Supplemental Data

The Influence of Anemia on Clinical Outcomes in Venous Thromboembolism: Results from GARFIELD-VTE

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Supplemental Table S1. Confounders for adjusted hazard ratios

|  |  |
| --- | --- |
| **Outcome** | **Confounders** |
| **Mortality** | Age, sex, ethnicity, BMI, VTE type, smoking, creatinine serum, cancer, chronic heart failure, acute medical illness, surgery, chronic immobilization, history of cancer, and anticoagulation treatment. |
| **Recurrent VTE** | Age, sex, ethnicity, BMI, VTE type, smoking, creatinine serum, cancer, acute medical illness, surgery, family history of VTE, oral contraception, and anticoagulation treatment. |
| **Major bleeding** | Age, sex, ethnicity, BMI, VTE type, smoking, creatinine serum, cancer, acute medical illness, chronic immobilization, history of cancer, and anticoagulation treatment. |
| **Any bleeding** | Age, sex, ethnicity, BMI, VTE type, smoking, creatinine serum, cancer, chronic heart failure, acute medical illness, surgery, chronic immobilization, history of cancer, and anticoagulation treatment. |
| **Cancer** | Age, sex, ethnicity, BMI, VTE type, smoking, creatinine serum, cancer, history of cancer, and anticoagulation treatment. |
| **MI/ACS** | Age, sex, ethnicity, BMI, VTE type, smoking, creatinine serum, cancer, and anticoagulation treatment. |
| **Stroke/TIA**  | Age, sex, ethnicity, BMI, VTE type, smoking, creatinine serum, cancer, and anticoagulation treatment. |

Supplemental Table S2. Hemoglobin by anemia status Mild/Moderate vs Severe

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| --- | --- | --- |
|  | **Mild/Moderate (N=1958)** | **Severe (N=813)** |
| **Haemoglobin [g/dL], median (IQR)** | 11.3 (10.7, 11.9)  | 8.9 (8.0, 9.4)  |
| **Haemoglobin categories [g/dL]** |   |   |
| **Low (males: <13·0; females: <12·0)** | 1958 (100.0%)  | 813 (100.0%)  |

Supplemental Table S3. Daily dosages of DOACs according to anticoagulant type

|  |  |  |
| --- | --- | --- |
| **OAC Type,** **n (%)** |  | **Daily Dose of OAC (mg)** |
|  |  | 2.5 | 5 | 10 | 15 | 20 | 30 | 40 | 60 | 75 | 110 | 150 | 220 | 330 |
| **Apixaban** | Anemia (n=2,771) | 0 (0.0) | 12 (1.2) | 74 (7.1) | 0 (0.0) | 65 (6.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0)  | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| No-anemia (n=4,927) | 1 (0.0) | 17 (0.7) | 128 (5.0) | 0 (0.0) | 198 (7.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Dabigatran** | Anemia (n=2,771) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 3 (0.3) | 1 (0.1) | 11 (1.1) | 48 (4.6) |
| No-anemia (n=4,927) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) | 1 (0.0) | 11 (0.4) | 124 (4.8) |
| **Edoxaban** | Anemia (n=2,771) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 14 (1.3) | 0 (0.0) | 10 (1.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| No-anemia (n=4,927) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.1) | 0 (0.0) | 10 (0.4) | 0 (0.0) | 26 (1.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Rivaroxaban** | Anemia (n=2,771) | 0 (0.0) | 0 (0.0) | 23 (2.2) | 57 (5.5) | 228 (22.0) | 482 (46.4) | 4 (0.4) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| No-anemia (n=4,927) | 0 (0.0) | 0 (0.0) | 17 (0.7) | 77 (3.0) | 358 (13.9) | 1,595 (61.8) | 15 (0.6) | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Supplemental Table S4. Rate of major bleeding per 100 person years in VTE patients with anemia by treatment type

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| --- | --- | --- |
|  | **Mild-Moderate Anemia****(n=1,962)** | **Severe Anemia****(n=817)** |
| **Treatment** | **No. of patients** | **Events** | **Rate % (95% CI)** | **No. of patients** | **Events** | **Rate % (95% CI)** |
| **Parenteral therapy** | 469 | 35 | 5.28 (3.79-7.36) | 255 | 21 | 7.01 (4.57-10.75) |
| **VKA** | 596 | 23 | 2.34 (1.56-3.53) | 255 | 29 | 8.21 (5.71-11.82) |
| **NOAC** | 789 | 27 | 1.96 (1.34-2.86) | 258 | 20 | 5.16 (3.33-8.00) |

Supplemental Table S5. Sites of major and non-major bleeds in anemia and no-anemia VTE patients

|  |  |  |
| --- | --- | --- |
| Site of bleed, n (%) | Anemia (n = 164) | No-anemia (n = 84) |
| Intra-Spinal | 1 (0·6) | 3 (3·6) |
| Subconjuctival | 0 (0·0) | 0 (0·0) |
| Intra-ocular/Retinal | 3 (1·9) | 5 (6·0) |
| GI upper | 28 (17·1) | 9 (10·7) |
| GI lower | 29 (17·7) | 11 (13·1) |
| Macroscopic haematuria | 11 (6·7) | 5 (6·0) |
| Abnormal uterine (metorrhagia and menorrhagia) | 21 (12.8) | 9 (10·5) |
| Intra-articular | 0 (0·0) | 0 (0·0) |
| Intra-muscular (no compartment syndrome) | 4 (2·4) | 3 (3·6) |
| Intra-muscular (with compartment syndrome) | 2 (1·2) | 1 (1·2) |
| Epistaxis | 1 (0·6) | 2 (2·4) |
| Gingival | 2 (1·2) | 0 (0·0) |
| Intra-peritoneal | 4 (2·4) | 0 (0·0) |
| Retro-peritoneal | 7 (4·3) | 2 (2·4) |
| Puncture site | 1 (0·6) | 0 (0·0) |
| Skin (Ecchymosis other than instrument site) | 1 (0·6) | 1 (1·2) |
| Haemoptysis | 4 (2·4) | 3 (3·6) |
| Haemopericardium | 0 (0·0) | 3 (3·6) |
| Haemothorax | 2 (1·2) | 0 (0·0) |
| Hemorrhagic stroke | 7 (4·3) | 8 (9·5) |
| Other | 27 (16·5) | 16 (19·0) |
| Unknown | 9 (5·5) | 3 (3·6) |

Supplemental table S6. Cause of death over 24-months follow-up

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| --- | --- | --- |
| Cause of death, n (%) | Anemia (n = 488) | No-anemia (n = 247) |
| Stroke | 12 (2·5) | 4 (1·6) |
| Cardiac | 35 (7·2) | 22 (8·9) |
| Cancer-related | 270 (55·3) | 117 (47·4) |
| Bleed | 7 (1·4) | 3 (1·2) |
| VTE | 13 (2·6) | 9 (3·6) |
| Other | 88 (18·0) | 46 (18·6) |
| Unknown | 63 (12·9) | 46 (18·6) |

Supplemental Table S7. Unadjusted 24-month clinical outcomes after VTE diagnosis in patients with mild/moderate anemia and severe anemia. Event rates are shown per 100 person-years (95% confidence interval). CI; confidence interval, VTE; venous thromboembolism, MI; myocardial infarction, ACS; acute coronary syndrome, TIA; transient ischemic attack.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcome |  | Mild/moderate anemia(n = 1,958) |  | Severe anemia(n = 813) |
| Event | n | Event rate (95% CI) | n | Event rate (95% CI) |
| All-cause mortality | 289 | 8·85 (7·89 to 9·94) | 199 | 17·10 (14·88 to 19·65) |
| Recurrent VTE | 144 | 4·64 (3·94 to 5·46) | 15 | 4·66 (3·54 to 6·13) |
| Major bleed | 91 | 2·86 (2·33 to 3·51) | 73 | 6·66 (5·30 to 8·38) |
| Any bleed | 287 | 9·80 (8·73 to 11·00) | 138 | 13·61 (11·51 to 16·08) |
| MI/ACS | 24 | 0·74 (0·50 to 1·11) | 10 | 0·87 (0·47 to 1·61) |
| Stroke/TIA | 33 | 1·02 (0·72 to 1·43) | 12 | 1·04 (0·59 to 1·82) |

Supplemental Figure S1. Adjusted hazard ratios for mortality with 95% CIs for 24-month outcomes after VTE diagnosis between patients with mild/moderate anemia (reference group) and severe anemia. Event rates are shown per 100 person-years. Abbreviations: VTE; venous thromboembolism, TIA; transient ischemic attack, MI; myocardial infarction, ACS; acute coronary syndrome, HR; hazard ratio, CI; confidence interval.



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