Efficacy and Safety of Non-vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Patients with Atrial Fibrillation and Cancer: a meta-analysis of randomized controlled trials

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Short Title: Anticoagulants in AF and Cancer

Word count: 2223
ABSTRACT

Background: The efficacy and safety of non-vitamin K antagonist oral anticoagulants (NOACs) in atrial fibrillation (AF) patients with cancer are unclear. The present study aims to assess the efficacy and safety of NOACs in AF patients with cancer.

Methods: To find all randomized controlled trials (RCTs) in which NOACs were compared against vitamin K antagonists (VKA) in AF with cancer, we have searched the Cochrane Library, PubMed, Embase databases and so on. Risk ratio (RR) was chosen as the statistic for dichotomous variables. Interval estimates use a 95% confidence interval (95%CI). Heterogeneity was evaluated in the I² statistic. Differences between groups were examined statistically significant at P<0.05.

Results: Four RCTs with a total of 3135 participants (male 67.5%) were included. Regarding the risk of stroke or systemic embolism (SE) [risk ratio (RR) 0.75, 95% confidence interval (95% CI) 0.52-1.09; P=0.14], venous thromboembolism (VTE) [RR 0.91, 95% CI 0.33-2.50; P=0.86] and all-cause death [RR 0.95, 95% CI 0.65-1.38; P=0.78], there was no significant difference between DOACs and VKAs in patients with AF and cancer. However, the NOACs group had a significantly lower incidence of major bleeding [RR 0.80, 95% CI 0.64-0.98; P=0.03], and anti-Xa were more effective than VKAs in reducing major bleeding [RR 0.79, 95% CI 0.62-0.99; P=0.04].

Conclusions: The present study for the first time finds that NOACs and VKAs are equally effective in preventing VTE and stroke in patients with AF and cancer, but the former has a lower risk of major bleeding. The efficacy and safety of NOACs in patients with AF and cancer still requires more trials to provide information.
**Introduction**

Atrial fibrillation (AF) is the commonest sustained arrhythmia, and the prevalence of AF increases with age, up to 10% over 80 years of age[1]. Compared with those in sinus rhythm, patients with AF have a 5-fold increase in the stroke risk, and anticoagulation therapy is the main treatment method for patients with AF[2]. Recent data indicate that the incidence of atrial fibrillation in cancer patients is increasing, and in certain cancer patients (eg, thoracic) new-onset AF can reach 30%[3]. Cancer patients and AF patients often share the same clinical characteristics, such as advanced age, electrolyte disorder, hypoxia, metabolic disorder and so on, but the mechanism of association between cancer and AF remains unclear[4]. The mechanism of cancer-related thrombosis has been well demonstrated[5,6]. However, due to frequent thrombocytopenia stemming from chemotherapy, endothelial dysfunction and tumour invasion, cancer may increase the risk of bleeding in AF patients[3], which is potentiated further with anticoagulant. Therefore, AF may be a major obstacle to cancer prognosis and treatment.

To date, NOACs have limited data of safety and efficacy in patients with AF and cancer. Existing study have compared efficacy and safety of various NOACs with Warfarin in this population, but with different results[7,8,9,10]. Due to lack of the guideline recommendations for antithrombotic therapy in patients with AF and cancer, which may bring obstacles to clinical treatment. In this meta-analysis, our goal is to determine the existence of any statistical significant difference in the safety and efficacy between NOAC and warfarin in the treatment of patients with AF and cancer, with a view to assisting in clinical anticoagulation decisions.

**Methods**

According to Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and
Meta-Analyses (PRISMA) statements, we designed the present meta-analysis\textsuperscript{[11]}.

**Search strategy**

PubMed, Embase, and Cochrane Central Register of Clinical Trials (Cochrane Library, Issue 02, 2017) databases were searched from January 2000 through March 2019 to identify RCTs comparing efficacy and safety of NOACs with Warfarin in patients with AF and cancer.

We used the following terms: (‘new oral anticoagulants’ OR ‘direct oral anticoagulants’ OR ‘non-vitamin K antagonist oral anticoagulants’ OR ‘dabigatran’ OR ‘rivaroxaban’ OR ‘apixaban’ OR ‘edoxaban’ OR ‘vitamin K antagonist oral anticoagulants’ OR ‘warfarin’) AND (‘malignancy’ OR ‘cancer’) AND (‘atrial fibrillation’ OR ‘persistent atrial fibrillation’ OR ‘paroxysmal atrial fibrillation’). No language restriction was set. In addition, bibliographies of identified articles were reviewed in order to find other sources.

**Eligibility criteria**

Inclusion criteria: (1) The subjects were all patients with atrial fibrillation and cancer who met the indications of using anticoagulants; (2) The type of study was randomized controlled trials (RCTs); (3) Intervention measures: the experimental group and the control group all use anticoagulants, and the types of anticoagulants are not limited; (4) Compared the clinical outcomes of stroke/systemic embolism(SE) and/or deep venous thromboembolism and/or major bleeding and/or all-cause mortality events between NOAC and warfarin in the treatment of patients with AF and cancer.

Exclusion criteria: (1) Case reports, editorials, reviews, retrospective study and PS-matched were excluded from our analysis. (2) We excluded the duplicate result and papers were determined to be unrelated to the study question. (3) We did not consider the summaries presented at major
international conferences that haven’t been published as full papers.

**Primary outcomes**

The primary outcomes of this study were (1) major bleeding events, (2) deep venous thromboembolism events, (3) stroke/systemic embolism(SE) events and (4) all-cause mortality events. The definition of major bleeding events was based on the Bleeding Academic Research Consortium (BARC) criteria. The score BARC \( \geq 2 \) was considered to be the main bleeding event\(^{[12]}\).

**Data extractions**

According to the inclusion and exclusion criteria, 2 researchers (W-CX and Y-PP) independently screened the literature, extracted the data and cross-checked. If there were any differences, they could be resolved through discussion or listening to the opinions of third parties (W-QH). The references to the retrieved articles were independently reviewed to further identify potential related studies. The contents of data extraction include: (1) basic information of the paper, including the first author, publication time, country/region; (2) intervention measures of experimental group and control group; (3) outcome indicators included stroke/systemic embolism, major bleeding, deep venous thromboembolism and all-cause death.

**Quality assessment**

Using the Cochrane Risk of Bias Tool to assess the quality and reporting of the included RCTs. The analysis includes six categories: the generation method of random sequences, whether to use blind method, allocation concealment, outcome data integrity, whether to selectively report results and other sources of bias.\(^{[13]}\). Quality of the included RCTs was summarized clearly.

**Statistical analysis**
According to recommendations of the Cochrane Collaboration and PRISMA guidelines, we have used Review Manager 5.3 to statistical analysis. RR was selected as the statistic for dichotomous variables, and the continuous variables used the mean difference (MD) as the statistic. Interval estimates use 95% CI. Differences between groups were considered statistically significant at P<0.05. Heterogeneity was assessed by the $I^2$ statistic, which is the ratio of total variation observed among the studies attributable to differences between studies rather than sampling errors\[^{14}\]. We considered $I^2 < 25\%$ as low and $I^2 > 75\%$ as high. If $I^2 < 25\%$, we will use the Mantel-Haenszel Risk Ratio (RR) Fixed-Effect model, and the random effects model was used if $I^2 > 25\%$\[^{15}\]. Using funnel plots to visually estimate publication bias\[^{15,16}\].

**Results**

Using the specified search criteria (Figure 1), we have identified a total of 197 studies. After screening step by step, 4 RCTs were finally included\[^{7,8,9,10}\], these four RCTs incorporated a total of 3135 participants (male 67.5\%). And five drugs were included in this study: dabigatran, rivaroxaban, apixaban, edoxaban and warfarin. The basic characteristics and interventions of each study are shown in Table 1, and bias risk assessment is shown in Figure 2 and Figure 3.

**Characteristics of included studies**

We summarized the baseline features of four RCTs in Table 1. A total of 1766 patients (56.33\%) with AF and cancer received NOACs, dabigatran in 84 (4.76\%), apixaban in 615 (34.82\%), rivaroxaban in 640 (36.24\%) and edoxaban in 1153 (65.29\%). 1369 patients (43.67\%) took Warfarin, and due to lack of data, the quality of control of the target international normalized ratio (INR) of warfarin-treated patients is unclear.

**The result of major bleeding events**
Four articles were included, including 3135 patients. Compared with warfarin, the NOACs group had significantly lower incidences of major bleeding in patients with AF and cancer [RR 0.80, 95% CI 0.64-0.98], and the results have statistical significance ($P=0.03$) (Figure 4A). It indicates that NOACs group has a lower risk of major bleeding in AF patients with cancer versus warfarin group.

**The result of all-cause death**

Three articles were included, including 3087 patients. No significant differences were found between NOACs group and warfarin group in the all-cause death[RR 0.95, 95% CI 0.65-1.38; $P=0.79$]. The all-cause death in the DOACs and VKA groups were 18.76% and 15.62%, respectively (Figure 4D).

**The result of VTE events**

Two articles were included, including 1872 patients. There were no between groups regarding the VTE events [RR 0.91, 95% CI 0.33-2.50; $P=0.86$]. Respectively, the VTE rates in the DOACs and warfarin groups were 0.76% and 0.84% (Figure 4B).

**The result of stroke/SE events**

Three articles were included, including 3025 patients. Regarding the stroke/SE events, there were no significant differences between groups [RR 0.75, 95% CI 0.52-1.09; $P=0.14$]. The stroke/SE rates in the DOACs and VKA groups were 3.33% and 4.01%, respectively (Figure 4C).

**Quality assessment and publication bias**

All RCTs included in this meta-analysis have good methodological quality, and indicating a low risk of bias (Figure 2 and Figure 3).

**Discussion**
Cancer and AF often coexist in elderly patients, the mechanism of association between AF and cancer has been reported, but remains unclear. Due to the development of tumor-targeted therapies technology, the life expectancy of cancer patients is becoming longer. Therefore, effective and safe strategies to reduce major bleeding events, VTE and stroke/SE events in patients with AF and cancer are much needed, yet few data can be used to guide care, which creates an unpredictable response about the best antithrombotic therapy for stroke prevention in this population.

Our study is the first meta-analysis available using all published RCTs data that compares the outcomes of NOACs with Warfarin in patients with AF and cancer on major bleeding events, VTE, stroke/SE and all-cause death. In this study, four RCTs and 3135 patients were included, involving four NOACs. The main results of this study included: (1) In patients with AF and cancer, NOACs users experienced lower rates in major bleeding events. (2) There are no significant differences between NOACs and warfarin for patients with AF and cancer in stroke/SE, VTE and all-cause death.

Anticoagulation has always been the main treatment for patients with AF, especially in cancer patients with high risk of thrombosis. However, cancer patients are often at high risk of bleeding, so the choice of antithrombotic therapy strategies in this population becomes very challenging. In the past 60 years, warfarin have been the first choice for anticoagulation therapy in patients with AF, so do as cancer patients. However, due to the shortcomings of warfarin in clinical use, some NOACs have been introduced in recent years. There are two main types of NOACs: (1) Direct thrombin inhibitors (dabigatran, et al); (2) Factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban, et al); Factor IIa (activated prothrombin) is the last link in the
coagulation cascade. Direct thrombin inhibitor (DIT) targets thrombin and directly binds to the activation site of thrombin to inhibit thrombin. Factor Xa inhibitor plays an anticoagulant role by inhibiting the conversion of thrombin pump into thrombin and inhibiting tissue factor-mediated thrombin production. Since factor Xa has been shown to promote procoagulant activity in cancer, the value of factor Xa inhibitors in these patients deserves special consideration[21].

During anticoagulation therapy, major bleeding is a very lethal complication. Using a large healthcare claims database, a current published observational research showed that stroke and bleeding rates in patients with AF and active cancer treated with NOACs were similar to those treated with warfarin, while VTE incidence was lower[22]. In our study, NOACs users experienced lower rates in major bleeding events, whereas there are no significant differences between NOACs and warfarin for patients with AF and cancer in stroke/SE, VTE and all-cause death. In the large phase 3 trial, patients with NOACs had almost half the frequency of intracerebral hemorrhage compared to warfarin, although their efficacy was similar[23]. Similar to our results, which NOACs still maintains an advantage in the risk of major bleeding in patients with AF and cancer.

At present, there is insufficient evidence to support specific recommendations for direct oral anticoagulants for patients with AF and cancer. However, considering the increasing prevalence of cancer and AF, it is necessary to better understand the safety and efficacy of NOACs in this population. Through our research, it has been preliminarily found that NOACs has a lower risk of major bleeding than warfarin in patients with AF and cancer. It should be noted that how to choose NOACs in patients with AF and cancer depends on the patient's specific situation and the advantages and disadvantages of various NOACs. Through our research, we hope our study can bring more attention to this field, rather than excluding cancer patients from enrolling in the trial.
Limitations

This meta-analysis has the following limitations. First, cancer populations included in the study were heterogeneous because there was very limited information about cancer stages and classification, diagnosis time or response to chemotherapy in these patients, in particular, exclusion criteria for some RCTs (ROCKET AF) may preclude patients with advanced malignancies, remote cancers, or those who significantly increase the risk of bleeding. Therefore, the current research population may not be able to extend to all cancer patients in clinical practice.

Second, due to data on end-point events for assessing safety and efficacy are limited, this study is limited to major bleeding, VTE, stroke/SE and all-cause mortality. As such, there is a lack of safety and efficacy evaluation for other endpoint events, such as non-major clinically relevant bleeding or overall bleeding and pulmonary embolism. Third, the number of samples included in the study varies greatly. Fourth, due to lack of data, the quality of control of the target INR of warfarin-treated patients is unclear, which may have a potential impact on the related endpoint events. Finally, we believe the main limitation of our analysis is that the subjects in the control group were heterogeneous.

Conclusions

After analysing efficacy and safety of anticoagulant therapy in patients with AF and cancer, we found there are no significant differences between NOACs and warfarin in stroke/SE, VTE and all-cause death, whereas NOACs users experienced lower rates in major bleeding events. Given NOACs have a wide therapeutic window, fewer drug interactions and no need for frequent laboratory monitoring and adjustment, NOACs should be considered first line therapy in patients with AF and cancer.
**Acknowledgements**

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**Disclosures**

The authors declare that there is no conflict of interest.
References


Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-34.


Figure Legends

Figure 1 Literature selection. Abbreviations: RCTs: randomized controlled trials.

Figure 2 Risk of bias summary.

Figure 3 Risk of bias graph. Review authors’ judgements about each risk of bias item presented as percentages across all included studies.

Figure 4A Forest plots of study outcomes. Forest plot of study outcomes for the comparison of NOACs with Warfarin for major bleeding in patients with AF and cancer. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI); width of the shaded square, size of the population. Abbreviations: AF: atrial fibrillation; NOACs: Non-vitamin K antagonist oral anticoagulants; CI: confidence interval.

Figure 4B Forest plot of study outcomes for the comparison of NOACs with Warfarin for VTE in patients with AF and cancer. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI); width of the shaded square, size of the population. Abbreviations: AF: atrial fibrillation; NOACs: Non-vitamin K antagonist oral anticoagulants; VTE: venous thromboembolism; CI: confidence interval.

Figure 4C Forest plot of study outcomes for the comparison of NOACs with Warfarin
for stroke/SE in patients with AF and cancer. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI); width of the shaded square, size of the population. Abbreviations: AF: atrial fibrillation; NOACs: Non-vitamin K antagonist oral anticoagulants; SE: systemic embolism. CI: confidence interval.

Figure 4D Forest plot of study outcomes for the comparison of NOACs with Warfarin for all-cause death. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI); width of the shaded square, size of the population. Abbreviations: AF: atrial fibrillation; NOACs: Non-vitamin K antagonist oral anticoagulants; CI: confidence interval.
Table 1. Characteristics of clinical trials involved in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Sample size (n)</th>
<th>Male (%)</th>
<th>Mean age</th>
<th>NOACs (n)</th>
<th>Treatment vs. Control</th>
<th>CHA₂DS₂-VASc</th>
<th>HAS-BLED</th>
<th>Follow-up</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flack[11], 2017 RE-LY</td>
<td>RCT</td>
<td>106</td>
<td>69 (65.1%)</td>
<td>76.8±6.7</td>
<td>84 (79.2%)</td>
<td>Dabigatran vs. Warfarin</td>
<td>NA</td>
<td>NA</td>
<td>3.3y</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Melloni[12], 2017 ARISTOTLE</td>
<td>RCT</td>
<td>1236</td>
<td>831 (67.2%)</td>
<td>75 (68-80)</td>
<td>615 (49.8%)</td>
<td>Apixaban vs. Warfarin</td>
<td>3.6 ± 2.2</td>
<td>1.8</td>
<td>1.8y</td>
<td>Stroke, death, bleeding</td>
</tr>
<tr>
<td>Chen[13], 2018 ROCKET AF</td>
<td>RCT</td>
<td>640</td>
<td>423 (66.1%)</td>
<td>76.5±4.5</td>
<td>309 (48.3%)</td>
<td>Rivaroxaban vs. Warfarin</td>
<td>3.5 ± 2.9</td>
<td>0.9</td>
<td>1.9y</td>
<td>Stroke, death, bleeding</td>
</tr>
<tr>
<td>Fanola[14], 2018 ENGAGE AF-TIMI 48</td>
<td>RCT</td>
<td>1153</td>
<td>794 (68.9%)</td>
<td>75 (68-79)</td>
<td>758 (65.7%)</td>
<td>Edoxaban vs. Warfarin</td>
<td>4.4 ± 2.7</td>
<td>2.8</td>
<td>2.8y</td>
<td>Stroke, death, bleeding</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; NOACs: non-vitamin K antagonist oral anticoagulants; CHA₂DS₂-VASc Score: (Congestive Heart Failure, Hypertension, Age ≥75 [Doubled], Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack [Doubled], Vascular Disease, Age 65-74, Female); HAS-BLED: (Hypertension, kidney function, abnormal liver function, stroke, history of bleeding, INR fluctuations, Age ≥65, smoking, drink).
We searched Pubmed, Embase and Cochrane Central Register of Clinical Trials, and reference lists were screened for relevant studies.

197 results

150 papers excluded based on title and abstract evaluation. Duplicate result (n=34). Not related to our study (n=103). Case reports or Review (n=13).

47 results

41 papers were excluded, as they were determined to be unrelated to the study question.

6 results

2 papers were excluded after careful reading of the full text. Retrospective (n=1).

4 RCTs included in the meta-analysis and qualitative synthesis.

Figure 1 Literature selection. RCTs: randomized controlled trials.
Figure 2 Risk of bias summary.

Figure 3 Risk of bias graph. Review authors’ judgements about each risk of bias item presented as percentages across all included studies.
Figure 4A Forest plots of study outcomes. Forest plot of study outcomes for the comparison of NOACs with Warfarin for major bleeding in patients with AF and cancer. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI); width of the shaded square, size of the population.

Abbreviations: AF: atrial fibrillation; NOACs: Non-vitamin K antagonist oral anticoagulants; CI: confidence interval.
Figure 4B Forest plot of study outcomes for the comparison of NOACs with Warfarin for VTE in patients with AF and cancer. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI); width of the shaded square, size of the population. Abbreviations: AF: atrial fibrillation; NOACs: Non-vitamin K antagonist oral anticoagulants; VTE: venous thromboembolism; CI: confidence interval.

Figure 4C Forest plot of study outcomes for the comparison of NOACs with Warfarin for stroke/SE in patients with AF and cancer. Diamond indicates overall summary
estimate for the analysis (width of the diamond represents the 95% CI); width of the shaded square, size of the population. Abbreviations: AF: atrial fibrillation; NOACs: Non-vitamin K antagonist oral anticoagulants; SE: systemic embolism. CI: confidence interval.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOACs</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>4.2.1 Rivaroxaban</td>
<td>Chen 2018</td>
<td>32</td>
<td>370</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>370</td>
<td>48</td>
<td>328</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>32</td>
<td>48</td>
<td>328</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
<td>32</td>
<td>48</td>
<td>328</td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 2.44 (P = 0.01)</td>
<td>32</td>
<td>48</td>
<td>328</td>
</tr>
<tr>
<td>4.2.2 Edoxaban</td>
<td>Fon Holz 2018</td>
<td>241</td>
<td>758</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>758</td>
<td>120</td>
<td>395</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>241</td>
<td>120</td>
<td>395</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
<td>241</td>
<td>120</td>
<td>395</td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 0.49 (P = 0.62)</td>
<td>241</td>
<td>120</td>
<td>395</td>
</tr>
<tr>
<td>4.2.3 Apixiban</td>
<td>Mallon 2017</td>
<td>54</td>
<td>615</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>615</td>
<td>42</td>
<td>621</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>54</td>
<td>42</td>
<td>621</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
<td>54</td>
<td>42</td>
<td>621</td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 1.32 (P = 0.19)</td>
<td>54</td>
<td>42</td>
<td>621</td>
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<tr>
<td></td>
<td>Total (95% CI)</td>
<td>1743</td>
<td>1344</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>327</td>
<td>210</td>
<td>0.95 [0.65, 1.38]</td>
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<tr>
<td></td>
<td>Heterogeneity: Tau² = 0.00; Chi² = 7.99, df = 2 (P = 0.02); I² = 75%</td>
<td>327</td>
<td>210</td>
<td>0.95 [0.65, 1.38]</td>
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<tr>
<td></td>
<td>Test for overall effect: Z = 0.28 (P = 0.79)</td>
<td>327</td>
<td>210</td>
<td>0.95 [0.65, 1.38]</td>
</tr>
<tr>
<td></td>
<td>Test for subgroup differences: Chi² = 7.95, df = 2 (P = 0.02), I² = 74.8%</td>
<td>327</td>
<td>210</td>
<td>0.95 [0.65, 1.38]</td>
</tr>
</tbody>
</table>

Figure 4D Forest plot of study outcomes for the comparison of NOACs with Warfarin for all-cause death. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI); width of the shaded square, size of the population. Abbreviations: AF: atrial fibrillation; NOACs: Non-vitamin K antagonist oral anticoagulants; CI: confidence interval.