



Dementia Risk of Direct Oral Anticoagulants Versus Warfarin for Atrial Fibrillation

A Systematic Review & Meta-Analysis



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COI Disclosure

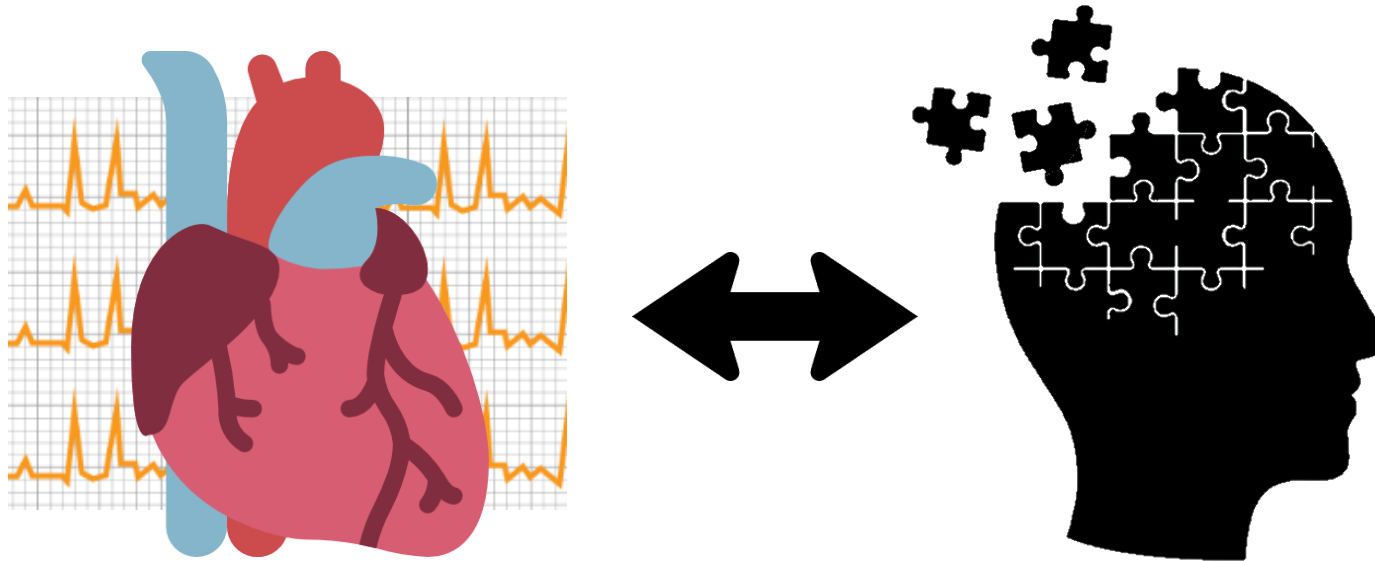
Khi Yung Fong:

The authors have no financial conflicts of interest
to disclose concerning the presentation



Introduction

Atrial fibrillation (AF): a prevalent condition among older people



- Association between AF and dementia thought to be independent of stroke events
- Unknown whether AF is a direct causal factor for cognitive decline, or simply a marker of global vascular disease burden



Introduction

Oral anticoagulants: central for stroke prevention in AF

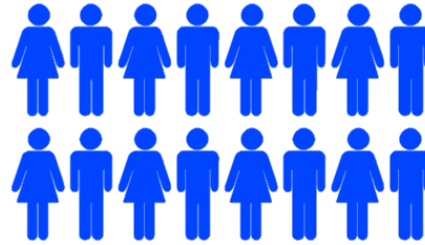


DOAC ↓ stroke, death, hemorrhage compared to warfarin
Effect on dementia not well characterized



Methods: meta-analysis

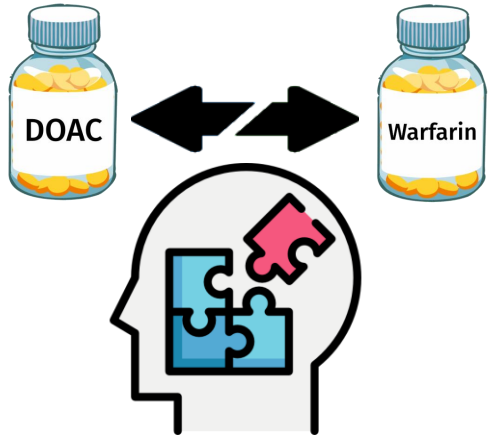
Electronic literature search retrieved:



10 large cohort studies

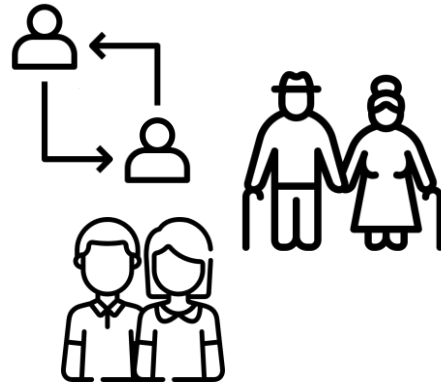
342,624 patients

Mean age: 70.4-75.7 years



Primary outcome:

Hazard ratio (HR) for new-onset dementia (DOAC vs warfarin)

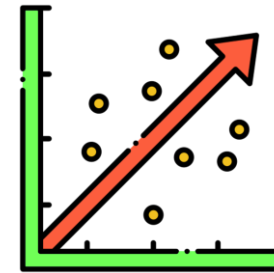


Subgroup analysis

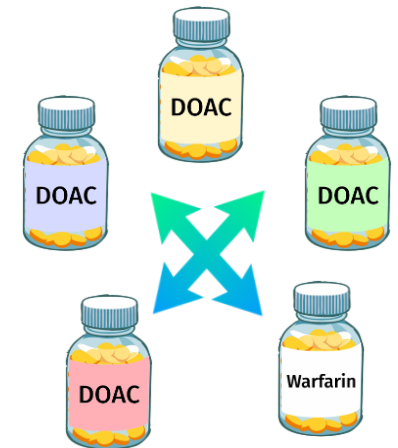
PSM studies

≥75 y/o

65-75 y/o



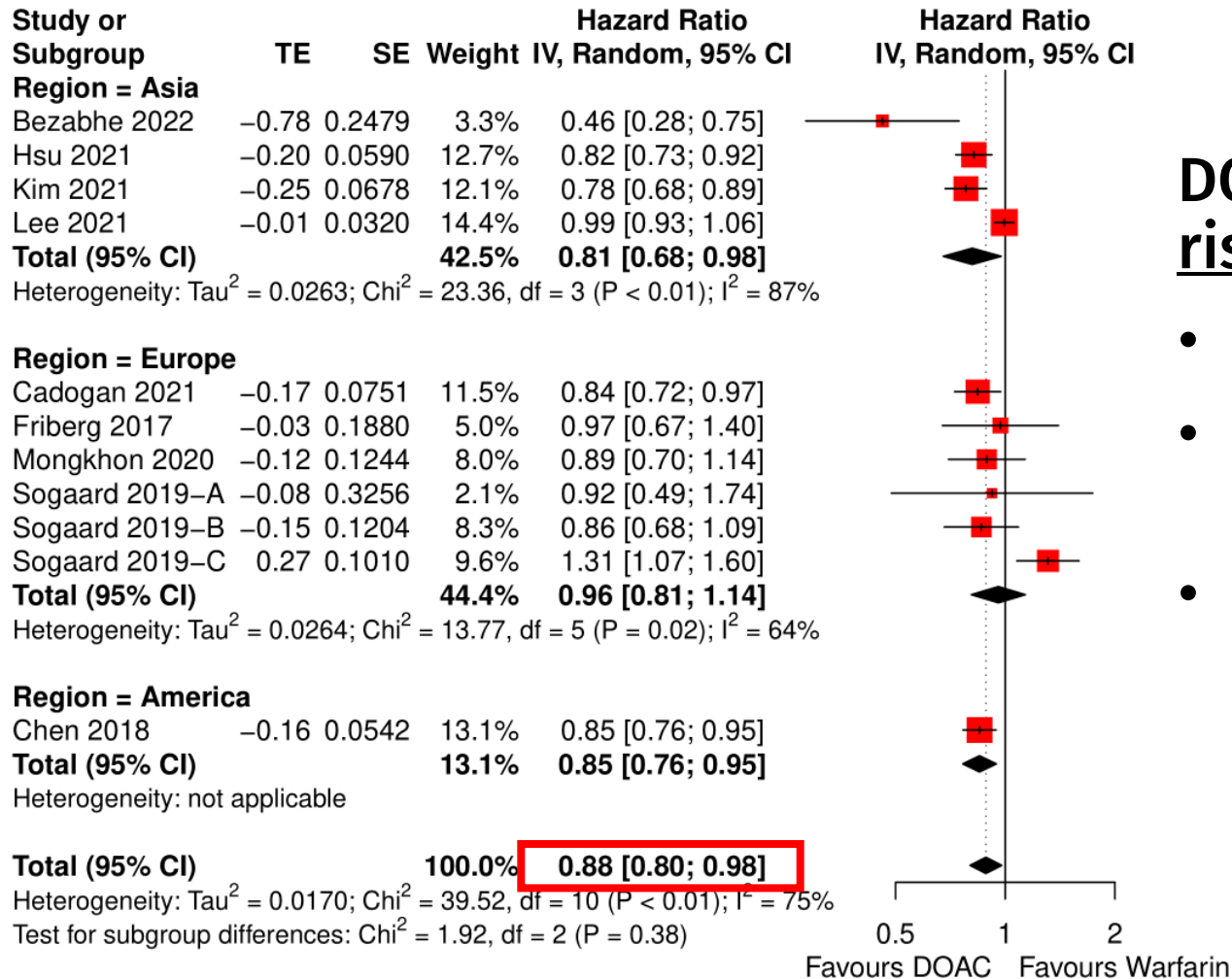
Meta-regression of
baseline characteristics



Network meta-analysis (NMA) of
individual DOACs vs warfarin



Results: meta-analysis



DOAC significantly reduced dementia risk compared to warfarin

- Effect most pronounced in Asians
- Similar benefit seen in subgroup analyses of PSM studies & 65-75 y/o
- No significant benefit seen in ≥75 y/o patients



Results: meta-regression

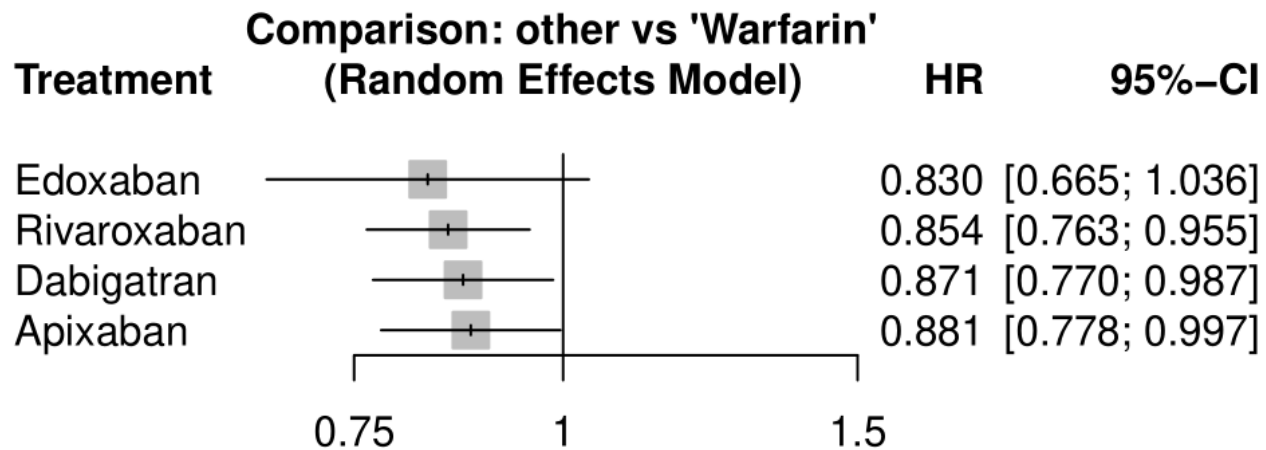


Benefit of DOAC over warfarin decreases with age (p=0.03)

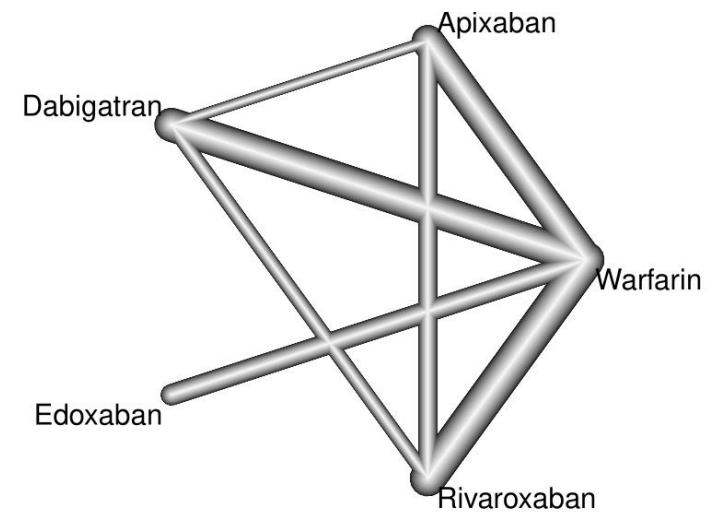
No significant associations with publication year, mean age, follow-up time, % males, CHA₂DS₂-VASc, heart failure, DM, HTN, previous stroke, statin use



Results: network meta-analysis



$I^2=62\%$, $Q=24$, $p=0.004$



Significant ↓ in dementia vs warfarin for all DOAC except edoxaban
No differences between individual DOACs



Discussion

Several mechanisms linking AF to ↑ dementia risk have been proposed



Stroke-dependent risk: ↓ risk of intracranial bleed, stroke with DOAC

- Superior stroke reduction with DOAC → less vascular dementia*

**JSCVD* 2014;23(7):1821-1829;
Lancet Neurology 2009;8(11):1006-1018



Stroke-independent risk (subclinical cerebral hypoperfusion, inflammation)

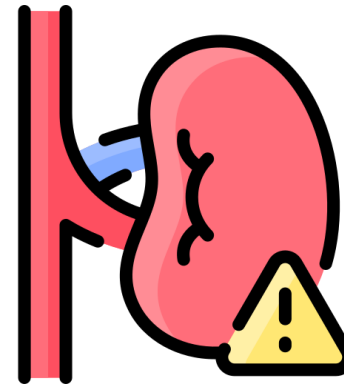
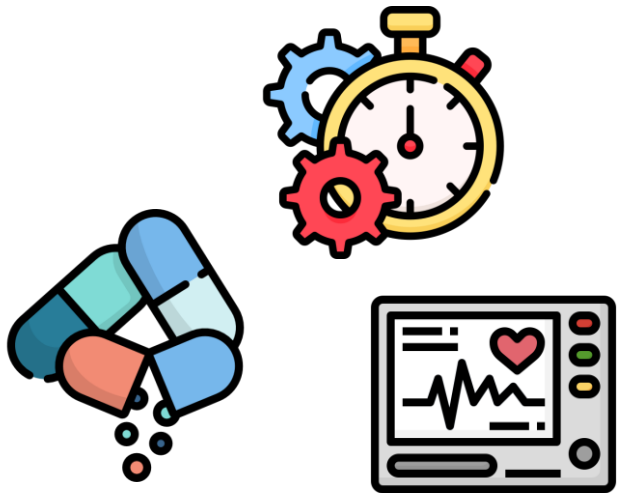
- Marked influence of TTR, labile INR on dementia in patients on warfarin, compared to DOAC[^]

[^]*Europace* 2018;20(8):1252-1258;
Am J Med 2018;131(12):1408-1417



Discussion

Suggestion of reversal of DOAC benefit with increasing age



Possible confounders: dosage variations, TTR of warfarin arm, nature of AF

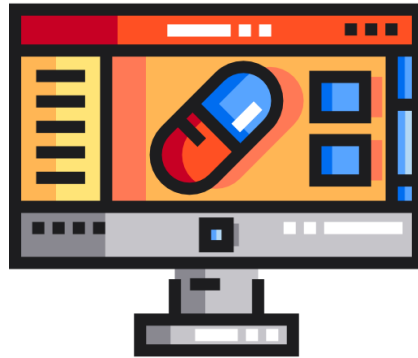
↓GFR, ↑ CKD with age – DOAC is renally cleared, possibly leading to suboptimal dosing



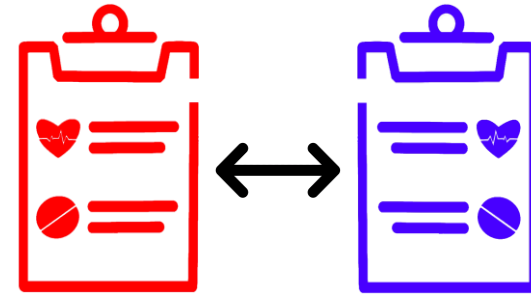
Limitations



Use of nonrandomized studies – needs further RCTs

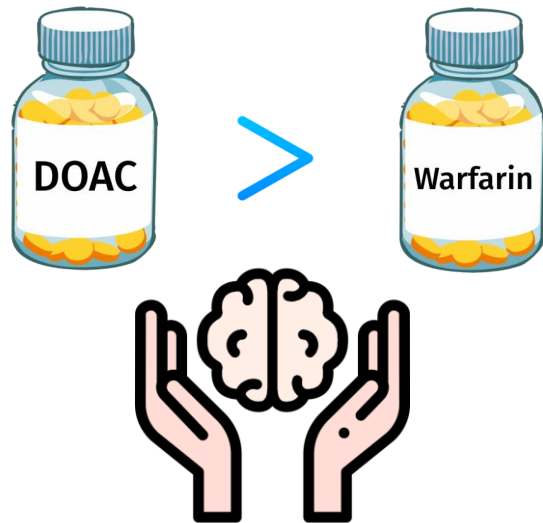


Use of disease codes may not encompass all dementia cases

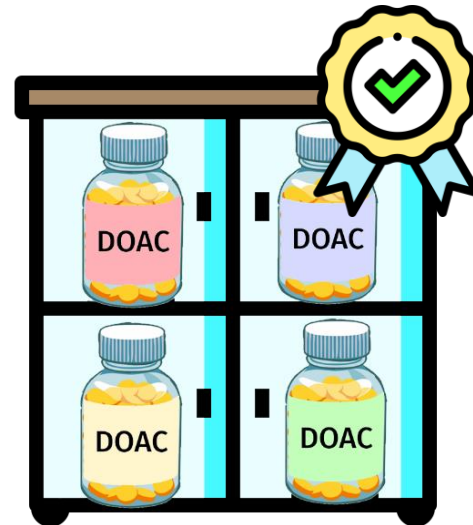


NMA: assumption of similarity among study designs

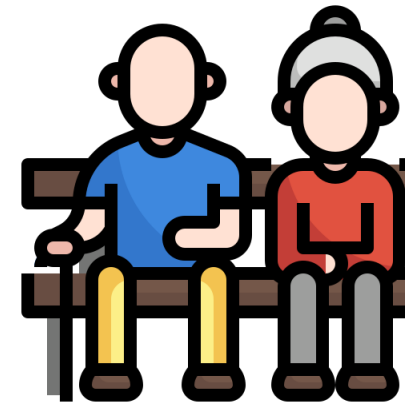
Closing Remarks



DOAC significantly reduces dementia risk compared to warfarin



No difference in hazard reduction between individual DOACs



Suggestion of lower benefit for DOAC with increasing age merits further research





Thank you!

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