# Supplementary Material

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Methods

eMethods I – Search strategy
Studies were searched through November 20th, 2019.

Search terms were as follows:
- Atrial fibrillation OR Atrial arrhythmia OR Heart failure
- Anticoagulant OR Anti-coagulant OR Anticoagulation OR anti thrombin OR Anti-thrombin OR Warfarin OR Rivaroxaban OR Edoxaban OR Apixaban OR Dabigatran OR Acenocoumarol OR Ximelagatran OR Coumarin
- Placebo OR Aspirin OR Clopidogrel OR Triflusal OR Ticagrelor OR Prasugrel
- Randomized controlled trial OR Randomised controlled trial OR Controlled clinical trial OR Randomized OR Randomised OR placebo OR Drug therapy OR Randomly OR Trial OR Groups
- Animals NOT Humans

The search was conducted through Pubmed and EMBASE.
## eTable I – Definitions of composite and major hemorrhage outcomes

| Trial                  | Composite outcome                                                                 | Major haemorrhage                                                                                                                                 |
|------------------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| **Atrial fibrillation trials** |                                                                                    |                                                                                        |
| AVERROES (2011)         | Occurrence of stroke (ischaemic or haemorrhagic) or systemic emboli.               | Major bleeding defined as clinically overt bleeding accompanied by one or more of the following: a decrease in the haemoglobin level of 2g/dL or more over a 24 hour period, transfusion of 2 or more units of packed red cells, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding. |
| WASPO (2007)            | Comparative frequency of combined endpoints comprising of death, thromboembolism, serious bleeding and withdrawal from the study. | Serious bleeding defined as intracranial haemorrhage, fall in haemoglobin by >2g/dL, need for blood transfusion. |
| BAFTA (2007)            | First occurrence of fatal or non-disabling stroke (ischaemic or hemorrhagic), other intracranial hemorrhage, or clinically significant arterial embolism. | Major hemorrhage was defined as extracranial haemorrhage defined as a fatal haemorrhage, or one that resulted in the need for transfusion or surgery, or intracranial haemorrhage (including haemorrhagic stroke). |
| Vemmos et al (2006)     | Ischaemic stroke or systemic emboli.                                               | Major bleeding was defined as intracranial hemorrhage, fatal bleeding, or bleeding leading to hospital admission, emergency procedures, or urgent transfusion. |
| ACTIVE W (2006)         | First occurrence of stroke, non-CNS systemic embolism, myocardial infarction, or vascular death. | Major bleeding was defined as any bleeding requiring transfusion of at least two units of red blood cells or equivalent of whole blood, or which was severe (severe bleeding was bleeding associated with any of the following: death, drop in haemoglobin of at least 50g/L, substantial hypotension with the need for inotropic agents, intraocular bleeding leading to substantial loss of vision, bleeding requiring surgical intervention (other than vascular site repair), symptomatic intracranial hemorrhage, or requirement for a transfusion of at least four units of blood). |
| SPEAF (intermediate risk group) (2004) | Composite of vascular death, transient ischaemic attack (TIA), and nonfatal stroke or systemic embolism, whichever came first. | Bleeding considered severe when requiring hospital admission, blood transfusion or surgery. |
| PATAF-stratum 1 (1999)  | Stroke (ischaemic or hemorrhagic), systemic arterial embolism, major hemorrhage or vascular death. | Major hemorrhage defined as requiring hospital admission and blood transfusion or causing fall in haemoglobin concentration or 2.0mmol/L or more. |
| AFASAK II (1998)        | Stroke (ischaemic or hemorrhagic) or a systemic thromboembolic event.              | Major bleeding was defined as fatal, life-threatening, or potentially life-threatening, requiring surgical treatment or blood transfusion. |
| SPAF II (all ages) (1994) | Ischaemic stroke or systemic emboli.                                               | Major hemorrhage was assessed by the criteria of Landefeld et al. |
| EAF (1993)              | Death from vascular disease, non-fatal stroke (including intracranial haemorrhage), non-fatal myocardial infarction, or systemic embolism. | Major bleeding was defined as requiring hospital admission, blood transfusion or surgery, or when it caused permanent increase in disability. |
| BAATAF (1992)           | Not applicable.                                                                    | Not applicable.                                                                         |
| Veterans (1992)         | Primary event(cerebral infarction) or death.                                       | A major hemorrhage was defined as one that required a blood transfusion, an emergency procedure, or both to terminate bleeding or remove a hematoma or that led to admission to an intensive care unit. |
| SPAF (1991)             | Primary event(ischaemic stroke or systemic emboli) or death.                      | Bleeding that involved the central nervous system, management requiring hospitalization with transfusion and/or surgery, or permanent residual impairment. |
| CAFA (1991)             | First occurrence of any of the following: ischaemic stroke except lacunar, other systemic embolism or intracranial or fatal hemorrhage. | A major bleeding event was defined as any bleeding episode associated with 20g/L decrease or more in serum haemoglobin or requiring a blood transfusion or bleeding into a sensitive location such as the pericardium or retinal. |
| AFASAK (1989)           | Stroke (ischaemic or hemorrhagic) or a systemic thromboembolic event.             | Major bleeding was defined as requiring medical intervention. |
| HFrEF trials                       | Event of interest                                                                 | Major bleeding definition                                                                                                                                                                                                 |
|------------------------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Compass (2019)                     | Composite of cardiovascular death, stroke, or myocardial infarction.                | All bleeding that led to presentation to an acute care facility or hospitalization was considered as major. This included fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to hospitalization (including presentation to an acute care facility without an overnight stay). |
| Commander HF (2018)                | Composite of death from any cause, myocardial infarction, or stroke.                | Major bleeding is defined as overt bleeding associated with a decrease in haemoglobin level of at least 2g/dL, transfusion of two or more units of packed red cells or whole blood, a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome or retroperitoneal), or a fatal outcome. |
| WARCEF (2012)                      | Composite end point of ischaemic stroke, intracerebral haemorrhage, or death from any cause. | Major hemorrhage was defined as intracerebral, epidural, subdural, subarachnoid, spinal intramedullary, or retinal haemorrhage; any other bleeding causing a decline in the haemoglobin level of more than 2 g per decilitre in 48 hours; or bleeding requiring transfusion of 2 or more units of whole blood, hospitalization, or surgical intervention. |
| WATCH (2009)                       | All-cause mortality, nonfatal MI and nonfatal stroke.                               | Major bleeding was defined as bleeding episodes leading to death or disability (including loss of neurological or special senses function), requiring surgical intervention, or associated with an acute decline of haemoglobin of greater than 2gm/dL or transfusion of more than 1 unit of packed red cells or whole blood. |
| HELAS (2006)                       | Non-fatal stroke, peripheral or pulmonary embolism, myocardial (re)infarction, re-hospitalisation, exacerbation of heart failure, or death from any cause. | Not reported.                                                                                                                                                                                                             |
| WASH (2004)                        | The composite outcome of death, nonfatal myocardial infarction, and nonfatal stroke. | Major bleeding was defined as hemorrhage requiring transfusion.                                                                                                                                                           |
| Trial                  | No. of participants | Trial design                        | Study Population                                                                 | Intervention group | Control group | Dose/INR target | Follow-up (months) |
|-----------------------|---------------------|-------------------------------------|----------------------------------------------------------------------------------|--------------------|---------------|-----------------|--------------------|
| **Atrial fibrillation trials** |                     |                                     |                                                                                  |                    |               |                 |                    |
| AVERROES, 2011        | 5599                | Randomized, double-blind, double-dummy | Atrial fibrillation and ≥1 risk factor; prior stroke or TIA, >75 years, HTN, DM, HF EF <35% or PVD. | Apixaban           | Aspirin       | -               | 13.2              |
| WASPO, 2007           | 75                  | Randomized, open label trial.       | Permanent atrial fibrillation, age 80-90 years of age, ambulatory.              | Warfarin           | Aspirin       | 2-3             | 12                 |
| BAFTA, 2007           | 973                 | Randomized, open label trial, blinded endpoints. | Atrial fibrillation, age over 75 years.                                        | Warfarin           | Aspirin       | 2-3             | 32.4               |
| Vemmos et al., 2006   | 31                  | Randomized, open label trial.       | Atrial fibrillation, age over 75 years.                                        | Adjusted dose coumadin v Fixed dose coumadin | Aspirin       | 1.6-2.5         | 3.7                |
| ACTIVE W, 2006        | 6706                | Randomized, open label, blinded adjudication of outcomes. | Atrial fibrillation and ≥1 risk factor: >75 years, HTN, previous stroke, TIA, or non-CNS systemic embolus, LV dysfunction with EF <45%, PVD. | Warfarin           | Aspirin and clopidogrel | 2-3             | 15.4               |
| Study                  | Randomized, open label trial | Atrial fibrillation. | Warfarin | Aspirin | **p**-Value |
|------------------------|-------------------------------|----------------------|----------|---------|-------------|
| SPEAF (intermediate risk group), 2004 | 479                           | Chronic or documented paroxysmal AF, medium or high risk according to Stroke Prevention in Atrial Fibrillation (SPAF) III stratification. | Acenocoumarol vs Triflusual and Acenocoumarol | Triflusual | 2.3-3.3  |
| PATAF-stratum 1, 1999 | 272                           | Chronic or intermittent atrial fibrillation, age over 60. | Adjusted dose coumadin vs Low dose coumadin | Aspirin | 2.5-3.5  |
| AFASAK II, 1998       | 339                           | Non-valvular chronic atrial fibrillation. | Minidose warfarin vs Minidose warfarin and aspirin vs Aspirin vs Warfarin | Aspirin | 2.3 |
| SPAF II (all ages), 1994 | 1100                          | Atrial fibrillation. | Warfarin | Aspirin | 2.45-24 |
| EAFT, 1993            | 1007                          | Atrial fibrillation, TIA or ischaemic stroke (Rankin 3 or less) within 3 months of enrolment. | Oral anticoagulant (coumarin derivative) | Aspirin vs Placebo | 2.5-4 |
| BAATAF, 1992          | 420                           | Atrial fibrillation (chronic or paroxysmal). | Warfarin | Placebo** | 1.5-2.7 |
| Veterans, 1992        | 525                           | Atrial fibrillation without rheumatic heart disease | Warfarin | Placebo | 1.4-2.8 |

**p**-values are indicated where appropriate.
| Study            | N   | Design                           | Eligibility                                      | intervention | Comparator        | HR(95%CI) |
|------------------|-----|----------------------------------|--------------------------------------------------|--------------|-------------------|-----------|
| SPAF, 1991 27    | 421 | Randomized, open label anticoagulation arm, blinded aspirin/placebo arms. | Documented atrial fibrillation.                  | Warfarin     | Aspirin v Placebo | 2.45 (1.7) |
| CAFA, 1991 28    | 378 | Randomized, triple blinded trial. | Atrial fibrillation (chronic or paroxysmal).     | Warfarin     | Placebo           | 2.3 (1.6) |
| AFASAK, 1989 29  | 1007| Randomized controlled trial, open label anticoagulation arm, blinded aspirin/placebo arms. | Chronic atrial fibrillation.                     | Warfarin     | Aspirin v Placebo | 2.8-4.2  |

**HFpEF trials**

| Study            | N   | Design                           | Eligibility                                      | intervention | Comparator        | HR(95%CI) |
|------------------|-----|----------------------------------|--------------------------------------------------|--------------|-------------------|-----------|
| COMPASS, 2019 30 | 476 | Randomized, double-blind trial.  | Chronic coronary artery disease or peripheral artery disease. Subgroup- EF <40% | Rivaroxaban and Aspirin | Aspirin   | - (23)   |
| Commander HF, 2018 6 | 5022| Randomized, double-blind trial.  | Chronic heart failure, a left ventricular ejection fraction of 40% or less and coronary artery disease and an episode of heart failure within 21 days. | Rivaroxaban | Placebo*          | - (21.1)  |
| WARCEF, 2012 31  | 2305| Randomized, double-blind, double-dummy, control trial. | Heart failure (NYHA I-IV), sinus rhythm.         | Warfarin     | Aspirin           | 2.35 (42) |
| Study         | Patients | Design                              | Primary Diagnoses                              | Treatment                     | Comparator                        | Outcome | Clot Prevention |
|--------------|----------|-------------------------------------|-----------------------------------------------|-------------------------------|-----------------------------------|---------|-----------------|
| WATCH, 2009  | 1587     | Randomized control trial. Open label-warfarin, double blind-aspirin/clopidogrel. | Heart failure (NYHA II-IV), sinus rhythm.      | Warfarin                      | Aspirin v Clopidogrel              | 2.5-3   | 22.8            |
| HELAS, 2006  | 115      | Randomized, double-blind, placebo control | Heart failure (NYHA II-IV), ejection fraction of less than 35%, sinus rhythm | Ischaemic heart disease       | Warfarin                          | Aspirin | 2-3 | 18.6 |
|             |          |                                     |                                               | Dilated cardiomyopathy        | Warfarin                        | Placebo |                 |
|             | 82       |                                     |                                               |                               |                                   |         |                 |
| WASH, 2004   | 279      | Randomized, open-label trail, blinded end point. | Heart failure (NYHA II-IV), sinus rhythm.      | Warfarin                      | Aspirin v No antithrombotic therapy | 2-3    | 27              |

*Aspirin taken by 93.1\% of all patients.
†Only aspirin control arm was included in the analysis.
‡Only triflusal control arm was included in the analysis.
**Placebo group may take aspirin.
††Stratum 2 excluded from analysis as therapy evaluated was low dose anticoagulation versus aspirin.
‡‡ All values for follow-up are reported as mean with the exception of SPEAF, this follow-up value is reported as median as mean was not reported.

Abbreviations: DCM, dilated cardiomyopathy; IHD, ischaemic heart disease; TIA, transient ischaemic attack.
eTable III – Baseline characteristics

| Trial                                | Mean Age | Female Participants, No. (%) | Subjects (Anticoagulant) | Subjects (Control) |
|--------------------------------------|----------|------------------------------|--------------------------|-------------------|
| AVERROES, 2011                        | 70       | 41.5                         | 2808                     | 2791              |
| WASPO, 2007                           | 83       | 53.3                         | 36                       | 39                |
| BAFTA, 2007                           | 81.5     | 45.4                         | 488                      | 485               |
| Vemmso et al., 2006                   | 80       | 49                           | 16                       | 15                |
| ACTIVE W, 2006                        | 70.2     | 33.9                         | 3371                     | 3335              |
| SPEAF (intermediate risk group), 2004 | 69       | 43.6                         | 237                      | 242               |
| PATAF-stratum 1, 1999                 | 74.8     | 55.1                         | 131                      | 141               |
| AFASAK II, 1998                       | 76.5     | 40                           | 170                      | 169               |
| SPAF II (all ages), 1994              | 64       | 24                           | 555                      | 545               |
| SPAF, 1991                            | 67       | 29                           | 210                      | 211               |
| CAFA, 1991                            | 67.7     | 25.4                         | 187                      | 191               |
| AFASAK, 1989                          | 74.2     | 46.3                         | 335                      | 672               |
| **Heart failure trials**              |          |                              |                          |                   |
| COMPASS, 2019                         | 65.5     | 23.2                         | 236                      | 240               |
| Commander HF, 2018                    | 66.4     | 22.9                         | 2507                     | 2515              |
| WARCEF, 2012                          | 61       | 19.9                         | 1142                     | 1163              |
| WATCH, 2009                           | 63       | 15                           | 540                      | 1047              |
| HELAS, 2006                           | 61.7     | 11                           | 54                       | 61                |
| WASH, 2004                            | 62.6     | 25.7                         | 89                       | 190               |
### eTable IV – Risk of Bias Summary Table

| Trial                        | Randomization process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall Bias |
|------------------------------|-----------------------|-----------------------------------------|----------------------|-----------------------------|---------------------------------|--------------|
| **Atrial Fibrillation Trials** |                       |                                         |                      |                             |                                 |              |
| AVERROES (2011)              | Low                   | Low                                     | Low                  | Low                         | Low                             | Low          |
| WASPO (2007)                 | Low                   | Low                                     | Low                  | Low                         | Low                             | Low          |
| BAFTA (2007)                | Low                   | Low                                     | Low                  | Low                         | Low                             | Low          |
| Vemmos et al (2006)         | Some Concerns         | Low                                     | Low                  | Some Concerns               | Low                             | Some Concerns |
| ACTIVE W (2006)             | Low                   | Low                                     | Low                  | Low                         | Low                             | Low          |
| SPEAF (2004)                | Low                   | High                                    | Low                  | Low                         | Low                             | Low          |
| PATAF (1999)                | Low                   | Low                                     | Low                  | Low                         | Low                             | Low          |
| AFASAK II (1998)            | Low                   | Low                                     | Low                  | Low                         | Low                             | Low          |
| SPAF II (1994)              | Low                   | Low                                     | Low                  | Low                         | Low                             | Low          |
| EAF (1993)                  | Low                   | Low                                     | Low                  | Low                         | Low                             | Low          |
| BAATAF (1992)               | Some Concerns         | High                                    | Low                  | Low                         | Low                             | Low          |
| Veterans (1992)             | Low                   | Low                                     | Low                  | Low                         | Low                             | Low          |
| SPAF (1991)                 | Low                   | Low                                     | Low                  | Low                         | Low                             | Low          |
| CAFA (1991)                 | Some Concerns         | Low                                     | Low                  | Low                         | Low                             | Some Concerns |
| AFASAK (1989)               | Low                   | Low                                     | High                 | Low                         | Low                             | High         |
| **HFrEF**                   |                       |                                         |                      |                             |                                 |              |
| COMPASS (2019)              | Low                   | Low                                     | Low                  | Low                         | Low                             | Low          |
| COMMANDER HF (2018)         | Low                   | Low                                     | Low                  | Low                         | Low                             | Low          |
| WARCEF (2012)               | Low                   | Low                                     | Low                  | Low                         | Low                             | Low          |
| WATCH (2009)                | Low                   | Low                                     | Low                  | Low                         | Low                             | Low          |
| HELAS (2006)                | Low                   | Some Concerns                           | Low                  | Low                         | Low                             | Some Concerns |
| WASH (2004)                 | Low                   | Low                                     | Low                  | Low                         | Low                             | Low          |
# eTable V – Prisma checklist

| Section/topic | # | Checklist Item                                                                                                                                                                                                                                                                                                                                 | Reported on page # |
|---------------|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| **TITLE**     |   |                                                                                                                                ---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|                   |
| Title         | 1 | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                                                                                                                                                             | 1                 |
| **ABSTRACT**  |   |                                                                                                                                                                                                                                                                                                                                                  |                   |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3-4               |
| **INTRODUCTION** |   |                                                                                                                                                                                                                                                                                                                                                 |                   |
| Rationale     | 3 | Describe the rationale for the review in the context of what is already known.                                                                                                                                                                                                         | 5                 |
| Objectives    | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                                                                                                                                                                   | 6-7               |
| **METHODS**   |   |                                                                                                                                                                                                                                                                                                                                                  |                   |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. (PROSPERO identifier: CRD42020153013)                                                                                                      |                   |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                                                                                                                                                        | 7                 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                                                                                                                                                                   | 7                 |
| Search        | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                                                                                                                                                  | 7                 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                                                                                                                                                                  | 7                 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                                                                                                                                                                   | 8                 |
| Data items    | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                                                                                                                                                                 | 8                 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.                                                                                                                                                                                                 | 9                 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                                                                                               | 9                 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I$^2$) for each meta-analysis.                                                                                                                                                                                                 | 8-9               |
| Guideline                             | Atrial fibrillation (Year)                                                                                                                                                                                                 | HFrEF (Year)                                                                                                                                                                                                 |
|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| European Society of Cardiology       | Grade 1A recommendation for oral anticoagulation to prevent thromboembolism in those with a CHA₂DS-VASc ≥ 2 (2020)                                                                                                          | Grade IIa recommendation for chronic cardiac syndrome in sinus rhythm at high stroke risk (IIb for moderate risk) to consider dual antiplatelet therapy or low dose rivaroxaban (2019)                                          |
| American Heart Association           | Class 1 recommendation for oral anticoagulation for primary stroke prevention (warfarin 1A, DOAC 1B) (2019)                                                                                                                                                                    | Do not recommend anticoagulation in patients with heart failure with reduced ejection fraction in the absence of atrial fibrillation (level B) (2013)                                                    |
| Canadian Cardiovascular Society      | Recommend anticoagulation for those with a CHA₂DS-VASc ≥ 1 (2018)                                                                                                                                                      |                                                                                                                                                                                                             |
| The American College of Chest Physicians | Recommend anticoagulation for a three-month period following an anterior myocardial infarction and left ventricular thrombus or an ejection fraction of ≤40%. Grade 2C recommendation against anticoagulation for those with non-ischaemic LV dysfunction (2012) |                                                                                                                                                                                                             |
| Heart failure society of America     | Treatment with warfarin (goal INR 2.0-3.0) is recommended for all patients with HF and a history of systemic or pulmonary emboli, including stroke or transient ischaemic attack, (Strength of Evidence C) (2010)                                |                                                                                                                                                                                                             |
Figures

eFigure I – Contour enhanced funnel plot for atrial fibrillation trials, all stroke outcome.

Different levels of statistical significance for studies are indicated by the shaded regions, detailed within the figure. The grey vertical line represents the summary estimate for oral anticoagulation and all stroke.

eFigure II – Contour enhanced funnel plot for HFrEF trials, all stroke outcome.
eFigure II – Contour enhanced funnel plot for HFrEF trials, all stroke outcome. Different levels of statistical significance for studies are indicated by the shaded regions, detailed within the figure. The grey vertical line represents the summary estimate for oral anticoagulation and all stroke.
### eFigure III – Cross Tabulation Risk of Bias

| Unique ID  | Outcome | Weight | Randomization process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall |
|------------|---------|--------|-----------------------|----------------------------------------|----------------------|---------------------------|----------------------------------|---------|
| 1 WARCEF   | All stroke | 9.79   | +                     | +                                      | +                    | +                         | +                                 | Low risk|
| 2 WATCH    | All stroke | 1.61   | +                     | +                                      | +                    | +                         | +                                 | Some concerns|
| 3 WASH     | All stroke | 0.28   | +                     | +                                      | +                    | +                         | +                                 | High risk|
| 4 WASPO    | All stroke | 0.16   | +                     | +                                      | +                    | +                         | +                                 |               |
| 5 BAFTA    | All stroke | 9.43   | +                     | +                                      | +                    | +                         | +                                 |               |
| 6 AFASAK II| All stroke | 2.64   | +                     | +                                      | +                    | +                         | +                                 |               |
| 7 ACTIVE W | All stroke | 14.57  | +                     | +                                      | +                    | +                         | +                                 |               |
| 8 SPAF II  | All stroke | 10.13  | +                     | +                                      | +                    | +                         | +                                 |               |
| 9 AVERROES | All stroke | 13.6   | +                     | +                                      | +                    | +                         | +                                 |               |
| 10 EAFT    | All stroke | 8.11   | +                     | +                                      | +                    | +                         | +                                 |               |
| 11 COMMANDER HF | All stroke | 12.8  | +                     | +                                      | +                    | +                         | +                                 |               |
| 12 AFASAK  | All stroke | 2.53   | +                     | +                                      | +                    | +                         | +                                 |               |
| 13 HELAS   | All stroke | 0.73   | +                     | ?                                      | +                    | +                         | +                                 |               |
| 14 SPEAF   | All stroke | 2.25   | +                     | -                                      | +                    | +                         | -                                 |               |
| 15 BAATAF  | All stroke | 1.05   | ?                     | -                                      | +                    | +                         | -                                 |               |
| 16 SPAF    | All stroke | 2.78   | +                     | +                                      | +                    | +                         | +                                 |               |
| 17 Vemmos et al | All stroke | 0.25  | ?                     | +                                      | ?                    | +                         | ?                                 |               |
| 18 PATAF   | All stroke | 1.03   | +                     | +                                      | +                    | +                         | +                                 |               |
| 19 Veterans| All stroke | 2.29   | +                     | +                                      | +                    | +                         | +                                 |               |
| 20 CAFA    | All stroke | 2.26   | ?                     | +                                      | +                    | +                         | !                                 |               |
| 21 COMPASS | All stroke | 1.72   | +                     | +                                      | +                    | +                         | +                                 |               |

eFigure III was generated using the Cochrane Risk of Bias 2 tool.
https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials
eFigure IV – Risk of Bias Summary

As percentage (intention-to-treat)

Overall Bias
Selection of the reported result
Measurement of the outcome
Mising outcome data
Deviations from intended interventions
Randomization process

86 88 90 92 94 96 98 100

Low risk  Some concerns  High risk

eFigure IV was generating using the Cochrane Risk of Bias 2 tool.
https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials
eFigure V – Prisma flow diagram

Records identified through database searching (n = 2162)

Additional records identified through other sources (n = 0)

Records after duplicates removed (n = 1046)

Records screened (n = 1046)

Records excluded (n = 978)

Full-text articles assessed for eligibility (n = 68)

Studies included in qualitative synthesis (n = 21)

Studies included in quantitative synthesis (meta-analysis) (n = 21)

Full-text articles excluded, with reasons:
Not RCT comparing OAC with Control in population of interest (n = 43)
Unable to locate English translation (n = 2)
RCT not completed (n = 2)
### Association of Oral Anticoagulation with Hemorrhagic Stroke

| Study, Year | OAC Event Total | Control Event Total | ARR (95% CI) | Favors | Favors | Odds Ratio (95% CI) |
|-------------|-----------------|---------------------|--------------|--------|--------|---------------------|
| _Atrial fibrillation_ | | | | | | |
| AVERROES, 2011 [15] | 6 2808 | 9 2791 | 0.11 [-0.16 to 0.38] | 17.97% | 0.66 [0.24, 1.86] | |
| BAFFO, 2007 [17] | 6 488 | 5 485 | -0.20 [-1.53 to 1.13] | 14.11% | 1.20 [0.36, 3.94] | |
| WASPS, 2007 [16] | 0 36 | 0 39 | -0.10 [-5.17 to 4.97] | 1.47% | 1.08 [0.02, 55.96] | |
| Veemms et al, 2006 [18] | 0 16 | 0 15 | 0.18 [-11.53 to 11.90] | 1.45% | 0.94 [0.02, 50.31] | |
| ACTIVE W, 2006 [19] | 15 3371 | 5 3335 | -0.30 [-0.56 to -0.03] | 18.59% | 2.98 [1.08, 8.20] | |
| SPEA (intermed), 2004 [20] | 1 237 | 2 242 | 0.40 [-1.00 to 1.81] | 3.86% | 0.51 [0.05, 5.65] | |
| PATAF-stratum 1, 1999 [21] | 1 131 | 1 141 | -0.05 [-2.09 to 1.98] | 2.92% | 1.08 [0.07, 17.39] | |
| AFASAKI, 1998 [22] | 1 170 | 1 169 | 0.00 [-1.63 to 1.63] | 2.92% | 0.99 [0.06, 16.02] | |
| EAF, 1993 [24] | 0 225 | 3 782 | 0.23 [-0.54 to 1.00] | 2.58% | 0.49 [0.03, 9.60] | |
| Veterans, 1992 [26] | 1 260 | 0 265 | -0.39 [-1.44 to 0.67] | 2.22% | 3.07 [0.12, 75.69] | |
| BAATF, 1992 [25] | 0 212 | 0 208 | 0.00 [-0.92 to 0.93] | 1.49% | 0.98 [0.02, 49.68] | |
| SPAF (Group I), 1991 [27] | 1 210 | 0 211 | -0.48 [-1.78 to 0.83] | 2.21% | 3.03 [0.12, 74.77] | |
| RE Model for Subgroup (Q = 5.86, df = 11, p = 0.88; I² = 9.3%) | -0.092 [-0.3 to 0.086] | | 1.24 [0.69, 2.25] | |

### HFREF

| Study, Year | OAC Event Total | Control Event Total | ARR (95% CI) | Favors | Favors | Odds Ratio (95% CI) |
|-------------|-----------------|---------------------|--------------|--------|--------|---------------------|
| COMMANDER HF, 2018 [6] | 6 2507 | 8 2515 | 0.08 [-0.21 to 0.37] | 17.26% | 0.75 [0.26, 2.17] | |
| WARCEF, 2012 [31] | 5 1142 | 2 1163 | -0.27 [-0.72 to 0.19] | 7.97% | 2.55 [0.49, 13.18] | |
| WATCH, 2009 [4] | 0 540 | 0 1047 | -0.04 [-0.33 to 0.24] | 1.49% | 1.94 [0.04, 97.80] | |
| WASH, 2004 [5] | 0 89 | 0 190 | -0.29 [-1.99 to 1.40] | 1.49% | 2.13 [0.04, 108.13] | |
| RE Model for Subgroup (Q = 1.69, df = 3, p = 0.64; I² = 7.9%) | -0.024 [-0.2 to 0.018] | | 1.20 [0.47, 3.07] | |

**Heterogeneity:** $\chi^2 = 0.06$, $\chi^2 = 7.58$, P = 0.94, I² = 6.0

**Test for overall effect:** z = 0.84, P = 0.40

P for interaction = 0.05

Continuity correction: OR 1.20 [0.69, 2.09]

| Odds Ratio (95% CI) |
|---------------------|
| 0.65 0.25 1 4 |

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eFigure VI – Forest plot demonstrating the association of oral anticoagulant with hemorrhagic stroke events compared to control. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the size of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect. Int-Intervention, CI-Confidence Interval, ARR-Absolute risk reduction.
### Association of Oral Anticoagulation with All-cause Mortality

| Study, Year  | Int Event Total | Control Event Total | ARR (95% CI) | Favors Int | Favors Control | Odds Ratio (95% CI) |
|--------------|-----------------|---------------------|--------------|------------|----------------|-------------------|
| AVERROES, 2011 [15] | 111 2808 | 140 2791 | 1.06 [-0.02 to 2.1] | 8.85% 0.78 [0.60, 1.01] | 0.05 0.25 1 4 |
| BAFTA, 2007 [17] | 107 488 | 108 485 | 0.34 [-4.87 to 5.6] | 6.27% 0.98 [0.72, 1.33] | 0.05 0.25 1 4 |
| WASPO, 2007 [16] | 1 36 | 2 39 | 2.35 [-6.41 to 11.1] | 0.10% 0.53 [0.05, 6.09] | 0.05 0.25 1 4 |
| Vennos et al, 2006 [18] | 0 16 | 0 15 | 0.18 [-11.53 to 11.9] | 0.04% 0.94 [0.02, 50.3] | 0.05 0.25 1 4 |
| ACTIVE W, 2006 [19] | 158 3371 | 159 3335 | 0.08 [-0.94 to 1.1] | 11.30% 0.98 [0.78, 1.23] | 0.05 0.25 1 4 |
| SPEAF (intermed), 2004 [20] | 20 237 | 15 242 | -2.24 [-6.90 to 2.4] | 1.19% 1.39 [0.70, 2.79] | 0.05 0.25 1 4 |
| PATAF-stratum 1, 1999 [21] | 12 131 | 17 141 | 2.90 [-4.40 to 10.2] | 0.94% 0.74 [0.34, 1.61] | 0.05 0.25 1 4 |
| AFAASK II, 1998 [22] | 17 170 | 14 169 | -1.72 [-7.95 to 4.4] | 1.04% 1.23 [0.59, 2.58] | 0.05 0.25 1 4 |
| SPAF II (>75), 1994 [23] | 26 197 | 24 188 | -0.43 [-7.15 to 6.3] | 1.63% 1.04 [0.57, 1.88] | 0.05 0.25 1 4 |
| SPAF II (<75), 1994 [23] | 36 358 | 41 357 | 1.43 [-3.11 to 6.0] | 2.56% 0.96 [0.54, 1.38] | 0.05 0.25 1 4 |
| EAFT, 1993 [24] | 41 225 | 201 782 | 7.48 [1.58 to 13.4] | 4.10% 0.64 [0.44, 0.94] | 0.05 0.25 1 4 |
| Veterans, 1992 [26] | 15 260 | 22 265 | 2.53 [-1.83 to 6.9] | 1.24% 0.68 [0.34, 1.33] | 0.05 0.25 1 4 |
| SPAF (Group I), 1991 [27] | 6 210 | 8 211 | 0.93 [-2.49 to 4.4] | 0.50% 0.75 [0.25, 2.19] | 0.05 0.25 1 4 |
| CAFA, 1991 [28] | 10 187 | 8 191 | -1.16 [-5.46 to 3.1] | 0.63% 1.29 [0.50, 3.35] | 0.05 0.25 1 4 |

**Heterogeneity:** $\chi^2 = 11.76, P = 0.09, I^2 = 0.03$

**Test for overall effect:** $z = -1.44, P = 0.15$

**P for interaction** = 0.18

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eFigure VII – Forest plot demonstrating the association of oral anticoagulant with all-cause mortality events compared to control. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the size of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect. Int-Intervention, CI-Confidence Interval, ARR-Absolute risk reduction.
eFigure VIII – Oral anticoagulation and Cardiovascular Mortality

Association of Oral Anticoagulation with Cardiovascular Mortality

| Study, Year | Int Event | Control Event | ARR (95% CI) | Favors Int | Favors Control | Odds Ratio (95% CI) |
|-------------|-----------|---------------|--------------|------------|----------------|-------------------|
| AVERROES, 2011 [15] | 84 2808 | 96 2791 | 0.45 [-0.48 to 1.4] | | | 11.46% 0.87 [0.64, 1.17] |
| BAFTA, 2007 [17] | 56 488 | 57 485 | 0.28 [-3.75 to 4.3] | | | 6.60% 0.97 [0.66, 1.44] |
| Vermmos et al, 2006 [18] | 0 16 | 0 15 | 0.18 [-11.53 to 11.9] | | | 0.06% 0.94 [0.02, 50.31] |
| ACTIVE W, 2006 [19] | 106 3371 | 120 3335 | 0.45 [-0.41 to 1.3] | | | 14.37% 0.87 [0.67, 1.13] |
| SPEAF (intermed), 2004 [20] | 11 237 | 8 242 | -1.34 [-4.84 to 2.2] | | | 1.18% 1.42 [0.56, 3.60] |
| PATAF-stratum 1, 1999 [21] | 9 131 | 9 141 | -0.49 [-6.41 to 5.4] | | | 1.11% 1.08 [0.42, 2.81] |
| AFASAK II, 1998 [22] | 5 170 | 4 169 | -0.57 [-4.00 to 2.9] | | | 0.57% 1.25 [0.33, 4.74] |
| SPAF II (>75), 1994 [23] | 16 197 | 14 188 | -0.68 [-6.03 to 4.7] | | | 1.82% 1.10 [0.52, 2.32] |
| SPAF II (<75), 1994 [23] | 20 358 | 25 357 | 1.42 [-2.14 to 5.0] | | | 2.75% 0.79 [0.43, 1.44] |
| EAFT, 1993 [24] | 30 225 | 156 782 | 6.62 [1.38 to 11.9] | | | 5.69% 0.62 [0.40, 0.94] |
| SPAF (Group B), 1991 [27] | 4 210 | 7 211 | 1.41 [-1.63 to 4.5] | | | 0.66% 0.57 [0.16, 1.96] |
| CAFA, 1991 [28] | 9 187 | 6 191 | -1.67 [-5.81 to 2.3] | | | 0.91% 1.56 [0.54, 4.47] |
| AFASAK, 1989 [29] | 3 335 | 27 672 | 3.12 [1.33 to 4.9] | | | 0.70% 0.22 [0.07, 0.72] |

RE Model for Subgroup \( Q = 11.66, df = 12, p = 0.47, \ i^2 = 0.0% \) 0.73 [0.1 to 1.3] 0.86 [0.74, 0.99]

Heart failure

| Study, Year | Int Event | Control Event | ARR (95% CI) | Favors Int | Favors Control | Odds Ratio (95% CI) |
|-------------|-----------|---------------|--------------|------------|----------------|-------------------|
| COMPASS, 2019 [30] | 16 236 | 19 240 | 1.14 [-3.55 to 5.8] | | | 2.13% 0.85 [0.42, 1.69] |
| COMMANDER HF, 2018 [6] | 453 2507 | 476 2515 | 0.86 [-1.29 to 3.0] | | | 49.99% 0.94 [0.82, 1.09] |

RE Model for Subgroup \( Q = 0.09, df = 1, p = 0.78, \ i^2 = 0.0% \) 0.88 [-1 to 2.9] 0.94 [0.82, 1.08]

Heterogeneity: \( r^2 = 0.00, \chi^2 = 12.81, P = 0.58, \ i^2 = 0.0% \) 0.76 [0.1 to 1.4] 100.00% 0.90 [0.81, 0.99]

Test for overall effect: \( z = -2.08, P = 0.04 \)

P for interaction = 0.36

0.05 0.25 1 4

Odds Ratio (95% CI)

eFigure VIII – Forest plot demonstrating the association of oral anticoagulant with cardiovascular mortality events compared to control. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the size of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect. Int-Intervention, CI-Confidence Interval, ARR-Absolute risk reduction.
eFigure IX – Oral anticoagulation and Total Myocardial Infarction

**Association of Oral Anticoagulation with Total Myocardial Infarction**

| Study, Year | Int Event Total | Control Event Total | ARR (95% CI) | Favors Int | Favors Control | Odds Ratio (95% CI) |
|-------------|-----------------|---------------------|--------------|------------|---------------|-------------------|
| AVERROES, 2011 [15] | 24 2808 28 2791 | 0.15 [-0.35 to 0.60] | 8.97% 0.45 [0.49, 1.47] |
| BAFTA, 2007 [17] | 15 488 15 485 | 0.02 [-2.15 to 2.19] | 5.09% 0.99 [0.48, 2.06] |
| Vennmos et al, 2006 [18] | 0 16 0 15 | 0.18 [-11.53 to 11.90] | 0.17% 0.94 [0.02, 50.31] |
| ACTIVE W, 2006 [19] | 23 3371 36 3335 | 0.40 [-0.05 to 0.84] | 9.75% 0.63 [0.37, 1.06] |
| SPEAF (Intemred.), 2004 [20] | 0 237 1 242 | 0.41 [-0.74 to 1.55] | 0.26% 0.34 [0.01, 8.36] |
| AFASAK II, 1998 [22] | 4 170 4 169 | 0.01 [-3.22 to 3.25] | 1.37% 0.99 [0.24, 4.04] |
| SPAF II (>75), 1994 [23] | 5 197 5 188 | 0.12 [-3.06 to 3.30] | 1.71% 0.95 [0.27, 3.35] |
| SPAF II (<75), 1994 [23] | 10 358 14 357 | 1.13 [-1.51 to 3.77] | 3.95% 0.70 [0.31, 1.61] |
| EAFT, 1993 [24] | 17 225 81 782 | 2.80 [-1.26 to 6.86] | 9.05% 0.71 [0.41, 1.22] |
| Veterans, 1992 [26] | 1 260 4 265 | 1.12 [-0.52 to 2.77] | 0.56% 0.25 [0.03, 2.27] |
| SPAF (Group I), 1991 [27] | 2 210 2 211 | 0.00 [-1.86 to 1.85] | 0.69% 1.00 [0.14, 7.20] |
| RE Model for Subgroup (Q = 2.84, df = 10, p = 0.98; I² = 0%) | 0.42 [0.06 to 0.79] | 0.76 [0.59, 0.97] |

**Heart failure**

| Study, Year | Int Event Total | Control Event Total | ARR (95% CI) | Favors Int | Favors Control | Odds Ratio (95% CI) |
|-------------|-----------------|---------------------|--------------|------------|---------------|-------------------|
| COMPASS, 2019 [30] | 6 236 10 240 | 1.62 [-1.60 to 4.85] | 2.54% 0.60 [0.21, 1.68] |
| COMMANDER HF, 2018 [6] | 98 2507 118 2515 | 0.78 [-0.34 to 1.90] | 35.89% 0.83 [0.63, 1.09] |
| WARCEF, 2012 [31] | 28 1142 31 1163 | 0.21 [-1.08 to 1.50] | 10.04% 0.92 [0.55, 1.54] |
| WATCH, 2009 [4] * | 21 540 27 1047 | -1.31 [-3.20 to 0.58] | 8.00% 1.53 [0.86, 2.73] |
| HELAS, 2006 [32] | 2 92 0 105 | -2.22 [-5.75 to 1.32] | 0.29% 5.83 [0.28, 122.99] |
| WASH, 2004 [5] | 3 89 15 190 | 4.52 [-0.84 to 9.89] | 1.68% 0.41 [0.11, 1.44] |
| RE Model for Subgroup (Q = 7.13, df = 5, p = 0.21; I² = 18.2%) | 0.41 [-0.3 to 1.2] | 0.91 [0.69, 1.20] |

**Heterogeneity:** $\chi^2 = 10.94, P = 0.81, I^2 = 0$

**Test for overall effect:** $z = -2.18, P = 0.03$

**P for interaction = 0.33**

- Odds Ratio (95% CI)
  - 0.05 0.25 1 4

eFigure IX – Forest plot demonstrating the association of oral anticoagulant with total myocardial infarction events compared to control. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the size of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect. Int-Intervention, CI-Confidence Interval, ARR-Absolute risk reduction, MI-Myocardial Infarction.

*WATCH reports non-fatal MI.*
**eFigure X – Oral anticoagulation and Major Haemorrhage**

### Association of Oral Anticoagulation with Major Hemorrhage

| Study, Year | Int Event Total | Control Event Total | ARR (95% CI) | Favors Int | Favors Control | Odds Ratio (95% CI) |
|-------------|-----------------|---------------------|--------------|------------|---------------|-------------------|
| AVERROES, 2011 [15] | 44 2808 | 39 2791 | -0.17 [-0.60 to 0.46] | ![Image](image.png) | ![Image](image.png) | 10.23% [1.12 [0.73, 1.73]] |
| BAFTA, 2007 [17] | 25 488 | 25 485 | 0.03 [-2.74 to 2.81] | ![Image](image.png) | ![Image](image.png) | 9.18% [0.99 [0.56, 1.76]] |
| WASPO, 2007 [16] | 0 36 | 3 39 | 7.40 [-2.12 to 16.91] | ![Image](image.png) | ![Image](image.png) | 1.21% [0.14 [0.01, 2.67]] |
| Vermeers et al, 2006 [18] | 0 16 | 0 15 | 0.18 [-11.53 to 11.90] | ![Image](image.png) | ![Image](image.png) | 0.72% [0.94 [0.02, 50.31]] |
| ACTIVE W, 2006 [19] | 93 3371 | 101 3335 | 0.27 [-0.53 to 1.07] | ![Image](image.png) | ![Image](image.png) | 11.25% [0.91 [0.68, 1.21]] |
| SPEAF (Intermediate), 2004 [20] | 10 237 | 2 242 | -3.39 [-6.20 to -0.59] | ![Image](image.png) | ![Image](image.png) | 3.63% [5.29 [1.15, 24.39]] |
| PATAF-stratified, 1999 [21] | 2 131 | 1 141 | -0.82 [-3.33 to 1.70] | ![Image](image.png) | ![Image](image.png) | 1.78% [2.17 [0.19, 24.22]] |
| AFASAK II, 1998 [22] | 4 170 | 5 169 | 0.61 [-2.82 to 4.03] | ![Image](image.png) | ![Image](image.png) | 4.37% [0.79 [0.21, 3.00]] |
| EAF, 1993 [24] | 13 225 | 10 782 | -4.60 [-7.65 to -1.55] | ![Image](image.png) | ![Image](image.png) | 7.13% [4.73 [2.05, 10.95]] |
| Veterans, 1992 [26] | 6 260 | 4 265 | -0.80 [-3.14 to 1.54] | ![Image](image.png) | ![Image](image.png) | 4.61% [1.54 [0.43, 5.53]] |
| SPAF (Group I), 1991 [27] | 4 210 | 14 211 | 4.73 [0.89 to 8.56] | ![Image](image.png) | ![Image](image.png) | 5.34% [0.27 [0.09, 0.84]] |
| CAFA, 1991 [28] | 5 167 | 1 191 | -2.15 [-4.68 to 0.36] | ![Image](image.png) | ![Image](image.png) | 2.14% [5.22 [0.60, 45.11]] |
| RE Model for Subgroup (Q = 27.93, df = 11, p = 0.00; I² = 74.0%) | ![Image](image.png) | ![Image](image.png) | -0.16 [-0.6 to 0.32] | ![Image](image.png) | ![Image](image.png) | 1.27 [0.74, 2.18] |

### Heart failure

| Study, Year | Int Event Total | Control Event Total | ARR (95% CI) | Favors Int | Favors Control | Odds Ratio (95% CI) |
|-------------|-----------------|---------------------|--------------|------------|---------------|-------------------|
| COMPASS, 2019 [30] | 11 236 | 5 240 | -2.58 [-5.82 to 0.66] | ![Image](image.png) | ![Image](image.png) | 5.64% [2.30 [0.79, 6.72]] |
| COMMANDER HF, 2018 [8] | 82 2507 | 50 2515 | -1.28 [-2.17 to -0.40] | ![Image](image.png) | ![Image](image.png) | 10.79% [1.67 [1.17, 2.38]] |
| WARCEF, 2012 [31] | 72 1142 | 35 1163 | -3.30 [-6.01 to -1.56] | ![Image](image.png) | ![Image](image.png) | 10.39% [2.17 [1.44, 3.28]] |
| WATCH, 2009 [4] | 28 540 | 30 1047 | -2.32 [-4.45 to 0.15] | ![Image](image.png) | ![Image](image.png) | 9.52% [1.85 [1.10, 3.14]] |
| WASH, 2004 [5] | 4 89 | 1 190 | -3.97 [-8.39 to 0.46] | ![Image](image.png) | ![Image](image.png) | 2.06% [8.89 [0.98, 80.77]] |
| RE Model for Subgroup (Q = 2.92, df = 4, p = 0.57; I² = 0.0%) | ![Image](image.png) | ![Image](image.png) | -2.1 [-3 to -1.3] | ![Image](image.png) | ![Image](image.png) | 1.91 [1.52, 2.42] |

Heterogeneity: $\chi^2 = 44.59, P = 0.00, I^2 = 69.4$

Test for overall effect: $z = 2.39, P = 0.02$

P for interaction = 0.17

0.05 0.25 1 4

Odds Ratio (95% CI)

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eFigure X – Forest plot demonstrating the association of oral anticoagulant with major haemorrhage events compared to control. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the size of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect. Int-Intervention, CI-Confidence Interval, ARR-Absolute risk reduction.

Definitions of major haemorrhage for individual trials can be found in eTable I.
### Association of Oral Anticoagulation with Fatal Hemorrhage

| Study, Year | OAC Event Total | Control Event Total | ARR (95% CI) | Favors OAC | Favors Control | Weight (95% CI) |
|-------------|-----------------|---------------------|--------------|------------|----------------|----------------|
| AVERROES, 2011 [15] | 4 2808 | 6 2791 | 0.07 [-0.15 to 0.29] |          |                | 17.50% [0.19, 2.35] |
| Venmors et al, 2006 [18] | 0 16 | 0 15 | 0.18 [-11.53 to 11.90] |          |                | 1.77% [0.94, 0.02] |
| ACTIVE W, 2006 [19] | 11 3371 | 7 3335 | -0.12 [-0.36 to 0.13] |          |                | 31.16% [1.56, 0.60] |
| SPEAF (intermed), 2004 [20] | 0 237 | 0 242 | 0.00 [-0.82 to 0.81] |          |                | 1.82% [1.02, 51.67] |
| AFASAK II, 1998 [22] | 1 170 | 1 169 | 0.00 [-1.63 to 1.63] |          |                | 3.63% [0.99, 0.06] |
| Veterans, 1992 [26] | 0 260 | 1 265 | 0.37 [-0.67 to 1.42] |          |                | 2.73% [0.34, 8.35] |
| SPAF (Group I), 1991 [27] | 1 210 | 0 211 | -0.48 [-1.78 to 0.83] |          |                | 2.73% [3.03, 74.77] |
| CAFA, 1991 [28] | 2 187 | 0 191 | -1.07 [-2.86 to 0.72] |          |                | 3.03% [0.16, 108.24] |
| RE Model for Subgroup (Q = 2.98, df = 7, p = 0.89; I² = 0.0%) | -0.054 [-0.2 to 0.1] |          | | | 1.20 [0.62, 2.31] |

**HFrEF**

| Study, Year | OAC Event Total | Control Event Total | ARR (95% CI) | Favors OAC | Favors Control | Weight (95% CI) |
|-------------|-----------------|---------------------|--------------|------------|----------------|----------------|
| COMMANDER HF, 2018 [6] | 3 2507 | 7 2515 | 0.16 [-0.09 to 0.41] |          |                | 15.31% [0.11, 1.66] |
| WARCEF, 2012 [31] | 7 1142 | 4 1163 | -0.27 [-0.83 to 0.30] |          |                | 18.51% [0.52, 6.12] |
| HELAS, 2006 [32] | 0 92 | 0 105 | -0.07 [-2.04 to 1.91] |          |                | 1.82% [1.14, 58.05] |
| RE Model for Subgroup (Q = 2.34, df = 2, p = 0.31; I² = 33.2%) | 0.023 [-0.2 to 0.26] |          | | | 0.93 [0.28, 3.05] |

**Heterogeneity:** $\chi^2 = 5.49, P = 0.86, I^2 = 0.0$

Test for overall effect: $z = 0.35, P = 0.72$

$P$ for interaction = 0.71

Continuity correction: OR 1.05 [0.58, 1.88]

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**eFigure XI – Forest plot demonstrating the association of oral anticoagulant with fatal hemorrhage events compared to control. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the size of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect. Int-Intervention, CI-Confidence Interval, ARR-Absolute risk reduction.**
### Association of Oral Anticoagulation with Primary Outcome

| Study, Year | Event Total | Control Event Total | ARR (95% CI) | Favors Int | Favors Control | Odds Ratio (95% CI) |
|-------------|-------------|---------------------|--------------|------------|----------------|-------------------|
| AVERROES, 2011 [15] | 51 | 2080 | 113 | 2791 | 2.23 [1.35 to 3.1] | 7.03% | 0.44 [0.31, 0.61] |
| BAFTA, 2007 [17] | 76 | 488 | 100 | 485 | 5.04 [2.22 to 9.9] | 7.10% | 0.71 [0.51, 0.99] |
| WASPO, 2007 [16] | 9 | 36 | 17 | 39 | 18.59 [-2.44 to 39.6] | 2.19% | 0.43 [0.16, 1.15] |
| Vemmos et al, 2006 [18] | 10 | 131 | 12 | 141 | 0.88 [-5.60 to 7.3] | 0.27% | 0.18 [0.01, 3.71] |
| ACTIVE W, 2006 [19] | 165 | 3371 | 234 | 3335 | 2.12 [0.96 to 3.2] | 8.57% | 0.68 [0.56, 0.84] |
| SPEAF (intermed), 2004 [20] | 14 | 223 | 17 | 242 | 1.12 [3.28 to 5.5] | 3.36% | 0.72 [0.40, 1.33] |
| PATAF-stratum 1, 1999 [21] | 10 | 113 | 12 | 124 | 1.04 [2.09 to 1.1] | 2.62% | 0.69 [0.37, 2.13] |
| AFASAK II, 1998 [22] | 12 | 200 | 10 | 169 | -1.14 [-6.38 to 4.1] | 2.65% | 1.21 [0.51, 2.88] |
| SPAF II (>75), 1994 [23] | 29 | 197 | 27 | 188 | 0.31 [-7.40 to 6.7] | 4.56% | 1.03 [0.58, 1.81] |
| SPAF II (<75), 1994 [23] | 32 | 358 | 40 | 357 | 2.21 [2.14 to 6.7] | 5.29% | 0.78 [0.48, 1.27] |
| EAFT, 1993 [24] | 43 | 225 | 266 | 782 | 14.90 [8.79 to 21.0] | 6.68% | 0.46 [0.32, 0.66] |
| Veterans, 1992 [26] | 4 | 260 | 19 | 265 | 5.65 [2.18 to 9.1] | 1.66% | 2.07 [0.67, 0.86] |
| BAATAF, 1992 [25] | 2 | 212 | 13 | 208 | 3.61 [1.77 to 8.8] | 3.08% | 0.14 [0.03, 0.54] |
| SPAF (Group I), 1991 [27] | 10 | 210 | 24 | 211 | 0.61 [1.45 to 11.6] | 3.17% | 0.39 [0.18, 0.84] |
| CAFA, 1991 [28] | 8 | 187 | 11 | 191 | 1.48 [-2.92 to 5.9] | 2.38% | 0.73 [0.29, 1.86] |
| AFASAK, 1989 [29] | 5 | 335 | 41 | 472 | 4.61 [2.38 to 6.8] | 2.36% | 0.23 [0.08, 0.67] |
| RE Model for Subgroup (Q = 30.24, df = 15, p = 0.01; I² = 49.2%) | 3.1 [2 to 3.6] | 0.58 [0.47, 0.72] |

### Heart Failure

| Study, Year | Event Total | Control Event Total | ARR (95% CI) | Favors Int | Favors Control | Odds Ratio (95% CI) |
|-------------|-------------|---------------------|--------------|------------|----------------|-------------------|
| COMPASS, 2019 [30] | 24 | 236 | 29 | 240 | 1.91 [3.73 to 7.6] | 4.51% | 0.82 [0.46, 1.46] |
| COMMANDER HF, 2018 [6] | 626 | 2507 | 658 | 2515 | 1.19 [-1.22 to 3.6] | 9.34% | 0.94 [0.83, 1.07] |
| WARCEF, 2012 [31] | 302 | 1142 | 320 | 1163 | 1.07 [2.55 to 4.7] | 8.80% | 0.95 [0.79, 1.14] |
| WATCH, 2009 [4] | 106 | 540 | 221 | 1047 | 1.48 [2.68 to 5.6] | 7.95% | 0.91 [0.70, 1.18] |
| HELAS, 2006 [32] | 19 | 92 | 24 | 105 | 2.20 [-3.32 to 13.7] | 3.69% | 0.88 [0.45, 1.73] |
| WASH, 2004 [5] | 23 | 89 | 55 | 190 | 3.10 [-0.04 to 14.2] | 4.55% | 0.89 [0.48, 1.51] |
| RE Model for Subgroup (Q = 0.36, df = 5, p = 1.00; I² = 0.0%) | 1.3 [0.4 to 3] | 0.93 [0.65, 1.52] |

Heterogeneity: $\chi^2 = 60.14$, $P = 0.00$, $I^2 = 66.5$

Test for overall effect: $z = -3.66$, $P = 0.00$

For interaction: $\chi^2 = 0.00$

Odds Ratio (95% CI)

| Odds Ratio (95% CI) |
|---------------------|
| 0.05 0.25 1 4 |

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eFigure XII – Forest plot demonstrating the association of oral anticoagulant with original primary outcome reported within trials compared to control. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the size of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect. Int-Intervention, CI-Confidence Interval, ARR-Absolute risk reduction.
**All Stroke Sensitivity analysis**

| Outcome | No. of studies | No. of patients | OAC | Control | I² | Favors OAC | Favors Control | Odds Ratio (95% CI) | P for interaction |
|---------|----------------|-----------------|-----|---------|----|------------|---------------|---------------------|------------------|
| **Low risk of bias** | | | | | | | | | |
| Atrial fibrillation | 10 | 17017 | 224 | 535 | 31.9 | | | 0.53 [0.43, 0.67] | |
| Heart failure | 5 | 9669 | 93 | 168 | 0 | | | 0.61 [0.47, 0.79] | |
| Overall | 15 | 26686 | 317 | 703 | 16.5 | | | 0.55 [0.46, 0.65] | 0.47 |
| **Control - Aspirin** | | | | | | | | | |
| Atrial fibrillation | 10 | 10824 | 165 | 451 | 36.6 | | | 0.53 [0.40, 0.70] | |
| Heart failure | 5 | 4762 | 44 | 94 | 0 | | | 0.56 [0.39, 0.81] | |
| Overall | 15 | 15586 | 209 | 545 | 21.8 | | | 0.53 [0.42, 0.66] | 0.81 |
| **Intervention - Warfarin** | | | | | | | | | |
| Atrial fibrillation | 13 | 13254 | 189 | 487 | 34.8 | | | 0.52 [0.40, 0.68] | |
| Heart failure | 4 | 4366 | 39 | 88 | 6.9 | | | 0.52 [0.32, 0.85] | |
| Overall | 17 | 177622 | 228 | 575 | 22.2 | | | 0.52 [0.42, 0.65] | 0.97 |
| **INR target (2-3.5)** | | | | | | | | | |
| Atrial fibrillation | 7 | 9222 | 118 | 194 | 0 | | | 0.58 [0.47, 0.71] | |
| Heart failure | 4 | 4366 | 39 | 88 | 6.9 | | | 0.52 [0.32, 0.85] | |
| Overall | 11 | 13590 | 157 | 282 | 0 | | | 0.58 [0.47, 0.71] | 0.63 |

eFigure XIII – Combined Forest Plot showing sensitivity analysis for all stroke outcome: [1] Low risk of bias, [2] aspirin as control, [3] warfarin as intervention, [4] INR target (2-3.5). The analysis is divided by population group; overall, atrial fibrillation trials, heart failure trials. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. Int-Intervention, CI-Confidence Interval, ARR-Absolute risk reduction.
Ischaemic Stroke Sensitivity analysis

| Outcome                     | No. of studies | No. of patients | OAC | Control | I² | Favors OAC | Favors Control | Odds Ratio (95% CI) | P for interaction |
|-----------------------------|----------------|-----------------|-----|---------|----|------------|------------------|-------------------|------------------|
| **Low risk of bias**        |                |                 |     |         |    |            |                  |                   |                  |
| Atrial fibrillation         | 10             | 17017           | 146 | 435     | 0  |           |                  | 0.42 [0.35, 0.51] | 0.13             |
| Heart failure               | 4              | 9193            | 73  | 146     | 0  |           |                  | 0.56 [0.42, 0.74] |                  |
| Overall                     | 14             | 26210           | 219 | 581     | 10.3 |           |                  | 0.46 [0.38, 0.55] |                  |
| **Control - Aspirin**       |                |                 |     |         |    |            |                  |                   |                  |
| Atrial fibrillation         | 9              | 9817            | 100 | 328     | 0  |           |                  | 0.42 [0.33, 0.53] |                  |
| Heart failure               | 3              | 4171            | 32  | 83      | 17.8 |           |                  | 0.43 [0.23, 0.79] |                  |
| Overall                     | 12             | 13988           | 132 | 411     | 0  |           |                  | 0.43 [0.35, 0.53] |                  |
| **Intervention - Warfarin** |                |                 |     |         |    |            |                  |                   |                  |
| Atrial fibrillation         | 12             | 12247           | 119 | 366     | 0  |           |                  | 0.43 [0.35, 0.54] |                  |
| Heart failure               | 3              | 4171            | 32  | 83      | 17.8 |           |                  | 0.43 [0.23, 0.79] |                  |
| Overall                     | 15             | 16418           | 151 | 449     | 0  |           |                  | 0.44 [0.36, 0.54] |                  |
| **INR target (2-3.5)**      |                |                 |     |         |    |            |                  |                   |                  |
| Atrial fibrillation         | 7              | 9222            | 70  | 150     | 0  |           |                  | 0.46 [0.35, 0.62] |                  |
| Heart failure               | 3              | 4171            | 32  | 83      | 17.8 |           |                  | 0.43 [0.23, 0.79] |                  |
| Overall                     | 10             | 13393           | 102 | 233     | 0  |           |                  | 0.46 [0.37, 0.59] |                  |

Observed Outcome

0.2 0.6

eFigure XIV – Combined Forest Plot showing sensitivity analysis for ischaemic stroke outcome: [1] Low risk of bias, [2] aspirin as control, [3] warfarin as intervention, [4] INR target (2-3.5). The analysis is divided by population group; overall, atrial fibrillation trials, heart failure trials. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. Int-Intervention, CI-Confidence Interval, ARR-Absolute risk reduction.
eFigure XV – Oral anticoagulation and Haemorrhagic stroke - Sensitivity analyses

Hemorrhagic Stroke Sensitivity Analysis

| Outcome                     | No. of studies | No. of patients | OAC | Control | I² | Favors OAC | Favors Control | Odds Ratio [95% CI] | P for interaction |
|-----------------------------|----------------|-----------------|-----|---------|----|------------|------------------|----------------------|------------------|
| **Low risk of bias**        |                |                 |     |         |    |            |                  |                      |                  |
| Atrial fibrillation         | 9              | 15917           | 31  | 24      | 13.7|             | 1.33 [0.70, 2.54] |                      |                  |
| Heart failure               | 4              | 9193            | 11  | 10      | 7.9 |             | 1.20 [0.47, 3.07] |                      |                  |
| Overall                     | 13             | 25110           | 42  | 34      | 9.1 |             | 1.37 [0.81, 2.33] |                      | 0.86             |
| **Control - Aspirin**       |                |                 |     |         |    |            |                  |                      |                  |
| Atrial fibrillation         | 8              | 8717            | 15  | 19      | 0  |             | 0.90 [0.46, 1.77] |                      |                  |
| Heart failure               | 3              | 4171            | 5   | 2       | 0  |             | 2.41 [0.59, 9.88] |                      |                  |
| Overall                     | 11             | 12228           | 20  | 20      | 0  |             | 1.08 [0.59, 1.98] |                      | 0.22             |
| **Intervention - Warfarin** |                |                 |     |         |    |            |                  |                      |                  |
| Atrial fibrillation         | 10             | 10769           | 25  | 15      | 0  |             | 1.73 [0.91, 3.28] |                      |                  |
| Heart failure               | 3              | 4171            | 5   | 2       | 0  |             | 2.41 [0.59, 9.88] |                      |                  |
| Overall                     | 13             | 14940           | 30  | 17      | 0  |             | 1.83 [1.02, 3.28] |                      | 0.68             |
| **INR target (2-3.5)**      |                |                 |     |         |    |            |                  |                      |                  |
| Atrial fibrillation         | 6              | 8844            | 24  | 14      | 5  |             | 1.77 [0.96, 3.26] |                      |                  |
| Heart failure               | 3              | 4171            | 5   | 2       | 0  |             | 2.41 [0.59, 9.88] |                      |                  |
| Overall                     | 9              | 13015           | 29  | 16      | 0  |             | 1.77 [0.96, 3.26] |                      | 0.62             |

Observed Outcome

0.4  2.04  3.67

eFigure XV – Combined Forest Plot showing sensitivity analysis for hemorrhagic stroke outcome: [1] Low risk of bias, [2] aspirin as control, [3] warfarin as intervention, [4] INR target (2-3.5). The analysis is divided by population group; overall, atrial fibrillation trials, heart failure trials. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. Int-Intervention, CI-Confidence Interval, ARR-Absolute risk reduction.
eFigure XVI – Oral anticoagulation and All-cause mortality - Sensitivity analyses

All-cause Mortality Sensitivity analysis

| Outcome                        | No. of studies | No. of patients | OAC  | Control | I² | Favors OAC | Favors Control | Odds Ratio (95% CI) | P for interaction |
|--------------------------------|----------------|-----------------|------|---------|----|------------|-----------------|-------------------|------------------|
| Low risk of bias               | 10             | 17017           | 530  | 736     | 4.5|             |                 | 0.87 [0.76, 0.99]  | 0.11              |
| Atrial fibrillation            | 5              | 9669            | 958  | 1090    | 0  |             |                 | 0.99 [0.90, 1.09]  |                  |
| Overall                        | 15             | 266686          | 1488 | 1826    | 0  |             |                 | 0.94 [0.87, 1.01]  |                  |
| Control - Aspirin              | 9              | 9817            | 357  | 555     | 0  |             |                 | 0.83 [0.72, 0.97]  |                  |
| Atrial fibrillation            | 5              | 4762            | 423  | 543     | 0  |             |                 | 1.01 [0.87, 1.16]  | 0.08              |
| Overall                        | 14             | 14579           | 780  | 1098    | 6.7|             |                 | 0.91 [0.82, 1.02]  |                  |
| Intervention - Warfarin        | 11             | 11827           | 429  | 604     | 0  |             |                 | 0.90 [0.79, 1.04]  |                  |
| Atrial fibrillation            | 5              | 4368            | 402  | 525     | 0  |             |                 | 1.00 [0.86, 1.16]  |                  |
| Overall                        | 16             | 16195           | 831  | 1129    | 0  |             |                 | 0.95 [0.86, 1.05]  | 0.33              |
| INR target (2-3.5)             | 7              | 9222            | 325  | 323     | 0  |             |                 | 1.00 [0.85, 1.18]  |                  |
| Atrial fibrillation            | 5              | 4368            | 402  | 525     | 0  |             |                 | 1.00 [0.86, 1.16]  |                  |
| Overall                        | 12             | 13590           | 727  | 848     | 0  |             |                 | 1.00 [0.90, 1.12]  | 0.96              |

0.7 1 1.2

Observed Outcome

eFigure XVI – Combined forest plot reporting sensitivity analyses for the all-cause mortality outcome: [1] Low risk of bias, [2] control - aspirin, [3] intervention - warfarin, [4] INR target (2-3.5). The analysis is divided by population group; atrial fibrillation trials, heart failure trials, and overall. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. Int-Intervention, CI-Confidence Interval, ARR-Absolute risk reduction.
### eFigure XVII – Composite MACE outcome (non-fatal MI, non-fatal stroke, all-cause mortality)

**Association of Oral Anticoagulation with MACE Composite outcome**

| Study, Year       | Int Event Total | Control Event Total | ARR (95% CI) | Favors Int | Favors Control | Odds Ratio (95% CI) |
|-------------------|-----------------|---------------------|--------------|------------|----------------|-------------------|
| AVERROES, 2011 [15] | 157 2808 228 2791 | 2.6 [1.2 to 3.90] | 11.57% | 0.67 [0.64, 0.82] |
| BAFTA, 2007 [17]  | 126 488 147 485 | 4.5 [-1.1 to 10.13] | 9.80% | 0.80 [0.60, 1.06] |
| Vermeulen et al, 2006 [18] | 0 16 2 15 | 12.7 [-6.8 to 32.20] | 0.22% | 0.16 [0.01, 3.71] |
| ACTIVE W, 2006 [19] | 255 3371 213 3335 | -1.2 [-2.4 to 0.04] | 12.13% | 1.20 [0.99, 1.45] |
| SPEAF (intermed), 2004 [20] | 24 237 25 242 | 0.2 [-5.2 to 5.63] | 4.44% | 0.98 [0.54, 1.77] |
| PATAF-stratum 1, 1999 [21] | 16 131 22 141 | 3.4 [-4.8 to 11.59] | 3.51% | 0.75 [0.38, 1.51] |
| AFASAK II, 1998 [22] | 30 170 24 169 | -3.5 [-11.2 to 4.33] | 4.50% | 1.29 [0.72, 2.32] |
| EAF, 1993 [24] | 53 225 296 782 | 14.3 [7.8 to 20.80] | 8.41% | 0.51 [0.36, 0.71] |

**RE Model for Subgroup (Q = 30.50, df = 7, p = 0.00; I² = 73.8%)**

| Heart failure | 1.4 [0.5 to 2.3] | 0.82 [0.63, 1.07] |

| COMPASS, 2019 [30] | 30 236 34 240 | 1.4 [-4.7 to 7.58] | 5.18% | 0.88 [0.52, 1.50] |
| COMMANDER HF, 2018 [6] | 626 2507 658 2515 | 1.2 [-1.2 to 3.61] | 13.59% | 0.94 [0.63, 1.07] |
| WARCEF, 2012 [31] | 208 1142 232 1163 | 1.7 [-1.5 to 4.94] | 11.63% | 0.89 [0.73, 1.10] |
| WATCH, 2009 [4] | 106 540 221 1047 | 1.5 [-2.7 to 5.64] | 10.33% | 0.91 [0.70, 1.18] |
| WASH, 2004 [5] | 23 89 55 190 | 3.1 [-0.8 to 14.25] | 4.68% | 0.86 [0.48, 1.51] |

**RE Model for Subgroup (Q = 0.27, df = 4, p = 0.99; I² = 0.0%)**

| Heterogeneity: r² = 0.04, χ² = 31.86, P = 0.00, I² = 65.1 % |
|-----------------------------------------------------------------|
| Test for overall effect: z = -2.01, P = 0.04 |
| P for interaction = 0.42 |

**Odds Ratio (95% CI)**

- 0.05
- 0.25
- 1
- 4

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*Upper limit of confidence interval is 0.996 corrected to three decimal places.*

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**Figure XVII – Forest plot demonstrating the effect of oral anticoagulant on MACE composite events compared to control.** The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the size of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect. Int-Intervention, CI-Confidence Interval, ARR-Absolute risk reduction.
**eFigure XVIII – Composite of Non-fatal Cardiovascular events in HFrEF Trials**

**Primary composite outcome removing all-cause mortality**

| Study               | Int Event | Total | Control Event | Total | Favors | Weight | Odds Ratio (95% CI) |
|---------------------|-----------|-------|---------------|-------|--------|--------|---------------------|
| Commander HF        | 149       | 2507  | 194           | 2515  | 1      | 66.14% | 0.76 [0.61, 0.94]   |
| HELAS(DCM)          | 5         | 38    | 5             | 44    | -      | 1.85%  | 1.18 [0.31, 4.44]   |
| HELAS(HD)           | 5         | 54    | 5             | 61    | -      | 1.92%  | 1.14 [0.31, 4.18]   |
| WARCEF              | 34        | 1142  | 57            | 1163  | -      | 17.26% | 0.60 [0.39, 0.92]   |
| WASH                | 1         | 89    | 11            | 190   | -      | 0.76%  | 0.18 [0.02, 1.46]   |
| WATCH               | 22        | 540   | 47            | 1047  | -      | 12.08% | 0.90 [0.54, 1.52]   |

Heterogeneity: $I^2 = 0.00$, $Q = 4.22$, $P = 0.52$, $I^2 = 0.0$

Test for overall effect: $z = -3.30$, $P = 0.00$

**eFigure XVIII – Forest plot demonstrating the effect of oral anticoagulant on non-fatal cardiovascular events in HFrEF trials compared to control.** The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the size of the squares reflects the weight of the studies. The combined effect appear as a diamond and the vertical dashed line represents the line of no effect. Int-Intervention, CI-Confidence Interval.