -                                   | 86.73 ± 27.57                                                        | 42.8     |
### Table S8. Apixaban: demographic data

| Study | Sample/patient | Age (Median, range) | Weight (Median, range) | Ethnicity (%) | Hepatic U/L | Clearance Creatinine (ml/min) (Cockroft) | Female (%) |
|-------|----------------|---------------------|------------------------|---------------|-------------|------------------------------------------|------------|
| Leil TA et al (2014) | - | - | - | - | - | - | - |
| Byon W et al (2017) Phase I subjects | 22.67 | 33 (18–85) | 71.2 (37.7–175) | Diverse | - | 112.8 (15-318) | 33 |
| Byon W et al (2017) VTE treatment subjects | 3.14 | 61 (18–89) | 84 (46.9–210) | Predominently caucasian | - | 99.2 (25.3–322) | 39.7 |
| Ueshima S et al (2018) | 3 | 68.1 (40.5–84.9) | 65.0 (41.0–92.2) | Asian | ASAT 23 (13-97), ALAT 19 (5-115) Median, (range) | 69.8 (30.6-145.5) | 25 |
| Cirincione B et al (2018) | 2.73 | 68 (18–94) | 81.4 (32-198.2) | Predominently caucasian | - | 79.3 (11.9-319.7) | 29.76 |
### Table S9. Edoxaban: demographic data

| Study                     | Sample/patient | Age (years) (mean±SD or median (range)) | Weight (kg) (mean±SD or median (range)) | Ethnicity (%) | Hepatic (mean±SD or median (range))(IU/l) | Clearance Creatinine (ml/min) (Cockroft) (mean±SD or median (range)) | % Female |
|---------------------------|----------------|------------------------------------------|------------------------------------------|---------------|------------------------------------------|---------------------------------------------------------------------|----------|
| **Salazar DE et al** (2012) | 10.55          | -                                        | -                                        | -             | -                                        | -                                                                   | 35.70    |
| **Rohatagi S et al** (2012) | -              | 55 (18-88)                               | 76 (43-128)                              | Predominently caucasian | AST 20 (5-120) ALT 16 (3-156) | 81.1 (21.8-203.5)                                                   | 47.68    |
| **Yin O et al** (2014)     | 28.95          | 31.4 (18–51)                             | 76.9 (48.8–107.0)                        | Diverse       | -                                        | -                                                                   | 12       |
| **Yin O et al** (2014)     | 7.64           | 59.8 (18–105)                            | 81.8 (31.0–165.3)                       | Diverse       | -                                        | 88.98 (7.69–246.80)                                                 | 35.4     |
| **Song SH et al** (2014)   | 7.05           | 56.2 (18-88)                             | 77.6 (40.0-165.3)                       | Diverse       | -                                        | 91.5 (14.1-246.8)                                                   | 23.7     |
| **Niebecker R et al** (2015) | 4.21           | 32 (18–67)                              | 79 (50–111)                              | Diverse       | -                                        | 130 (14–247)                                                       | 20       |
| **Jönsson S et al** (2015) | 9.5            | 50.1 (30.0–64.0), 56.8 (38.0–65.0), 50.8 (30.8–67.0), 53.1 (41.0–63.0), 74.4 (58.9–89.4), 76.5 (60.3–91.0), 78.6 (58.0–90.0), 71.7 (56.0–95.0) | -                                      | -             | 94.6 (83.0–123.0), 64.7 (54.0–77.0), 42.0 (33.0–49.0) and 21.8 (14.0–27.0) | 33¹, 50², 37.5³, 62.5⁴ |
| **Krekels EH et al** (2016) | 2.59           | 71 (27–95)                              | 83 (32–231)                              | Predominently caucasian | -                                        | 73 (23–434)                                                        | 38       |
| **Shimizu T et al** (2017) | 4.35¹          | 81 (64-91)³, 69 (36-82)², 73 (63-79)⁶ | 54 (35-85)³, 68 (48-85)², 68 (50-90)⁶ | Asian (Japanese) | -                                        | 26.3 (17.8-29.9)³, 67.6 (50.3-141)², 62.5 (52.0-92.3)⁸ | 21⁵, 4⁶, 7⁷ |

¹ Normal kidney function ² Mild renal impairment ³ moderate renal impairment ⁴ severe renal impairment ⁵ for the severe renal impairment study ⁶ patients with Severe Renal Impairment (15mg edoxaban) ⁷ patients with Normal and Mild Renal Impairment (30mg edoxaban) ⁸ patients with Normal and Mild Renal Impairment (60mg edoxaban)
Table S10. Dabigatran: Population estimates for CL/F

| Study                | Model description                                      | CL/F estimate for a typical patient of the study (l/h) (RSE) | CL/F interindividual variability (%CV, RSE) | Intraindividual variability (%CV, RSE) if proportional; (ng/ml, RSE) if additive error |
|----------------------|---------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------|-----------------------------------------------------------------------------------|
| Trocóniz IF et al    | 2 compartments, first-order absorption with a linear elimination | 43.4 (0.27) (<24h) 82.1 (0.06) (>24h)                        | 108.6 (0.16)                                | 66.9 (0.03) proportional, <24h 0.375 (0.12) Additive, <24h 36.61 (0.05) proportional >24h |
| (2007)               |                                                         |                                                             |                                             |                                                                                  |
| Liesenfeld KH et al  | 2 compartments, first-order absorption with a linear elimination | 124 (0.70) (CL/F_{max})                                     | -                                           | 32.8 (1.02) proportional 6.68 (7.81) (additive)                                   |
| (2011)               |                                                         |                                                             |                                             |                                                                                  |
| Dansirikul et al     | 2 compartments, first-order absorption with a linear elimination | 107 (5.85) (healthy) 111 (2.13) (AF+OS)                     | -                                           | 18.4 (7.01) proportional 1.01 (25.5) (additive)                                   |
| (2012)               |                                                         |                                                             |                                             |                                                                                  |
| Delavenne X et al    | 2 compartments, first-order absorption with a linear elimination | 14.8 (7)                                                     | -                                           | 10.5 (11) (proportional) 4.65 (16) (additive)                                     |
| (2013)               |                                                         |                                                             |                                             |                                                                                  |
| Liesenfeld KH et al  | 2 compartments, first-order absorption with a linear elimination | 12.4 (28.71)                                                | 40.4 (43.01)                                | 8.5 (24.00) (proportional)                                                      |
| (2013)               |                                                         |                                                             |                                             |                                                                                  |
| Ollier E et al       | 1 compartment, first-order absorption with a linear elimination | 13.7 (10)                                                   | 0.156 (standard error) (32)                 | 10.5 (7) (proportional) 2.09 (11) (additive)                                     |
| (2015)               |                                                         |                                                             |                                             |                                                                                  |
### Table S11. Rivaroxaban: Population estimates for CL/F

| Study            | Model description                                      | CL/F estimate for a typical patient of the study (l/h) (RSE) | CL/F interindividual variability (%CV, RSE) | Intraindividual variability (%CV, RSE) if proportional; (ng/ml, RSE) if additive error |
|------------------|---------------------------------------------------------|---------------------------------------------------------------|------------------------------------------------|----------------------------------------------------------------------------------|
| Mueck et al (2007) | 2 compartments, first-order absorption with a linear elimination | 9.17 (3.1) | 17.4 (19.1) | 25.4 (8.2) (proportional) |
| Mueck W et al (2008) | 1 compartment first-order absorption with a linear elimination | 7.51 (4.1) | 38.2 (10) | 52.6 (3.0) (proportional) |
| Mueck W et al (2008) | 1 compartment first-order absorption with a linear elimination | 7.3 (4.0) | 38.6 (8.3) | 37.1 (4.0) (proportional) |
| Mueck et al (2011) | 1 compartment first-order absorption with a linear elimination | 5.67 (3.70) | 39.9 (7.60) | 40.7 (3.20) (proportional) |
| Tanigawa T et al (2012) | 1 compartment first-order absorption with a linear elimination | 4.72 (3.69) | 21.3 (27.66) | 40.2 (7.78) (proportional) |
| Xu XS et al (2012) | 1 compartment first-order absorption with a linear elimination | 6.48 (2.21) | 31.3 (4.72) | 0.35 (1.09) (additive) |
| Kaneko M et al (2013) | 1 compartment first-order absorption with a linear elimination | 4.73 (3.8) | 41 (16.6) | 13.1 (6.5) (proportional) |
| Girgis IG et al (2014) | 1 compartment first-order absorption with a linear elimination | 6.10 (3.9) | 35.2 (14.3) | 47.9 (6.2) (proportional) |
| Barsam SJ et al (2017) | 1 compartment first-order absorption with a linear elimination | 8.86 (7) | 48 (99) | 31 (215) (proportional); 0.016 (112) (additive error) |
| Zhang et al (2017) | 1 compartment first-order absorption with a linear elimination | 6.31 (4.01) | 34.6 (11.8) | 47.5 (5.22) (proportional) |
| Suzuki S et al (2017) | 1 compartment first-order absorption with a linear elimination | 4.40 (4.7%) (RSE/mean) | 20.6 (28.7) (RSE/mean) | - |
| Willmann S et al (2018) | 1 compartment first-order absorption with a linear elimination | 6.58 (2.33) | 26.2 (39.2) | 46.6 (14.1) (proportional) |
| Willmann S et al (2018) | 2 compartments, first-order absorption with a linear elimination | 7.26 (9.38) | 39.0 (2.96) | 20.3 (1.54) (proportional) |
| Wiesen MH-J et al (2018) | 2 compartments, first-order absorption with a linear elimination | 4.9 (-) | 27.0 (-) | - |
| Zdovc J et al (2019) | 1 compartment first-order absorption with a linear elimination | 6.12 (17.7) | 80.8 (15.4) | 59.5 (12.3) (proportional) |
| Speed V et al (2020) | 1 compartment first-order absorption with a linear elimination | 5.57 (5.34-5.82 95%CI) | 23.02 (37.9) | 46.37 (15.6) |
Table S12. Apixaban: Population estimates for CL/F

| Study                  | Model description                              | CL/F value (l/h) (RSE) | CL/F interindividual variability (%CV, RSE) | Intraindividual variability (%CV, RSE) |
|------------------------|------------------------------------------------|------------------------|---------------------------------------------|---------------------------------------|
| Leil TA et al (2014)   | 2 compartments, first-order absorption with a linear elimination | -                      | 14.1 (37.5)                                 | 34.1 (0.328-0.356 95%CI) (proportional) |
| Byon W et al (2017)    | 2 compartments, first-order absorption with a linear elimination | 4.35                   | 33.1                                        | Not reported                           |
| Ueshima S et al (2018) | 1 compartment first-order absorption with a linear elimination | 3.06                   | 26.6 (21.5)                                 | 34 (12.0) (proportional)               |
| Cirincione B et al (2018)| 2 compartments, first-order absorption with a linear elimination | 3.62                   |                                              | 31.00 ± 0.284 (± SE) (HV and Studies Japan NVAF phase II8, Japan ACS phase II); 66.7 ± 1.87 (± SE) (Study APPRAISE I); 45.7 ± 1.65 (± SE) (Study ARISTOTLE) (proportional) |
Table S13. Edoxaban: Population estimates for CL/F

| Study            | Model description                                                                 | CL/F estimate (l/h) (RSE) | CL/F interindividual variability (%CV, RSE) | Intraindividual variability (%CV, RSE) if proportional; (ng/ml, RSE) if additive error |
|------------------|------------------------------------------------------------------------------------|---------------------------|--------------------------------------------|---------------------------------------------------------------------------------------|
| Salazar DE et al 2012 | 2 compartments, first-order absorption (with delayed absorption) with a linear elimination | 36 (1.4)                  | 18.1 (12.8)                               |                                                                                       |
| Rohatagi S et al (2012) | 2 compartments, first-order absorption (with delayed absorption) with a linear elimination | 32.3 (1.2)                | 20.2 (12.0)                               | 11.3 (11.0) (phase I) 66.1 (6.0) phase IIa 97.4 (5.2) phase Iib, hip study (proportional) |
| Yin O et al 2014 | 2 compartments, first-order absorption (with delayed absorption) with a linear elimination | 22.6 (2.42)               | 9.42 (26.7)                               | 32.1 (4.30) (proportional)                                                             |
| Yin O et al 2014 | 2 compartments, first-order absorption (with delayed absorption) with a linear elimination | 11.4 (5.60)               | 10.1 (12.5)                               | 30.2 (3.99) (phase I) 79.5 (5.37) phase II (proportional) 50.3 (5.06) (phase III) (proportional) |
| Song SH et al 2014 | 2 compartments, first-order absorption (with delayed absorption) with a linear elimination | 32.1 (1.06)               | 29.1 (3.68)                               | 20.6 (0.563) for healthy volunteers study 37.3 (7.99) for PRT018 phase II study 33.9 (5.17) for the rest of studies (proportional) |
| Niebecker R et al 2015 | 2 compartments, first-order absorption (with delayed absorption) with a linear elimination | -                         | 14.9 (7.94)                               | 33.3 (3.95) (proportional)                                                             |
| Jönsson S et al 2015 | 2 compartments, first-order absorption (with delayed absorption) with a linear elimination | -                         | -                                         | -                                                                                      |
| Krekels EH et al 2016 | 2 compartments, first-order absorption (with delayed absorption) with a linear elimination | -                         | 13.6 (23.5)                               | 28.2 (7.62) (proportional)                                                             |
| Shimizu T et al 2017 | 2 compartments, first-order absorption (with delayed absorption) with a linear elimination | -                         | -                                         | -                                                                                      |

NE: not estimated
# Table S14. Dabigatran: Population estimates for pharmacokinetic parameters

| Study                      | Vc/F estimate (l) (RSE) | V/F interindividual variability (%CV, RSE) | Vp/F estimate (l) (RSE) | Q/F (l/h) (RSE) | F   | T lag (h) | ka (h−1) (RSE) | Interindividual variability Ka (%CV, RSE) |
|----------------------------|-------------------------|---------------------------------------------|-------------------------|----------------|-----|-----------|----------------|------------------------------------------|
| Trocóniz IF et al (2007)   | 30.8 (0.17)             | -                                           | 136 (0.42)              | 13.6 (0.35)    | -   | -         | 0.022 (<24h) 0.265 (>24h)                 | 29.83 (0.23) (>24h)                     |
| Liesenfeld KH et al (2011) | 673 (0.98)              | 20.5 (13.21)                                | 345 (fixed)             | 35.5 (fixed)   | 1.00 (fixed) | 0.634 (fixed) | 0.754 (fixed) | -                                       |
| Dansiriker et al (2012)    | 756 (6.73 (healthy) 726 (3.42) (AF+OS) | 25.2 (32.2)                                | 345 (7.83)              | 35.5 (12.3 (healthy) 35.5 (fixed) (AF+OS)) | 1.00 (fixed) | -         | 2.08 (20.0) healthy 0.754 (4.73) (AF+OS) | 105.4 (33.7)                            |
| Delavenne X et al (2013)   | 48.3 (12)               | 0.105 (standard error) (41)                 | 68.7 (6)                | 20.6 (8)       | 0.065 (fixed); 0.101 (1.4) in presence of clarithromycin | - | - | - | - |
| Liesenfeld KH et al (2013) | 531 (22.60)             | 14.3 (43.07)                                | 499 (9.42)              | 152 (14.34)    | 1.00 (fixed) | 1.67 (4.56) | 0.821 (16.81) | 64.0 (30.24)                           |
| Ollier E et al (2015)      | 69.5 (6)                | -                                           | -                       | -              | -   | 0.0565 (10) (normal absorption group) 0.0114 (6) (poor absorption group) | - | - | - | - |
### Table S15. Rivaroxaban: Population estimates for pharmacokinetic parameters

| Study                      | Vc/F value (l) (mean, RSE) | V/F interindividual variability (%CV, RSE) | Vp/F value (l) (mean, RSE) | Q/F (l/h) (mean, RSE) | ka (h⁻¹) | Interindividual variability Ka (%CV, RSE) |
|----------------------------|-----------------------------|--------------------------------|-----------------------------|------------------------|----------|----------------------------------------|
| Mueck et al (2007)         | <30mg 55.3 (4.3) 30mg 79.2 (9.4) Vc/F: 30.7 (27.6) Vp/F: 38.6 (38.2) | <30mg 12.6 (11.4) 30mg 23.5 (18.6) | 0.97 (15.2) | 52.9 (75.4) |
| Mueck W et al (2008)       | 58.2 (4.9) 32.4 (23.0) | - | 1.49 (10) | - |
| Mueck W et al (2008)       | 49.1 (4.3) 49.1 (4.3) | - | 1.81 (8.3) | - |
| Mueck et al (2011)         | 54.4 (3.80) 28.8 (11.4) | - | 1.23 (5.00) | - |
| Tanigawa T et al (2012)    | 42.9 (6.22) 24.4 (39.93%) | - | 0.6 (11.43%) 68 (35.21%) |
| Xu XS et al (2012)         | 57.9 (1.16) 10.0 (3.66) | - | 1.24 (3.28) 139 (0.30) |
| Kaneko M et al (2013)      | 43.8 (6.9) 63.6 (24.4%) | - | 0.617 (10.7%) 58.2 (40.7%) |
| Girgis IG et al (2014)     | 79.7 (6.1) 17.6 (61.5) | - | 1.16 (14.1) |
| Barsam SJ et al (2017)     | 101 (12) 60 (247) | - | 1.21 (34) |
| Zhang et al (2017)         | 7.16 (3.70) 15.5 (46.2) | - | 0.982 (14.0) |
| Suzuki S et al (2017)      | 38.2 (5.6%) (RSE/mean) 63.6 (fixed) | - | 1.37 (58.9%) (RSE/mean) 44.6 (24) (RSE/mean) |
| Willmann S et al (2018)    | 62.5 (2.04) | - | 0.821 (2.36) 39.7 (63.9) |
| Willmann S et al (2018)    | 50.9 (12) 16.7 (3.91) 13.5 (51.5) | - | 0.717 (21.3) a for tablet and diluted suspension 0.208 (15.4) for undiluted suspension 62.8 (5.39) |
| Wiesen MHJ et al (2018)     | 39.3 (-) | - | 0.97 (-) 1.24 (fixed) |
| Zdovc J et al (2019)       | 96.8 (9.70) | - | 0.147 (14.8) 794 (14.9) |
| Speed V et al (2020)       | 59.4 (54.6-64.2 95%CI) | - | 0.707 (0.552-0.862 95%CI) | - |
### Table S16. Apixaban: Population estimates for pharmacokinetic parameters

| Study                  | Vc/F value (l) (RSE) | Vp/F value (l) (RSE) | V/F interindividual variability (%CV) mean (%CV, RSE) | Q/F (l/h) (RSE) | ka (h⁻¹) (RSE) | Interindividual variability Ka (%CV, RSE) |
|------------------------|----------------------|----------------------|---------------------------------------------------|----------------|----------------|-----------------------------------------|
| Leil TA et al (2014)   | 22.9 (18.8-26.5 95%CI) | 22.2 (19.8-25.3 95%CI) | 6.35 (25.2) | 2.60 (2.27-2.94 95%CI) | 0.188 (0.161-0.215 95%CI) | 28.3 (53.2) |
| Byon W et al (2017)    | 32.1±1.16(±SE)    | 19.8±1.3(±SE)         | 23.5     | 1.62 (0.125)       | 0.44 ± 0.0209 (±SE)   | 50.2 |
| Total subjects         |                      |                      |          |                           |                           |                               |
| Ueshima S et al (2018) | 24.7 (15.8-33.6) (95%CI) ±4.54 (±SE) | 56.6 (35.0) | 17 | 1.92 (0.020) | 0.471±0.0218 (±SE) | 51.4 |
| Cirincione B et al (2018) | 30±1.04 (±SE)    | 27.3±2.78 (±SE)       | 17 |                             |                           |                               |
**Table S17. Edoxaban: Population estimates for pharmacokinetic parameters**

| Study                  | Vc/F estimate (l) (RSE) | Vp/F estimate (l) (RSE) | Vc/F interindividual variability (%CV, RSE) | Q/F (L/h) (RSE) | tlag (h) | ka (h−1) (RSE) | Interindividual variability KA (%CV, RSE) |
|------------------------|-------------------------|-------------------------|---------------------------------------------|-----------------|----------|----------------|-----------------------------------------|
| Salazar DE et al (2012)| 244 (2.2)               | 90.3 (3.6)              | 31.0 (10.0)                                 | 6.42 (4.0)      | 0.421 (2.1)| 5.87 (19.1)   | 127.7 (17.2)                             |
| Rohatagi S et al (2012)| 243 (2.2)               | 116 (10.0)              | 12.2 (8.3)                                  | 5.86 (3.1)      | 0.425 (2.5)| 7.21 (47.9)  | 2.787 (10.4)                             |
| Yin O et al (2014)     | 142 (4.31) oral 78.7 (5.64) IV | 55.1 (3.94)             | 34.9 (9.71)                                 | 5.18 (6.93)     | 0.233 (NE) | 1.89 (4.13)  | 72.8 (7.05)                              |
| Yin O et al (2014)     | 151 (3.63) oral 82.2 (3.65) IV | 42.9 (4.59)             | 18.6 (8.83)                                 | 2.73 (5.64)     | 0.250 (NE) | 1.08 (9.35)  | 79.4 (6.77)                              |
| Song SH et al (2014)   | 214 (1.87)               | 134 (4.53)              | 36.1 (4.97)                                 | 8.85 (5.29)     | 0.391 (0.108)| 3.54 (5.96)  | 102 (11.3)                               |
| Niebecker R et al (2015)| 209 (1.21)               | 92.3 (2.43)             | 23.2 (NE)                                   | 5.92 (2.49)     | 0.250 fixed (NE) | 3.35 (4.15) | -                                        |
| Jönsson S et al (2015) | 95.4 (11.6)              | 54.3 (16.3)             | -                                           | 5.19 (13.1)     | -        | -              | -                                        |
| Krekels EH et al (2016) | 194 (1.14)               | 88.6 (4.04)             | 21.5 (not estimated)                        | 5.75 (4.66)     | 0.250 fixed (NE) | 2.16 (5.24) | 794 (14.9)                             |
| Shimizu T et al (2017) | -                       | -                        | -                                           | -               | -        | -              | -                                        |
Table S18. Dabigatran: Significant covariates on CL/F

| Study                  | CLcr | Serum creatinine | Age | Weight | Other                                                                 |
|------------------------|------|------------------|-----|--------|-----------------------------------------------------------------------|
| Troconiz IF et al      | ↑    | -                | -   | -      | ↑ with gastrin concentration                                          |
| (2007)                 |      |                  |     |        |                                                                       |
| Liesenfeld KH et al    | ↑    | -                | ↓   | -      | ↓ in female patients                                                   |
| (2011)                 |      |                  |     |        | ↓ in patients with heart failure of class II, III, or IV              |
| Dansirikul et al       | ↑    | -                | ↓   | -      | ↓ in female patients                                                   |
| (2012)                 |      |                  |     |        | ↓ in female patients                                                   |
| Delavenne X et al      | -    | -                | -   | -      |                                                                       |
| (2013)                 |      |                  |     |        |                                                                       |
| Liesenfeld KH et al    | -    | -                | -   | -      |                                                                       |
| (2013)                 |      |                  |     |        |                                                                       |
| Ollier E et al         | -    | -                | -   | -      |                                                                       |
| (2015)                 |      |                  |     |        |                                                                       |

CrCL: creatinine clearance (Cockcroft-Gault) AF=atrial fibrillation, OS=orthopedic surgery
Nb: effect if the covariates increase compared to median
Table S19. Rivaroxaban : Significant covariates on CL/F

| Study                  | CLcr | Serum creatinine | Age | Weight | Other |
|------------------------|------|------------------|-----|--------|-------|
| Mueck et al (2007)     | -    | -                | -   | -      | -     |
| Mueck W et al (2008)   | ↑    | -                | ↓   | -      | -     |
|                       | Study day : ↑ at steady state compared to first post-operative day |       |
|                       | ↑ with ↑ serum albumin concentration |       |
|                       | ↑ with ↑ hematocrit |       |
| Mueck W et al (2008)   | ↑ (knee study) | ↓ (hip study) | ↓ (hip study) | - | - |
|                       | ↑ with ↑ hematocrit (only after surgery) (knee study) |       |
|                       | ↓ If Female vs male (knee study) |       |
| Mueck et al (2011)     | -    | ↓                | ↓   | -      | -     |
| Tanigawa T et al (2012)| -    | -                | -   | -      | -     |
|                       | ↓ if blood urea nitrogen ↑ |       |
| Xu XS et al (2012)     | -    | ↓                | ↓   | -      | -     |
| Kaneko M et al (2013)  | ↑    | -                | -   | -      | -     |
|                       | ↑ with ↑ hematocrit |       |
| Girgis IG et al (2014) | -    | ↓                | ↓   | -      | -     |
| Suzuki S et al (2017)  | ↑    | -                | -   | -      | -     |
|                       | ↓ if Mild CYP3A4/5 or Pgp inhibitors |       |
|                       | ↓ with ↑ ALT |       |
| Barsam SJ et al (2017) | ↑    | -                | -   | -      | -     |
| Zhang et al (2017)     | -    | ↓                | ↓   | -      | -     |
|                       | no effect of food time (evening and morning) |       |
| Willmann S et al (2018)| ↑    | -                | -   | ↓      | -     |
|                       | ↑ if CYP3A4 inducers |       |
|                       | ↓ if weak-moderate CYP3A4 inhibitors |       |
|                       | ↑ if VPE vs VTE |       |
|                       | ↓ if AF vs VTE |       |
|                       | ↑ ACS vs VTE |       |
| Willmann S et al (2018)| -    | -                | -   | -      | -     |
| Wiesen MHJ et al (2018)| ↑    | -                | -   | -      | -     |
| Zdovc J et al (2019)   | -    | -                | -   | -      | -     |
|                       | ↓ if Low ABCB1 expression |       |
|                       | ↑ if high ABCB1 expression. |       |
| Speed V et al (2020)   | ↑    | -                | -   | -      | -     |

Nb: effect if the covariates increase compared to median
VPE : venous pulmonary embolism, VTE : Venous thromboembolism, ACS : acute coronary syndrome, AF : Atrial fibrillation
# Table S20. Apixaban: Significant covariates on CL/F

| Study                   | CLcr | Serum creatinine | Age | Weight | Other                                                                 |
|-------------------------|------|-----------------|-----|--------|----------------------------------------------------------------------|
| Leil TA et al (2014)    | -    | -               | -   | -      | ↓ if surgery <4d vs ≥4d                                               |
| Byon W et al (2017)     | -    | -               | -   | -      | ↓ if Asian vs non-Asian    ↓ if strong or moderate CYP3A4/P-gp inhibitors vs no inhibitors For CL\(_{\text{NR}}\)/F: ↓ if female |
| Total subjects          | -    | -               | -   | -      | ↓ if surgery <4d vs ≥4d                                               |
| Ueshima S et al (2018)  | ↑    | -               | -   | -      | ↑ if CYP3A5*1/*1 vs CYP3A5*1/*3 or *3/*3 genotype ↑ if ABCG2 421C/C or C/A genotype vs ABCG2 421A/A genotype |
| Cirincione B et al (2018)| ↑   | -               | -   | -      | ↓ if strong or moderate CYP3A4/P- gp inhibitors vs no inhibitors ↓ if Asian, Korean, and other Asian ethnicities vs non-Asian ↓ if male ↓ if healthy vs ACS patients ↓ if AF vs healthy patients For CL\(_{\text{NR}}\)/F: ↓ if female |

Nb: effect if the covariates increase compared to median
AF = atrial fibrillation
Table S21. Edoxaban: Significant covariates on CL/F

| Study                  | CLcr     | Serum             | Age     | Weight | Other                                                                 |
|------------------------|----------|-------------------|---------|--------|----------------------------------------------------------------------|
| Salazar DE et al (2012)| ↑        | -                 | -       | -      | ↓ if P-gp inhibitors (including quinidine, ketoconazole, erythromycin and amiodarone) |
| Rohatagi S et al (2014)| ↑        | -                 | -       | -      | -                                                                      |
| Yin O et al 2014       |          | -                 | -       | -      | ↓ if female                                                          |
| Yin O et al 2014       | ↑        | -                 | -       | -      | For CL/Fₚk: ↓ if P-gp inhibitors (including quinidine, ketoconazole, erythromycin, verapamil, and amiodarone) (IV only) For CL/Fₚk: ↑ age and ↓ with weight |
| Song SH et al (2014)   | NP       | NP                | NP      | NP     | NP                                                                      |
| Niebecker R et al (2015)| -       | -                 | -       | -      | ↓ if Pgp inhibitors (only for phase 1 studies)                         |
| Jönsson S et al (2015) | ↑        | -                 | -       | -      | For CL/Fₚk: ↑ in Asian race ↓ in AF patients                          |
| Krekels EH et al (2016)| -        | -                 | -       | -      | For CL/Fₚk: ↓ in AF patients vs healthy volunteers                     |
| Shimizu T et al (2017) |          | -                 | -       | -      | -                                                                      |

Nb: effect if the covariates increase compared to median
NP: not pursued
### Table S22. Dabigatran: Significant covariates on $V_\text{C/F}$

| Study                        | Age | Weight | Other                                      |
|------------------------------|-----|--------|--------------------------------------------|
| Trocóniz IF et al (2007)     | -   | -      | -                                          |
| Liesenfeld KH et al (2011)   | -   | ↑      | ↑ with hemoglobin concentration             |
| Dansirikul et al (2012)      | -   | ↑      | -                                          |
| Delavenne X et al (2013)     | -   | -      | -                                          |
| Liesenfeld KH et al (2013)   | -   | -      | -                                          |
| Ollier E et al (2015)        | -   | -      | -                                          |

*Note: effect if the covariates increase compared to median*
### Table S23. Rivaroxaban: Significant covariates on $V_c/F$

| Study                  | Age | Weight                        | Other                        |
|------------------------|-----|-------------------------------|------------------------------|
| Mueck et al (2007)     | -   | -                            | -                            |
| Mueck W et al (2008)   | -   | ↑ (body surface area)         | -                            |
| Mueck W et al (2008)   | -   | ↑ (Lean body mass)            | (hip study)                  |
|                        |     | ↑ (body surface area)         |                              |
| Mueck et al (2011)     | ↓   | ↑                             | ↓ If Female                  |
| Tanigawa T et al (2012)| -   | -                            | -                            |
| Xu XS et al (2012)     | ↓   | ↑ (Lean body mass)            | -                            |
| Kaneko M et al (2013)  | -   | -                            | -                            |
| Girgis IG et al (2014) | ↓   | ↑ (Lean body mass)            | -                            |
| Zhang et al (2017)     | ↓   | ↑ (Lean body mass)            | -                            |
| Barsam SJ et al (2017) | -   | -                            | -                            |
| Suzuki S et al (2017)  | -   | -                            | -                            |
| Willmann S et al (2018)| ↓   | ↑                             | ↓ If Female                  |
| Willmann S et al (2018)| -   | -                            | -                            |
| Wiesen MHJ et al (2018) | -   | -                            | -                            |
| Zdovc J et al (2019)   | -   | -                            | -                            |
| Speed V et al (2020)   | -   | ↑ (Lean body mass)            | -                            |

Nb: effect if the covariates increase compared to median
### Table S24. Apixaban: Significant covariates on Vc/F

| Study                        | Age | Weight | Other                      |
|------------------------------|-----|--------|----------------------------|
| Leil TA et al (2014)         | -   | ↑      | ↑ if hematocrit ↑          |
| Byon W et al (2017)          | -   | ↑      |                            |
| Total subjects               | -   | -      | -                          |
| Ueshima S et al (2018)       | -   | -      | -                          |
| Cirincione B et al (2018)    | -   | ↑      | -                          |

Nb: effect if the covariates increase compared to median
### Table S25. Edoxaban: Significant covariates on Vc/F

| Study                        | Age | Weight | Other                                                                 |
|------------------------------|-----|--------|----------------------------------------------------------------------|
| Salazar DE et al (2012)      | -   | ↑      | ↓ if AF patients                                                     |
| Rohatagi S et al (2012)      | -   | -      |                                                                      |
| Yin O et al (2014)           | -   | -      |                                                                      |
| Yin O et al (2014)           | -   | -      | ↓ if P-gp inhibitors (including quinidine, ketoconazole, erythromycin, verapamil, and amiodarone) (both IV and po) |
| Song SH et al (2014)         | NP  | NP     |                                                                      |
| Niebecker R et al (2015)     | -   | -      | ↑ in Asian race                                                      |
| Jönsson S et al (2015)       | -   | -      |                                                                      |
| Krekels EH et al (2016)      | -   | -      | ↑ in Asian race                                                      |
| Shimizu T et al (2017)       | -   | -      |                                                                      |

Nb: effect if the covariates increase compared to median  
NP: not pursued
Table S26. Apixaban: Significant covariates on CL$_{B/F}$

| Study                  | CLcr | Serum creatinine | Age | Weight | Other  |
|------------------------|------|------------------|-----|--------|--------|
| Leil TA et al (2014)   | ↑    | -                | -   | -      | -      |
| Byon W et al (2017)    | ↑    | -                | -   | -      | -      |
| Total subjects         |      |                  |     |        |        |
| Ueshima S et al (2018) | -    | -                | -   | -      | -      |
| Cirincione B et al (2018) | -  | -                | -   | -      | -      |

Nb: effect if the covariates increase compared to median
Table S27. Apixaban: Significant covariates on CL_{NR/F}

| Study                        | CLcr | Serum creatinine | Age | Weight | Other                                      |
|------------------------------|------|------------------|-----|--------|--------------------------------------------|
| Leil TA et al (2014)         | -    | ↓                | -   | -      | ↓ if female; ↓ dose (>25mg/d); ↓ if surgery <4d vs ≥4d |
| Byon W et al (2017) Total subjects | -    | -                | ↓   | -      | ↓ if female                                |
| Ueshima S et al (2018)       | -    | -                | -   | -      |                                            |
| Cirincione B et al (2018)    | -    | -                | -   | -      | ↓ if female                                |

Nb: effect if the covariates increase compared to median
Table S28. Edoxaban: Significant covariates on CL\(_R/F\)

| Study                     | CLcr | Serum creatinine | Age | Weight | Other |
|---------------------------|------|------------------|-----|--------|-------|
| Salazar DE et al (2012)   | -    | -                | -   | -      | -     |
| Rohatagi S et al (2012)   | -    | -                | -   | -      | -     |
| Yin O et al (2014)        | -    | -                | -   | -      | -     |
| Yin O et al (2014)        | -    | -                | -   | -      | ↓ if P-gp inhibitors (including quinidine, ketoconazole, erythromycin, verapamil, and amiodarone) (IV only) |
| Song SH et al (2014)      | NP   | NP               | NP  | NP     | NP    |
| Niebecker R et al (2015)  | ↑    | -                | -   | -      | -     |
| Jönsson S et al (2015)    | -    | -                | -   | -      | -     |
| Krekels EH et al (2016)   | ↑    | -                | -   | -      | ↑ in Asian race |
| Shimizu T et al (2017)    | -    | -                | -   | -      | ↓ in AF patients |

Nb: effect if the covariates increase compared to median
AF: atrial fibrillation
NP: not pursued
**Table S29. Edoxaban : Significant covariates on CL<sub>NR/F</sub>**

| Study                  | CLcr | Serum creatinine | Age | Weight | Other |
|------------------------|------|------------------|-----|--------|-------|
| Salazar DE et al (2012) | -    | -                | -   | -      | -     |
| Rohatagi S et al (2012) | -    | -                | -   | -      | -     |
| Yin O et al (2014)     | -    | -                | ↓   | ↑      | -     |
| Yin O et al (2014)     | NP   | NP               | NP  | NP     | NP    |
| Song SH et al (2014)   | NP   | NP               | NP  | NP     | NP    |
| Niebecker R et al (2015)| -    | -                | -   | -      | -     |
| Jönsson S et al (2015) | -    | -                | -   | -      | -     |
| Krekels EH et al (2016) | -    | -                | -   | -      | ↓ in AF patients |
| Shimizu T et al (2017) | -    | -                | -   | -      | -     |

Nb: effect if the covariates increase compared to median
NP : not pursued
Table S30. Dabigatran: Significant covariates on F

| Study                     | Age | Weight | Other                                                                 |
|---------------------------|-----|--------|-----------------------------------------------------------------------|
| Trocóniz IF et al (2007)  | -   | -      | -                                                                     |
| Liesenfeld KH et al (2011)| -   | -      | ↑ with verapamil, amiodarone, ↓ with coadministration of pump proton inhibitor |
| Dansirikul et al (2012)   | -   | -      | -                                                                     |
| Delavenne X et al (2013)  | -   | -      | -                                                                     |
| Liesenfeld KH et al (2013)| -   | -      | -                                                                     |
| Ollier E et al (2015)     | -   | -      | -                                                                     |

Nb: effect if the covariates increase compared to median
**Table S31. Dabigatran: Significant covariates on Ka**

| Study                              | Age | Weight | Other                                      |
|------------------------------------|-----|--------|--------------------------------------------|
| Trocóniz IF et al (2007)           | ↓   | -      | ↓ Serum creatinine                          |
| Liesenfeld KH et al (2011)         | -   | -      |                                            |
| Dansirikul et al (2012)            | -   |        | ↑ with P-gp inhibitor                      |
|                                    |     |        | ↓ with proton pump inhibitors               |
| Delavenne X et al (2013)           | -   | -      |                                            |
| Liesenfeld KH et al (2013)         | -   | -      |                                            |
| Ollier E et al (2015)              | -   | -      |                                            |

**Nb:** effect if the covariates increase compared to median
Table S32. Apixaban: Significant covariates on Ka

| Study                         | Administration in the evening vs administration in the morning or afternoon |
|-------------------------------|------------------------------------------------------------------------------|
| Leil TA et al (2014)          | -                                                                            |
| Byon W et al (2017)           | ↓                                                                            |
| Total subjects                |                                                                              |
| Ueshima S et al (2018)        | -                                                                            |
| Cirincione B et al (2018)     | ↓                                                                            |

Nb: effect if the covariates increase compared to median
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Table S33. Edoxaban Significant covariates on Ka

| Study                     | Age | Weight | Other                                    |
|---------------------------|-----|--------|------------------------------------------|
| Salazar DE et al (2012)   | -   | -      |                                          |
| Rohatagi S et al (2012)   | -   | -      | ↓ with food 6h prior to surgery vs 12h   |
| Yin O et al (2014)        | -   | -      |                                          |
| Yin O et al (2014)        | -   | -      |                                          |
| Song SH et al (2014)      | -   | -      |                                          |
| Niebecker R et al (2015)  | -   | -      |                                          |
| Jönsson S et al (2015)    | -   | -      |                                          |
| Krekels EH et al (2016)   | -   | -      |                                          |
| Shimizu T et al (2017)    | -   | -      |                                          |

Nb: effect if the covariates increase compared to median
NP: not pursued
Table S34. Quality of the models used for simulations: Dabigatran.

| Models                  | Phases of clinical trials | Population size | Blood sample/patients | POPPK results | Relevant covariates tested | Internal validation | External validation |
|-------------------------|---------------------------|-----------------|-----------------------|---------------|---------------------------|---------------------|---------------------|
| Trocóniz IF et al (2007)| No                        |                 |                       |               |                           |                     | No                  |
| Liesenfeld KH et al (2011)| No                    |                 |                       |               |                           |                     | No                  |
| Dansirikul et al (2012)  | Yes                      |                 |                       |               |                           |                     | Yes                 |

Legends. High, medium, weak classification defined in table S1
## Table S35. Quality of the models used for simulations: Rivaroxaban

| Models                    | Phases of clinical trials | Population size | Blood sample size | POPPK results | Relevant covariates | Internal validation | External validation |
|---------------------------|---------------------------|-----------------|-------------------|----------------|--------------------|---------------------|---------------------|
| Barsam SJ et al (2017)    |                           |                 |                   |                |                    | No                  | No                  |
| Willmann S et al (2018)   |                           |                 |                   |                |                    | Yes                 |                     |
| Kaneko M et al (2013)     |                           |                 |                   |                |                    | No                  |                     |
| Xu XS et al (2012)        |                           |                 |                   |                |                    | No                  |                     |
| Suzuki S et al (2017)     |                           |                 |                   |                |                    | No                  |                     |
| Speed V et al (2020)      |                           |                 |                   |                |                    | No                  |                     |

**Legends.** High, medium, weak classification defined in table S1
### Table S36. Quality of the models used for simulations: Apixaban

| Models                  | Phases of clinical trials | Population size | Blood sample size | POPPK results | Relevant covariates | Internal validation | External validation |
|-------------------------|---------------------------|-----------------|-------------------|---------------|--------------------|---------------------|---------------------|
| Ueshima S et al (2018)  | High                      | Medium          | Low               | High          | Yes                | Yes                 | No                  |
| Leil TA et al (2014)    | High                      | Medium          | Not available     | High          | Yes                | Yes                 | No                  |

**Legends.** **High**, **medium**, **weak** classification defined in table S1
Table S37. Quality of the models used for simulations: Edoxaban

| Models                  | Phases of clinical trials | Population size | Blood sample size | POPPK results | Relevant covariates | Internal validation | External validation |
|-------------------------|---------------------------|-----------------|-------------------|---------------|--------------------|---------------------|---------------------|
| Krekels EH et al (2016) | No                        | Yes             | No                | No            | No                 | Yes                 | No                  |
| Niebecker R et al (2015)| No                        | Yes             | No                | No            | No                 | No                  | No                  |
| Yin O et al (2014)      | No                        | Yes             | No                | No            | No                 | No                  | No                  |
| Salazar DE et al (2012) | No                        | Yes             | No                | No            | No                 | No                  | No                  |
| Rohatagi S et al (2012) | No                        | Yes             | No                | No            | No                 | No                  | No                  |

Legends. High, medium, weak classification defined in table S1
Table S38. Mean increases in AUC detailed for each model and different covariates: dabigatran

| Study                  | Simulation conditions                  | drug dose | n= | AUC normalized to a typical patient mean [95% Confidence Interval] |
|------------------------|---------------------------------------|-----------|----|-----------------------------------------------------------------|
| Liesenfeld KH et al (2011) | CLCr [50-130] ml/min, Age=70           | 150 mg BID | 1000 | 1.31 [1.15 – 1.47]                                               |
|                        | CLCr [50-130] ml/min, Age=80           | 110mg BID | 1000 | 1.09 [0.88 – 1.30]                                               |
|                        | CLCr [30-49] ml/min, Age=70            | 110mg BID | 1000 | 1.60 [1.39 – 1.81]                                               |
|                        | CLCr [30-49] ml/min, Age=80            | 110mg BID | 1000 | 1.67 [1.45 – 1.89]                                               |
|                        | CLCr [15-29] ml/min, Age=70            | 110mg BID | 1000 | 2.77 [2.16 – 3.37]                                               |
|                        | CLCr [15-29] ml/min, Age=80            | 110mg BID | 1000 | 2.88 [2.25 – 3.51]                                               |
|                        | CLCr [15-29] ml/min, Age=70 (US recommendation) | 75mg BID | 1000 | 1.89 [1.47 – 2.30]                                               |
|                        | CLCr [15-29] ml/min, Age=80 (US recommendation) | 75mg BID | 1000 | 1.97 [1.53 – 2.39]                                               |
| Trocóniz IF et al (2007) | Post-surgery thrombophylaxis patient, >24h, Gastrine=69.16 pmol/L, CLCr [50-130] ml/min | 220mg OD | 1000 | 1.21 [0.46 – 1.96]                                               |
|                        | Post-surgery thrombophylaxis patient, >24h, Gastrine=69.16 pmol/L, CLCr [30-49] ml/min | 220mg OD | 1000 | 1.46 [0.58 – 2.34]                                               |
|                        | Post-surgery thrombophylaxis patient, >24h, Gastrine=69.16 pmol/L, CLCr [15-29] ml/min | 220mg OD | 1000 | 2.77 [1.56 – 3.98]                                               |
|                          | Post-surgery thrombophylaxis patient, >24h, Gastrine=34.58 pmol/L, CLCr [50-130] ml/min | 220mg OD | 1000 | 3.08 [1.79 – 4.37] |
|-------------------------|-----------------------------------------------------------------------------------------------|----------|------|---------------------|
|                         | Post-surgery thrombophylaxis patient, >24h, Gastrine=34.58 pmol/L, CLCr [30-49] ml/min       | 220mg OD | 1000 | 4.41 [2.94 – 5.88]  |
|                         | Post-surgery thrombophylaxis patient, >24h, Gastrine=34.58 pmol/L, CLCr [15-29] ml/min       | 220mg OD | 1000 | 6.00 [4.25 – 7.76]  |

|                          | AF patients, CLCr [50-130] ml/min, aged [80-100] year, P-gp inhibitor=0                      | 110mg BID | 1000 | 1.34 [1.016 – 1.67] |
|-------------------------|-----------------------------------------------------------------------------------------------|----------|------|---------------------|
|                         | AF patients, CLCr [50-130] ml/min, aged [80-100] year, P-gp inhibitor=1                      | 110mg BID | 1000 | 1.54 [1.17 – 1.92]  |
|                         | AF patients, CLCr [50-130] ml/min, aged [40-79] years, P-gp inhibitor=0                      | 150mg BID | 1000 | 1.48 [1.10 – 1.86]  |
|                         | AF patients, CLCr [50-130] ml/min, aged [40-79] years, P-gp inhibitor=1                      | 150mg BID | 1000 | 1.70 [1.26 – 2.14]  |
|                         | AF patients, CLCr [30-49] ml/min, aged [80-100] year, P-gp inhibitor=0                      | 110mg BID | 1000 | 1.80 [1.51 – 2.08]  |
|                         | AF patients, CLCr [30-49] ml/min, aged [80-100] year, P-gp inhibitor=1                      | 110mg BID | 1000 | 2.07 [1.74 – 2.39]  |
|                         | AF patients, CLCr [30-49] ml/min, aged [40-79] years, P-gp inhibitor=0                      | 110mg BID | 1000 | 2.20 [1.93 – 2.48]  |
|                         | AF patients, CLCr [30-49] ml/min, aged [40-79] years, P-gp inhibitor=1                      | 110mg BID | 1000 | 2.53 [2.22 – 2.85]  |
|                         | AF patients, CLCr [15-29] ml/min, aged [80-100] year, P-gp inhibitor=0                      | 110mg BID | 1000 | 2.34 [1.98 – 2.71]  |
|                         | AF patients, CLCr [15-29] ml/min, aged [80-100] year, P-gp inhibitor=1                      | 110mg BID | 1000 | 2.70 [2.27 – 3.12]  |
|                         | AF patients, CLCr [15-29] ml/min, aged [40-79] years, P-gp inhibitor=0                      | 110mg BID | 1000 | 2.89 [2.53 – 3.24]  |
Table S39. Mean increases in AUC detailed for each model and different covariates: rivaroxaban

| Study                  | Simulation conditions          | n=  | drug dose | AUC normalized to a typical patient mean [95% Confidence Interval] |
|------------------------|-------------------------------|-----|-----------|---------------------------------------------------------------|
| Barsam SJ et al (2017) | VTE patient, CLCr [50-130] ml/min | 1000| 20mg OD   | 1.12 [0.22 – 2.022]                                          |
|                        | VTE patient, CLCr [30-49] ml/min | 1000| 20mg OD   | 1.63 [0.66 – 2.60]                                          |
|                        | VTE patient, CLCr [15-29] ml/min | 1000| 15mg OD   | 1.56 [0.33 – 2.79]                                          |
| Willmann S et al (2018)| AF patient, CLCr [50-130] ml/min, Without co-medication | 1000| 20mg OD   | 1.17 [0.59 – 1.75]                                          |
|                        | AF patient, CLCr [50-130] ml/min, Moderate CYP3A4 inhibitor=1 | 1000| 20mg OD   | 1.23 [0.63 – 1.83]                                          |
|                        | AF patient, CLCr [50-130] ml/min, Strong CYP3A4 inhibitor=1 | 1000| 20mg OD   | 1.26 [0.64 – 1.87]                                          |
|                        | AF patient, CLCr [50-130] ml/min, Strong CYP3A4 inhibitor=1, P-gp inhibitor=1 | 1000| 20mg OD   | 1.33 [0.71 – 1.93]                                          |
|                        | AF patient, CLCr [30-49] ml/min, Without co-medication | 1000| 15mg OD   | 1.25 [0.66 – 1.86]                                          |
|                        | AF patient, CLCr [30-49] ml/min, Without co-medication | 1000| 20mg OD   | 1.42 [0.73 – 2.11]                                          |
|                        | AF patient, CLCr [30-49] ml/min, P-gp inhibitor=1 | 1000| 15mg OD   | 1.26 [0.86 – 2.42]                                          |
|                        | AF patient, CLCr [30-49] ml/min, P-gp inhibitor=1 | 1000| 20mg OD   | 1.64 [0.65 – 1.86]                                          |
| Condition | Dosage | Peak Concentration |
|-----------|--------|--------------------|
| AF patient, CLCr [30-49] ml/min, Moderate CYP3A4 inhibitor=1 | 1000 | 15 mg OD | 1.44 [0.77 – 2.12] |
| AF patient, CLCr [30-49] ml/min, Moderate CYP3A4 inhibitor=1 | 1000 | 20 mg OD | 1.73 [0.93 – 2.53] |
| AF patient, CLCr [30-49] ml/min, Strong CYP3A4 inhibitor=1 | 1000 | 15 mg OD | 1.27 [0.65 – 1.88] |
| AF patient, CLCr [30-49] ml/min, Strong CYP3A4 inhibitor=1 | 1000 | 20 mg OD | 1.92 [1.03 – 2.80] |
| AF patient, CLCr [30-49] ml/min, Strong CYP3A4 inhibitor=1, P-gp inhibitor=1 | 1000 | 15 mg OD | 1.32 [0.65 – 1.98] |
| AF patient, CLCr [30-49] ml/min, Strong CYP3A4 inhibitor=1, P-gp inhibitor=1 | 1000 | 20 mg OD | 2.01 [1.03 – 2.99] |
| AF patient, CLCr [15-29] ml/min, Without co-medication | 1000 | 15 mg OD | 1.58 [0.81 – 2.35] |
| AF patient, CLCr [15-29] ml/min, P-gp inhibitor=1 | 1000 | 15 mg OD | 1.61 [0.87 – 2.38] |
| AF patient, CLCr [15-29] ml/min, Moderate CYP3A4 inhibitor=1 | 1000 | 15 mg OD | 1.85 [1.01 – 2.69] |
| AF patient, CLCr [15-29] ml/min, Strong CYP3A4 inhibitor=1 | 1000 | 15 mg OD | 1.89 [1.23 – 2.54] |
| AF patient, CLCr [15-29] ml/min, Strong CYP3A4 inhibitor=1, P-gp inhibitor=1 | 1000 | 15 mg OD | 1.97 [1.21 – 2.73] |
| CLCr [50-130] ml/min | 1000 | 20 mg OD | 0.90 [0.46 – 1.36] |
| CLCr [30-49] ml/min | 1000 | 20 mg OD | 1.45 [0.70 – 2.14] |
| CLCr [30-49] ml/min | 1000 | 15 mg OD | 1.07 [0.53 – 1.61] |
| CLCr [15-29] ml/min | 1000 | 15 mg OD | 1.61 [0.81 – 2.43] |
| Patient Status | Fluid Body Weight (kg) | Partial Thromboplastin Time (s) | Initial DOAC Dose (mg) | Initial DOAC U. C. (mg/mL) |
|----------------|------------------------|---------------------------------|------------------------|---------------------------|
| Without DVT patient | SC=1.3 mg/dL | 1000 | 20mg OD | 1.06 [0.65 – 1.47] |
| Without DVT patient | BW=80 kg, SC=1.9 mg/dL | 1000 | 20mg OD | 1.17 [0.70 – 1.59] |
| Without DVT patient | BW=90 kg, SC=3.2 mg/dL | 1000 | 15 mg OD | 1.14 [0.69 – 1.84] |
| AF patient | CLCr [50-130] ml/min, ALT=25 U/L (normal level), P-gp inhibitor=0 | 1000 | 20mg OD | 1.01 [0.69 – 1.71] |
| AF patient | CLCr [50-130] ml/min, ALT=25 U/L (normal level), P-gp inhibitor=1 | 1000 | 20mg OD | 1.51 [1.06 – 1.87] |
| AF patient | CLCr [50-130] ml/min, ALT= 125 U/L (high level, 5x), P-gp inhibitor=0 | 1000 | 20mg OD | 1.49 [1.05 – 2.54] |
| AF patient | CLCr [50-130] ml/min, ALT= 125 U/L (high level, 5x), P-gp inhibitor=1 | 1000 | 20mg OD | 2.16 [1.50 – 3.65] |
| AF patient | CLCr [50-130] ml/min, ALT= 250 U/L (high level, 10x), P-gp inhibitor=0 | 1000 | 20mg OD | 1.90 [1.01 – 2.91] |
| AF patient | CLCr [50-130] ml/min, ALT= 250 U/L (high level, 10x), P-gp inhibitor=1 | 1000 | 20mg OD | 2.67 [1.23 – 3.90] |
| AF patient | CLCr [30-49] ml/min, ALT=25 U/L (normal level), P-gp inhibitor=0 | 1000 | 20mg OD | 1.33 [0.95 – 2.28] |
| AF patient | CLCr [30-49] ml/min, ALT=25 U/L (normal level), P-gp inhibitor=1 | 1000 | 20mg OD | 1.45 [1.04 – 2.49] |
| AF patient | CLCr [30-49] ml/min, ALT=125 U/L (high level, 5x), P-gp inhibitor=0 | 1000 | 20mg OD | 1.90 [1.32 – 3.22] |
| AF patient | CLCr [30-49] ml/min, ALT=125 U/L (high level, 5x), P-gp inhibitor=1 | 1000 | 20mg OD | 2.16 [1.50 – 3.65] |
| AF patient, CLCr [30-49] ml/min, ALT= 125 U/L (high level, 5x), P-gp inhibitor=1 | 1000 | 20mg OD | 2.78 [1.94 – 4.72] |
| AF patient, CLCr [30-49] ml/min, ALT= 125 U/L (high level, 5x), P-gp inhibitor=1 | 1000 | 15mg OD | 2.10 [1.50 – 3.60] |
| AF patient, CLCr [30-49] ml/min, ALT= 250 U/L (high level, 10x), P-gp inhibitor=0 | 1000 | 20mg OD | 2.24 [1.55 – 3.79] |
| AF patient, CLCr [30-49] ml/min, ALT= 250 U/L (high level, 10x), P-gp inhibitor=0 | 1000 | 15mg OD | 1.68 [1.18 – 2.85] |
| AF patient, CLCr [30-49] ml/min, ALT= 250 U/L (high level, 10x), P-gp inhibitor=1 | 1000 | 20mg OD | 3.24 [2.32 – 5.56] |
| AF patient, CLCr [30-49] ml/min, ALT= 250 U/L (high level, 10x), P-gp inhibitor=1 | 1000 | 15mg OD | 2.45 [1.74 – 4.20] |
| AF patient, CLCr [15-29] ml/min, ALT=25 U/L (normal level), P-gp inhibitor=0 | 1000 | 15mg OD | 1.64 [1.16 – 2.80] |
| AF patient, CLCr [15-29] ml/min, ALT=25 U/L (normal level), P-gp inhibitor=1 | 1000 | 15mg OD | 2.38 [1.70 – 4.08] |
| AF patient, CLCr [15-29] ml/min, ALT= 125 U/L (high level, 5x), P-gp inhibitor=0 | 1000 | 15mg OD | 2.34 [1.62 – 3.95] |
| AF patient, CLCr [15-29] ml/min, ALT= 125 U/L (high level, 5x), P-gp inhibitor=1 | 1000 | 15mg OD | 3.35 [2.43 – 5.78] |
| AF patient, CLCr [15-29] ml/min, ALT= 250 U/L (high level, 10x), P-gp inhibitor=0 | 1000 | 15mg OD | 2.73 [1.94 – 4.67] |
| AF patient, CLCr [15-29] ml/min, ALT= 250 U/L (high level, 10x), P-gp inhibitor=1 | 1000 | 15mg OD | 4.02 [2.82 – 6.85] |
| AF/VTE patients, CLCrLBW [50-130] ml/min | 1000 | 20mg OD | 1.06 [0.69 – 1.43] |
| AF/VTE patients, CLCrLBW [50-130] ml/min | 1000 | 15mg OD | 1.15 [0.69 – 1.43] |
| AF/VTE patients, CLCrLBW [30-49] ml/min | 1000 | 20mg OD | 1.53 [1.12 – 1.96] |
**Table S40. Mean increases in AUC detailed for each model and different covariates: apixaban**

| Study | Simulation conditions | n= | drug dose | AUC normalized to a typical patient mean [95% Confidence Interval] |
|-------|-----------------------|----|-----------|---------------------------------------------------------------|
| Ueshima S et al 2018 | CLCr [50-130] ml/min, CYP3A5=0, ABCG2 421A/A = 0 | 1000 | 5mg BID | 1.18 [0.74 – 1.63] |
| | CLCr [50-130] ml/min, CYP3A5=1, ABCG2 421A/A = 0 | 1000 | 5mg BID | 1.36 [0.80 – 1.91] |
| | CLCr [50-130] ml/min, CYP3A5=0, ABCG2 421A/A = 1 | 1000 | 5mg BID | 1.30 [0.80 – 1.81] |
| | CLCr [50-130] ml/min, CYP3A5=1, ABCG2 421A/A = 1 | 1000 | 5mg BID | 1.57 [0.91 – 2.07] |
| | CLCr [30-49] ml/min, CYP3A5=0, ABCG2 421A/A = 0 | 1000 | 5mg BID | 1.36 [0.85 – 1.87] |
| | CLCr [30-49] ml/min, CYP3A5=1, ABCG2 421A/A = 0 | 1000 | 5mg BID | 1.99 [1.24 – 2.75] |
| | CLCr [30-49] ml/min, CYP3A5=0, ABCG2 421A/A = 1 | 1000 | 5mg BID | 1.94 [1.17 – 2.71] |
| | CLCr [30-49] ml/min, CYP3A5=1, ABCG2 421A/A = 1 | 1000 | 5mg BID | 2.56 [1.52 – 3.61] |
| | CLCr [30-49] ml/min, CYP3A5=0, ABCG2 421A/A = 0 | 1000 | 2.5mg BID | 0.68 [0.42 – 1.12] |
| | CLCr [30-49] ml/min, CYP3A5=1, ABCG2 421A/A = 0 | 1000 | 2.5mg BID | 1.00 [0.62 – 1.44] |
| CLCr [30-49] ml/min, CYP3A5=0, ABCG2 421A/A = 1 | 1000 | 2.5mg BID | 0.97 [0.58 – 1.36] |
| CLCr [30-49] ml/min, CYP3A5=1, ABCG2 421A/A = 1 | 1000 | 2.5mg BID | 1.28 [0.76 – 1.80] |
| CLCr [15-29] ml/min, CYP3A5=0, ABCG2 421A/A = 0 | 1000 | 2.5mg BID | 0.91 [0.55 – 1.35] |
| CLCr [15-29] ml/min, CYP3A5=1, ABCG2 421A/A = 0 | 1000 | 2.5mg BID | 1.33 [0.81 – 1.77] |
| CLCr [15-29] ml/min, CYP3A5=0, ABCG2 421A/A = 1 | 1000 | 2.5mg BID | 1.25 [0.77 – 1.72] |
| CLCr [15-29] ml/min, CYP3A5=1, ABCG2 421A/A = 1 | 1000 | 2.5mg BID | 1.79 [1.10 – 2.48] |

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| Orthopedic surgery patient (>4 days), Age=60, CLCr [50-130] ml/min | 1000 | 2.5mg BID | 1.10 [0.44 – 1.77] |
| Orthopedic surgery patient (>4 days), Age=70, CLCr [50-130] ml/min | 1000 | 2.5mg BID | 1.12 [0.45 – 1.69] |
| Orthopedic surgery patient (>4 days), Age=80, CLCr [50-130] ml/min | 1000 | 2.5mg BID | 1.14 [0.46 – 1.70] |
| Orthopedic surgery patient (>4 days), Age=90, CLCr [50-130] ml/min | 1000 | 2.5mg BID | 1.16 [0.49 – 1.72] |
| Orthopedic surgery patient (>4 days), Age=60, CLCr [30-49] ml/min | 1000 | 2.5mg BID | 1.58 [0.71 – 2.25] |
| Orthopedic surgery patient (>4 days), Age=70, CLCr [30-49] ml/min | 1000 | 2.5mg BID | 1.59 [0.73 – 2.28] |
| Orthopedic surgery patient (>4 days), Age=80, CLCr [30-49] ml/min | 1000 | 2.5mg BID | 1.63 [0.69 – 2.37] |
| Orthopedic surgery patient (>4 days), Age=90, CLCr [30-49] ml/min | 1000 | 2.5mg BID | 1.69 [0.75 – 2.43] |
| Orthopedic surgery patient (>4 days), Age=60, CLCr [15-29] ml/min | 1000 | 2.5mg BID | 1.67 [0.75 – 2.38] |
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| Study | Simulation conditions | n= | drug dose | AUC normalized to a typical patient mean [95% Confidence Interval] |
|-------|-----------------------|----|-----------|---------------------------------------------------------------|
| KrekeH et al 2016 NVAF patient. CLCr [50-130] ml/min. P-gp Inhibitor=0<br>NVAF patient. CLCr [50-130] ml/min. P-gp Inhibitor=1<br>NVAF patient. CLCr [30-49] ml/min. P-gp Inhibitor=0<br>NVAF patient. CLCr [30-49] ml/min. P-gp Inhibitor=1<br>NVAF patient. CLCr [30-49] ml/min. P-gp Inhibitor=0<br>NVAF patient. CLCr [30-49] ml/min. P-gp Inhibitor=1<br>NVAF patient. CLCr [15-29] ml/min. P-gp Inhibitor=0<br>NVAF patient. CLCr [15-29] ml/min. P-gp Inhibitor=1 | 1000 | 60mg OD | 1.20 [0.88 – 1.53]<br>0.68 [0.51 – 0.85]<br>1.75 [0.70 – 2.80]<br>1.91 [0.92 – 2.90]<br>0.88 [0.70 – 1.10]<br>0.95 [0.85 – 1.05]<br>1.13 [0.88 – 1.37]<br>1.33 [0.98 – 1.68] |

If patients had the CYP3A51/3 or 3/3 genotype, then the dichotomous parameter CYP3A5=1, otherwise it was set to 0. If patients had the ABCG2 421A/A genotype, then the dichotomous parameter ABCG2=1, otherwise it was set to 0. CLCr: creatinine clearance calculated using the Cockcroft-Gault equation.

Table S41. Mean increases in AUC detailed for each model and different covariates: edoxaban
| Niebecker R et al 2015 | CLCr [50-130] ml/min. BW [60-120] kg. P-gp Inhibitor=0 | 1000 | 60mg OD | 1.03 [0.74 – 1.32] |
| --- | --- | --- | --- | --- |
| | CLCr [50-130] ml/min. BW [40-59] kg. P-gp Inhibitor=0 | 1000 | 60mg OD | 1.24 [0.33 – 2.16] |
| | CLCr [50-130] ml/min. BW [60-120] kg. P-gp Inhibitor=1 | 1000 | 30mg OD | 0.68 [0.40 – 0.94] |
| | CLCr [50-130] ml/min. BW [40-59] kg. P-gp Inhibitor=1 | 1000 | 30mg OD | 0.73 [0.45 – 1.01] |
| | CLCr [50-130] ml/min. BW [60-120] kg. P-gp Inhibitor=1 | 1000 | 30mg OD | 0.80 [0.49 – 1.10] |
| | CLCr [30-49] ml/min. BW [60-120] kg. P-gp Inhibitor=0 | 1000 | 60mg OD | 1.49 [0.52 – 4.27] |
| | CLCr [30-49] ml/min. BW [60-120] kg. P-gp Inhibitor=1 | 1000 | 60mg OD | 1.68 [0.58 – 2.78] |
| | CLCr [30-49] ml/min. BW [40-59] kg. P-gp Inhibitor=1 | 1000 | 60mg OD | 1.86 [0.72 - 3.00] |
| | CLCr [30-49] ml/min. BW [40-59] kg. P-gp Inhibitor=0 | 1000 | 60mg OD | 2.04 [0.80 – 3.27] |
| | CLCr [30-49] ml/min. BW [60-120] kg. P-gp Inhibitor=0 | 1000 | 30mg OD | 0.80 [0.52 – 1.09] |
| | CLCr [30-49] ml/min. BW [60-120] kg. P-gp Inhibitor=1 | 1000 | 30mg OD | 0.89 [0.58 – 1.19] |
| | CLCr [30-49] ml/min. BW [40-59] kg. P-gp Inhibitor=0 | 1000 | 30mg OD | 0.94 [0.72 – 1.15] |
| | CLCr [30-49] ml/min. BW [40-59] kg. P-gp Inhibitor=1 | 1000 | 30mg OD | 1.04 [0.80 – 1.28] |
| | CLCr [15-29] ml/min. BW [60-120] kg. P-gp Inhibitor=0 | 1000 | 30mg OD | 0.91 [0.60 – 1.21] |
| | CLCr [15-29] ml/min. BW [60-120] kg. P-gp Inhibitor=1 | 1000 | 30mg OD | 1.00 [0.67 – 1.32] |
| Study | CLCr [ml/min] | BW [kg] | P-gp Inhibitor | Dose [mg] | ATC [mg] |
|-------|--------------|---------|----------------|-----------|---------|
| Terrier J, Gaspard F et al | CLCr [15-29] ml/min, BW [40-59] kg, P-gp Inhibitor=0 | 1000 | 30 mg OD | 1.14 [0.86 – 1.41] |
| | CLCr [15-29] ml/min, BW [40-59] kg, P-gp Inhibitor=1 | 1000 | 30 mg OD | 1.27 [0.96 – 1.58] |
| Yin O et al 2014 | CLCr [50-130] ml/min, BW [60-120] kg, Amiodarone=0 | 1000 | 60 mg OD | 1.06 [0.82 – 1.30] |
| | CLCr [50-130] ml/min, BW [40-59] kg, Amiodarone=0 | 1000 | 60 mg OD | 1.25 [0.95 – 1.54] |
| | CLCr [50-130] ml/min, BW [40-59] kg, Amiodarone=0 | 1000 | 30 mg OD | 0.82 [0.49 – 1.06] |
| | CLCr [50-130] ml/min, BW [60-120] kg, Amiodarone=1 | 1000 | 60 mg OD | 1.36 [1.06 – 1.66] |
| | CLCr [50-130] ml/min, BW [40-59] kg, Amiodarone=1 | 1000 | 30 mg OD | 0.92 [0.64 – 1.20] |
| | CLCr [30-49] ml/min, BW [60-120] kg, Amiodarone=0 | 1000 | 60 mg OD | 1.51 [0.53 – 2.49] |
| | CLCr [30-49] ml/min, BW [60-120] kg, Amiodarone=1 | 1000 | 60 mg OD | 1.77 [0.69 – 2.85] |
| | CLCr [30-49] ml/min, BW [40-59] kg, Amiodarone=0 | 1000 | 60 mg OD | 2.01 [0.46 – 2.38] |
| | CLCr [30-49] ml/min, BW [40-59] kg, Amiodarone=1 | 1000 | 60 mg OD | 2.19 [0.91 – 3.47] |
| | CLCr [30-49] ml/min, BW [60-120] kg, Amiodarone=0 | 1000 | 30 mg OD | 0.76 [0.54 – 0.98] |
| | CLCr [30-49] ml/min, BW [60-120] kg, Amiodarone=1 | 1000 | 30 mg OD | 0.88 [0.69 – 1.06] |
| | CLCr [30-49] ml/min, BW [40-59] kg, Amiodarone=0 | 1000 | 30 mg OD | 0.90 [0.46 – 1.34] |
| | CLCr [30-49] ml/min, BW [40-59] kg, Amiodarone=1 | 1000 | 30 mg OD | 1.09 [0.91 – 1.28] |
| Condition | CLCr [15-29] ml/min. | BW [60-120] kg. | Amiodarone | Dose | AUC | Range |
|-----------|----------------------|----------------|-------------|------|-----|-------|
| Control   | 1000                 | 30mg OD        | 0           | 0.73 | [0.59 – 0.88] |
| Control   | 1000                 | 30mg OD        | 1           | 0.96 | [0.79 – 1.13] |
| Control   | 1000                 | 30mg OD        | 0           | 0.95 | [0.76 – 1.14] |
| Control   | 1000                 | 30mg OD        | 1           | 1.25 | [1.02 – 1.47] |

**Salazar DE et al 2012**

| Condition | CLCr [50-130] ml/min. | P-gp Inhibitor | Dose | AUC | Range |
|-----------|----------------------|----------------|------|-----|-------|
| Control   | 1000                 | 60mg OD        | 0.97 | [0.71 – 1.24] |
| Control   | 1000                 | 30mg OD        | 0.79 | [0.60 – 0.98] |
| Control   | 1000                 | 30mg OD        | 0.95 | [0.71 – 1.19] |
| Control   | 1000                 | 60mg OD        | 1.40 | [1.14 – 1.66] |

| Condition | CLCr [30-49] ml/min. | P-gp Inhibitor | Dose | AUC | Range |
|-----------|----------------------|----------------|------|-----|-------|
| Control   | 1000                 | 60mg OD        | 2.01 | [1.68 – 2.34] |
| Control   | 1000                 | 60mg OD        | 2.22 | [1.83 – 2.62] |
| Control   | 1000                 | 30mg OD        | 0.72 | [0.56 – 0.88] |
| Control   | 1000                 | 30mg OD        | 1.01 | [0.77 – 1.24] |
| Control   | 1000                 | 30mg OD        | 1.11 | [0.82 – 1.41] |
| Control   | 1000                 | 30mg OD        | 0.92 | [0.57 – 1.26] |
| Control   | 1000                 | 30mg OD        | 1.20 | [0.91 – 1.50] |
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| NVAF patient. CLCr [15-29] ml/min. P-gp Inhibitor=1 (Ketoconazole) | 1000 | 30mg OD | 1.40 [1.05 – 1.75] |
|---|---|---|---|
| CLCr [50-130] ml/min | 1000 | 60mg OD | 1.11 [0.77 – 1.46] |
| CLCr [30-49] ml/min | 1000 | 60mg OD | 1.47 [1.05 – 1.76] |
| CLCr [30-49] ml/min | 1000 | 30mg OD | 0.73 [0.53 – 0.96] |
| CLCr [15-29] ml/min | 1000 | 30mg OD | 0.90 [0.65 – 1.15] |

CLCr: creatinine clearance calculated using the Cockcroft–Gault equation. NVAF: nonvalvular atrial fibrillation. AF: atrial fibrillation. VTE: venous thromboembolism. Pgp: P-glycoprotein

Data S1: Equations for CL/F simulations for dabigatran

Trocóniz IF et al (2007) 17322149

\[
\frac{CL}{F_{c24h}} = \left(1 + \theta_{AGE} \cdot \left[\frac{AGE}{72} - 1\right]\right) \cdot \theta_{GAST1} \cdot \theta_{GAST2} \cdot \theta_{GAST3}
\]

\[
\frac{CL}{F_{s24h}} = \left(1 + \theta_{AGE} \cdot \left[\frac{AGE}{72} - 1\right]\right) \cdot \theta_{GAST1} \cdot \theta_{GAST2} \cdot \theta_{GAST3}
\]

\[
\theta_{CL(<24h)} = 43.4 \text{ mL/min} ; \theta_{GAST1} = 0.633 \text{ pmol/L} ; \theta_{CL(>24h)} = 82.1 \text{ mL/min} ; \theta_{GAST2} = 0.294 \text{ pmol/L}
\]

Liesenfeld KH et al (2011) PMID 21972820

\[
\frac{CL}{F} = \theta_{CL_{max}} \cdot CRCL \cdot \theta_{POWERCL}/(\theta_{EC50DCCL} \cdot \theta_{POWERCL} + CRCL) \cdot \theta_{AGE} \cdot \theta_{SEX} \cdot \theta_{ET} \cdot \theta_{H1}
\]

\[
\theta_{CL_{max}} = 12.4 \text{ L/h} ; \theta_{POWERCL} = 1.29 ; \theta_{EC50DCCL} = 56.7 \text{ mL/min} ; \theta_{AGE} = -0.41 \% / \text{ year} ; \theta_{ET} = 0.797 ; \theta_{H1} = 0.933 ; \theta_{SEX} = 0.917
\]

Dansirikul et al (2012) PMID 22398858

\[
\frac{CL}{F} = \theta_{CL} \cdot \left(1 + \theta_{AGE} \cdot \left[\frac{AGE}{68} - 1\right]\right) \cdot \theta_{ET} \cdot \theta_{SEX} \cdot \theta_{FEMALE}
\]

If \( CL/F < 120 \text{ mL/min} \):

\[
\frac{CL}{F} = \theta_{CL} \cdot \left(1 + \theta_{CL_{CR}} \cdot \left[CLCR - 120\right]\right) \cdot \left(1 + \theta_{AGE} \cdot \left[AGE - 68\right]\right) \cdot \theta_{ET} \cdot \theta_{SEX} \cdot \theta_{FEMALE}
\]
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\[ F = \theta_f \cdot \theta_{PP} \cdot \theta_{PP}\]

\[ \theta_{CL} = 111 \ (l/hr) ; \ \theta_{AGE} = -0.00662 ; \ \theta_{AF} = 0.939 ; \ \theta_{FEMALE} = 0.875 ; \ \theta_{F} = 1 ; \ \theta_{PP} = 1.150 ; \ \theta_{PP} = 0.854 \]

\((15-29, 30-49, 50-130 \) ml/min), Age <80 ou > 80, Pgp inhibitor or not, 110mg od or bid, 150mg od or bid

Data S2: Equations for CL/F simulations for rivaroxaban

Barsam SJ et al (2017) PMID 30046688

\[ CL = CL_{POP} \cdot \left( \frac{CrCL}{79} \right)^{0.434} \]

\[ CL_{POP} = 8.86 \ (L/h) \]

Willmann S et al (2018) PMID 29660785

\[ \frac{CL/F}{CL/F} = \frac{CL_{TV}/F \cdot \left( CrCL \right)^{0.434}}{\left( \frac{CrCL}{79} \right)^{0.434}} \cdot \theta_{CO\text{MED}} \cdot \theta_{STUDY} \]

\[ \theta_{CO\text{MED}} = \begin{cases} 1 & \text{if no co-medication} \\ \theta_{CL/F,PGP} = 0.966 & \text{co-medication with PGP inhibitor} \\ \theta_{CL/F,Strong\_3A4\_inh} = 0.978 & \text{co-medication with strong CYP 3A4 inhibitor} \\ \theta_{CL/F,Medium\_3A4\_inh} = 0.863 & \text{co-medication with medium CYP 3A4 inhibitor} \\ \theta_{CL/F,Weak\_3A4\_inh} = 0.939 & \text{co-medication with weak CYP 3A4 inhibitor} \\ \theta_{CL/F,3A4\_ind} = 1.30 & \text{co-medication with CYP 3A4 inducer} \end{cases} \]

\[ \theta_{STUDY} = \begin{cases} 1 & \text{if DVT (Studies 11223 and 11528)} \\ \theta_{CL/F,AF} = 0.849 & \text{AF (Study 3001)} \\ \theta_{CL/F,ACS} = 1.14 & \text{ACS (Study 2001)} \\ \theta_{CL/F,VTE\_\leq72h} = 1.04 & \text{VTE (Studies 10933, 10945 and 11527), \leq72 h} \\ \theta_{CL/F,VTE\_>72h} = 1.29 & \text{VTE, >72 hr after first dose} \end{cases} \]

Kaneko M et al (2013) PMID 23337693

\[ CL/F = CL_{pop} \cdot \left( \frac{CrCL}{67.11} \right)^{0.159} \]
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\[
CL/F = CL_{pop} \cdot (1 - 0.0132 \cdot [HCT - 42.14])
\]

\[
CL_{pop}/F = 4.73 \text{ (L/h)}
\]

CrCL, creatinine clearance; HCT, hematocrit

Xu XS et al (2012) PMID 22242932

\[
CL/F = CL_{F_{pop}} \cdot (1 - 0.00112 \cdot [\text{Age} - 57] - 0.151 \cdot [\text{Scr} - 0.95])
\]

\[
CL_{F_{pop}}/F = 6.48 \text{ (L/h)}
\]

SCR, serum creatinine; LBM, lean body mass

Suzuki S et al (2017) PMID 29773500

\[
CL/F = 4.40 \cdot \left(\frac{\text{CrCL}}{75}\right)^{0.324} \cdot \left(\frac{\text{ALT}}{22}\right)^{-0.225} \cdot (1 - 0.319(\text{INH}))
\]

CrCL, creatinine clearance; ALT, alanine aminotransferase; INH: CYP3A4/5 or Pgp moderate inhibitors

Speed V et al (2020) PMID 32511863

\[
CL/F = CL_{F_{pop}} \cdot \left(\frac{\text{CrCL}_{LBW}}{55}\right)^{0.446}
\]

\[
CL_{F_{pop}}/F = 5.57 \text{ (L/h)}
\]

CrCL, creatinine clearance calculated using CG applying lean body weight to calculation

Data S3: Equations for CL/F simulations for apixaban

Ueshima S et al 2018 PMID 29457840

\[
CL/F = 1.53 \times \left(\frac{\text{CrCL}}{70}\right)^{0.7} + 0.312^{\text{CYP3A5}} \times 0.341^{\text{ABCG2}}
\]

If patients had the CYP3A5*1/*3 or *3/*3 genotype, then the dichotomous parameter CYP3A5 was equal to 1, otherwise it was set to 0. If patients had the ABCG2 421A/A genotype, then the dichotomous parameter ABCG2 was equal to 1, otherwise it was set to 0. CrCl: creatinine clearance calculated using the Cockcroft–Gault equation.

Leil TA et al (2014) PMID 25229619

\[
CL/F = 1.53 \times \left(\frac{\text{CrCL}}{70}\right)^{0.7} + 0.312^{\text{CYP3A5}} \times 0.341^{\text{ABCG2}}
\]
POPPK models for DOAC: a systematic review and clinical appraisal using exposure simulation

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\[
\frac{CL}{F} = \left[ \frac{CL_{R,MAX}/F \times cCrCL_{G1}}{cCrCL_{S0} + cCrCL_{G1}} + CL_{NR,REF}/F \times \left( \frac{Age}{Age_{REF}} \right)^{CL_{NR,Age}} \times e^{(CL_{Sex,Sex})} \times e^{(CL_{D0,Sw2})} \right] 
\]

where \( CL_{R,MAX}/F \) is typical value of \( CL_R \) for a male non-surgical subject receiving a total daily dose of apixaban that is not greater than 25 mg, \( CL_{MAX}/F \) is the maximum \( CL_R/F \), \( cCrCL_{S0} \) is the cCrCL value at 50% for an CLR/F that is half of \( CL_R/F \), and \( G1 \) is the shape parameter controlling the steepness of the \( CL_R/F - cCrCL \) relationship. \( CL_{Sex}, CL_{D0}, CL_{D4}, CL_{TDD} \) are the coefficients for the effects of sex, surgery and dose on \( CL_{NR}/F \).

Data S4: Equations for CL/F simulations for edoxaban

Krekels EH et al (2016) PMID 26951208

\[
CL/F = CL_{nr}/F + CL_r/F
\]

\( CL_{nr} \) is the value of \( CL_n \) for NVAF patients, \( CL_r \) is the value of \( CL_r \) for healthy volunteers

\[
Fraction (\theta_{2b}) \ of \ apparent \ non-renal \ clearance \ (CL_{nr}/F) \ for \ NVAF \ patients = 0.845
\]

\( CL_{nr}/F = slope_{2b} \cdot CLCr\)

\( \theta_{2b} = 0.196 \)

The fraction change in \( CL/F \) with concomitant inhibitor: Typical \( CL/F \) without \( Pg + Pp \) inhibitor = \( (1 + \theta_{17}) \)

Fractional change (1 + \( \theta_{17} \)) in total apparent clearance \( (CL/F) \) with coadministration of \( P + Pg \) inhibitors for healthy volunteers = 0.315

Typical \( CL/F \) with \( Pg + Pp \) inhibitor NVAF patients = \( CL/F \) without \( Pg + Pp \) inhibitor NVAF patients \( \times (1 + \theta_{18} \cdot \theta_{25}) \)

\( (1 + \theta_{18}) = fractional \ change \ in \ relative \ F \ with \ coadministration \ of \ Pgp \ inhibitors \ for \ healthy \ volunteers = 1.20 \)

\( \theta_{25} = fraction \ of \ change \ in \ relative \ F \ with \ concomitant \ P + Pg \ inhibitor \ for \ NVAF \ patient = 0.134 \)

CLCr, creatinine clearance; CL/F, apparent total clearance; CL/Fnr, apparent non renal clearance; CL/Fr, apparent renal clearance; NVAF, non-valvular atrial fibrillation

Niebecker R et al (2015) PMID 26218447

\[
CL/F = CL_{nr}/F + CL_r/F
\]

\( CL_{nr}/F = \theta_1 \cdot CLCr\)

\( \theta_1 = 0.199 \) (slope 1)
POPPK models for DOAC: a systematic review and clinical appraisal using exposure simulation

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\[
\frac{\text{CL}_{nr}/F}{\text{CL}_{nr, pop}} = \left(\frac{\text{WT}}{70}\right)^{3/4}
\]

*Only for phase 3:* Typical \( F_{\text{with PG-p inhibitor}} = \text{Typical } F_{\text{without PG-p inhibitor}} \times (1 + \theta_{F-gp}) 

\( P-gp \) inhibitors on \( F \) phase 3(%) = -11.5

\[
\text{CLCr}, \text{creatinine clearance}; \text{CL}/F, \text{apparent total clearance}; \text{CL/F}_{nr}, \text{apparent non renal clearance}; \text{CL/F}_{r}, \text{apparent renal clearance}; \text{WT}, \text{weight}
\]

\[
\frac{\text{CL}_{nr}/F}{\text{CL}_{nr, typ}} = \left(\frac{\text{WT}}{70}\right)^{3/4}
\]

Yin O et al (2014) PMID 25168620

\[
\text{CL} = 11.4 \times \left(\frac{\text{BW}^{1.320}}{81}\right)^{6.3} + 0.0822 \times \text{CLCr}
\]

\( F_1 = 0.583 \)

Amiodarone on \( F_1 = 0.300 \)

Verapamil on \( F_1 = 0.382 \)

Ketoconazole on \( F_1 = 0.57 \)

BW, body weight, CLCr, creatinine clearance, \( F_1 \), Bioavailability

Salazar DE et al (2012) PMID 22398655

\[
\frac{\text{CL} / F}{\text{CL}_{F, pop}} = \text{CL} / \text{CL}_{F, pop} \times \left(\frac{\text{CLCr}}{91}\right) \times e^{-(\text{Keto}0.18)} \times e^{-(\text{Ery}0.199)} \times e^{-(\text{Qnd}0.212)} \times e^{-(\text{Amin}0.436)}
\]

\( F_1 = 1 \times e^{(\text{Keto}0.792)} \times e^{(\text{Ery}0.781)} \times e^{(\text{Qnd}0.727)} \times e^{(\text{Amin}0.751)} 

\( \text{CL}/F_{pop} = 36 \text{ L/h} \)

CLCr, creatinine clearance, \( F_1 \), Bioavailability

Rohatagi S et al (2012) PMID 23014669

\[
\frac{\text{CL}/F}{\text{CL}_{F, pop}} = \text{CL}/\text{CL}_{F, pop} \times \left(\frac{\text{CLCr}}{81}\right)^{K_{\text{CL}/F-CLCr}}
\]

\( K_{\text{CL}/F-CLCr} = 0.350 \)
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