

## ORIGINAL RESEARCH ARTICLE

# Cardiovascular outcomes of non-vitamin K antagonist oral anticoagulants among patients with atrial fibrillation

## Supplementary File

**Table S1. Number of patients screened and reasons for exclusion**

| Reasons                                    | Dabigatran | Rivaroxaban | Apixaban |
|--------------------------------------------|------------|-------------|----------|
| Total screened                             | 1,293      | 667         | 460      |
| Rheumatic heart disease                    | 5          | 1           | 1        |
| Planned finite duration                    | 5          | 6           | 3        |
| Hypertrophic cardiomyopathy                | 8          | 2           | 0        |
| Indications other than atrial fibrillation | 42         | 90          | 15       |
| Not anticoagulant naive                    | 315        | 275         | 199      |
| Not taking the drug                        | 53         | 23          | 17       |
| Drug initiation before study start date    | 19         | N/A         | N/A      |
| Others / more than one reason              | 131        | 31          | 18       |

**Table S2. Dose distribution**

| Dose                          | Number of patients |
|-------------------------------|--------------------|
| Dabigatran 150 mg twice daily | 313                |
| Dabigatran 110 mg twice daily | 402                |
| Rivaroxaban 20 mg daily       | 200                |
| Rivaroxaban 15 mg daily       | 39                 |
| Apixaban 5 mg twice daily     | 113                |
| Apixaban 2.5 mg twice daily   | 94                 |

**Table S3. Baseline characteristics of the factor Xa inhibitors vs. dabigatran**

| Variables              | Before IPTW   |             |       | After IPTW    |             |       |
|------------------------|---------------|-------------|-------|---------------|-------------|-------|
|                        | FXa inhibitor | Dabigatran  | ASMD  | FXa inhibitor | Dabigatran  | ASMD  |
| <i>n</i>               | 446           | 715         | -     | 446           | 715         | -     |
| Age (years), mean ± SD | 72.7 ± 10.9   | 72.5 ± 10.0 | 0.018 | 72.6 ± 10.1   | 72.6 ± 10.1 | 0.004 |
| Sex (Male)             | 51.6          | 51.6        | 0.001 | 51.6          | 51.0        | 0.012 |
| Race (Chinese)         | 99.1          | 99.2        | 0.006 | 98.9          | 99.2        | 0.024 |
| History of MI          | 7.0           | 4.2         | 0.123 | 5.5           | 4.5         | 0.046 |
| History of CVA         | 34.8          | 30.2        | 0.097 | 33.4          | 31.3        | 0.044 |

(cont'd...)

Table S3. (Continued)

| Variables                                             | Before IPTW   |               |       | After IPTW    |               |       |
|-------------------------------------------------------|---------------|---------------|-------|---------------|---------------|-------|
|                                                       | FXa inhibitor | Dabigatran    | ASMD  | FXa inhibitor | Dabigatran    | ASMD  |
| History of PCI                                        | 8.1           | 4.8           | 0.139 | 6.4           | 5.4           | 0.041 |
| History of CABG                                       | 1.1           | 1.1           | 0.000 | 1.2           | 1.0           | 0.014 |
| DM                                                    | 30.0          | 32.3          | 0.049 | 30.3          | 31.5          | 0.027 |
| Hypertension                                          | 69.1          | 70.6          | 0.034 | 69.0          | 70.0          | 0.022 |
| CHF                                                   | 13.9          | 14.4          | 0.014 | 13.4          | 13.7          | 0.009 |
| PVD                                                   | 1.6           | 1.8           | 0.019 | 1.5           | 1.8           | 0.019 |
| Proteinuria                                           | 0.9           | 0.3           | 0.086 | 0.7           | 0.3           | 0.058 |
| Thyrotoxicosis                                        | 2.9           | 2.0           | 0.063 | 2.4           | 2.0           | 0.028 |
| Cirrhosis                                             | 0.7           | 0.3           | 0.060 | 0.6           | 0.3           | 0.054 |
| OSA                                                   | 3.4           | 2.7           | 0.042 | 2.8           | 2.7           | 0.007 |
| COPD                                                  | 2.2           | 3.4           | 0.066 | 2.7           | 3.1           | 0.022 |
| Depression                                            | 2.7           | 2.0           | 0.049 | 2.1           | 1.9           | 0.012 |
| Cancer                                                | 1.6           | 2.1           | 0.039 | 1.7           | 2.0           | 0.027 |
| Gout                                                  | 9.0           | 7.4           | 0.057 | 8.2           | 7.3           | 0.034 |
| Smoking                                               | 30.2          | 35.9          | 0.120 | 32.6          | 33.4          | 0.039 |
| Drinking                                              | 6.9           | 9.3           | 0.086 | 7.9           | 8.6           | 0.026 |
| Antiplatelet                                          | 21.7          | 16.1          | 0.147 | 18.4          | 17.1          | 0.035 |
| NSAID                                                 | 2.5           | 1.5           | 0.068 | 2.0           | 1.7           | 0.020 |
| ACEI/ARB                                              | 48.7          | 43.1          | 0.112 | 45.4          | 44.0          | 0.028 |
| Statin                                                | 64.1          | 59.6          | 0.093 | 62.1          | 60.6          | 0.031 |
| Beta-blocker                                          | 49.3          | 49.4          | 0.001 | 49.7          | 48.9          | 0.017 |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc, mean ± SD     | 3.62 ± 1.70   | 3.56 ± 1.61   | 0.039 | 3.58 ± 1.68   | 3.57 ± 1.6    | 0.009 |
| HAS-BLED, mean ± SD                                   | 2.18 ± 1.06   | 2.14 ± 0.98   | 0.045 | 2.15 ± 1.03   | 2.14 ± 0.99   | 0.013 |
| Baseline eGFR (mL/min/1.73m <sup>2</sup> ), mean ± SD | 70.00 ± 18.53 | 72.02 ± 16.50 | 0.116 | 71.41 ± 17.18 | 71.80 ± 16.67 | 0.023 |

Notes: Data expressed as percentages (%) unless stated otherwise. ASMD > 0.1 is considered significant.

Abbreviations: ACEI/ARB: Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; ASMD: Absolute standardized mean difference; CABG: Coronary artery bypass grafting; CHF: Congestive heart failure; CVA: Cerebrovascular accident; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; IPTW: Inverse probability of treatment weighting; MI: Myocardial infarction; NSAID: Non-steroidal anti-inflammatory drug; OSA: Obstructive sleep apnea; PCI: Percutaneous coronary intervention; PVD: Peripheral vascular disease; SD: Standard deviation.

Table S4. Baseline characteristics of the group rivaroxaban vs. dabigatran

| Variables                                                     | Before IPTW       |                   |       | After IPTW        |                   |       |
|---------------------------------------------------------------|-------------------|-------------------|-------|-------------------|-------------------|-------|
|                                                               | Rivaroxaban       | Dabigatran        | ASMD  | Rivaroxaban       | Dabigatran        | ASMD  |
| <i>n</i>                                                      | 239               | 715               | -     | 239               | 715               | -     |
| Age (years), mean $\pm$ SD                                    | 72.0 $\pm$ 11.0   | 72.5 $\pm$ 10.0   | 0.053 | 72.6 $\pm$ 9.9    | 72.4 $\pm$ 10.1   | 0.017 |
| Sex (Male)                                                    | 51.5              | 51.6              | 0.003 | 53.4              | 51.3              | 0.042 |
| Race (Chinese)                                                | 99.2              | 99.2              | 0.000 | 99.1              | 99.2              | 0.007 |
| History of MI                                                 | 4.6               | 4.2               | 0.020 | 3.4               | 4.1               | 0.038 |
| History of CVA                                                | 37.7              | 30.2              | 0.159 | 34.7              | 31.4              | 0.072 |
| History of PCI                                                | 6.3               | 4.8               | 0.069 | 4.4               | 4.7               | 0.016 |
| History of CABG                                               | 0.8               | 1.1               | 0.028 | 0.8               | 1.1               | 0.025 |
| DM                                                            | 26.4              | 32.3              | 0.129 | 27.9              | 30.9              | 0.067 |
| Hypertension                                                  | 71.5              | 70.6              | 0.020 | 71.9              | 70.5              | 0.031 |
| CHF                                                           | 10.5              | 14.4              | 0.116 | 12.8              | 13.6              | 0.024 |
| PVD                                                           | 1.3               | 1.8               | 0.044 | 1.0               | 1.7               | 0.060 |
| Proteinuria                                                   | 0.4               | 0.3               | 0.025 | 0.3               | 0.3               | 0.003 |
| Thyrotoxicosis                                                | 3.3               | 2.0               | 0.093 | 2.4               | 2.1               | 0.023 |
| Cirrhosis                                                     | 0.4               | 0.3               | 0.025 | 0.4               | 0.3               | 0.016 |
| OSA                                                           | 2.5               | 2.7               | 0.009 | 2.0               | 2.6               | 0.040 |
| COPD                                                          | 1.3               | 3.4               | 0.127 | 2.2               | 3.1               | 0.057 |
| Depression                                                    | 3.3               | 2.0               | 0.093 | 2.0               | 2.1               | 0.006 |
| Cancer                                                        | 0.8               | 2.1               | 0.095 | 1.9               | 2.0               | 0.006 |
| Gout                                                          | 7.9               | 7.4               | 0.020 | 8.3               | 7.3               | 0.035 |
| Smoking                                                       | 30.5              | 35.9              | 0.113 | 33.7              | 34.9              | 0.025 |
| Drinking                                                      | 10.7              | 9.3               | 0.047 | 9.3               | 9.4               | 0.004 |
| Antiplatelet                                                  | 21.3              | 16.1              | 0.139 | 16.4              | 16.4              | 0.002 |
| NSAID                                                         | 2.1               | 1.5               | 0.043 | 1.8               | 1.5               | 0.018 |
| ACEIARB                                                       | 49.8              | 43.1              | 0.135 | 45.9              | 43.8              | 0.042 |
| Statin                                                        | 62.3              | 59.6              | 0.056 | 60.6              | 59.9              | 0.014 |
| Beta-blocker                                                  | 45.6              | 49.4              | 0.075 | 47.4              | 48.5              | 0.022 |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc, mean $\pm$ SD         | 3.56 $\pm$ 1.72   | 3.56 $\pm$ 1.61   | 0.003 | 3.57 $\pm$ 1.74   | 3.54 $\pm$ 1.63   | 0.013 |
| HAS-BLED, mean $\pm$ SD                                       | 2.23 $\pm$ 1.06   | 2.14 $\pm$ 0.98   | 0.091 | 2.19 $\pm$ 1.01   | 2.14 $\pm$ 0.99   | 0.053 |
| Baseline eGFR (mL/<br>min/1.73m <sup>2</sup> ), mean $\pm$ SD | 72.00 $\pm$ 18.40 | 72.02 $\pm$ 16.51 | 0.001 | 72.38 $\pm$ 16.64 | 72.17 $\pm$ 16.68 | 0.012 |

Notes: Data expressed as percentages (%) unless stated otherwise. ASMD > 0.1 is considered significant.

Abbreviations: ACEI/ARB: Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; ASMD: Absolute standardized mean difference; CABG: Coronary artery bypass grafting; CHF: Congestive heart failure; CVA: Cerebrovascular accident; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; IPTW: Inverse probability of treatment weighting; MI: Myocardial infarction; NSAID: Non-steroidal anti-inflammatory drug; OSA: Obstructive sleep apnea; PCI: Percutaneous coronary intervention; PVD: Peripheral vascular disease; SD: Standard deviation.

Table S5. Baseline characteristics of the group apixaban vs. dabigatran

| Variables                                             | Before IPTW   |                         |       | After IPTW    |                         |       |
|-------------------------------------------------------|---------------|-------------------------|-------|---------------|-------------------------|-------|
|                                                       | Apixaban      | Dabigatran <sup>a</sup> | ASMD  | Apixaban      | Dabigatran <sup>a</sup> | ASMD  |
| <i>n</i>                                              | 207           | 619                     |       | 207           | 619                     |       |
| Age (years), mean ± SD                                | 73.5 ± 10.8   | 72.5 ± 10.0             | 0.105 | 73.5 ± 9.7    | 72.7 ± 10.0             | 0.080 |
| Sex (Male)                                            | 51.7          | 52.9                    | 0.024 | 51.0          | 52.0                    | 0.020 |
| Race (Chinese)                                        | 99.0          | 99.3                    | 0.025 | 98.5          | 99.3                    | 0.076 |
| History of MI                                         | 9.7           | 4.3                     | 0.232 | 6.4           | 5.1                     | 0.055 |
| History of CVA                                        | 31.4          | 29.7                    | 0.036 | 30.7          | 29.7                    | 0.021 |
| History of PCI                                        | 10.1          | 4.8                     | 0.225 | 7.3           | 5.8                     | 0.062 |
| History of CABG                                       | 1.4           | 1.2                     | 0.023 | 1.9           | 1.2                     | 0.056 |
| DM                                                    | 34.3          | 31.7                    | 0.056 | 31.8          | 31.8                    | 0.001 |
| Hypertension                                          | 66.2          | 69.7                    | 0.075 | 67.0          | 69.2                    | 0.049 |
| CHF                                                   | 17.9          | 15.1                    | 0.076 | 15.4          | 15.4                    | 0.000 |
| PVD                                                   | 1.9           | 1.9                     | 0.001 | 1.7           | 2.0                     | 0.022 |
| Proteinuria                                           | 1.4           | 0.1                     | 0.193 | 1.1           | 0.1                     | 0.124 |
| Thyrototoxicosis                                      | 2.4           | 1.9                     | 0.033 | 1.7           | 1.8                     | 0.014 |
| Cirrhosis                                             | 1.0           | 0.3                     | 0.099 | 2.6           | 0.3                     | 0.195 |
| OSA                                                   | 4.3           | 2.8                     | 0.086 | 3.1           | 3.0                     | 0.007 |
| COPD                                                  | 3.4           | 3.4                     | 0.003 | 2.9           | 3.4                     | 0.024 |
| Depression                                            | 1.9           | 1.9                     | 0.001 | 2.2           | 1.9                     | 0.019 |
| Cancer                                                | 2.4           | 2.1                     | 0.022 | 2.8           | 2.3                     | 0.028 |
| Gout                                                  | 10.1          | 7.3                     | 0.104 | 7.7           | 7.4                     | 0.011 |
| Smoking                                               | 29.9          | 37.2                    | 0.151 | 30.7          | 35.8                    | 0.108 |
| Drinking                                              | 3.2           | 9.0                     | 0.219 | 5.7           | 7.9                     | 0.089 |
| Antiplatelet                                          | 22.2          | 16.1                    | 0.160 | 18.6          | 17.1                    | 0.040 |
| NSAID                                                 | 2.9           | 1.2                     | 0.136 | 1.9           | 1.4                     | 0.042 |
| ACEI/ARB                                              | 47.3          | 42.8                    | 0.093 | 43.9          | 43.2                    | 0.014 |
| Statin                                                | 66.2          | 59.8                    | 0.131 | 62.3          | 60.7                    | 0.034 |
| Beta-blocker                                          | 53.6          | 49.2                    | 0.089 | 51.4          | 49.9                    | 0.031 |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc, mean ± SD     | 3.69 ± 1.67   | 3.52 ± 1.61             | 0.100 | 3.61 ± 1.66   | 3.55 ± 1.63             | 0.033 |
| HAS-BLED, mean ± SD                                   | 2.13 ± 1.05   | 2.12 ± 0.98             | 0.014 | 2.15 ± 1.02   | 2.12 ± 0.97             | 0.027 |
| Baseline eGFR (mL/min/1.73m <sup>2</sup> ), mean ± SD | 67.69 ± 18.45 | 72.14 ± 16.53           | 0.260 | 69.75 ± 16.20 | 71.50 ± 16.58           | 0.017 |

Notes: Data expressed as percentages (%) unless stated otherwise. ASMD > 0.1 is considered significant. <sup>a</sup>Some of the patients in the dabigatran group were excluded.

Abbreviations: ACEI/ARB: Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; ASMD: Absolute standardized mean difference; CABG: Coronary artery bypass grafting; CHF: Congestive heart failure; CVA: Cerebrovascular accident; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; IPTW: Inverse probability of treatment weighting; MI: Myocardial infarction; NSAID: Non-steroidal anti-inflammatory drug; OSA: Obstructive sleep apnea; PCI: Percutaneous coronary intervention; PVD: Peripheral vascular disease; SD: Standard deviation.

Table S6. Baseline characteristics of the group apixaban vs. rivaroxaban

| Variables                                             | Before IPTW   |                          |       | After IPTW    |                          |       |
|-------------------------------------------------------|---------------|--------------------------|-------|---------------|--------------------------|-------|
|                                                       | Apixaban      | Rivaroxaban <sup>a</sup> | ASMD  | Apixaban      | Rivaroxaban <sup>a</sup> | ASMD  |
| <i>n</i>                                              | 207           | 231                      | -     | 207           | 231                      | -     |
| Age (years), mean ± SD                                | 73.5 ± 10.8   | 71.8 ± 11.0              | 0.163 | 73.3 ± 10.7   | 72.7 ± 10.7              | 0.055 |
| Sex (Male)                                            | 51.7          | 52.4                     | 0.014 | 52.2          | 51.9                     | 0.005 |
| Race (Chinese)                                        | 99.0          | 99.1                     | 0.011 | 98.9          | 99.2                     | 0.024 |
| History of MI                                         | 9.7           | 4.8                      | 0.191 | 8.1           | 5.8                      | 0.089 |
| History of CVA                                        | 31.4          | 37.2                     | 0.122 | 32.8          | 34.3                     | 0.031 |
| History of PCI                                        | 10.1          | 6.5                      | 0.133 | 9.2           | 7.3                      | 0.069 |
| History of CABG                                       | 1.4           | 0.9                      | 0.055 | 1.2           | 0.9                      | 0.026 |
| DM                                                    | 34.3          | 26.8                     | 0.162 | 31.3          | 27.9                     | 0.071 |
| Hypertension                                          | 66.2          | 71.0                     | 0.104 | 67.2          | 70.4                     | 0.070 |
| CHF                                                   | 17.9          | 10.8                     | 0.202 | 14.6          | 12.6                     | 0.058 |
| PVD                                                   | 1.9           | 1.3                      | 0.050 | 1.7           | 1.0                      | 0.065 |
| Proteinuria                                           | 1.4           | 0.0                      | 0.176 | 1.5           | 0.0                      | 0.176 |
| Thyrototoxicosis                                      | 2.4           | 3.5                      | 0.062 | 2.4           | 3.0                      | 0.034 |
| Cirrhosis                                             | 1.0           | 0.4                      | 0.065 | 2.6           | 0.6                      | 0.155 |
| OSA                                                   | 4.3           | 2.2                      | 0.124 | 3.6           | 2.4                      | 0.070 |
| COPD                                                  | 3.4           | 1.3                      | 0.139 | 2.6           | 1.4                      | 0.082 |
| Depression                                            | 1.9           | 3.5                      | 0.094 | 2.6           | 3.2                      | 0.034 |
| Cancer                                                | 2.4           | 0.9                      | 0.123 | 2.5           | 1.0                      | 0.109 |
| Gout                                                  | 10.1          | 7.8                      | 0.083 | 9.2           | 8.6                      | 0.019 |
| Smoking                                               | 29.9          | 30.8                     | 0.018 | 28.7          | 29.2                     | 0.011 |
| Drinking                                              | 3.2           | 11.0                     | 0.305 | 5.7           | 7.5                      | 0.072 |
| Antiplatelet                                          | 22.2          | 21.2                     | 0.024 | 20.3          | 21.5                     | 0.029 |
| NSAID                                                 | 2.9           | 2.2                      | 0.047 | 2.9           | 2.1                      | 0.046 |
| ACEI/ARB                                              | 47.3          | 49.8                     | 0.049 | 47.9          | 50.0                     | 0.055 |
| Statin                                                | 66.2          | 62.3                     | 0.080 | 65.2          | 62.2                     | 0.063 |
| Beta-blocker                                          | 53.6          | 45.0                     | 0.172 | 50.9          | 47.8                     | 0.063 |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc, mean ± SD     | 3.69 ± 1.67   | 3.53 ± 1.73              | 0.090 | 3.61 ± 1.66   | 3.57 ± 1.71              | 0.028 |
| HAS-BLED, mean ± SD                                   | 2.13 ± 1.04   | 2.22 ± 1.07              | 0.078 | 2.17 ± 1.05   | 2.20 ± 1.04              | 0.026 |
| Baseline eGFR (mL/min/1.73m <sup>2</sup> ), mean ± SD | 67.69 ± 18.45 | 72.34 ± 18.48            | 0.250 | 69.33 ± 18.16 | 70.27 ± 18.55            | 0.051 |

Notes: Data expressed as percentages (%) unless stated otherwise. ASMD > 0.1 is considered significant. <sup>a</sup>Some of the patients in the rivaroxaban group were excluded.

Abbreviations: ACEI/ARB: Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; ASMD: Absolute standardized mean difference; CABG: Coronary artery bypass grafting; CHF: Congestive heart failure; CVA: Cerebrovascular accident; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; IPTW: Inverse probability of treatment weighting; MI: Myocardial infarction; NSAID: Non-steroidal anti-inflammatory drug; OSA: Obstructive sleep apnea; PCI: Percutaneous coronary intervention; PVD: Peripheral vascular disease; SD: Standard deviation.

**Table S7. Causes of cardiovascular death**

| Cause of death        | Dabigatran ( <i>n</i> = 715) | Rivaroxaban ( <i>n</i> = 239) | Apixaban ( <i>n</i> = 207) |
|-----------------------|------------------------------|-------------------------------|----------------------------|
| Myocardial infarction | 0                            | 1                             | 1                          |
| Heart failure         | 2                            | 3                             | 1                          |
| Ischemic stroke       | 2                            | 4                             | 0                          |
| Hemorrhagic stroke    | 1                            | 2                             | 2                          |
| Sudden death          | 10                           | 5                             | 1                          |

**Table S8. Causes of fatal bleeding**

| Cause of fatal bleeding | Dabigatran ( <i>n</i> = 715) | Rivaroxaban ( <i>n</i> = 239) | Apixaban ( <i>n</i> = 207) |
|-------------------------|------------------------------|-------------------------------|----------------------------|
| Haemoptysis             | 1                            | 0                             | 0                          |
| Hemorrhagic stroke      | 1                            | 1                             | 2                          |
| Subdural hemorrhage     | 2                            | 2                             | 0                          |
| Subarachnoid hemorrhage | 1                            | 1                             | 0                          |
| Pneumohemoperitoneum    | 0                            | 0                             | 1                          |