Direct Oral Anticoagulants Vs. Warfarin

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Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care

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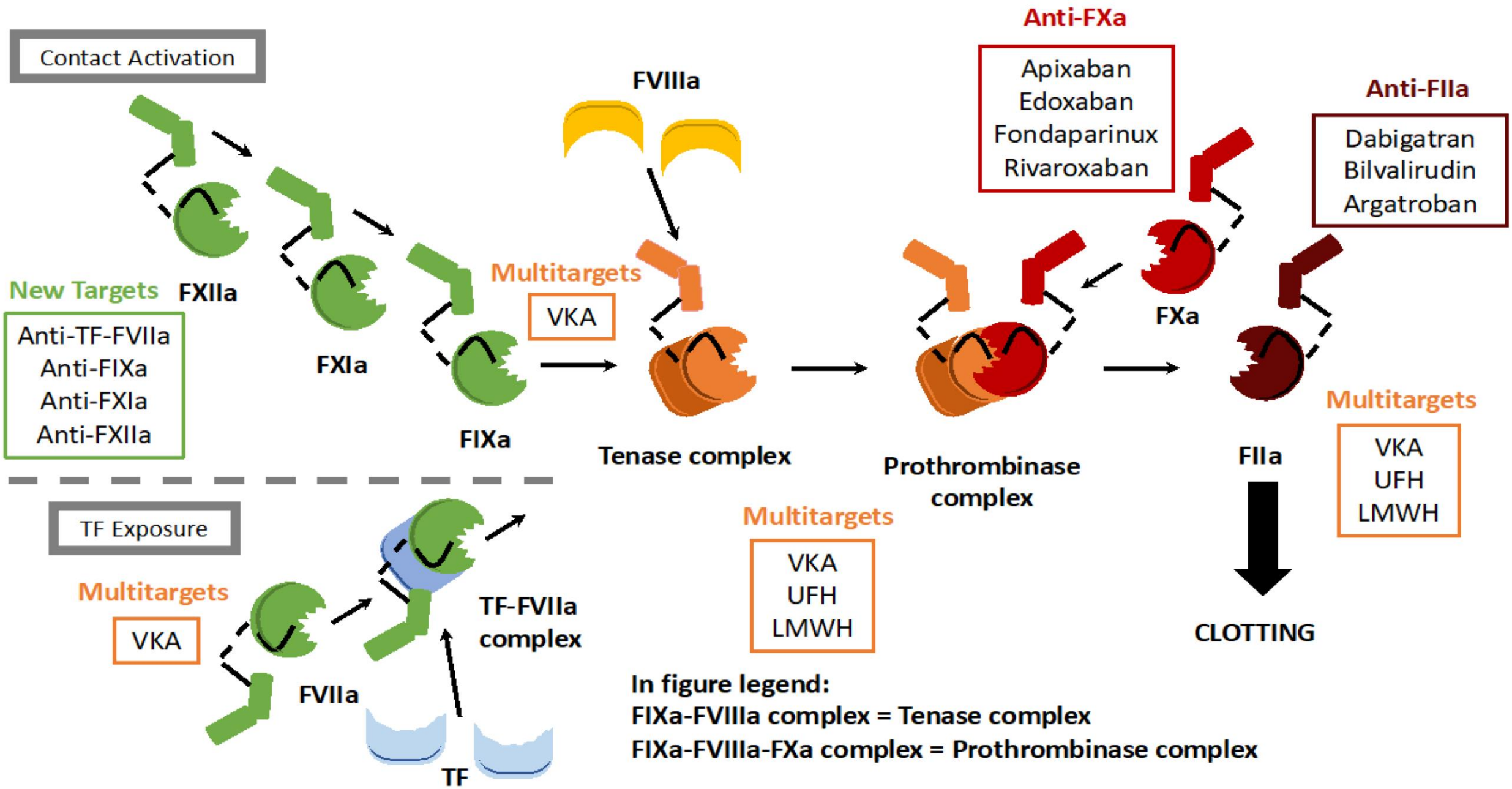
Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care [published correction appears in BMJ. 2018 Oct 18;363:k4413. doi: 10.1136/bmj.k4413.]. *BMJ*. 2018;362:k2505. Published 2018 Jul 4. doi:10.1136/bmj.k2505

- **Background:** Anticoagulants prevent stroke and treat venous thromboembolism (VTE).
  - AF, PE, DVT, and TKR

- **Why Compare DOACs & Warfarin?**
  - Warfarin: Long-established, requires INR monitoring, variable dose adjustments.
  - DOACs: Fixed dose, no routine monitoring, fewer drug interactions.
  - Lack of effective antidote

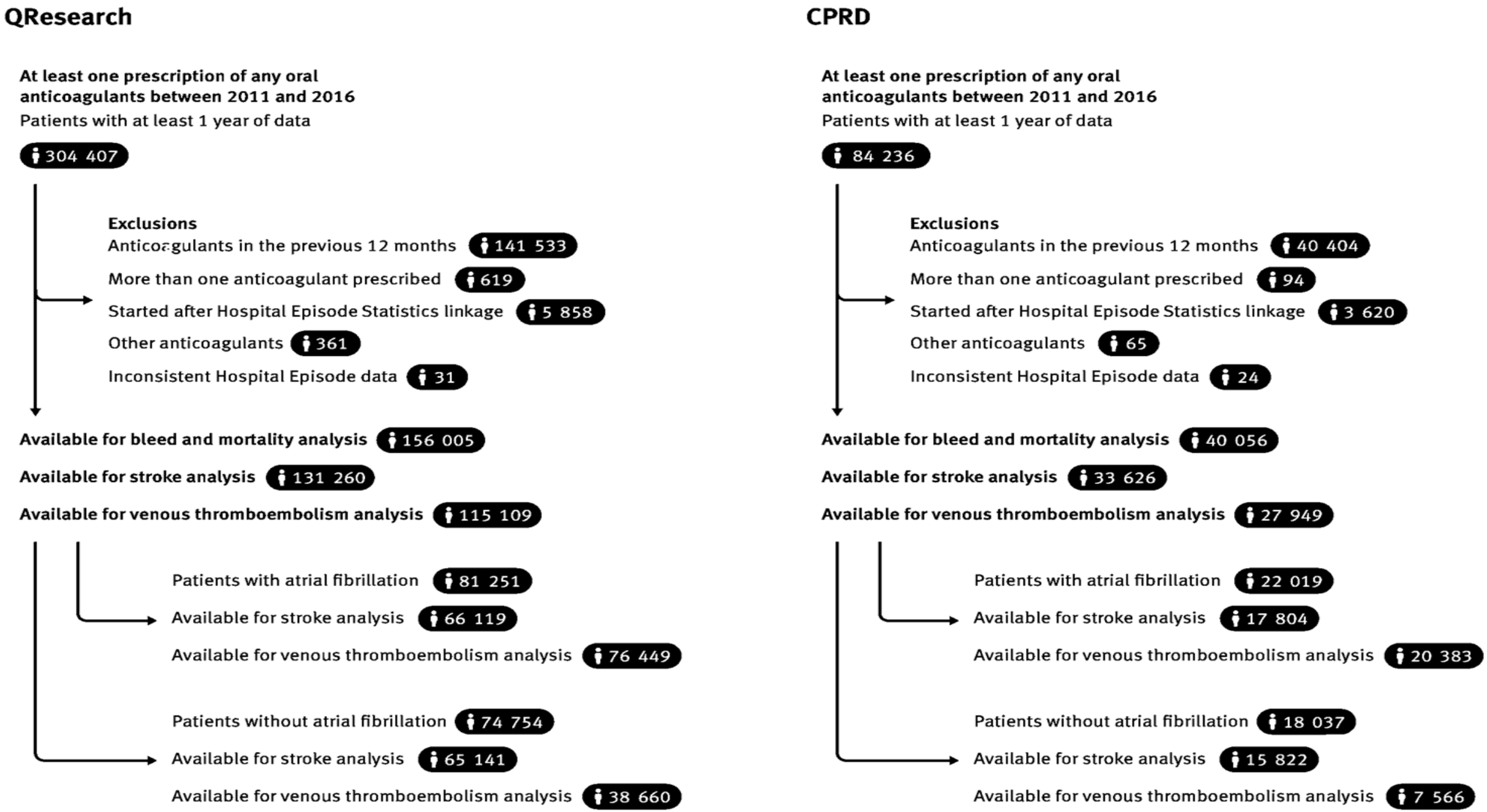
- **Study Objective:** Investigate the safety and efficacy of DOACs compared with warfarin in a real-world setting.

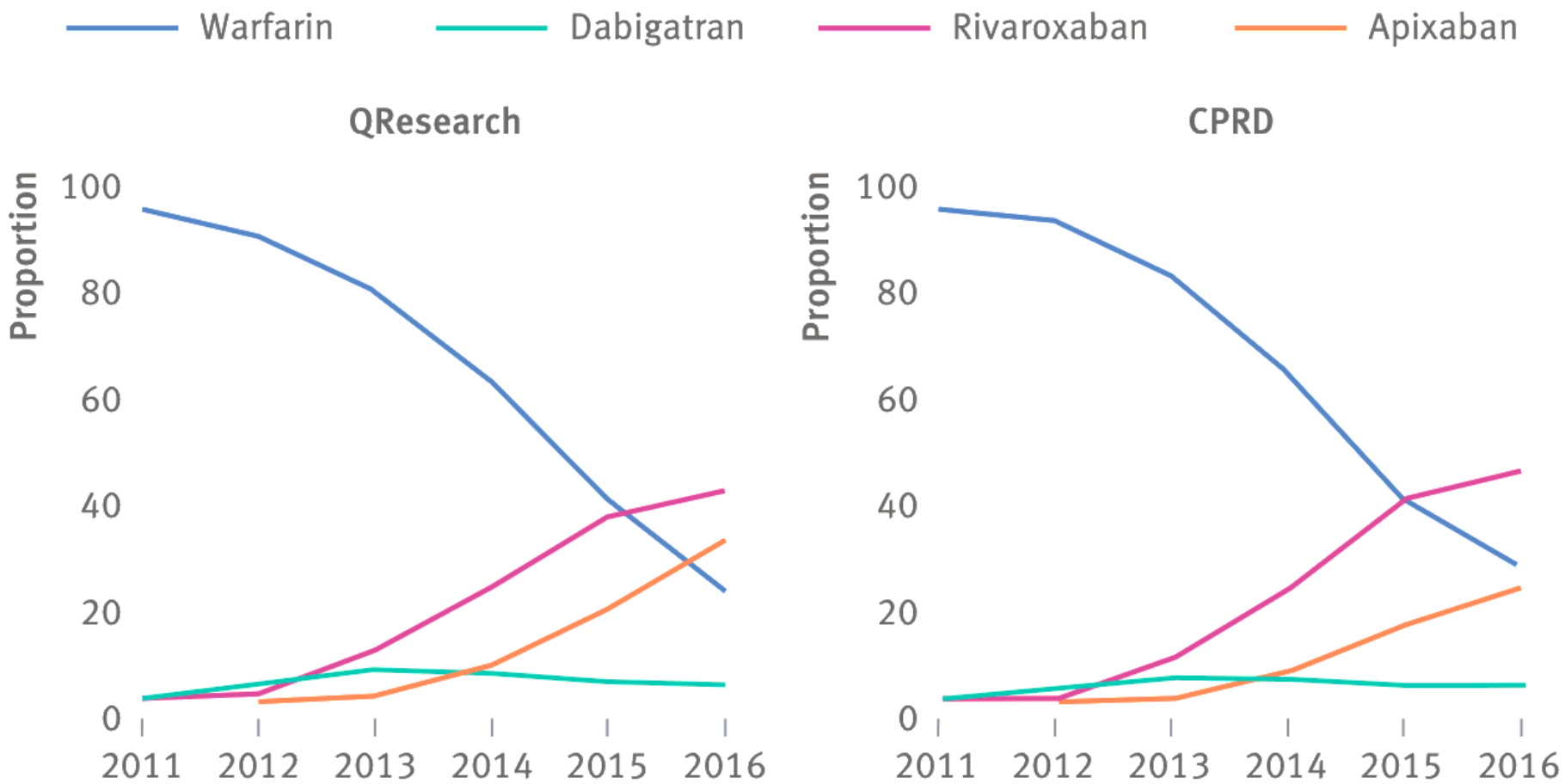


Heestermans M, Poenou G, Hamzeh-Cognasse H, Cognasse F, Bertoletti L. Anticoagulants: A Short History, Their Mechanism of Action, Pharmacology, and Indications. *Cells.* 2022; 11(20):3214. https://doi.org/10.3390/cells11203214

Study Design & Methods

- **Study Type:** Prospective cohort study
- **Data Sources:** QResearch & CPRD (UK primary care databases).
- **Study Period:** 2011-2016.
- **Participants:**
  - Excluded if taken any anticoagulant in last 12 months or lack of record
  - 132,231 warfarin users
  - 7,744 dabigatran users
  - 37,863 rivaroxaban users
  - 18,223 apixaban users
  - Dosage: 300 mg for dabigatran, 20 mg for rivaroxaban, and 10 mg for apixaban.
  - Edoxaban, Acenocoumarol, and phenindione were excluded.
- **Outcomes Measured:**
  - **Primary:** Major bleeding (hospitalization or death)
  - **Secondary:** Intracranial bleeding, gastrointestinal bleeding, ischemic stroke, venous thromboembolism (VTE), all-cause mortality.


QResearch
At least one prescription of any oral anticoagulants between 2011 and 2016
Patients with at least 1 year of data
304 407
Exclusions
Anticoagulants in the previous 12 months 141 533
More than one anticoagulant prescribed 619
Started after Hospital Episode Statistics linkage 5 858
Other anticoagulants 361
Inconsistent Hospital Episode data 31
Available for bleed and mortality analysis 156 005
Available for stroke analysis 131 260
Available for venous thromboembolism analysis 115 109
Patients with atrial fibrillation 81 251
Available for stroke analysis 66 119
Available for venous thromboembolism analysis 76 449
Patients without atrial fibrillation 74 754
Available for stroke analysis 65 141
Available for venous thromboembolism analysis 38 660
CPRD
At least one prescription of any oral anticoagulants between 2011 and 2016
Patients with at least 1 year of data
84 236
Exclusions
Anticoagulants in the previous 12 months 40 404
More than one anticoagulant prescribed 94
Started after Hospital Episode Statistics linkage 3 620
Other anticoagulants 65
Inconsistent Hospital Episode data 24
Available for bleed and mortality analysis 40 056
Available for stroke analysis 33 626
Available for venous thromboembolism analysis 27 949
Patients with atrial fibrillation 22 019
Available for stroke analysis 17 804
Available for venous thromboembolism analysis 20 383
Patients without atrial fibrillation 18 037
Available for stroke analysis 15 822
Available for venous thromboembolism analysis 7 566



QResearch, version 42

Clinical Practice Research Datalink (CPRD), November 2016

Fig 2 | Proportion of patients prescribed different anticoagulants in each year by database

Results – Major Bleeding Risks

- **Apixaban:** Lowest risk of major bleeding events.
- **Dabigatran:** Moderate bleeding risk; lower intracranial but higher gastrointestinal bleeding risk.
- **Rivaroxaban:** Highest risk of major bleeding and gastrointestinal bleeding.
- **Clinical Interpretation:** Apixaban shows superior safety in bleeding outcomes.

Results – Intracranial & Gastrointestinal Bleeding Risks

- **Intracranial Bleeding:**
    - Dabigatran and apixaban associated with lower risk than warfarin.
    - Rivaroxaban had a similar risk to warfarin.
- **Gastrointestinal Bleeding:**
    - Rivaroxaban and dabigatran had higher risks compared to warfarin.
    - Apixaban had the lowest gastrointestinal bleeding risk.

Results – Ischemic Stroke & VTE Risks

- **Ischemic Stroke Prevention:**
    - DOACs were **non-inferior to warfarin** in preventing ischemic stroke.
- **VTE Risks:**
    - **Apixaban & Dabigatran:** Lower VTE risk than warfarin.
    - **Rivaroxaban:** Higher VTE risk compared to warfarin.

- **Key Takeaway**

Apixaban appears to balance safety and efficacy better than other DOACs.

Results – Mortality Risks

- **Rivaroxaban:** Associated with **increased all-cause mortality** compared to warfarin.
- **Low-Dose Apixaban:** Also associated with **increased all-cause mortality** in both AF and non-AF patients.
- **Apixaban (Standard Dose) & Dabigatran:** Did not show increased mortality risk.
- **Clinical Considerations:** Caution is needed when prescribing low-dose apixaban, particularly for high-risk patients.

Results – Clinical Implications

- **Patient Selection:**
    - **Apixaban (standard dose)** preferred for patients at high bleeding risk.
    - **Low-dose Apixaban & Rivaroxaban** should be used cautiously due to mortality concerns.
- **Warfarin Remains Viable:**
    - Useful for patients requiring close monitoring or with severe renal impairment.
- **DOACs vs. Warfarin:**
    - DOACs generally have better safety profiles but require individualized prescribing.

Real-World vs. Clinical Trials

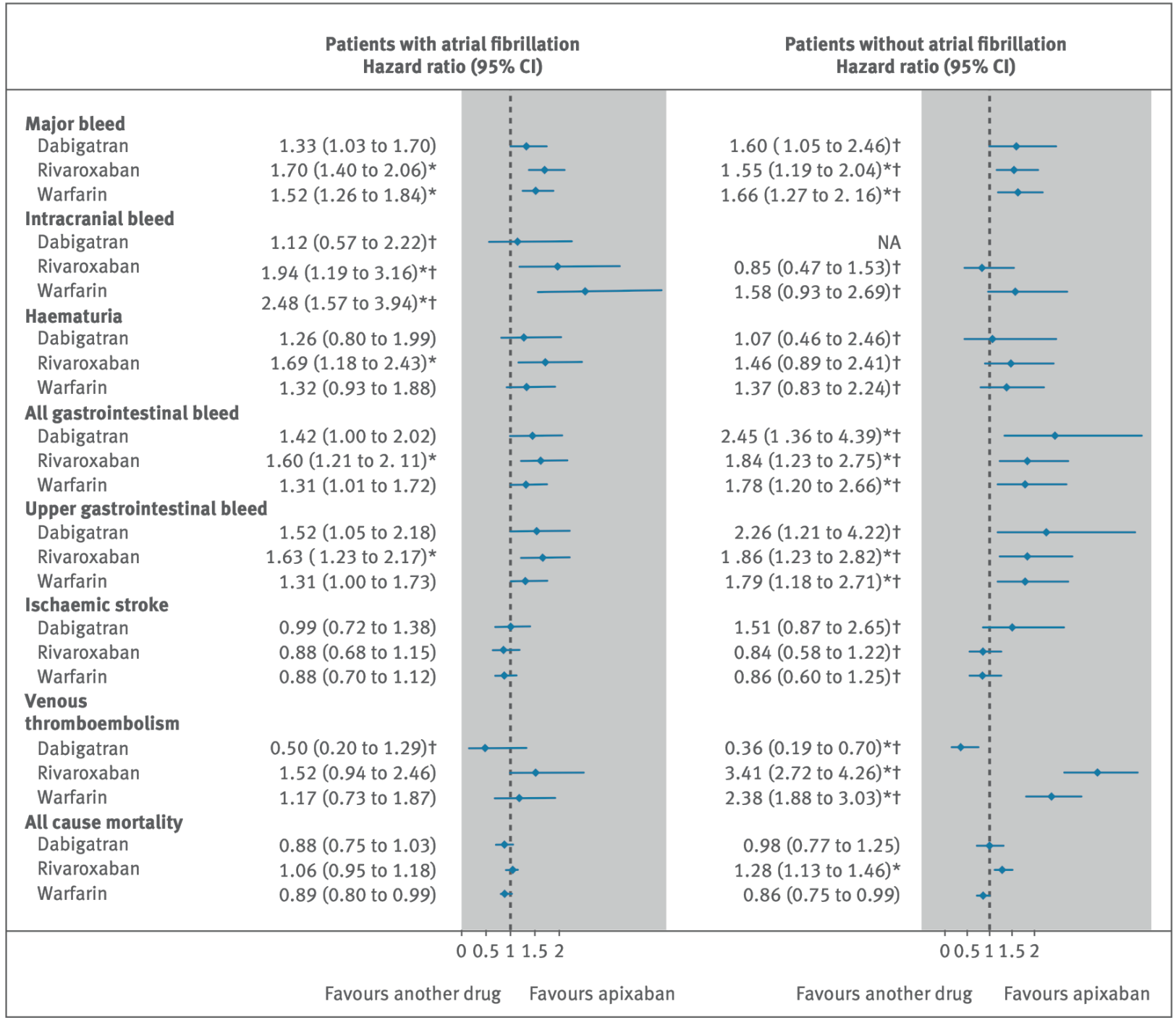
- **Why This Study Matters?**
  - Randomized controlled trials (RCTs) often have strict criteria, excluding high-risk patients.
  - This real-world study includes **a broader patient population**, giving more applicable clinical insights.

- **Strengths of Observational Data:**
  - Large sample size
  - Representative of routine clinical practice

- **Limitations:**
  - Potential confounders despite adjustments.
  - Variability in real-world adherence to medication.

Comparison of Anticoagulants in AF and Non-AF Patients

Outcome	Warfarin (Reference)	Dabigatran	Rivaroxaban	Apixaban
Major Bleeding (AF Patients)	Baseline risk	↓ Intracranial Bleeding (HR 0.45)	No significant reduction	**↓ Major Bleeding (HR 0.66), ↓ Intracranial Bleeding (HR 0.40)**
Major Bleeding (Non-AF Patients)	Baseline risk	No significant reduction	↓ Intracranial Bleeding (HR 0.54)	**↓ Major Bleeding (HR 0.60), ↓ GI Bleeding (HR 0.55)**
Intracranial Bleeding (AF Patients)	Reference	**↓ HR 0.45**	**↑ HR 1.94 vs. Apixaban**	**↓ HR 0.40**
Intracranial Bleeding (Non-AF Patients)	Reference	No significant difference	**↓ HR 0.54**	No significant difference
GI Bleeding (AF Patients)	Reference	No significant difference	**↑ HR vs. Apixaban**	**↓ HR 0.55**
GI Bleeding (Non-AF Patients)	Reference	**↑ HR vs. Apixaban**	**↑ HR vs. Apixaban**	**↓ HR 0.55**
All-Cause Mortality (AF Patients)	Reference	No significant difference	**↑ HR 1.19**	**↑ HR 1.27 (low-dose)**
All-Cause Mortality (Non-AF Patients)	Reference	No significant difference	**↑ HR 1.51**	**↑ HR 1.34 (low-dose)**
Ischaemic Stroke (AF & Non-AF Patients)	Reference	No significant difference	No significant difference	No significant difference
Venous Thromboembolism (AF Patients)	Reference	No significant difference	No significant difference	No significant difference
Venous Thromboembolism (Non-AF Patients)	Reference	No significant difference	**↑ HR 1.49**	No significant difference


Patients with atrial fibrillation
Hazard ratio (95% CI)
Patients without atrial fibrillation
Hazard ratio (95% CI)
Major bleed
Dabigatran 1.33 (1.03 to 1.70) 1.60 (1.05 to 2.46)†
Rivaroxaban 1.70 (1.40 to 2.06)* 1 .55 (1.19 to 2.04)*†
Warfarin 1.52 (1.26 to 1.84)* 1.66 (1.27 to 2. 16)*†
Intracranial bleed
Dabigatran 1.12 (0.57 to 2.22)† NA
Rivaroxaban 1.94 (1.19 to 3.16)*† 0.85 (0.47 to 1.53)†
Warfarin 2.48 (1.57 to 3.94)*† 1.58 (0.93 to 2.69)†
Haematuria
Dabigatran 1.26 (0.80 to 1.99) 1.07 (0.46 to 2.46)†
Rivaroxaban 1.69 (1.18 to 2.43)* 1.46 (0.89 to 2.41)†
Warfarin 1.32 (0.93 to 1.88) 1.37 (0.83 to 2.24)†
All gastrointestinal bleed
Dabigatran 1.42 (1.00 to 2.02) 2.45 (1 .36 to 4.39)*†
Rivaroxaban 1.60 (1.21 to 2. 11)* 1.84 (1.23 to 2.75)*†
Warfarin 1.31 (1.01 to 1.72) 1.78 (1.20 to 2.66)*†
Upper gastrointestinal bleed
Dabigatran 1.52 (1.05 to 2.18) 2.26 (1.21 to 4.22)†
Rivaroxaban 1.63 (1.23 to 2.17)* 1 .86 (1.23 to 2.82)*†
Warfarin 1.31 (1.00 to 1.73) 1.79 (1.18 to 2.71)*†
Ischaemic stroke
Dabigatran 0.99 (0.72 to 1.38) 1.51 (0.87 to 2.65)†
Rivaroxaban 0.88 (0.68 to 1.15) 0.84 (0.58 to 1.22)†
Warfarin 0.88 (0.70 to 1.12) 0.86 (0.60 to 1.25)†
Venous thromboembolism
Dabigatran 0.50 (0.20 to 1.29)† 0.36 (0.19 to 0.70)*†
Rivaroxaban 1.52 (0.94 to 2.46) 3.41 (2.72 to 4.26)*†
Warfarin 1.17 (0.73 to 1.87) 2.38 (1.88 to 3.03)*†
All cause mortality
Dabigatran 0.88 (0.75 to 1.03) 0.98 (0.77 to 1.25)
Rivaroxaban 1.06 (0.95 to 1.18) 1.28 (1.13 to 1.46)*
Warfarin 0.89 (0.80 to 0.99) 0.86 (0.75 to 0.99)
0 0.5 1 1.5 2
0 0.5 1 1.5 2
Favours another drug
Favours apixaban
Favours another drug
Favours apixaban

Conclusion

- **Apixaban is the safest DOAC overall.**
- **Dabigatran has a mixed profile with lower intracranial bleeding but higher GI bleeding.**
- **Low-dose Apixaban Rivaroxaban is associated with increased mortality and should be used cautiously.**
- **DOACs are a valuable alternative to warfarin, but patient-specific risks must be assessed.**

Thank you for your attention!

Questions?