Direct oral anticoagulants versus vitamin K antagonists in left ventricular thrombi

A systematic review and meta-analysis

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Affiliations
I have no relationships with for-profit or not-for-profit organizations.

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Outline

1. Background
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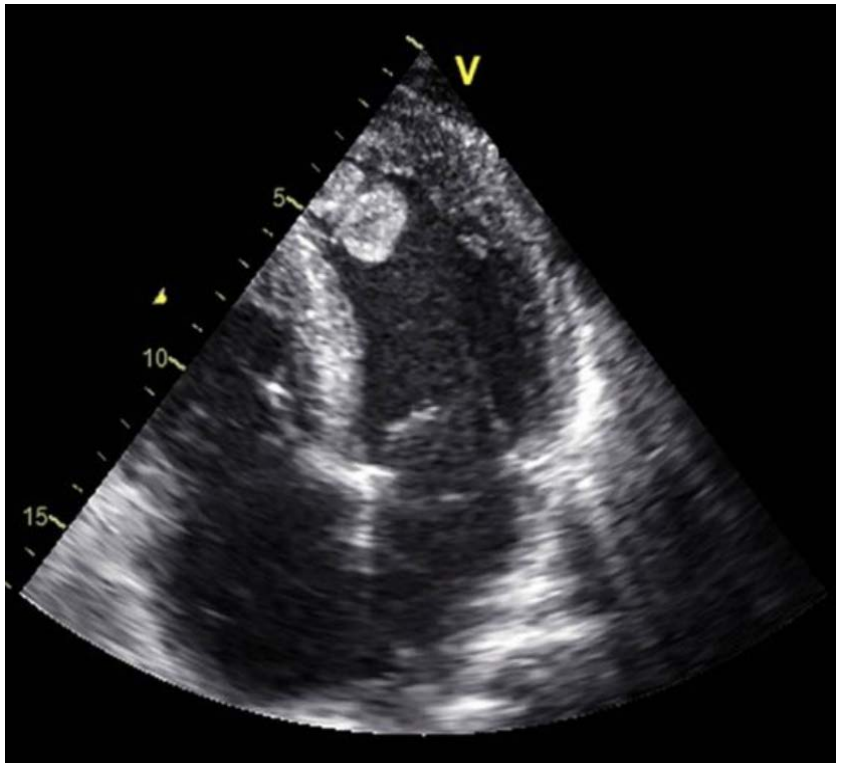
BACKGROUND

About Left Ventricular (LV) Thrombi

- Occur in conditions where left ventricular systolic function is impaired
    - E.g. post-anterior myocardial infarction, dilated cardiomyopathy
- Associated with thromboembolic events
    - E.g. stroke, peripheral arterial emboli



Management of Left Ventricular Thrombi

European Society of Cardiology (2012)

"Mural thrombi, once diagnosed, require oral anticoagulant therapy with vitamin K antagonists for up to 6 months"

American College of Cardiology (2013)

"Anticoagulant therapy with a vitamin K antagonist is reasonable for patients with STEMI and asymptomatic LV mural thrombi"

Limitations of Current Consensus Guidelines

No recent updates to the guidelines

Recommendations based on low quality of evidence; primarily expert opinion

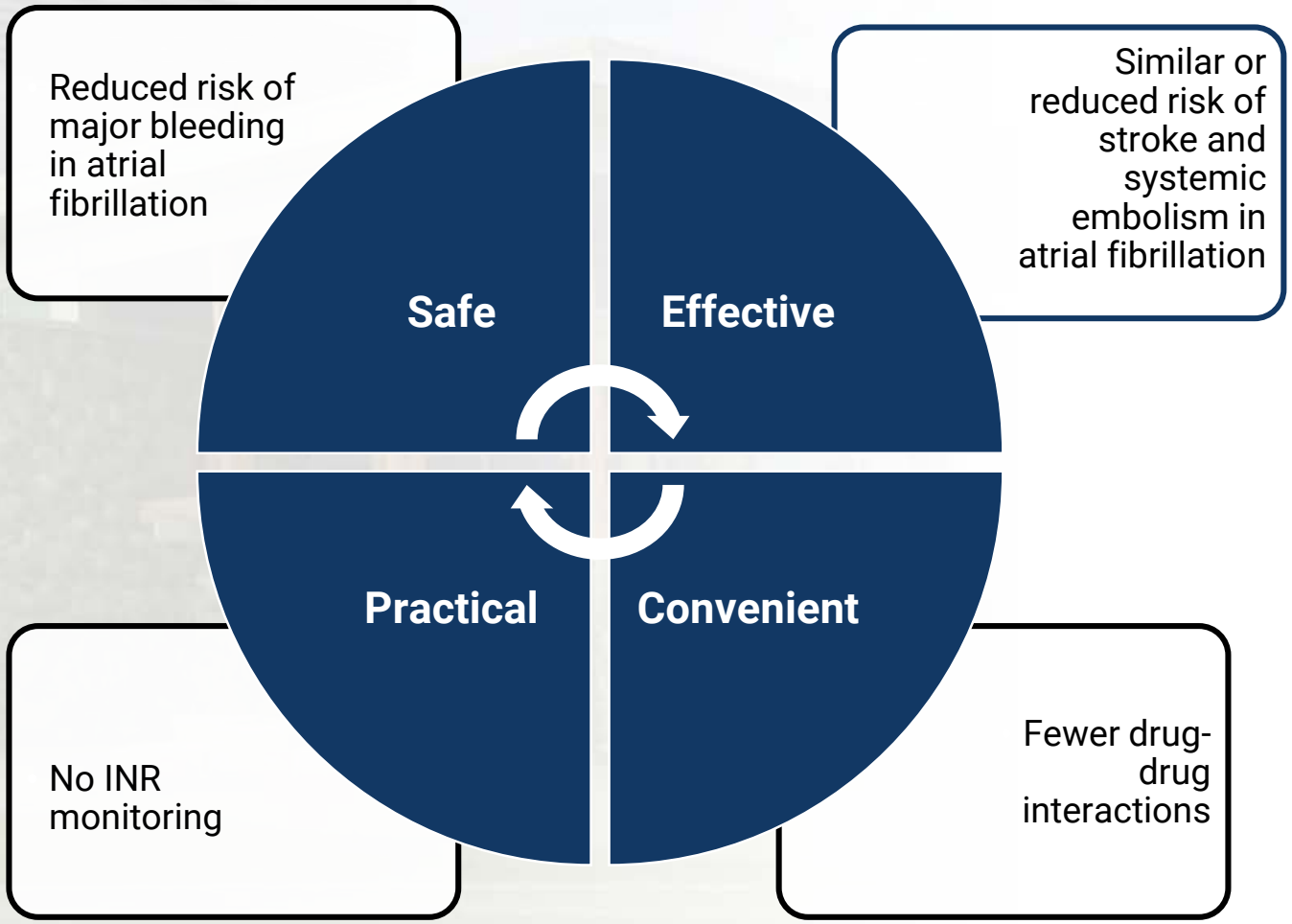
Current Recommendations for DOACs

American Heart Association/American Stroke Association (2014)

“In those with LV thrombus who are intolerant to VKA therapy, treatment with LMWH, dabigatran, rivaroxaban, or apixaban for 3 months may be considered as an alternative to VKA therapy”

(Class 2B recommendation, Level of Evidence C)

Benefits of DOACs vs. VKAs



Evidence for DOACs in LV Thrombi

- Many small retrospective studies have demonstrated that DOACs and VKAs have similar outcomes in treatment of LVT

- E.g. Robinson *et al.* 2020:
  - Multicenter retrospective cohort study
  - n = 121 DOAC; n = 236 warfarin
  - Increased stroke and systemic embolism with DOACs (HR 2.88; 95% CI 1.22-6.80; *p* = 0.02)

Rationale for Our Study

- Conflicting data exists regarding the safety & efficacy of DOACs for the treatment of LV thrombi
- No recent guidelines to recommend the use of DOACs for this indication
- DOACs are a well-established alternative to VKAs in the treatment of other thromboembolic phenomenon, but conflicting literature for LV thrombi to date

Research Objectives

To compare the safety and efficacy of DOACs to VKAs in the management of LV thrombi with respect to:

- Stroke
- Bleeding
- Systemic embolism (SE)
- Stroke or systemic embolism (SSE)
- Mortality
- LV thrombus resolution

Primary Outcomes

Secondary Outcomes

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RESEARCH METHODS

Methodology

Databases

- PubMed, Embase, CENTRAL, Scopus, and OpenGrey

Inclusion Criteria

- Comparative study of DOACs to VKAs in LV thrombi
- Must report on: stroke, bleeding, SE, SSE, mortality or LV thrombus resolution

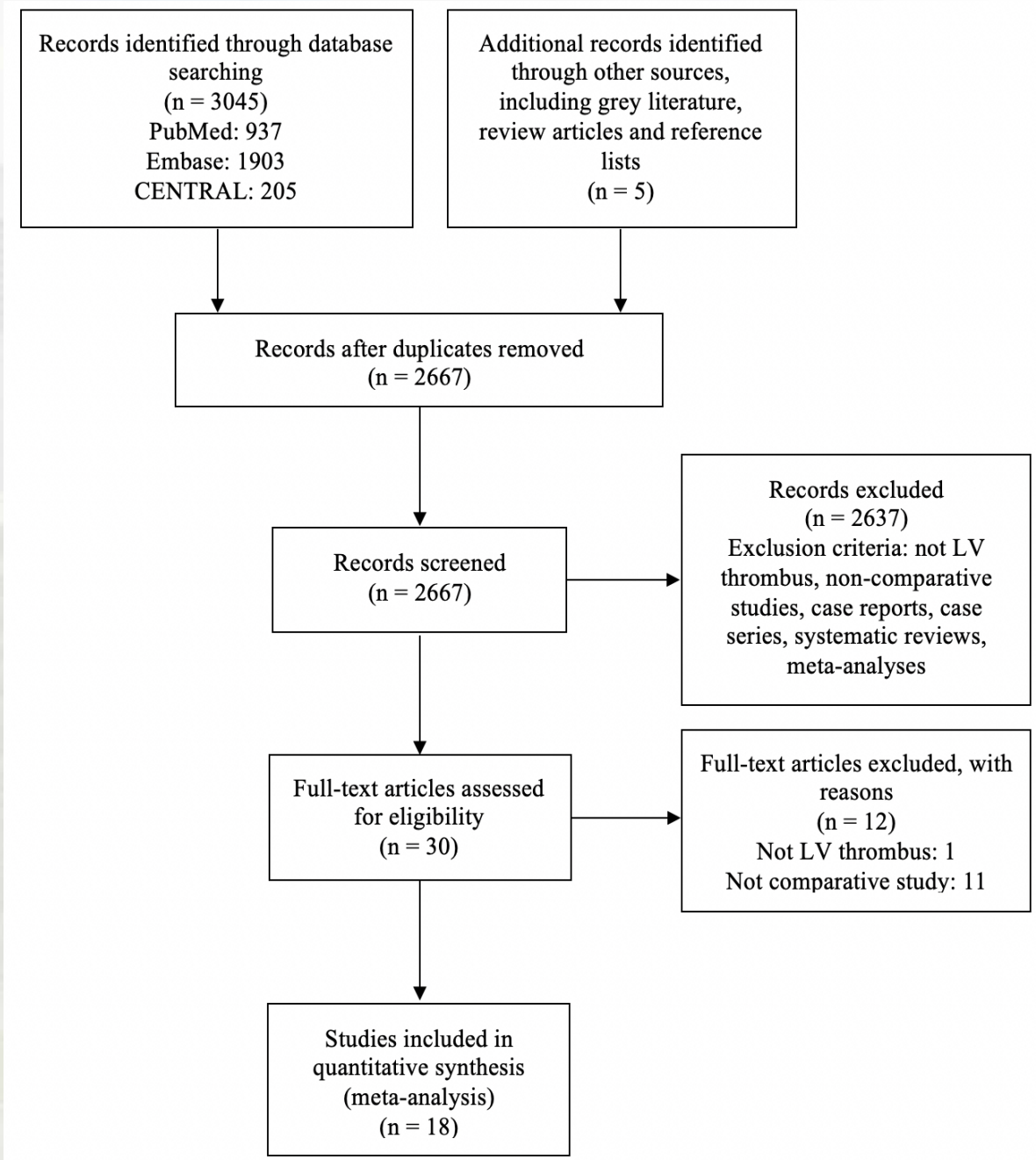
Exclusion Criteria

- Case reports, case series, non-comparative trials & review articles

Statistical Analysis

- Random-effects model used to report odds ratios

RESULTS



Included Studies

18 studies (including 8 abstracts)

- 14 retrospective cohorts
- 2 prospective cohorts
- 2 preliminary RCTs

2666 patients

- 674 on DOAC, 1992 on VKA
- Mean age 49-63 years
- Significant cardiovascular comorbidities
- Most LV thrombi due to acute MI or ischemic cardiomyopathy

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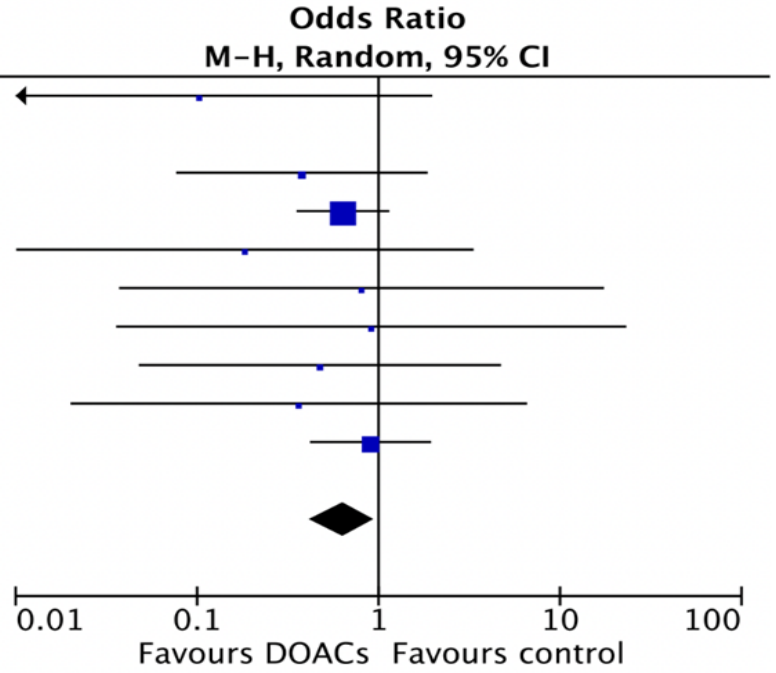
Stroke

Study or Subgroup	DOACs Events	DOACs Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdelnabi	0	39	4	40	2.0%	0.10 [0.01, 1.97]
Alcalai	0	13	0	12		Not estimable
Ali	2	32	9	60	6.9%	0.38 [0.08, 1.87]
Bass	14	180	90	769	50.6%	0.64 [0.35, 1.15]
Cochran	0	14	9	59	2.1%	0.18 [0.01, 3.34]
Guddeti	0	19	2	80	1.8%	0.81 [0.04, 17.46]
Iqbal	0	22	1	62	1.7%	0.91 [0.04, 23.19]
Jones	1	41	3	60	3.3%	0.47 [0.05, 4.73]
Willeford	0	22	7	129	2.1%	0.36 [0.02, 6.58]
Yunis	10	64	34	200	29.6%	0.90 [0.42, 1.95]
Total (95% CI)		**446**		**1471**	**100.0%**	**0.63 [0.42, 0.96]**
Total events	27		159			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.72$, df = 8 (P = 0.88); $I^2 = 0\%$

Test for overall effect: Z = 2.14 (P = 0.03)



6.0% in DOAC vs. 10.8% in VKA (OR 0.63, 95% CI 0.42-0.96, *p* = 0.03)

Sensitivity analysis

OR 0.57, 95% CI 0.35-0.95, *p* = 0.03

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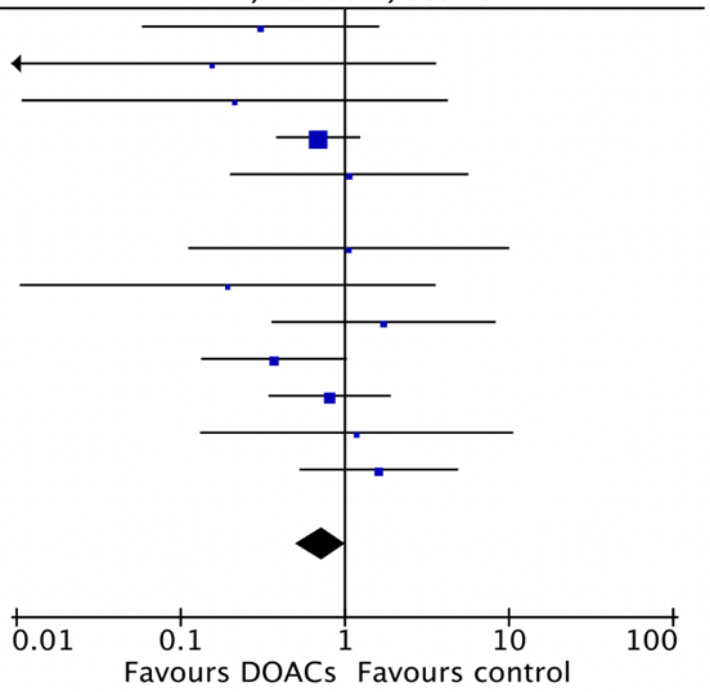
Bleeding

Study or Subgroup	DOACs Events	DOACs Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdelnabi	2	39	6	40	4.6%	0.31 [0.06, 1.62]
Alcalai	0	13	2	12	1.3%	0.16 [0.01, 3.60]
Alizadeh	0	38	3	60	1.4%	0.21 [0.01, 4.25]
Bass	14	180	84	769	36.5%	0.69 [0.38, 1.24]
Cochran	2	14	8	59	4.6%	1.06 [0.20, 5.66]
Durrer-Ariyakuddy	0	20	0	33		Not estimable
Guddeti	1	19	4	80	2.5%	1.06 [0.11, 10.02]
Iqbal	0	22	6	62	1.5%	0.19 [0.01, 3.57]
Jaidka	3	12	6	37	5.2%	1.72 [0.36, 8.30]
Jones	6	41	19	60	12.2%	0.37 [0.13, 1.03]
Robinson	8	121	19	236	17.4%	0.81 [0.34, 1.90]
Willeford	1	22	5	129	2.6%	1.18 [0.13, 10.62]
Yunis	5	64	10	200	10.3%	1.61 [0.53, 4.90]
Total (95% CI)		**605**		**1777**	**100.0%**	**0.72 [0.50, 1.02]**
Total events	42		172			

Heterogeneity: Tau² = 0.00; Chi² = 8.85, df = 11 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.83 (P = 0.07)



7.0% in DOAC vs. 9.7% in VKA (OR 0.72, 95% CI 0.50-1.02, *p* = 0.07)

Sensitivity analysis

OR 0.67, 95% CI 0.45-1.00, *p* = 0.05

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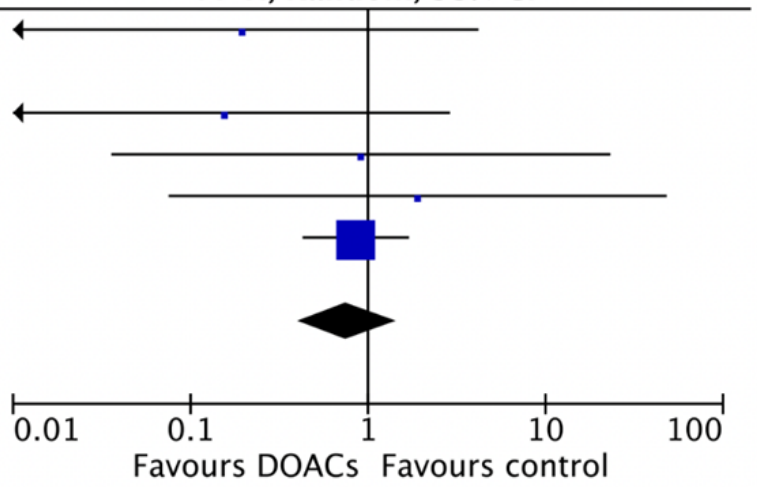
Systemic Embolism

Study or Subgroup	DOACs Events	DOACs Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdelnabi	0	39	2	40	4.2%	0.19 [0.01, 4.19]
Alcalai	0	13	0	12		Not estimable
Ali	0	32	5	60	4.7%	0.16 [0.01, 2.90]
Iqbal	0	22	1	62	3.8%	0.91 [0.04, 23.19]
Willeford	0	22	1	129	3.8%	1.90 [0.08, 48.21]
Yunis	13	64	46	200	83.4%	0.85 [0.43, 1.71]
Total (95% CI)		**192**		**503**	**100.0%**	**0.77 [0.41, 1.44]**
Total events	13		55			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.38$, df = 4 (P = 0.67); $I^2 = 0\%$

Test for overall effect: Z = 0.83 (P = 0.41)



6.7% in DOAC vs. 10.7% in VKA

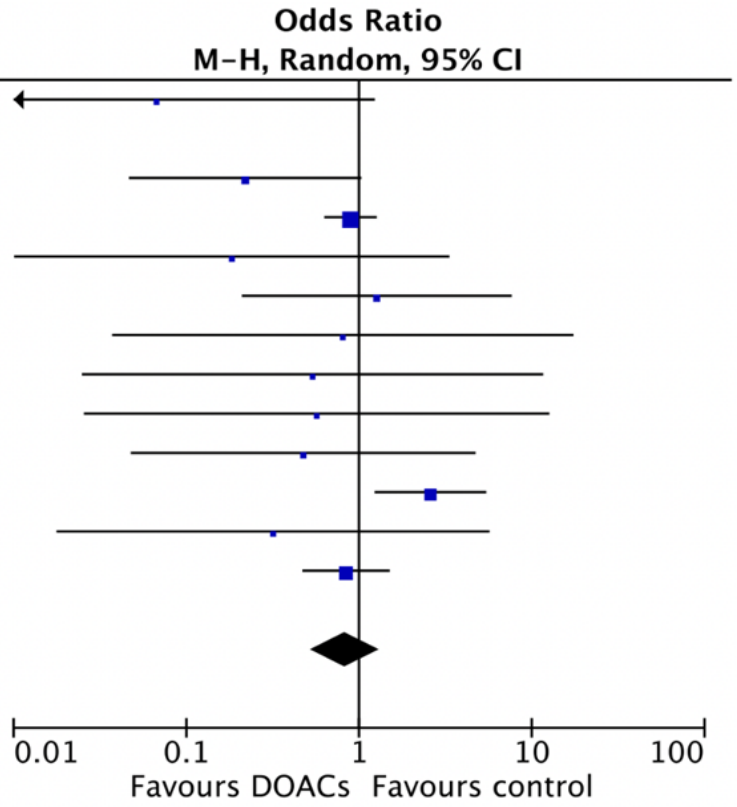
OR 0.77, 95% CI 0.41-1.44, *p* = 0.41

Stroke or Systemic Embolism

Study or Subgroup	DOACs Events	DOACs Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdelnabi	0	39	6	40	2.4%	0.07 [0.00, 1.24]
Alcalai	0	13	0	12		Not estimable
Ali	2	32	14	60	7.1%	0.22 [0.05, 1.03]
Bass	55	180	254	769	29.2%	0.89 [0.63, 1.27]
Cochran	0	14	9	59	2.4%	0.18 [0.01, 3.34]
Daher	2	17	4	42	5.6%	1.27 [0.21, 7.66]
Guddeti	0	19	2	80	2.1%	0.81 [0.04, 17.46]
Iqbal	0	22	2	62	2.1%	0.54 [0.02, 11.64]
Jaidka	0	12	2	37	2.1%	0.57 [0.03, 12.66]
Jones	1	41	3	60	3.6%	0.47 [0.05, 4.73]
Robinson	17	121	14	236	18.4%	2.59 [1.23, 5.46]
Willeford	0	22	8	129	2.4%	0.32 [0.02, 5.70]
Yunis	23	64	80	200	22.5%	0.84 [0.47, 1.51]
Total (95% CI)		**596**		**1786**	**100.0%**	**0.83 [0.53, 1.33]**
Total events	100		398			

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 16.54$, df = 11 (P = 0.12); $I^2 = 33\%$

Test for overall effect: Z = 0.76 (P = 0.45)



16.8% in DOAC vs. 22.2% in VKA

OR 0.83, 95% CI 0.53-1.33, *p* = 0.45

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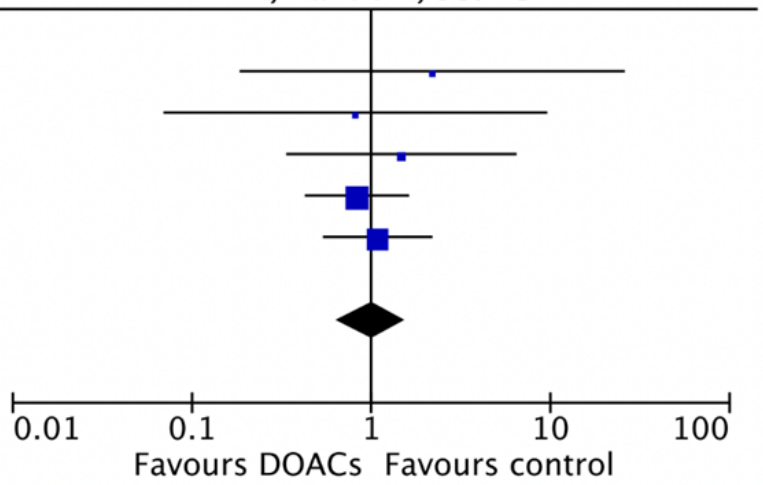
Mortality

Study or Subgroup	DOACs Events	DOACs Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Alcalai	0	13	0	12		Not estimable
Cochran	1	14	2	59	3.2%	2.19 [0.18, 26.05]
Durrer-Ariyakuddy	1	20	2	33	3.3%	0.82 [0.07, 9.62]
Iqbal	3	22	6	62	9.1%	1.47 [0.34, 6.48]
Robinson	14	121	32	236	44.3%	0.83 [0.43, 1.63]
Yunis	13	64	38	200	40.1%	1.09 [0.54, 2.20]
Total (95% CI)		**254**		**602**	**100.0%**	**1.01 [0.64, 1.57]**
Total events	32		80			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.01$, df = 4 (P = 0.91); $I^2 = 0\%$

Test for overall effect: Z = 0.03 (P = 0.98)



12.8% in DOAC vs. 13.3% in VKA

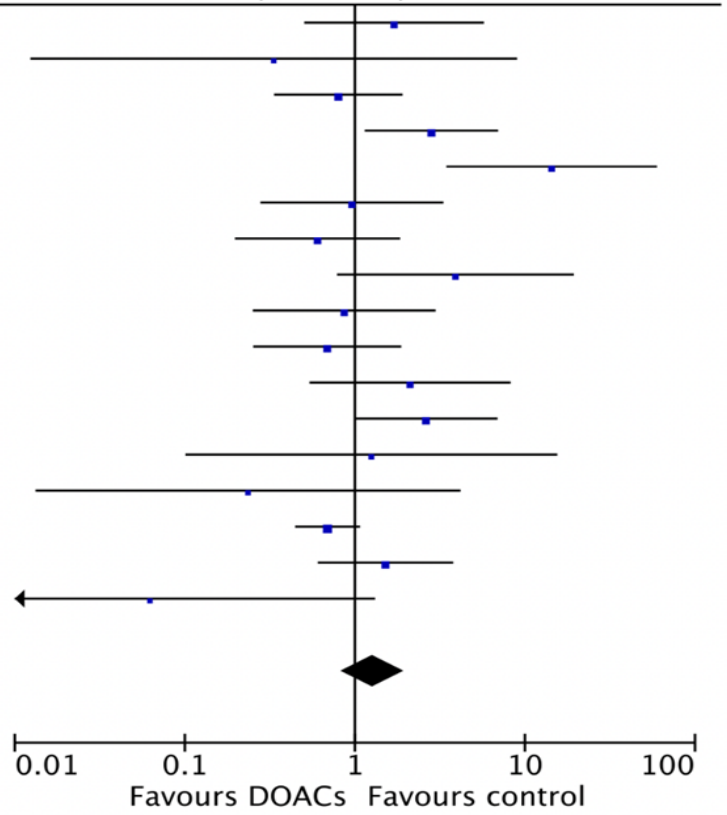
OR 1.01, 95% CI 0.64-1.57, *p* = 0.98

LV Thrombus Resolution

Study or Subgroup	DOACs Events	DOACs Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdelnabi	34	39	32	40	6.3%	1.70 [0.50, 5.74]
Alcalai	12	13	12	12	1.5%	0.33 [0.01, 8.99]
Ali	18	32	37	60	8.4%	0.80 [0.33, 1.91]
Alizadeh	29	38	32	60	8.2%	2.82 [1.14, 6.96]
Cochran	11	14	12	59	5.4%	14.36 [3.45, 59.73]
Daher	12	17	30	42	6.2%	0.96 [0.28, 3.32]
Durrer-Ariyakuddy	9	20	19	33	6.9%	0.60 [0.20, 1.85]
Gama	11	13	31	53	4.6%	3.90 [0.79, 19.38]
Guddeti	15	19	65	80	6.2%	0.87 [0.25, 2.98]
Iqbal	13	22	42	62	7.5%	0.69 [0.25, 1.88]
Jaidka	8	12	18	37	5.6%	2.11 [0.54, 8.25]
Jones	34	41	39	60	7.7%	2.62 [0.99, 6.91]
Lim	1	5	3	18	2.4%	1.25 [0.10, 15.50]
Ratnayake	1	2	34	42	1.9%	0.24 [0.01, 4.18]
Robinson	56	121	131	236	11.2%	0.69 [0.44, 1.07]
Willeford	13	22	63	129	8.1%	1.51 [0.60, 3.79]
Yunis	62	64	200	200	1.8%	0.06 [0.00, 1.32]
Total (95% CI)		**494**		**1223**	**100.0%**	**1.29 [0.83, 1.99]**
Total events	339		800			

Heterogeneity: $Tau^2 = 0.39$; $Chi^2 = 35.96$, df = 16 (P = 0.003); $I^2 = 56\%$

Test for overall effect: Z = 1.13 (P = 0.26)



69.3% in DOAC vs. 69.6% in VKA

OR 1.29, 95% CI 0.83-1.99, *p* = 0.26

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Summary of Results

Outcome	Weighted average (%)		OR (95% CI)	P-value	I^2 (%)
	DOAC	VKA			
Stroke	6.0	10.8	0.63 (0.42-0.96)	0.03	0
Bleeding	7.0	9.7	0.72 (0.50-1.02)	0.07	0
Systemic embolism	6.7	10.7	0.77 (0.41-1.44)	0.41	0
Stroke or systemic embolism	16.8	22.2	0.83 (0.53-1.33)	0.45	33
Mortality	12.8	13.3	1.01 (0.64-1.57)	0.98	0
LV thrombus resolution	69.3	69.6	1.29 (0.83-1.99)	0.26	56

STRENGTHS & LIMITATIONS

Strengths

Largest meta-analysis to date	Inclusion of RCT data	Examined stroke as individual outcome
2666 patients across 18 primary studies (>600 on DOAC)	First meta-analysis to include data from two RCTs	First meta-analysis to examine stroke, SE & SSE

Limitations

Primary Study Design

- Most included studies
  - were cohorts

Variability in Definitions

- Outcome definitions varied
  - across studies

CONCLUSIONS

Summary of Evidence

1. At this time, there is no concrete recommendation for/against use of DOACs in treatment of LV thrombi

2. DOACs and VKAs are comparable in the odds of systemic embolism, stroke or systemic embolism, mortality and LV thrombus resolution

3. DOACs are associated with a statistically significant reduction in the odds of stroke without an increase in bleeding

4. In the appropriate clinical context, it may be reasonable to use DOACs for treatment of LV thrombi after shared decision-making with the patient

5. Large, high-quality RCTs are required to corroborate our findings and inform future guidelines

THANK YOU

Questions?

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SUPPLEMENTARY TABLES

TABLES

Table 1: Summary of study characteristics

Author	Study design	Groups		Etiology of LV thrombus	Average follow-up (months)	Outcome definitions
		VKA (n)	DOAC[a] (n)			
Abdelnabi (2020)[17]	RCT	40 (all warfarin)	39 (all rivaroxaban 20 mg daily)	Ischemic cardiomyopathy (78.5%) Idiopathic (20.3%) Peripartum (1.2%)	6	***Stroke:*** Any type of stroke ***SE:*** Any type of systemic embolism ***Bleeding:*** Major bleeding according to ISTH ***LV thrombus resolution:*** Determined by TTE
Alcalai (2020)[18]	RCT	12 (all warfarin)	13 (all apixaban 5 mg BID)	Acute MI (100%)	3	***Bleeding:*** Major bleeding ***LV thrombus resolution:*** Determined by TTE
Ali (2020)[21]	Retrospective cohort	60 (all warfarin)	32 (rivaroxaban = 18, apixaban = 13, dabigatran = 1)	Ischemic cardiomyopathy (58%) Non-ischemic cardiomyopathy (23%) Acute MI (15%) Takotsubo cardiomyopathy (3%)	12	Not defined

Alizadeh (2019)[19]	Prospective cohort	60 (VKA not specified)	38 (rivaroxaban = 22, apixaban = 14, edoxaban = 2)	Acute MI (100%)	21.6	***Bleeding:*** Major bleeding, including intracranial bleed, major gastrointestinal bleed and bleed requiring hospital admission ***LV thrombus resolution:*** Determined by echocardiography or CMR
Bass (2021)[22]	Retrospective cohort	769 (all warfarin)	180 (rivaroxaban = 77, apixaban = 79, dabigatran = 29)	Not specified	3	***Stroke:*** Thromboembolic stroke ***Bleeding:*** GUSTO criteria
Cochran (2020)[7]	Retrospective cohort	59 (all warfarin)	14 (DOAC not specified)	Acute MI (48%)	12	***Stroke:*** Clinically documented ***Bleeding:*** Minimal, minor and major bleeding according to TIMI ***LV thrombus resolution:*** Determined by TTE with contrast
Daher (2020)[23]	Retrospective cohort	42 (warfarin = 14, acenocoumarol = 12, fluindione = 16)	17 (rivaroxaban = 4, apixaban = 12, dabigatran = 1)	Acute MI or ischemic cardiomyopathy (37.3%)	3	***LV thrombus resolution:*** Determined by TTE
Durrer-Ariyakuddy (2019)[24]	Retrospective cohort	33 (VKA not specified)	20 (DOAC not specified)	Acute MI (47%) Non-ischemic cardiomyopathy (40%) Ischemic heart disease (13%)	20	***Bleeding:*** Major bleeding ***LV thrombus resolution:*** Determined by echocardiography

Gama (2019)[25]	Retrospective cohort	53 (all warfarin)	13 (DOAC not specified)	All patients post-acute MI or heart failure with reduced ejection fraction	Unknown	***LV thrombus resolution:*** Determined by echocardiography and complemented by CMR when needed
Guddeti (2020)[8]	Retrospective cohort	80 (all warfarin)	19 (rivaroxaban = 2, apixaban = 15, dabigatran = 2)	Acute MI (20.2%) Ischemic cardiomyopathy (58.6%)	12	***Stroke:*** Confirmed by neuroimaging ***Bleeding:*** Life-threatening bleed requiring hospitalization, reduction in hemoglobin by ≥ 2 g/dL, or bleed requiring endoscopic evaluation ***LV thrombus resolution:*** Determined by echocardiogram
Iqbal (2020)[9]	Retrospective cohort	62 (all warfarin)	22 (rivaroxaban 20 mg daily = 13, apixaban 5 mg BID = 8, dabigatran 150 mg BID = 1)	Ischemic cardiomyopathy (86.9%) Dilated cardiomyopathy (4.76%) Hypertrophic cardiomyopathy (3.57%) Myocarditis (2.4%) Unknown (2.4%)	36 ± 17	***Bleeding:*** Any episode of documented bleeding, including presentation to the emergency department, hospitalization, or described in subsequent correspondence ***LV thrombus resolution:*** Determined by TTE or CMR
Jaidka (2018)[26]	Retrospective cohort	37 (all warfarin)	12 (DOAC not specified)	Acute MI (100%)	6	***LV thrombus resolution:*** Determined by echocardiography

Jones (2020)[20]	Prospective cohort	60 (all warfarin)	41 (rivaroxaban = 24, apixaban = 15, edoxaban = 2)	Acute MI (100%)	26.4 (median)	***Bleeding:*** BARC criteria ***LV thrombus resolution:*** Determined by TTE or CMR
Lim (2019)[27]	Retrospective cohort	18 (all warfarin)	5 (rivaroxaban = 2, dabigatran = 3)	Unknown	Unknown	***LV thrombus resolution:*** Determined by echocardiography
Ratnayake (2020)[28]	Retrospective cohort	42 (all warfarin)	2 (all dabigatran)	Acute MI (100%)	6	***LV thrombus resolution:*** Determined by TTE
Robinson (2020)[10]	Retrospective cohort	236	121 (apixaban, rivaroxaban and dabigatran)	Unknown	12	***Stroke:*** Clinically documented stroke ***SE:*** Clinically documented systemic embolism ***Bleeding:*** Event requiring cessation of anticoagulation ***LV thrombus resolution:*** Determined by TTE
Willeford (2020)[29]	Retrospective cohort	129 (all warfarin)	22 [rivaroxaban = 18 (15 mg BID followed by 20 mg BID = 11, 20 mg daily = 6, 15 mg daily = 1), apixaban = 4 (2.5 mg BID = 1, 5 mg BID = 3)]	Unknown	8.5	***Stroke:*** Ischemic or hemorrhagic stroke ***Bleeding:*** Hemorrhagic stroke and bleeding requiring transfusion ***LV thrombus resolution:*** Determined by TTE
Yunis (2020)[30]	Retrospective cohort	200 (all warfarin)	64 (DOAC not specified)	Unknown	24	Not defined

Table S1: Baseline characteristics of patients

Author (year)	Group	Age	Male	Hyper-tension	Diabetes Mellitus	Dyslipi-demia	CAD	HF	LVEF	PVD	Atrial Fibrillation	Prior Stroke/ TIA	Prior SE	Concurrent Antiplatelet Therapy (%)		
														ASA	P2Y12 Inhibitor	DAPT
Abdelnabi (2020)[17]	DOAC (n=39)	49.1 ±12.3	21 (53.8)	23 (59)	23 (59)	22 (56.4)	-	-	36.1 ±6.1	-	-	1 (2.6)	-	-	-	-
	VKA (n=40)	50.1 ±12.9	24 (60)	19 (47.5)	19 (47.5)	16 (40)	-	-	37.0 ±5.3	-	-	2 (5)	-	-	-	-
Ali (2020)[21]	DOAC (n=32)	59.2 ±11.9	26 (81.3)	-	12 (37.5)	-	-	25 (78.1)	23.0 ±9.4	2 (6.3)	9 (28.1)	-	-	65.45	17.3	-
	VKA (n=60)	58 ±16.3	49 (81.7)	-	18 (30)	-	-	45 (75)	23.2 ±11.2	14 (23.3)	18 (30)	-	-			-
Bass (2021)[22]	DOAC (n=180)	63.4 ±16.7	125 (69.4)	-	-	-	77 (42.8)	123 (68.3)	-	-	111 (61.7)	31 (17.2)	-	46.7		
	VKA (n=769)	61.6 ±15.3	545 (70.9)	-	-	-	443 (57.6)	573 (74.5)	-	-	352 (45.8)	158 (20.6)	-	55.7		
Cochran (2020)[7]	DOAC (n=14)	51.5 (39-73)[a]	11 (78.6)	-	7 (47)	-	7 (53)	10 (73)	-	-	-	-	-	-	-	-
	VKA (n=59)	62 (34-84)[a]	45 (76.3)	-	23 (39)	-	36 (61)	48 (81)	-	-	-	-	-	-	-	-
Daher (2020)[23]	DOAC (n=17)	57 ±14	14 (82.4)	10 (59)	2 (12)	5 (29.4)	-	-	41±8	-	-	-	-	58.8	64.7	-

	VKA (n=42)	61 ±13	35 (83)	17 (40.5)	9 (21.4)	18 (43)	-	-	36±12	-	-	-	-	66.7	40.5	-
Guddeti (2020)[8]	DOAC (n=19)	60.7 ±13.1	15 (79)	15 (79)	3 (15.8)	-	11 (57.9)	19 (100)	25	-	4 (21.1)	-	1 (11.1)	57.9	15.8	-
	VKA (n=80)	61.3 ±12.2	55 (68.8)	61 (76.3)	34 (43)	-	53 (66.3)	77 (96.3)	25	-	18 (22.5)	-	5 (6.25)	67.5	15	-
Iqbal (2020)[9]	DOAC (n=22)	62±13	20 (91)	9 (41)	19 (86)	4 (18)	-	21 (95)	31±13	4 (18)	3 (14)	1 (4.5)	1 (4.6)	41	-	38
	VKA (n=62)	62±14	55 (89)	18 (29)	19 (31)	9 (15)	-	60 (94)	35±13	2 (3)	3 (5)	9 (14.5)	2 (3.2)	65	-	
Jaidka (2018)[26]	DOAC (n=12)	57.2 ±9.3	9 (75)	2 (16.7)	1 (8.3)	2 (16.7)	0 (0)	-	36.7 ±10.1	-	-	0 (0)	-	75	100	-
	VKA (n=37)	61.3 ±12.1	28 (75.7)	18 (48.6)	7 (18.9)	13 (35.1)	3 (8.1)	-	20 ±20.7	-	-	4 (10.8)	-	89.9	100	-
Jones (2020)[20]	DOAC (n=41)	58.7 ±14.2	33 (80.4)	23 (60.5)	7 (18.4)	19 (50)	21 (55.3)	-	33.5 ±10	1 (2.6)	-	-	-	-	-	68.3
	VKA (n=60)	60.8 ±14.3	51 (85)	22 (36.4)	10 (16.7)	19 (31.7)	22 (36.7)	-	35.4 ±9	1 (1.7)	-	-	-	-	-	70
Robinson (2020)[10]	DOAC (n=121)	58.1 ±14.9	94 (77.7)	86 (71.1)	36 (29.8)	71 (58.7)	-	-	27.7 ±13.8	-	30 (24.8)	-	25 (20.7)	46.3	9.1	8.3
	VKA (n=236)	58.2 ±15.1	170 (72)	177 (75)	92 (39)	126 (53.4)	-	-	28.2 ±12.4	-	45 (19.1)	-	38 (16.1)	46.2	5.1	18.2
Willeford (2020)[29]	DOAC (n=22)	54 (48-64)[b]	17 (77.3)	8 (36.4)	4 (18.2)	-	15 (68.2)	19 (86.4)	-	4 (18.2)	3 (13.6)	1 (4.5)	-	22.7	13.6	-
	VKA (n=129)	56 (49-65.5)	104 (80.6)	54 (41.9)	37 (28.7)	-	68 (52.7)	110 (85.3)	-	9(7)	24 (18.6)	12 (9.3)	-	54.3	27.9	-