SUPPLEMENTAL MATERIAL

TITLE: Oral Anticoagulation in Patients With Chronic Kidney Disease: A Systematic Review and Meta-Analysis

Supplemental Methods

Complete Search algorithm used in MEDLINE database

Terms] OR "warfarin"[All Fields] OR "coumadin"[All Fields]) OR ("dabigatran"[MeSH Terms] OR "dabigatran"[All Fields]) OR ("rivaroxaban"[MeSH Terms] OR "rivaroxaban"[All Fields]) OR ("factor xa inhibitors"[Pharmacological Action] OR "factor xa inhibitors"[MeSH Terms]) OR ("factor"[All Fields] AND "xa"[All Fields] AND "inhibitors"[All Fields]) OR "factor xa inhibitors"[All Fields])

Complete Search algorithm used in ovid Embase and ovid MEDLINE databases

1 chronic renal insufficiency.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
2 chronic kidney disease.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
3 chronic renal failure.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
4 chronic kidney failure.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
5 oral anticoagulation.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
6 warfarin.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
7 coumadin.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
8 apixaban.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
9 eliquis.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
10 rivaroxaban.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
11 xarelto.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
12 dabigatran.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
13 pradaxa.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
14 1 or 2 or 3 or 4
15 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
16 14 and 15

Complete Search algorithm used in CENTRAL
#1 MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees

#2 MeSH descriptor: [Anticoagulants] explode all trees

#3 MeSH descriptor: [Warfarin] explode all trees

#4 MeSH descriptor: [Antithrombins] explode all trees

#5 MeSH descriptor: [Dabigatran] explode all trees

#6 MeSH descriptor: [Rivaroxaban] explode all trees

#7 MeSH descriptor: [Factor Xa Inhibitors] explode all trees

#8 #2 OR #3 OR #4 OR #5 OR #6 OR #7

#9 #1 AND #8
## Supplemental Tables

### Table e-1: Excluded studies with reasons for exclusion

<table>
<thead>
<tr>
<th>Study name</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knoll et al(^1)</td>
<td>No comparative groups</td>
</tr>
<tr>
<td>To et al(^2)</td>
<td>No comparative groups</td>
</tr>
<tr>
<td>Kooiman et al(^3)</td>
<td>No comparative groups</td>
</tr>
<tr>
<td>Szummer et al(^4)</td>
<td>No comparative groups</td>
</tr>
<tr>
<td>Hart et al(^5)</td>
<td>No comparative groups</td>
</tr>
<tr>
<td>Mahmoodi et al(^6)</td>
<td>No comparative groups</td>
</tr>
<tr>
<td>Khalid et al(^7)</td>
<td>No comparative groups</td>
</tr>
<tr>
<td>Wizemann et al(^8)</td>
<td>No comparative groups</td>
</tr>
<tr>
<td>Chan et al(^9)</td>
<td>No comparative groups</td>
</tr>
<tr>
<td>Koretsune et al(^10)</td>
<td>No comparative groups</td>
</tr>
<tr>
<td>Yamashita et al(^11)</td>
<td>Study not reporting stroke outcomes</td>
</tr>
<tr>
<td>Kumar et al(^12)</td>
<td>Study not reporting stroke outcomes</td>
</tr>
<tr>
<td>Bauersachs et al(^13)</td>
<td>Study not reporting stroke outcomes</td>
</tr>
<tr>
<td>Brancaccio et al(^14)</td>
<td>Study not reporting stroke outcomes</td>
</tr>
<tr>
<td>Genovesi et al(^15)</td>
<td>Study not reporting stroke outcomes</td>
</tr>
<tr>
<td>Connolly et al(^16)</td>
<td>Data unavailable</td>
</tr>
<tr>
<td>Ogawa et al(^17)</td>
<td>Data unavailable</td>
</tr>
<tr>
<td>Rao et al(^18)</td>
<td>Data unavailable</td>
</tr>
<tr>
<td>Oh et al(^19)</td>
<td>Data unavailable</td>
</tr>
<tr>
<td>Seeger et al(^20)</td>
<td>No CKD patients</td>
</tr>
<tr>
<td>Keskar et al(^21)</td>
<td>No clear OAC groups</td>
</tr>
</tbody>
</table>
### Table e-2: Baseline characteristics of the included patients (NOAC vs. warfarin)

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Age (years)</th>
<th>Males (%)</th>
<th>HTN (%)</th>
<th>HLD (%)</th>
<th>DM (%)</th>
<th>Smoker (%)</th>
<th>Prior AIS/TIA (%)</th>
<th>Prior MI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanton et al</td>
<td>73, 73</td>
<td>79 ±11.8, 79±13.5</td>
<td>29, 30</td>
<td>49.3, 56.2</td>
<td>N.A</td>
<td>52.1, 38.4</td>
<td>N.A</td>
<td>57.5, 45.2</td>
<td>N.A</td>
</tr>
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</tr>
<tr>
<td>Loo et al</td>
<td>2596, 2596</td>
<td>8.49, 8.49</td>
<td>53.0, 53.0</td>
<td>81.0, 81.5</td>
<td>65.1, 62.3</td>
<td>27.7, 28.7</td>
<td>52.5, 53</td>
<td>10.7, 9.4</td>
<td>14.5, 14.3</td>
</tr>
</tbody>
</table>

HTN indicates hypertension; HLD, hyperlipidemia; DM, diabetes mellitus; AIS, acute ischemic stroke; TIA, transient ischemic attack; NA, not available or reported; NOAC, Non-Vitamin K Antagonist Oral Anticoagulant
## Table e-3: Baseline characteristics of the included patients (Warfarin vs. No anticoagulation)

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Age (years) (Warfarin, no AC)</th>
<th>Males (%) (Warfarin, no AC)</th>
<th>HTN (%) (Warfarin, no AC)</th>
<th>HLD (%) (Warfarin, no AC)</th>
<th>DM (%) (Warfarin, no AC)</th>
<th>Smoker (%) (Warfarin, no AC)</th>
<th>Prior AIS/TIA (%) (Warfarin, no AC)</th>
<th>Prior MI (%) (Warfarin, no AC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiu et al</td>
<td>31, 73</td>
<td>74.5±7.4, 76.04 ± 8.64</td>
<td>N.A</td>
<td>90, 94.5</td>
<td>N.A</td>
<td>33.3, 52.1</td>
<td>13.3, 26</td>
<td>16.7, 11.1</td>
<td>33.3, 28.8</td>
</tr>
<tr>
<td>Lai et al</td>
<td>232, 167</td>
<td>73 ± 12, 77 ± 11</td>
<td>71, 63</td>
<td>64, 68</td>
<td>67, 65</td>
<td>47, 40</td>
<td>28, 25</td>
<td>8, 8</td>
<td>N.A</td>
</tr>
<tr>
<td>Lin et al</td>
<td>59, 144</td>
<td>60±17, 60±15</td>
<td>51, 55</td>
<td>93.2, 87.5</td>
<td>N.A</td>
<td>71.2, 64.6</td>
<td>N.A</td>
<td>6.8, 17.4</td>
<td>22, 54</td>
</tr>
<tr>
<td>Jun et al</td>
<td>7446, 7446</td>
<td>78.2± 6, 78.1±6, 7.1</td>
<td>49.8, 49.3</td>
<td>80.7, 80.4</td>
<td>N.A</td>
<td>25.6, 25.0</td>
<td>N.A</td>
<td>13.8, 13.9</td>
<td>14.9, 15.9</td>
</tr>
<tr>
<td>Study</td>
<td>Cases</td>
<td>Controls</td>
<td>Age</td>
<td>BMI</td>
<td>Gender</td>
<td>Inclusion Duration</td>
<td>Outcomes</td>
<td></td>
<td></td>
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<tr>
<td>--------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Carrero et al</td>
<td>5292, 19025 (Warfarin, no AC)</td>
<td>78 (29-98), 80 (32-103)</td>
<td>63.9, 58.2</td>
<td>54.0, 53.4</td>
<td>N.A</td>
<td>30.4, 27.5</td>
<td>10.0, 14.1</td>
<td>23.3, 17.8</td>
<td>39.2, 39.4</td>
</tr>
<tr>
<td>Olesen et al</td>
<td>899, 2688 (Warfarin, no AC)</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
</tr>
</tbody>
</table>

HTN indicates hypertension; HLD, hyperlipidemia; DM, diabetes mellitus; AIS, acute ischemic stroke; TIA, transient ischemic attack; NA, not available or reported; AC, anticoagulation
Table e-4: Quality assessment of included studies with the Newcastle–Ottawa Scale

<table>
<thead>
<tr>
<th>Study name</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Overall score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bohula et al (ENGAGE AF-TIMI 48, 2016)</td>
<td>****</td>
<td>**</td>
<td>***</td>
<td>9/9</td>
</tr>
<tr>
<td>Hori et al (J-ROCKET AF, 2013)</td>
<td>****</td>
<td>**</td>
<td>**</td>
<td>8/9</td>
</tr>
<tr>
<td>Hohnloser et al (ARISTOTLE, 2012)</td>
<td>****</td>
<td>**</td>
<td>**</td>
<td>8/9</td>
</tr>
<tr>
<td>Hori et al (J-ROCKET AF, 2013)</td>
<td>****</td>
<td>**</td>
<td>***</td>
<td>9/9</td>
</tr>
<tr>
<td>Hijazi et al (RE-LY, 2014)</td>
<td>****</td>
<td>**</td>
<td>**</td>
<td>8/9</td>
</tr>
<tr>
<td>Stanton et al</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>8/9</td>
</tr>
<tr>
<td>Loo et al</td>
<td>****</td>
<td>**</td>
<td>**</td>
<td>8/9</td>
</tr>
<tr>
<td>Banerjee et al</td>
<td>****</td>
<td>**</td>
<td>***</td>
<td>9/9</td>
</tr>
<tr>
<td>Chiu et al</td>
<td>***</td>
<td>**</td>
<td>**</td>
<td>7/9</td>
</tr>
<tr>
<td>Lai et al</td>
<td>****</td>
<td>**</td>
<td>**</td>
<td>8/9</td>
</tr>
<tr>
<td>Lin et al</td>
<td>***</td>
<td>**</td>
<td>**</td>
<td>7/9</td>
</tr>
<tr>
<td>Jun et al</td>
<td>****</td>
<td>**</td>
<td>**</td>
<td>8/9</td>
</tr>
<tr>
<td>Carrero et al</td>
<td>****</td>
<td>**</td>
<td>**</td>
<td>8/9</td>
</tr>
<tr>
<td>Olesen et al</td>
<td>****</td>
<td>**</td>
<td>**</td>
<td>8/9</td>
</tr>
<tr>
<td>Bonde et al</td>
<td>****</td>
<td>**</td>
<td>**</td>
<td>8/9</td>
</tr>
<tr>
<td>Total</td>
<td>56/64</td>
<td>26/28</td>
<td>33/48</td>
<td>119/135</td>
</tr>
</tbody>
</table>
Table e-5: Potential confounders used for adjusted analyses

<table>
<thead>
<tr>
<th>First author</th>
<th>Confounders used for adjusted analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bohula et al&lt;sup&gt;22&lt;/sup&gt; (ENGAGE AF-TIMI 48)</td>
<td>Renal impairment, interaction between renal impairment category and treatment groups</td>
</tr>
<tr>
<td>Bonde et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Age, baseline characteristics, CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-VASc score, HAS-BLED score, aspirin treatment</td>
</tr>
<tr>
<td>Banerjee et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Age, sex, CHADS&lt;sub&gt;2&lt;/sub&gt; risk factors, or baseline characteristics</td>
</tr>
<tr>
<td>Carrero et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Age, sex, eGFR, preexisting comorbidities (diabetes mellitus, hypertension, myocardial infarction, congestive heart failure, cerebrovascular disease, ischemic stroke, bleeding, chronic obstructive pulmonary disease, cancer within 3 years), patient presentation characteristics at admission (ST-segment elevation myocardial infarction decompensated heart failure [Killip class ≥2]), hospital course (percutaneous coronary intervention and coronary artery bypass graft), discharge medication (antiplatelet therapy [none, mono, or dual]), β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and statins), and center effect (as a random effect via a γ frailty distribution), left ventricular ejection fraction</td>
</tr>
<tr>
<td>Chiu et al&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Age, diabetes mellitus, hypertension, heart failure, GFR</td>
</tr>
<tr>
<td>Fordyce et al&lt;sup&gt;27&lt;/sup&gt; (ROCKET AF)</td>
<td>Randomized treatment, age, sex, body mass index, geographic region, paroxysmal AF, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease (myocardial infarction, peripheral artery disease, or carotid occlusive disease), congestive heart failure, hypertension, chronic obstructive pulmonary disorder, diastolic blood pressure, heart rate, and alcohol use</td>
</tr>
<tr>
<td>Hijazi et al&lt;sup&gt;28&lt;/sup&gt; (RE-LY)</td>
<td>Renal impairment, interaction between renal impairment category and treatment groups</td>
</tr>
<tr>
<td>Hohnlooser et al&lt;sup&gt;29&lt;/sup&gt; (ARISTOTLE)</td>
<td>Renal impairment, interaction between renal impairment category and treatment groups</td>
</tr>
<tr>
<td>Reference</td>
<td>Description</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hori et al $^{30}$ (J-ROCKET AF)</td>
<td>Renal impairment, interaction between renal impairment category and treatment groups</td>
</tr>
<tr>
<td>Jun et al $^{31}$</td>
<td>Baseline eGFR category, interaction between eGFR and warfarin use</td>
</tr>
<tr>
<td>Lai et al $^{32}$</td>
<td>Age, sex, GFR, hemodialysis, renal transplant, aspirin use, stroke or transient ischemic attack, coronary artery disease, valvular heart disease, peripheral arterial disease, smoking, hypertension, diabetes mellitus, hyperlipidemia</td>
</tr>
<tr>
<td>Lin et al $^{33}$</td>
<td>Age, gender, use of anti-platelets, and existing diabetes, hypertension, myocardial infarction/congestive heart failure, and stroke</td>
</tr>
<tr>
<td>Loo et al $^{34}$</td>
<td>Age, sex, CKD status, CKD stage, CHA$^2$DS$^2$-VASc score, HAS-BLED score, antiplatelet use</td>
</tr>
<tr>
<td>Olesen et al $^{35}$</td>
<td>CHA$^2$DS$^2$-VASc score, antithrombotic treatment, year of inclusion</td>
</tr>
<tr>
<td>Stanton et al $^{36}$</td>
<td>No adjusted analyses were available</td>
</tr>
</tbody>
</table>

CHADS$_2$ (congestive heart failure, hypertension, age $\geq$75 years, diabetes, prior stroke or transient ischemic attack); CHA$^2$DS$^2$-VASc (congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, and sex category); HAS-BLED (Hypertension, Abnormal renal function, abnormal liver function, Stroke, Bleeding, Labile international normalized ratio, Elderly, Drug therapy, alcohol intake)
Supplemental Figures

Figure e-1: Flow-Chart Diagram Presenting the Selection of Eligible Studies

Records identified through CENTRAL (N=71), Scopus (N=986), Embase (N=1422), MEDLINE (N=2107) → Additional Records identified through bibliography (N=2) → Records after duplicates removed (N=4405) → Records screened (N=4405) → Records excluded (N=4369) → Full text articles excluded (n=21): No comparative groups (n=10), stroke outcomes not provided (n=5), data unavailable (n=4), no distinct OAC subgroup (n=1), no CKD patients (n=1) → Studies included in qualitative synthesis (N=15) → Studies included in quantitative synthesis (meta-analysis) (N=15)
Figure e-2: Funnel plot of the included studies for the outcome of ischemic stroke
Figure e-3: Funnel plot of the included studies for stroke or systemic embolism
Figure e-4: Funnel plot of the included studies for major bleeding
**Figure e-5:** Pooled risk ratio of ischemic stroke for CKD patients on Warfarin vs. no anticoagulation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Warfarin Events</th>
<th>Total</th>
<th>no warfarin Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.1 CKD mild</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Banerjee et al, 2014</td>
<td>59</td>
<td>1425</td>
<td>49</td>
<td>1221</td>
<td>14.6%</td>
<td>1.03 [0.71, 1.50]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1425</td>
<td>1221</td>
<td>14.6%</td>
<td>1.03 [0.71, 1.50]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>59</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.16 (P = 0.87)</td>
<td></td>
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<tr>
<td><strong>1.1.2 CKD moderate</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Banerjee et al, 2014</td>
<td>78</td>
<td>1408</td>
<td>73</td>
<td>1233</td>
<td>17.0%</td>
<td>0.94 [0.69, 1.28]</td>
<td></td>
</tr>
<tr>
<td>Carrero et al, 2014</td>
<td>76</td>
<td>2270</td>
<td>484</td>
<td>7869</td>
<td>20.0%</td>
<td>0.54 [0.43, 0.69]</td>
<td></td>
</tr>
<tr>
<td>Jun et al, 2017</td>
<td>95</td>
<td>3064</td>
<td>141</td>
<td>3064</td>
<td>19.2%</td>
<td>0.67 [0.52, 0.87]</td>
<td></td>
</tr>
<tr>
<td>Lai et al, 2009</td>
<td>11</td>
<td>115</td>
<td>17</td>
<td>85</td>
<td>6.7%</td>
<td>0.48 [0.24, 0.97]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>6857</td>
<td>12251</td>
<td>62.9%</td>
<td>0.66 [0.51, 0.87]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>260</td>
<td>715</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Heterogeneity: Tau² = 0.04; Chi² = 8.27, df = 3 (P = 0.04); I² = 64%</td>
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</tr>
<tr>
<td>Test for overall effect: Z = 3.00 (P = 0.003)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.1.3 CKD severe</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Banerjee et al, 2014</td>
<td>11</td>
<td>372</td>
<td>81</td>
<td>1594</td>
<td>8.1%</td>
<td>0.58 [0.31, 1.08]</td>
<td></td>
</tr>
<tr>
<td>Carrero et al, 2014</td>
<td>2</td>
<td>31</td>
<td>4</td>
<td>73</td>
<td>1.5%</td>
<td>1.18 [0.23, 6.10]</td>
<td></td>
</tr>
<tr>
<td>Chiu et al, 2014</td>
<td>11</td>
<td>266</td>
<td>23</td>
<td>266</td>
<td>6.8%</td>
<td>0.48 [0.24, 0.96]</td>
<td></td>
</tr>
<tr>
<td>Jun et al, 2009</td>
<td>2</td>
<td>39</td>
<td>6</td>
<td>28</td>
<td>1.8%</td>
<td>0.24 [0.05, 1.10]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>850</td>
<td>2160</td>
<td>22.4%</td>
<td>0.55 [0.37, 0.81]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>32</td>
<td>127</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 2.27, df = 4 (P = 0.69); I² = 0%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 3.03 (P = 0.002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>9132</td>
<td>15632</td>
<td>100.0%</td>
<td>0.68 [0.55, 0.84]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>351</td>
<td>891</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.04; Chi² = 16.79, df = 9 (P = 0.05); I² = 46%</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.62 (P = 0.0003)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 5.86, df = 2 (P = 0.05), I² = 65.9%</td>
<td></td>
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</tr>
</tbody>
</table>

![Graph showing the pooled risk ratio of ischemic stroke for CKD patients on Warfarin vs. no anticoagulation](image-url)
Figure e-6: Pooled risk ratios of intracerebral hemorrhage for CKD patients on Warfarin vs. no anticoagulation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Warfarin Events</th>
<th>Total</th>
<th>no warfarin Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiu et al, 2014</td>
<td>3</td>
<td>31</td>
<td>1</td>
<td>73</td>
<td>24.7%</td>
<td>7.06 [0.76, 65.29]</td>
<td></td>
</tr>
<tr>
<td>Lai et al, 2009</td>
<td>11</td>
<td>32</td>
<td>3</td>
<td>15</td>
<td>59.8%</td>
<td>1.72 [0.56, 5.27]</td>
<td></td>
</tr>
<tr>
<td>Lin et al, 2017</td>
<td>0</td>
<td>59</td>
<td>3</td>
<td>144</td>
<td>15.5%</td>
<td>0.35 [0.02, 6.58]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>122</strong></td>
<td><strong>232</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1.90 [0.55, 6.62]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>14</td>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.35$; $\text{Chi}^2 = 2.67$, df = 2 ($P = 0.26$); $I^2 = 25\%$

Test for overall effect: $Z = 1.01$ ($P = 0.31$)
**Figure e-7:** Pooled risk ratios of stroke for CKD patients on NOAC vs. Warfarin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>Total Events</th>
<th>Warfarin Events</th>
<th>Total Events</th>
<th>Weight (%)</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4.1.1 CKD mild</strong></td>
<td>ARISTOTLE (CKD mild), 2012</td>
<td>56</td>
<td>7550</td>
<td>69</td>
<td>7363</td>
<td>16.8%</td>
<td>0.79 [0.56, 1.12]</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48 (CKD mild), 2013</td>
<td>156</td>
<td>4060</td>
<td>201</td>
<td>4148</td>
<td>49.4%</td>
<td>0.79 [0.65, 0.97]</td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>116</td>
<td>212</td>
<td>11511</td>
<td>270</td>
<td>66.2%</td>
<td>0.79 [0.66, 0.95]</td>
<td><img src="image3" alt="Graph" /></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>212</td>
<td>270</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong> Z = 2.58 (P = 0.010)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **4.1.2 CKD moderate** | ARISTOTLE (CKD moderate), 2012 | 35 | 7550 | 39 | 7363 | 10.0% | 0.88 [0.56, 1.38] | ![Graph](image4) |
| ENGAGE AF-TIMI 48 (CKD moderate), 2013 | 77 | 1379 | 82 | 1361 | 22.7% | 0.93 [0.69, 1.25] | ![Graph](image5) |
| J-ROCKET AF, 2012 | 4 | 141 | 4 | 143 | 1.1% | 1.01 [0.26, 3.98] | ![Graph](image6) |
| **Subtotal (95% CI)** | 9070 | 8867 | 33.8% | 0.91 [0.71, 1.17] | ![Graph](image7) |
| **Total events** | 116 | 125 | | | | | |
| **Heterogeneity:** Tau² = 0.00; Chi² = 0.07, df = 2 (P = 0.97); I² = 0% | | | | | | | |
| **Test for overall effect:** Z = 0.71 (P = 0.48) | | | | | | | |

| **Total (95% CI)** | 20680 | 20378 | 100.0% | 0.83 [0.72, 0.96] | ![Graph](image8) |
| **Total events** | 328 | 395 | | | |
| **Heterogeneity:** Tau² = 0.00; Chi² = 0.91, df = 4 (P = 0.92); I² = 0% | | | | | |
| **Test for overall effect:** Z = 2.51 (P = 0.01) | | | | | |
| **Test for subgroup differences:** Chi² = 0.84, df = 1 (P = 0.36); I² = 0% | | | | | |
**Figure e-8:** Pooled risk ratios of major bleeding for CKD patients on Warfarin vs. no anticoagulation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Warfarin Events</th>
<th>no warfarin Events</th>
<th>Weight</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6.4.1 CKD mild</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Banerjee et al, 2014</td>
<td>129</td>
<td>1425</td>
<td>65</td>
<td>1221 15.1%</td>
<td>1.70 [1.27, 2.27]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1425</td>
<td>1221</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>129</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.61 (P = 0.0003)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6.4.2 CKD moderate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Banerjee et al, 2014</td>
<td>126</td>
<td>1408</td>
<td>95</td>
<td>1233 16.6%</td>
<td>1.16 [0.90, 1.50]</td>
</tr>
<tr>
<td>Carrero et al, 2014</td>
<td>130</td>
<td>2270</td>
<td>396</td>
<td>7869 19.9%</td>
<td>1.14 [0.94, 1.38]</td>
</tr>
<tr>
<td>Jun et al, 2017</td>
<td>235</td>
<td>3064</td>
<td>256</td>
<td>3064 21.1%</td>
<td>0.92 [0.77, 1.09]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>6742</td>
<td>12166</td>
<td>57.7%</td>
<td>1.05 [0.90, 1.23]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>491</td>
<td>747</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.01; Chi² = 3.63, df = 2 (P = 0.16); I² = 45%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.61 (P = 0.54)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6.4.3 CKD severe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Banerjee et al, 2014</td>
<td>23</td>
<td>142</td>
<td>24</td>
<td>199 7.3%</td>
<td>1.34 [0.79, 2.28]</td>
</tr>
<tr>
<td>Carrero et al, 2014</td>
<td>25</td>
<td>372</td>
<td>107</td>
<td>1594 10.0%</td>
<td>1.00 [0.66, 1.52]</td>
</tr>
<tr>
<td>Jun et al, 2017</td>
<td>36</td>
<td>266</td>
<td>37</td>
<td>266 9.9%</td>
<td>0.97 [0.64, 1.49]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>780</td>
<td>2059</td>
<td>27.3%</td>
<td>1.06 [0.82, 1.38]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>84</td>
<td>168</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 2 (P = 0.61); I² = 0%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.46 (P = 0.64)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>8947</td>
<td>15446</td>
<td>100.0%</td>
<td>1.14 [0.96, 1.35]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>704</td>
<td>980</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.03; Chi² = 14.49, df = 6 (P = 0.02); I² = 59%</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.53 (P = 0.13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 8.70, df = 2 (P = 0.01), I² = 77.0%</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
**Figure e-9:** Pooled risk ratios of major or minor bleeding for CKD patients on NOAC vs. Warfarin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>NOAC Total</th>
<th>Warfarin Events</th>
<th>Warfarin Total</th>
<th>Weight</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>7.1.1 CKD mild</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENGAGE AF–TIMI 48 (CKD mild), 2013</td>
<td>649</td>
<td>4047</td>
<td>743</td>
<td>4130</td>
<td>49.5%</td>
<td>0.89 [0.81, 0.98]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>4047</td>
<td>4130</td>
<td>49.5%</td>
<td>0.89 [0.81, 0.98]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>649</td>
<td>743</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.35 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>7.1.2 CKD moderate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENGAGE AF–TIMI 48 (CKD moderate), 2013</td>
<td>220</td>
<td>1372</td>
<td>282</td>
<td>1356</td>
<td>37.8%</td>
<td>0.77 [0.66, 0.90]</td>
<td></td>
</tr>
<tr>
<td>I–ROCKET AF, 2012</td>
<td>39</td>
<td>141</td>
<td>33</td>
<td>143</td>
<td>12.7%</td>
<td>1.20 [0.80, 1.79]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1513</td>
<td>1499</td>
<td>50.5%</td>
<td>0.92 [0.60, 1.41]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>259</td>
<td>315</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\tau^2 = 0.07; \text{Chi}^2 = 4.02, \text{df} = 1 (P = 0.05); I^2 = 75%$</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.37 (P = 0.71)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>5560</td>
<td>5629</td>
<td>100.0%</td>
<td>0.88 [0.75, 1.03]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>908</td>
<td>1058</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\tau^2 = 0.01; \text{Chi}^2 = 4.90, \text{df} = 7 (P = 0.09); I^2 = 59%$</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.61 (P = 0.11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: $\text{Chi}^2 = 0.03, \text{df} = 1 (P = 0.87)$</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>$I^2 = 0%$</td>
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</tr>
</tbody>
</table>
Figure e-10: Pooled risk ratios of mortality for CKD patients on NOAC vs. Warfarin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>Total Events</th>
<th>Total Weight</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5.1.1 CKD mild</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48 (CKD mild), 2013</td>
<td>400</td>
<td>4060</td>
<td>435</td>
<td>4148</td>
<td>0.94 [0.83, 1.07]</td>
</tr>
<tr>
<td>RE-LY, 2014 (Dabigatran 110)</td>
<td>175</td>
<td>2803</td>
<td>244</td>
<td>2898</td>
<td>0.74 [0.62, 0.89]</td>
</tr>
<tr>
<td>RE-LY, 2014 (Dabigatran 150)</td>
<td>198</td>
<td>2852</td>
<td>244</td>
<td>2898</td>
<td>0.82 [0.69, 0.99]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>7175</strong></td>
<td><strong>9944</strong></td>
<td><strong>52.3%</strong></td>
<td><strong>0.84 [0.73, 0.97]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>773</td>
<td>923</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.01; Chi^2 = 4.43, df = 2 (P = 0.11); i^2 = 55%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.39 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **5.1.2 CKD moderate**            |             |              |              |                               |                               |
| ENGAGE AF-TIMI 48 (CKD moderate), 2013 | 251   | 1379         | 300          | 1361                          | 0.83 [0.71, 0.96]             |
| J-ROCKET AF, 2012                 | 4           | 141          | 4            | 143                           | 1.01 [0.26, 3.98]             |
| RE-LY, 2014 (Dabigatran 110)      | 176         | 1196         | 143          | 1126                          | 1.16 [0.94, 1.42]             |
| RE-LY, 2014 (Dabigatran 150)      | 159         | 1232         | 143          | 1126                          | 1.02 [0.82, 1.25]             |
| **Subtotal (95% CI)**             | **3948**    | **3756**     | **47.7%**    | **0.98 [0.81, 1.19]**          |                               |
| Total events                      | 590         | 590          |              |                               |                               |
| Heterogeneity: Tau^2 = 0.02; Chi^2 = 7.37, df = 3 (P = 0.06); i^2 = 59% |
| Test for overall effect: Z = 0.21 (P = 0.83) |

| **Total (95% CI)**                |             |              |              |                               |                               |
| 13663                             | 13700       | 100.0%       | 0.90 [0.81, 1.01] |                               |
| Total events                      | 1363        | 1513         |              |                               |                               |
| Heterogeneity: Tau^2 = 0.01; Chi^2 = 13.84, df = 6 (P = 0.03); i^2 = 57% |
| Test for overall effect: Z = 1.79 (P = 0.07) |
| Test for subgroup differences: Chi^2 = 1.56, df = 1 (P = 0.21), i^2 = 36.1% |
**Figure e-11**: Sensitivity analysis comparing the risk of stroke among CKD patients on Factor X inhibitors vs. Warfarin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Factor X Inhibitors</th>
<th>Warfarin</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>ARISTOTLE (CKD mild), 2012</td>
<td>56</td>
<td>7550</td>
<td>69</td>
<td>7363</td>
</tr>
<tr>
<td>ARISTOTLE (CKD moderate), 2012</td>
<td>35</td>
<td>7550</td>
<td>39</td>
<td>7363</td>
</tr>
<tr>
<td>ENGAGE AF–TIMI 48 (CKD mild), 2013</td>
<td>156</td>
<td>4060</td>
<td>201</td>
<td>4148</td>
</tr>
<tr>
<td>ENGAGE AF–TIMI 48 (CKD moderate), 2013</td>
<td>77</td>
<td>1379</td>
<td>82</td>
<td>1361</td>
</tr>
<tr>
<td>J-ROCKET AF, 2012</td>
<td>4</td>
<td>141</td>
<td>4</td>
<td>143</td>
</tr>
<tr>
<td>ROCKET-AF, 2011</td>
<td>38</td>
<td>1474</td>
<td>41</td>
<td>1476</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>22154</strong></td>
<td><strong>21854</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.84 [0.73, 0.96]</strong></td>
</tr>
</tbody>
</table>

Total events: 366

Heterogeneity: Tau² = 0.00; Chi² = 1.13, df = 5 (P = 0.95); I² = 0%

Test for overall effect: Z = 2.49 (P = 0.01)
**Figure e-12:** Sensitivity analysis comparing the risk of intracerebral hemorrhage among CKD patients on various NOAC categories vs. Warfarin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>Warfarin Events</th>
<th>Weight</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2.5.1 Factor X inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE, 2012</td>
<td>5</td>
<td>1493</td>
<td>27</td>
<td>1512</td>
<td>18.8%</td>
</tr>
<tr>
<td>ENGAGE AF–TIMI 48 (HDER), 2013</td>
<td>10</td>
<td>1372</td>
<td>19</td>
<td>1356</td>
<td>25.9%</td>
</tr>
<tr>
<td>J–ROCKET AF, 2012</td>
<td>2</td>
<td>141</td>
<td>4</td>
<td>143</td>
<td>7.2%</td>
</tr>
<tr>
<td>ROCKET–AF, 2011</td>
<td>10</td>
<td>1474</td>
<td>13</td>
<td>1476</td>
<td>23.3%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>4480</td>
<td>4487</td>
<td>75.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>27</td>
<td>63</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.17; Chi² = 5.14, df = 3 (P = 0.16); I² = 42%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.48 (P = 0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2.5.2 Direct Thrombin inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE–LY, 2014</td>
<td>11</td>
<td>2428</td>
<td>14</td>
<td>1126</td>
<td>24.8%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2428</td>
<td>1126</td>
<td>24.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>11</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.52 (P = 0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>6908</td>
<td>5613</td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>38</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.07; Chi² = 5.36, df = 4 (P = 0.25); I² = 25%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.50 (P = 0.0005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Figure e-13:** Sensitivity analysis comparing the risk of mortality among CKD patients on various NOAC categories vs. Warfarin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>Total</th>
<th>Warfarin Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5.5.1 Factor X inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE, 2012</td>
<td>107</td>
<td>1502</td>
<td>126</td>
<td>1515</td>
<td>35.1%</td>
<td>0.86 [0.67, 1.10]</td>
<td></td>
</tr>
<tr>
<td>ENGAGE AF–TIMI 48 (HDER), 2013</td>
<td>95</td>
<td>1379</td>
<td>116</td>
<td>1361</td>
<td>31.7%</td>
<td>0.81 [0.62, 1.05]</td>
<td></td>
</tr>
<tr>
<td>J–ROCKET AF, 2012</td>
<td>4</td>
<td>141</td>
<td>4</td>
<td>143</td>
<td>1.2%</td>
<td>1.01 [0.26, 3.98]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>3022</td>
<td>4383</td>
<td>3019</td>
<td>4383</td>
<td>68.0%</td>
<td>0.84 [0.70, 1.00]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>206</td>
<td>246</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 2 (P = 0.91); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.97 (P = 0.05)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5.5.2 Direct Thrombin inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE–LY, 2014</td>
<td>177</td>
<td>2428</td>
<td>76</td>
<td>1126</td>
<td>32.0%</td>
<td>1.08 [0.83, 1.40]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>2428</td>
<td>4156</td>
<td>1126</td>
<td>4156</td>
<td>32.0%</td>
<td>1.08 [0.83, 1.40]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>177</td>
<td>4156</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.58 (P = 0.56)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>3540</td>
<td>4145</td>
<td>100.0%</td>
<td></td>
<td>0.91</td>
<td>0.91 [0.78, 1.05]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>383</td>
<td>322</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 2.72, df = 3 (P = 0.44); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.30 (P = 0.19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 2.55, df = 1 (P = 0.11), I² = 60.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure e-14: Sensitivity analysis comparing the risk of major bleeding among CKD patients on various NOAC categories vs. Warfarin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC</th>
<th>Warfarin</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>6.5.1 Factor X inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE (CKD mild), 2012</td>
<td>136</td>
<td>7550</td>
<td>176</td>
<td>7363</td>
</tr>
<tr>
<td>ARISTOTLE (CKD moderate), 2012</td>
<td>43</td>
<td>1357</td>
<td>83</td>
<td>1380</td>
</tr>
<tr>
<td>ARISTOTLE (CKD severe), 2012</td>
<td>5</td>
<td>136</td>
<td>15</td>
<td>132</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48 (CKD mild), 2013</td>
<td>267</td>
<td>4947</td>
<td>309</td>
<td>4130</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48 (CKD moderate), 2013</td>
<td>50</td>
<td>1302</td>
<td>66</td>
<td>1305</td>
</tr>
<tr>
<td>J-ROCKET AF, 2012</td>
<td>7</td>
<td>141</td>
<td>8</td>
<td>143</td>
</tr>
<tr>
<td>ROCKET-AF, 2011</td>
<td>66</td>
<td>1474</td>
<td>69</td>
<td>1476</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>16007</strong></td>
<td><strong>15929</strong></td>
<td><strong>50.9%</strong></td>
<td><strong>0.76 [0.64, 0.91]</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>574</td>
<td>726</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.02; Chi² = 11.43, df = 6 (P = 0.08); I² = 48%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.03 (P = 0.002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.5.2 Direct Thrombin inhibitors

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC</th>
<th>Warfarin</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>RE-LY CKD mild (Dabigatran 110), 2014</td>
<td>158</td>
<td>2803</td>
<td>209</td>
<td>2898</td>
</tr>
<tr>
<td>RE-LY CKD mild (Dabigatran 150), 2014</td>
<td>188</td>
<td>2852</td>
<td>209</td>
<td>2898</td>
</tr>
<tr>
<td>RE-LY CKD moderate (Dabigatran 110), 2014</td>
<td>122</td>
<td>1196</td>
<td>116</td>
<td>1125</td>
</tr>
<tr>
<td>RE-LY CKD moderate (Dabigatran 150), 2014</td>
<td>129</td>
<td>1232</td>
<td>116</td>
<td>1125</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>8083</strong></td>
<td><strong>8048</strong></td>
<td><strong>49.1%</strong></td>
<td><strong>0.91 [0.81, 1.02]</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>597</td>
<td>650</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 3.53, df = 3 (P = 0.32); I² = 15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.61 (P = 0.11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>24090</td>
<td>23977</td>
</tr>
<tr>
<td>Total events</td>
<td>1171</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.01; Chi² = 17.68, df = 10 (P = 0.06); I² = 43%</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.16 (P = 0.002)</td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 2.70, df = 1 (P = 0.10), I² = 62.9%</td>
<td></td>
</tr>
</tbody>
</table>
Figure e-15: Sensitivity analysis comparing the risk of ischemic stroke among CKD patients on Factor X inhibitors vs. Warfarin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Factor X inhibitors</th>
<th>Warfarin</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARISTOTLE, 2012</td>
<td>26</td>
<td>25</td>
<td>1.05 [0.61, 1.81]</td>
</tr>
<tr>
<td>ENGAGE AF–TIMI 48 (CKD mild), 2013</td>
<td>132</td>
<td>146</td>
<td>0.92 [0.73, 1.16]</td>
</tr>
<tr>
<td>ENGAGE AF–TIMI 48 (CKD moderate), 2013</td>
<td>63</td>
<td>62</td>
<td>1.00 [0.71, 1.41]</td>
</tr>
<tr>
<td>J-ROCKET AF, 2012</td>
<td>2</td>
<td>3</td>
<td>0.68 [0.11, 3.99]</td>
</tr>
<tr>
<td>ROCKET–AF, 2011</td>
<td>34</td>
<td>34</td>
<td>1.00 [0.63, 1.60]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>8556</td>
<td>8643</td>
<td>0.96 [0.81, 1.14]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 4.5, df = 4 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.64)
Figure e-16: Sensitivity analysis comparing the risk of major or minor bleeding among CKD patients on Factor X inhibitors vs. Warfarin.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Factor X inhibitors</th>
<th>Warfarin</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENCAGE AF-TIMI 48 (CKD mild), 2013</td>
<td>649 events</td>
<td>4047</td>
<td>49.5% 0.89 [0.81, 0.98]</td>
</tr>
<tr>
<td>ENCAGE AF-TIMI 48 (CKD moderate), 2013</td>
<td>220 events</td>
<td>1372</td>
<td>37.8% 0.77 [0.66, 0.90]</td>
</tr>
<tr>
<td>J-ROCKET AF, 2012</td>
<td>39 events</td>
<td>141</td>
<td>12.7% 1.20 [0.80, 1.79]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>5560</strong></td>
<td><strong>5629</strong></td>
<td><strong>100.0%</strong> 0.88 [0.75, 1.03]</td>
</tr>
<tr>
<td>Total events</td>
<td>908</td>
<td>1058</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.01; Chi² = 4.90, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 1.61 (P = 0.11)

Figure e-17: Subgroup analysis after adjustment of potential confounders comparing the risk of ischemic stroke among CKD patients on Warfarin vs. no anticoagulation.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrero et al, 2014</td>
<td>-0.7133</td>
<td>0.1442</td>
<td>56.1%</td>
<td>0.49 [0.37, 0.65]</td>
</tr>
<tr>
<td>Lai et al, 2009</td>
<td>-1.273</td>
<td>0.2855</td>
<td>38.9%</td>
<td>0.28 [0.16, 0.49]</td>
</tr>
<tr>
<td>Lin et al, 2017</td>
<td>0.5653</td>
<td>1.1925</td>
<td>5.0%</td>
<td>1.76 [0.17, 18.22]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>0.42 [0.24, 0.72]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.12; Chi² = 4.41, df = 2 (P = 0.11); I² = 55%
Test for overall effect: Z = 3.13 (P = 0.002)
**Figure e-18:** Subgroup analysis after adjustment of potential confounders comparing the risk of major bleeding among CKD patients on Warfarin vs. no anticoagulation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banerjee et al, 2014</td>
<td>-0.0408</td>
<td>0.2825</td>
<td>14.3%</td>
<td>0.96 [0.55, 1.67]</td>
<td></td>
</tr>
<tr>
<td>Carrero et al (CKD moderate), 2014</td>
<td>0.0392</td>
<td>0.1255</td>
<td>30.8%</td>
<td>1.04 [0.81, 1.33]</td>
<td></td>
</tr>
<tr>
<td>Carrero et al (CKD severe), 2014</td>
<td>-0.1985</td>
<td>0.2693</td>
<td>15.3%</td>
<td>0.82 [0.48, 1.39]</td>
<td></td>
</tr>
<tr>
<td>Lin et al, 2017</td>
<td>1.5282</td>
<td>0.7768</td>
<td>2.7%</td>
<td>4.61 [1.01, 21.13]</td>
<td></td>
</tr>
<tr>
<td>Olesen et al (CKD), 2012</td>
<td>0.3075</td>
<td>0.0797</td>
<td>37.0%</td>
<td>1.36 [1.16, 1.59]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>1.14 [0.88, 1.47]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.04; \text{Chi}^2 = 9.30, \text{df} = 4 (P = 0.05); I^2 = 57\%$

Test for overall effect: $Z = 0.99 (P = 0.32)$
**Figure e-19:** Subgroup analysis after adjustment of potential confounders comparing the risk of mortality among CKD patients on NOAC vs. Warfarin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARISTOTLE (CKD mild), 2012</td>
<td>-0.0408</td>
<td>0.0877</td>
<td>16.2%</td>
<td>0.96 [0.81, 1.14]</td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE (CKD moderate), 2012</td>
<td>-0.1508</td>
<td>0.1018</td>
<td>14.4%</td>
<td>0.86 [0.70, 1.05]</td>
<td></td>
</tr>
<tr>
<td>Loo et al. 2018</td>
<td>0.131</td>
<td>0.1568</td>
<td>9.2%</td>
<td>1.14 [0.84, 1.55]</td>
<td></td>
</tr>
<tr>
<td>RE-LY CKD mild (Dabigatran 110), 2014</td>
<td>-0.3285</td>
<td>0.1024</td>
<td>14.4%</td>
<td>0.72 [0.59, 0.88]</td>
<td></td>
</tr>
<tr>
<td>RE-LY CKD mild (Dabigatran 150), 2014</td>
<td>-0.2107</td>
<td>0.0972</td>
<td>15.0%</td>
<td>0.81 [0.67, 0.98]</td>
<td></td>
</tr>
<tr>
<td>RE-LY CKD moderate (Dabigatran 110), 2014</td>
<td>0.1484</td>
<td>0.1103</td>
<td>13.5%</td>
<td>1.16 [0.93, 1.44]</td>
<td></td>
</tr>
<tr>
<td>RE-LY CKD moderate (Dabigatran 150), 2014</td>
<td>0</td>
<td>0.1139</td>
<td>13.1%</td>
<td>1.00 [0.80, 1.25]</td>
<td></td>
</tr>
<tr>
<td>ROCKET-AF, 2011</td>
<td>-0.1863</td>
<td>0.2631</td>
<td>4.3%</td>
<td>0.83 [0.50, 1.39]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.92 [0.82, 1.04]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.01; \ Chi^2 = 15.05, df = 7 (P = 0.04); I^2 = 53%$

Test for overall effect: $Z = 1.38 (P = 0.17)$
References


