Question 6 evidence tables

Question 6: Should a DOAC be preferred to a VKA in stroke prevention in AF?

NB Any discrepancies between reviewers in evidence quality and comment were discussed at the corresponding evidence review meeting

DOAC = direct oral anticoagulation, VKA = vitamin k antagonist, AF = atrial fibrillation, LAAOD = left atrial appendage occlusive device, ISSE = ischemic stroke and systemic embolism, VHD = valvular heart disease, TEE = thromboembolic events, GI = gastrointestinal, MI = myocardial infarction, ADR = adverse drug reactions, NOAC = novel oral anticoagulation, SR = systematic review, MA = meta-analysis, RCT = randomised controlled trial, IPDMA = individual patient data meta-analysis, MDT = multidisciplinary team, PICO = patient/population, intervention, comparison and outcomes, OR = odds ratio, CI = confidence interval, QoL = quality of life, ADL = activities of daily living, OR = odds ratio, RR = relative risk, aOR = adjusted odds ratio, cOR = crude odds ratio, CI = confidence interval, RoB = risk of bias, I2 = heterogeneity statistic.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
272	A. Ahmed et al. (2020). Intracerebral hemorrhage outcomes in patients using direct oral anticoagulants versus vitamin K antagonists: a meta-analysis. *Clin Neurol Neurosurg,* 198: 106146	· Systematic review and meta-analysis of mostly retrospective cohort studies (14/17). · All in high-income settings with a mixture of ethnicity (7/17 from Asian countries). · N=17 studies with n=25,354 patients · Mean age of the studies between 65.7 – 81.5 (most >75yrs); slightly over presented in male (most of the studies >50% male) · Search until 31/12/2019	DOAC-ICH (n=5631) vs. VKA-ICH (n=19,273)	· Haematoma volumes · Haematoma expansion · Mrs>3 at discharge · Case-fatality at discharge · Mrs>3 at 3 month · Case-fatality at 3 month	- Patients with DOAC-ICH had smaller haematoma volumes (weighted mean differences=-9.59, 95%CI -15.33-3.85) and reduced case fatality at discharge (RR=0.82, 0.71-0.96). -Non-significant trend for other outcomes, although the point estimate was in favour for DOAC-ICH (Haematoma expansion: RR=0.79; Mrs>3 at discharge: RR=0.82; Mrs>3 at 3m: RR=0.77 and death at 3m: RR=0.90)	**+** Acceptable as per paper quality but the evidence is still limited due to potential selection bias of each study as most of the studies included were retrospective and very small size (10/17 – both groups n<100).
272	A. Ahmed et al. (2020). Intracerebral hemorrhage outcomes in patients using direct oral anticoagulants versus vitamin K antagonists: a meta-	Metanalysis of studies including trials but prdominantly cohort studies. 25354 study subjects Quite a lot of heterogeneity. Excluded registers to avoid double counting	DOAC vs VKA looking at Haematoma expansion and outcome	Haematoma size, Haematoma expansion Mortality and Functional Outcome	Smaller haematoma Volume and lower mortality at discharge. Outcome benefit not sustained at 3/12	**+** Acceptable but bias potentially a problem due to small size of studies.

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	analysis. *Clin Neurol Neurosurg,* 198: 106146					
273	E. Antonucci et al. (2015). The Italian START-Register on Anticoagulation with Focus on Atrial Fibrillation. *PloS One,* 10:5 e0124719	· An independent observational cohort study based on a registry in Italy · N=3209 patient with non valvular AF on anticoagulation (mean age=76; 55.2% male) · Patient cohort 2012-2013	95.7% on VKA	Descriptive; cross-sectional analysis of baseline characteristics such as age, medical history	Not relevant (some background info: mean CHADSVASc 3.1; 39.5% had moderate renal failure and 5.3% severe renal failure)	- Low quality data out of date
273	E. Antonucci et al. (2015). The Italian START-Register on Anticoagulation with Focus on Atrial Fibrillation. *PloS One,* 10:5 e0124719	Registry Data. N=5252 with 3209 on Anticoagulation for AF. Only 2.1% from entire cohort on DOAC (n=109)	DOAC and VKA, Non-randomised, not compared	Descriptive of population characteristics including HASBLED and CHADS2	Descriptive. No comparison of outcomes made.	Relatively old data soon after EMA drug approval. Not fully relevant to this process
274	N. S. Bajaj et al. (2016). Comparison of Approaches for Stroke Prophylaxis in Patients with Non-Valvular Atrial Fibrillation: Network Meta-Analyses of Randomized Controlled Trials. *PloS One,* 11:10 e0163608	· Network meta-analysis including all the 6 available randomised controlled trials looking at stroke prophylaxis in non-valvular AF. · Mean age 70-75 and most with equal sex split (4/6) · N=59,627 patients · Median/mean follow-up mostly around 2 years (5/6)	VKA vs. -Watchman (382 vs. 732) -Apixaban (9081 vs. 9120) -Dabigatran (6022 vs. 6076) -Edoxaban (7036 vs. 7034) -Rivaroxaban (7133 vs. 7131)	· Ischaemic stroke · Major bleeding · Composite primary safety endpoints as per each trial	All are equally efficacious for ischaemic stroke prevention but have different safety profiles: Apixaban was associated with the least number of primary safety endpoints. In the cluster analyses assessing both safety and efficacy, apixaban, edoxaban, and dabigatran ranked best followed by VKA and rivaroxaban. WATCHMAN ranked the last.	+ Acceptable with the caveats as not being in the stroke population – most of the trials only had a ~20 % of patients with history of stroke 54.6% I, 19.7% (A), 19.8% (D), 28.3% I, 20.1% (W), 28.3% (W).
274	N. S. Bajaj et al. (2016). Comparison of Approaches for Stroke Prophylaxis in Patients	Network Metanalysis VKA, DOAC and LAAOD.	VKA vs Apixaban, Rivaroxaban, edoxaban and Dabigatran.	Ischaemic stroke, Composite safety and Major bleeding (noting that definition of this	No difference in efficacy. Apixaban seemed to have better safety.	+ Acceptable. Hard to correct for known differences in study

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	with Non-Valvular Atrial Fibrillation: Network Meta-Analyses of Randomized Controlled Trials. *PloS One,* 11:10 e0163608	Mainly looking at ROCKET, ARISTOTLE, ENGAGE and RELY from this review point of view	VKA vs. Watchman also included in study.	varies a bit between these studies)		designs and conducts in metanalysis design.
275	J. B. Briere et al. (2019). Number needed to treat based on real-world evidence for non-vitamin K antagonist oral anticoagulants versus vitamin K antagonist oral anticoagulants in stroke prevention in patients with non-valvular atrial fibrillation. *J Med Econ,* 22:8 760-765	· NNT calculated based on a previously published meta-analysis (2019 – Oxford doesn't have access to this meta-analysis …) · Included non-randomized non valvular AF studies comparing DOACs with VKAs, and reporting effectiveness, safety, or persistence. · Search until Dec 2016	VKS vs. -Apixaban (n=18 studies) -Dabigatran (n=79) -Rivaroxaban (n=49	· Ischaemic stroke and systemic embolism · Ischaemic stroke · Major bleeding · Intracranial bleeding · All-cause mortality	Superiority of DOACs over VKAs was observed in 10/15 comparisons: Rivaroxaban vs. VKA: one death prevented every 22 patients treated and one IS prevented every 206 patients treated Dabigatran: 32 and 166 respectively No significant difference for apixaban vs. VKA All DOACs were associated with reduced risk of ICH (205 R, 115 D and 108 A)	**+/-** Acceptable / low quality due to potential selection bias and heterogeneity across studies (although difficult to know as have no access to the meta-analysis that the current paper is based on). Not sure how many patients with stroke were included for example.
275	J. B. Briere et al. (2019). Number needed to treat based on real-world evidence for non-vitamin K antagonist oral anticoagulants versus vitamin K antagonist oral anticoagulants in stroke prevention in patients with non-valvular atrial fibrillation. *J Med Econ,* 22:8 760-765	Based on a previous Metanalysis, this looks at NNT for various DOACs vs VKA. Studies included are diverse. Much detail not in the paper and referred to previous publication. No data on Edoxaban.	VKA vs DOAC (Apixaban, Rivaroxaban and Dabigatran)	ISSE, IS, Mortality, Major bleeding , Intracranial Haemorrhage	DOACs generally superior, especially in terms of safety. Apixaban not associated with improved outcome.	- Low. Insufficient data in this paper to comment on publications that had been included. Journal of prior publication not available in TCD beyond 2014.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
276	D. Caldeira et al. (2018). Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease: systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother,* 4:2 111-118	· Systematic review and meta-analysis of randomised controlled trials (4/5post hoc subgroup analysis and 1 in bioprosthetic heart vavle) · Patients with AF+VHD (native valvular disease, bioprosthesis and valve repair). Patients with mechanical and rheumatic mitral valvular (moderate to severe mitral stenosis) +AF. · Search until November 2016 · N=5 studies with 12,653 AF patients with VHD · Mean age 71-75 in 4/5 trials and age=47 in DAWN-Pilot · Most common VHD: mitral valve regurgitation >70% in 4/5 trials	VKA vs. -Apixaban (2370/2438) -Dabigatran (1304/2646) -Edoxaban (955/910) -Rivaroxaban (1035/968) - Dabigatran (DAWN pilot – 12/15)	· Stroke and systemic embolism · Major bleeding · Intracranial haemorrhage	For VHD (HR, 95%CI): · Stroke and systemic embolism=0.73, 0.60-0.90; · Major bleeding=0.90, 0.68-1.20; (ROCKET AF an outlier) · ICH=0.45, 0.24-0.87)	Acceptable (+) and with the caveats being post-hoc subgroup analysis and also no analysis stratified by history of stroke/TIA
276	D. Caldeira et al. (2018). Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease: systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother,* 4:2 111-118	Systematic review and Metanalysis of RCTs. Also considered bioprosthesis and some patients with VAF. No specific analysis in previous history of stroke/TIA	VKA vs Apixaban, Edoxaban, Rivaroxaban and Dabigatran	Stroke (ischaemic and Haemorrhagic combined) Major bleeding Intracranial Haemorrhage	Combined DOAC associated with lower ISSE and Intracranial Haemorrhage in both VHD and Non-VHD. DOAC lower Major Haemorrhage in Non VHD	**++/+** High Quality/ Acceptable
277	R. Cappato et al. (2015). Uninterrupted rivaroxaban vs.	· Randomised controlled trial	Uninterrupted rivaroxaban (n=124) vs. uninterrupted VKA	Primary endpoint: incidence of major bleeding in the two	· Major bleeding 0.4% and only in the VKA arm	**++**

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	uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation. *Eur Heart J,* 36:28 1805-11	· Multinational, open-label, parallel-group IIIb · Patients with non-valvular AF undergoing catheter ablation (n=248) · Mean age=59.5, 71% male · 74% PAF	(n=124) prior to CA and for 4 weeks after	groups within the first 30+/- 5 days after catheter ablation Secondary endpoint: thromboembolic events	· Thromboembolic events 0.8% and only in the VKA arm	High but not relevant to the PICO of interest (i.e. short-term result and very specific scenatio)
277	R. Cappato et al. (2015). Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation. *Eur Heart J,* 36:28 1805-11	Randomised Controlled Trial specifically at anticoagulation in subjects undergoing catheter ablation. N=250	VKA vs Rivaroxaban	Bleeding following catheter ablation	No difference between groups but probably underpowered to find same.	**N/A** Not Relevant
278	C. I. Coleman et al. (2016). Real-world evidence of stroke prevention in patients with nonvalvular atrial fibrillation in the United States: the REVISIT-US study. *Curr Med Res Opin,* 32:12 2047-2053	· Retrospective study based on routinely collected data in the US · Jan 2012-Oct 2014 · Adults newly initiated with rivaroxaban, apixaban or warfarin · DOAC users matched with warfarin users using propensity score · Mean age=71yrs and 54% male	Rivaroxaban (11,411) vs. warfarin (11,411) Apixaban (4083) vs. warfarin (4083)	Ischaemic stroke (IS) or ICH combined and individually	Rivaroxaban vs. warfarin: IS/ICH HR=0.61, 95%CI 0.45-0.82 ICH=0.53, 0.35-0.79 IS=0.71, 0.47-1.07 Apixaban vs. warfarin: IS/ICH=0.63, 0.35-1.12 ICH=0.38, 0.17-0.88 IS=1.13, 0.49-2.63	- Low quality based on coding without dedicated adjudication and it seemed only inpatient events/outcomes were included hence might miss more minor outcomes. Most importantly patient with history of history of stroke were excluded so not relevant to our secondary prevention setting
278	C. I. Coleman et al. (2016). Real-world evidence of stroke prevention in patients with nonvalvular atrial fibrillation in the	Retrospective analysis of data from a US Insurance site. No information on patients with previous stroke or TIA. Performed on data from 2012-2014	Apixaban and Rivaroxaban.vs VKA. More Rivaroxaban (11,411) than Apixaban (4083)	IS and ICH	Rivaroxaban: ICH significantly lowered. Apixaban> No significant difference in Ischaemic or Haemorrhagic stroke	- Low Quality. Analysis of data collected for other purposes. No Data on secondary prevention

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	United States: the REVISIT-US study. *Curr Med Res Opin,* 32:12 2047-2053		reflecting later licencing.			
279	E. Crocetti et al. (2021). Effectiveness and Safety of Non-Vitamin K Oral Anticoagulants in Non-Valvular Atrial Fibrillation Patients: Results of A Real-World Study in a Metropolitan Area of Northern Italy. *J Clin Med,* 10:19	· Population-based retrospective cohort study in the area of Milan Health Protection Agency, Italy · Patients who were new users of oral anticoagulants and who did not switch during the study period · 2017-2019 · Outcome assessment based on hospital coding · AF patients with mitral stenosis, cardiac surgery with valve replacement were excluded · N=8543 patients, mean age 73-79 and 43.7-54.6% women · Propensity score Kernel weighting used to minimise indication bias · 2y follow-up	· Warfarin (n=1104) · Apixaban (n=2693) · Dabigatran (n=1636) · Edoxaban (n=1725) · Rivaroxaban (n=1385)	Mortality D vs. W HR=0.52, 0.42-0.64 R vs. W HR=0.51, 0.41-0.62 A vs. W HR=0.69, 0.60-0.79 E vs. W HR=0.75, 0.63-0.89 Stroke D vs. W=0.59, 0.40-0.88 R vs. W=0.77, 0.51-1.15 A vs. W=0.74, 0.56-0.98 E vs. W=0.72, 0.50-1.05 Bleeding D vs. W=0.81, 0.59-1.11 R vs. W=0.67, 0.46-0.95 A vs. W=0.80, 0.64-1.01 E vs. W=0.78, 0.57-1.05 MI D vs. W=0.84, 0.67-1.07 R vs. W=0.74, 0.56-0.97 A vs. W=0.73, 0.60-0.88 E vs. W=0.73, 0.57-0.94	No change directly on this paper but if taken into account Lancet systematic review in 2014 (Lancet 2014; 383: 955–62) then potentially yes (taking into account safety profile) "with a preference to DOAC over VKA in DOAC-eligible patients to reduce the risk of stroke"	**+** Acceptable although may lose outcomes if switching was due to the outcome of interest. Also unclear % with history of stroke/TIA
279	E. Crocetti et al. (2021). Effectiveness and Safety of Non-Vitamin K Oral Anticoagulants in Non-Valvular Atrial Fibrillation Patients: Results of A Real-	Retrospective Insurance dataset study of newly anticoagulated subjects in Milan. No real secondary prevention element.	VKA vs Dabigatran (no dose specified), Apixaban, Rivaroxaban, and Edoxaban	Mortality, myocardial infarction, Stroke and Hospitalised Bleeding	Lower rated for DOACs across all outcome measures. HR similar between DOACs	**-** Low Quality. No clarity on Secondary prevention. Retrospective analysis of an insurance dataset.

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	World Study in a Metropolitan Area of Northern Italy. *J Clin Med,* 10:19					
280	G. Denas et al. (2017). Effectiveness and safety of oral anticoagulation with non-vitamin K antagonists compared to well-managed vitamin K antagonists in naïve patients with non-valvular atrial fibrillation: Propensity score matched cohort study. *Int J Cardiol,* 249: 198-203	· Population-based retrospective cohort study in the Veneto Region in Italy · AF patients initiating oral anticoagulants · Based on hospital coding · N=40,411 patients · June 2013-Dec 2015 · Mean age ~75yrs and roughly even split for sex Propensity score matching also used (n=13480)	DOAC (n=6923) vs. VKA (n=33,488) Propensity score matching: both groups n=6740	Hospitalised events: · Death · MI · IS · All bleeding Intracranial bleeding	(identical results using stratification by propensity score or using matching and stratification results extracted below Death: HR=0.83, 0.74-0.93 MI: HR=0.80, 0.52-1.21 IS: HR=0.93 (0.68-1.28) All bleeding: HR=0.96, 0.78-1.17 ICH: HR=0.69, 0.48-0.99	**+** Acceptable, although ~20% had history of TIA/stroke/thromboembolism
280	G. Denas et al. (2017). Effectiveness and safety of oral anticoagulation with non-vitamin K antagonists compared to well-managed vitamin K antagonists in naïve patients with non-valvular atrial fibrillation: Propensity score matched cohort study. *Int J Cardiol,* 249: 198-203	Retrospective population based cohort study with propensity matching. July 2013-Dec 2015 Based on Hospital coding and from licensing of DOACs in Italy	DOAC vs VKA. DOACs not specifically identified	Hospitalised events Death MI IS All bleeding Intracranial Bleeding	Lower deaths in DOAC group on ITT Lower ICH in the DOAC on per-treatment analysis	- Low, limited secondary prevention data. Data collected for other purposes.
10	C. Escobar et al. Effectiveness and Safety of Dabigatran Compared to Vitamin K	Systematic review and meta-analysis to assess the effectiveness and safety of dabigatran, globally and stratified	Dabigatran (110/150 mg twice daily) for at least 3 months (safety outcomes) or 6	Primary outcome: Ischaemic stroke and the composite of ischaemic	Outcome: ischaemic stroke Dabigatran did not modify the hazard to develop an ischemic stroke compared to VKA (HR	- Low

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	Antagonists in Non-Asian Patients with Atrial Fibrillation: A Systematic Review and Meta-Analysis (2021). Clin Drug Investig 41 941-953.	by dose vs VKA in non-Asian patients. Observational comparative studies (prospective or retrospective). 34 studies, 1,600,722 participants (1,154,283 exposed to vitamin K antagonists and 446,439 to dabigatran) in real world patients diagnosed with non valvular atrial fibrillation. 32 studies were retrospective; 4 studies used a commercial database. In 12 studies data was extracted from a national healthcare database. Registers included limited to those using data source national or regional-wide registers (n>1000 patients) Studies had to report at least one of the following outcomes: ischaemic stroke, composite outcome of ischaemic stroke plus systemic embolism, major bleeding, intracranial bleeding, fatal bleeding, and/or gastrointestinal bleeding, systemic embolism, myocardial infarction, pulmonary embolism and all causes of mortality. One study supported by	months (effectiveness outcomes) vs vitamin K antagonists in patients with atrial fibrillation from "real word studies".	stroke/systemic embolism.	0.97, 95% CI 0.82-1.16; 24 comparison groups; I^2=94%). There was a subgroup effect suggesting the results are affected by the dose. Dabigatran at 150 mg significantly reduced the risk of ischaemic stroke (14% lower risk; HR 0.86, 95% CI 0.76-0.99; 12 comparisons; I^2=59%) whereas no difference was found with Dabigatran at 110 mg (HR 0.99, 95% CI 0.88-1.12, seven comparisons; I^2=52%) Composite ischaemic stroke/systemic embolism: Dabigatran (at either 150 mg or 110 mg) reduced the risk of stroke/systemic embolism compared with VKA (18% lower risk; HR 0.82, 95% CI 0.75-0.90, ten comparisons; I^2=28%) Mortality outcome: Globally, dabigatran reduced the risk of all-cause mortality compared to VKA (24% lower risk; HR CI 0.69-0.84; 22 comparisons; I^2= 90%). Greater effect with dabigatran at 150mg (35% lower mortality, HR 0.65, 95% CI 0.58-0.73; I^2=69%). Safety outcome: major bleeding Dabigatran (either at 150mg or 110 mg) reduced the risk of major bleeding compared to	This meta-analysis was founded by pharmaceutical company (Boehingher) and authors had conflicts of interest. Mainly observational studies which are at increased risk of bias as treatment allocation was not randomly decided. Mainly retrospective studies (32), and only 2 prospective studies. High heterogeneity among studies.

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					VKA (23% lower risk, HR 0.77, 95% CI 0.70-0.83, 29 comparisons; $I^{2=}$18%) and the reduction of major bleeding was higher with Dabigatran 150mg than with 110mg (HR 0.81, 95% CI 0.67-0.99; I^2=84%). Fatal bleeding: Dabigatran (either 150 or 110 mg) may reduce the risk of fatal bleeding (24% lower, HR 0.76, 95% CI 0.60-0.95; I^2=0%, 5 comparisons, only 3 studies) GI bleeding: Dabigatran (either 150 mg or 110 mg) increases slightly the risk of developing GI bleeding (HR 1.16, 95% CI 1.08-1.26; 32 comparisons; I^2=67%)	
281	C. Escobar et al. (2021). Effectiveness and Safety of Dabigatran Compared to Vitamin K Antagonists in Non-Asian Patients with Atrial Fibrillation: A Systematic Review and Meta-Analysis. *Clin Drug Investig,* 41:11 941-953	Systematic Review and Metanalysis using a range of sources including national datasets/ registers and corporate. Compared Dabigatran 110 BD and Dabigatran 150 BD against VKA. 34 studies total.	Dabigatran, both licenced doses against VKA.	IS, ISSE Major Bleeding ICH Fatal Bleeding GI Bleeding MI PE Mortality	No difference in IS but ?Dabigatran less ISSE. Less bleeds with Dabigatran except for GI bleeds. Quite a lot of 'nearly significant' reported.	- Low on initial review, Lower on subsequent review when I saw an erratum for the paper published. High risk of bias. No allocation of treatment.
282	S. Gupta et al. (2019). Direct Oral Anticoagulants Versus	Systematic review and meta-analysis of 24 studies, 3 RCT	DOACS vs VKAs in patients with AF	Outcomes: Thromboembolism,	Thromboembolic events in RCT occurred in 0.18% of DOACs patients vs 0.55% in	- Low

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	Vitamin K Antagonists in Patients Undergoing Cardioversion for Atrial Fibrillation: a Systematic Review and Meta-analysis. *Cardiovasc Drugs Ther,* 33:3 339-352	(n=5203) and 21 observational studies (n=11,855).	undergoing cardioversion	bleeding, mortality and thrombus on TEE.	VKAs (RR 0.40, 95% CI 0.13-1.24, p=0.11, I^2=7%, moderate quality). In observational studies DOACs were associated with significantly lower incidence of thromboembolism compared to VKAs (RR 0.51, 95% CI 0.26-0.99, p=0.005, I^2=27%, very low-quality evidence) Major bleeding occurred in 0.42% of patients receiving DOACs vs 0.64% receiving VKAs (RR 0.62, 95% CI 0.28-1.35, moderate quality). In RCTs, 1.8% of bleedings in DOACs group vs 2.5% in VKAs group (RR 0.85, 95% CI 0.58-1.23, p=0.38, I^2=0%, moderate quality evidence). In observational studies suggestion that DOACs are associated with lower incidence of bleeding compared to VKAs (RR 0.59, 95% CI 0.34-1.00, p=0.05, I^2=34%, very low-quality evidence) Death occurred in 0.28% of DOACs group vs 0.38% in VKAs group (RR 0.70, 95% CI 0.23-2.10, low quality). Mortality did not differ between groups (0.3% in the DOACs group vs 0.4% in VKAs group) in RCT (RR 0.70, 95% CI 0.23-2.10, p=0.52, I^2=5%, low quality evidence) or observational studies (RR 0.87,	This study only applies to the subset of patients that undergo cardioversion. RCT and observational studies analysed separately. 17 observational studies considered to be at high risk of bias and quality of evidence very low in some. 3 RCT and 4 out of 21 observational studies were at low risk of bias. Confidence in the estimates of effects for observational studies was very low. In RCT the quality of evidence was downgraded for serious imprecisions. In RCTs (mean follow up 30 days)

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					95% CI 0.42-1.78, p=0.69, I^2=0%, very low evidence)	
282	S. Gupta et al. (2019). Direct Oral Anticoagulants Versus Vitamin K Antagonists in Patients Undergoing Cardioversion for Atrial Fibrillation: a Systematic Review and Meta-analysis. *Cardiovasc Drugs Ther,* 33:3 339-352	Systematic review and Metanalysis of subjects undergoing cardioversion. 24 studies. RCTs and Observational studies 6536 DOAC vs 4994 VKA	DOACs vs VKA. DOACs undifferentiated. Only in subjects going for cardioversion. No data on secondary Prevention post TIA / stroke but likely limited.	Thrombus on TOE, Bleeds Thrombotic events, Mortality	Significantly less embolic events, TOE and Thrombus and bleeds with DOACs on observational studies. No significant differences on RCTs	**+/-** Adequate for this population. Low for the topic of the review, unlikely to be relevant
283	M. Hirschl & M. Kundi (2019). Safety and efficacy of direct acting oral anticoagulants and vitamin K antagonists in nonvalvular atrial fibrillation – a network meta-analysis of real-world data. *Vasa,* 48:2 134-147	Network meta-analysis. 88 studies including 3,351,628 patients providing 2.9 million patient-years of follow up.	DOACs vs VKAs in patients with nonvalvular atrial fibrillation	Outcomes: Efficacy (prevention of stroke and systemic embolism) and safety (bleeding, myocardial infarction and death) of DOACs vs VKAs	Primary efficacy outcome (stroke or stroke combined with systemic embolism): all DOACs were superior to VKAs; the HR were: Dabigatran= 0.870; 95% CI 0.813-0.931) Rivaroxaban= 0.779; 95% CI 0.713-0.850) Apixaban= 0.788; 95% CI 0.668-0.930) The overall HR (including studies that did not differentiate between DOACs): 0.824; 95% CI 0.783-0.866 against VKAs. Rivaroxaban was more effective in preventing stroke/stroke SE than Dabigatran (HR=0.940, 0.890-0.993); no other significant differences concerning	**+** Although all DOACS had an increased efficacy in avoiding strokes and systemic thromboembolism, the greater benefit comes from reduced rates of major bleeding compared to VKAs. There was high heterogeneity, but it did not affect the overall outcome. Meta-regression to detected reasons for heterogeneity found that it could be explained by only considering few factors such as lower efficacy of low-dose treatment in the real world and methodology in real world studies. Apixaban was found the safest anticoagulant drug in terms of bleeding prevention but is not

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					efficacy endpoints were found between the DOACs. For comparisons of absolute risk reduction between DOACs no statistically significant differences were determined. Safety outcomes: The overall comparison between DOACs and VKAs gave a HR of 0.796; 0.748-0.846) in favour of DOACs. Apixaban had the lowest HRs of major bleeding relative to VKAs (HR=0.603, 0.555-0.655) followed by Dabigatran (HR=0.800, 0.727-0.880). No difference to VKAs was seen for Rivaroxaban (HR=1.020, 0.931-1.117). All DOACs significantly reduced intracranial bleeding in comparison to VKAs: HR for dabigatran was 0.431 (0.391-0.475); for apixaban 0.583 (0.483-0.705) and for rivaroxaban 0.645 (0.556-0.749). Comparing all DOACs vs VKAs gave also a reduced risk for intracranial bleeding (HR= 0.487, 0.446-0.530). Risk of GI bleeding: The result for all DOACs combined against VKAs showed no differences (HR=1.045, 0.956-1.142). The only DOAC not associated with an increased risk of GI bleeding compared to VKAs	the most efficacious one and conversely rivaroxaban, which has the highest efficacy, is not the safest amongst DOACs.

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					was apixaban (HR=0.640, 0.547-0.749). Dabigatran showed an increased risk compared to VKAs (HR=1.111,1.004-1.229) as well as rivaroxaban (HR=1.247,1.092-1.423) The risk of MI was reduced with all NOACs compared to VKAs (HR=0.873, 0.783-0.974) but statistically not significant for rivaroxaban (HR=0.839, 0.683-1.030) in contrast to apixaban (HR=0.307,0.133-0.708) and dabigatran (HR=0.823,0.705-0.960). Mortality: Reduced mortality observed for all DOACs compared to VKAs (HR=0.741, 0.658-0.833), but statistical significance for specific DOACs was reached by dabigatran only (HR=0.622, 0.527-0.733)	
283	M. Hirschl & M. Kundi (2019). Safety and efficacy of direct acting oral anticoagulants and vitamin K antagonists in nonvalvular atrial fibrillation – a network meta-analysis of real-world data. *Vasa,* 48:2 134-147	Systematic Review and Metanalysis of 88 'Real world' studies.	Dabigatran, Rivaroxaban and Apixaban vs VKAs. No real-world studies of edoxaban identified.	ISSE Major Bleeding GI Bleeding ICH MI Death	DOACs all preferable to VKA on ISSE and ICH. Excess GI bleeds on Dabigatran. Less Mis on Apixaban	**+/-** Adequate. Most effects seem to be through greater safety. Hard to know how much faith in other analyses given study heterogeneity.
284	C. J. Klijn et al. (2019). Antithrombotic treatment for	Guideline from the European Stroke Organization (2019); used systematic-review and meta-	One of the questions addressed in the guidelines (relevant	Recurrent stroke or thromboembolism and safety outcomes (death,	Pooling the results of 4 trials on DOAC vs VKAs:	**++**

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: A European Stroke Organisation guideline. *Eur Stroke J,* 4:3 198-223	analysis of RCT to answer PICO questions. 4 RCT were identified: Re-LY (18,113 patients assigned to dabigatran or warfarin; ROCKET-AF (14,264 patients assigned to rivaroxaban or warfarin; ARISTOTELE (18,201 patients assigned to apixaban or warfarin; ENGAGE-AF-TIMI 48 (21,105 patients assigned to edoxaban or warfarin).	for this question) was the comparison of use of DOAC versus VKAs in patients with previous ischaemic stroke or TIA and non-valvular AF	major bleeds and intracranial bleeds)	there was no significant difference in the risk of stroke or thromboembolism (RR 0.91, 95% CI 0.81-1.02) and ischaemic stroke (RR 1.15; 95% CI 0.84-1.57) in DOAC vs VKAs. There was no significant heterogeneity across the trials in the efficacy outcomes, with the exception of moderate heterogeneity for ICH (I^2=34%, p=0.18). There was a significant reduction of stroke and systemic embolism and of stroke in favour of DOAC when higher dose regimens of dabigatran and edoxaban were included, while the reduction of haemorrhagic stroke remained similar. Safety outcomes: DOAC where were associated with a significant reduction of haemorrhagic stroke (RR 0.43, 95% CI 0.29-0.64) and death from any cause (RR 0.87, 95% CI 0.80-0.95) when compared to warfarin. DOAC were associated with a significant reduction of major bleeding (0.79, 95% CI 0.64-0.96) and more significantly of intracranial bleeding (RR 0.45, 95% CI 0.45-0.63). There was substantial heterogeneity across trials regarding major bleeding	DOAC are associated with a significant reduction of major bleeding, and have at least the same efficacy as VKAs in preventing thromboembolic events

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					complications (I^2=67%; p=0.01).	
284	C. J. Klijn et al. (2019). Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: A European Stroke Organisation guideline. *Eur Stroke J,* 4:3 198-223	A systematic review and Metanalysis of RCTS. The 4 main RCTS, ROCKET, ENGAGE, RE-LY and Aristotle were identified. This paper describes the ESO guideline development.	DOACs vs VKA in Subjects with AF and previous TIA or Stroke.	Stroke (all) or thromboembolism, Ischemic stroke, Intracerebral haemorrhage, Major bleeding complications, Non-fatal stroke, non-fatal myocardial infarction and vascular death, Death, Venous thromboembolism	No significant difference in risk of Stroke or thromboembolism with DOACs vs. warfarin but all DOACs seem to be significantly safer in terms of both major haemorrhage and ICH	**+** Good Quality, but essentially working from the 4 initial published RCTs.
285	R. C. P. Makam et al. (2018). Efficacy and safety of direct oral anticoagulants approved for cardiovascular indications: Systematic review and meta-analysis. *PloS One,* 13:5 e0197583	Systematic review and meta-analysis Included 4 studies on non-valvular AF (n=58,311) and 5 studies (n=22,040) on venous thromboembolism. Studies included: RE-LY, ARISTOTELES, ROCKET AF, ENGAGE AF-TIMI 48. Median duration of follow up ranged from 1.8-2.8 years.	Used data from Phase 3 RCT that compared FDA-approved DOACs (dabigatran, apixaban, rivaroxaban, or edoxaban) in dosages approved by FDA (dabigatran 150 mg twice daily, apixaban 5 mg twice daily, rivaroxaban 20mg daily and edoxaban 60 mg daily) vs VKAs for prevention of thromboembolism in patients with nonvalvular AF or for treatment of acute venous thromboembolism.	Outcomes: stroke and systemic embolism (primary efficacy outcome for nonvalvular AF), any stroke, fatal and non-fatal PE, myocardial infraction, death from vascular causes, recurrent DVT or PE, recurrent venous thromboembolism and related death, all cases of mortality, bleeding, and other adverse events.	Patients with nonvalvular AF who received DOAC had a lower risk of stroke or systemic embolism (Pooled OR 0.76, 95% CI 0.68-0.84); lower risk of systemic embolism (0.56, 0.34-0.93) and lower total mortality (0.89-0.84-0.95). Safety outcomes also showed that DOACs: had 15% lower odds of experiencing a major bleeding; 45% lower odds of experiencing a fatal bleeding; and 52% lower odds of experiencing intracranial bleeding compared to VKAs DOACs participants had ¼ higher risk of GI bleeding vs participants on VKAs; and	**++** This systematic review included the same studies included in the systematic review published by ESO for secondary prevention in patients with nonvalvular AF but only considered patients with DOACs treatment dose approved by FDA at the time. It showed that DOACs are associated with a significant reduction of major bleeding and have at least the same efficacy as VKAs in preventing thromboembolic events.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					greater risk of MI (OR 2.44-1.01-5.87) vs VKAs; and the relatively higher risk of MI persisted when analysis was restricted to the use of Factor Xa inhibitors alone (OR 3.0. 0.81-11.13)	
285	R. C. P. Makam et al. (2018). Efficacy and safety of direct oral anticoagulants approved for cardiovascular indications: Systematic review and meta-analysis. *PLoS One,* 13:5 e0197583	Metanalysis and Systemic Review. 4 trials for AF 5 for VTE	DOAC vs. VKA for AF and VTE. DOAC considered as a single entity	ISSE Stroke PE Mortality ADRs Bleeding Major Bleeding	DOAC superior for ISSE, IS, Mortality, Haemorrhagic Stroke, Major Fatal or Intracranial Bleeding. No difference on ADRs	+ Good, but grouped DOACs together as a single entity to add power. No specific consideration of Secondary Prevention No real surprise that analysis of the same trials repeatedly shows the same effect.
286	M. Schiavoni et al. (2018). Use of dabigatran and rivaroxaban in non-valvular atrial fibrillation: one-year follow-up experience in an Italian centre. *Blood Transfus,* 16:2 209-214	Single centre cohort of patients (112 women and 84 men), with Non-valvular AF and on VKAs were proposed for switching to NOAC and followed up prospectively from June 2013 to December 2014 in Italy.	Switch from VKAs to DOAC	To determine efficacy, safety and tolerability of DOAC use during one year of follow up compared to VKAs	78/196 patients completed 1-year follow up; 87 were given dabigatran and 91 rivaroxaban. 6 patients in the dabigatran group discontinued therapy and did not complete follow up; one patient had a major GI bleed on dabigatran 110 mg twice a day and another patient had abundant epistaxis that required hospitalization. The efficacy of the two DOAC was similar. Patients given Dabigatran had a higher frequency (n=32) of non-haemorrhagic complications (OR: 3.3; 95% CI 1.7-7.8) which occurred earlier	- Low Single centre, small numbers, not randomized, not blind for treatment allocation or outcome.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					(HR: 6.1; 95% CI 3.0-12.6) than those (n=7) in patients on rivaroxaban. The degree of satisfaction was higher in patients on rivaroxaban (mean score 9.1, SD 1.0) than among those on dabigatran (mean score 8.7; SD 0.9, p=0.01).	
286	M. Schiavoni et al. (2018). Use of dabigatran and rivaroxaban in non-valvular atrial fibrillation: one-year follow-up experience in an Italian centre. *Blood Transfus,* 16:2 209-214	Single centre study of subjects changed from VKA to Dabigatran or Rivaroxaban. N=196	Switch from Warfarin to Dabigatran or Rivaroxaban Not a specifically Secondary prevention Population.	ADRs, Bleeding events and patient satisfaction.	More ADRs and Bleeding events from Dabigatran than Rivaroxaban. Higher patient satisfaction with Rivaroxaban.	- Low. Single centre, non-randomised
287	N. N. Shen et al. (2020). Direct Oral Anticoagulants vs. Vitamin-K Antagonists in the Elderly With Atrial Fibrillation: A Systematic Review Comparing Benefits and Harms Between Observational Studies and Randomized Controlled Trials. *Front Cardiovasc Med,* 7: 132	Systematic review including RCT or observation studies (Oss) in patients older than 75 years; Included 32 studies, 547,419 patients that compared DOACs with VKAs; 27 Oss (519,267 patients) and 5 RCT (28,152 patients). Most studies conducted in the USA (n=11). For observational studies, only nationwide or health insurance database studies that reported adjusted or matched data using an authorized method to minimize confounding were included.	To compare the benefits and harms between observational studies and RCT in DOCs vs VKAs in the elderly. Only 2 studies were specifically designed to investigate clinical outcomes in the elderly; the remaining studies presented data from subgroup analysis. Dabigatran use was involved in 21 studies, rivaroxaban in 12, apixaban in 9 and	Outcomes: stroke or systemic embolism, ICH, major bleeding, GI bleeding, MI and all causes of mortality. Overall, the included observational studies and RCTs were of modest to high quality.	For observational studies compared with VKAs, DOACS significantly reduced risks for stroke/systemic embolism (HR:0.87; 95% CI: 0.81-0.94, I^2=67.7%); ICH (HR 0.47, 0.37-0.57, I^2=69.1%, major bleeding (HR 0.87, 0.77-0.98, I^2=91.6%) and MI (HR 0.89, 0.79-0.99, I^2=0%). DOACs had no significant effect on GI bleeding (HR 1.21, 0.98-1.43, I^2=89.4%) and all causes of mortality (HR 1.01, 0.92-1.11, I^2=89.2%) when compared with VKAs. For RCTs, DOACs significantly reduced risks for	**++** DOACS vs VKAs significantly reduced risks for stroke/systemic embolism and ICH in observational studies and RCTs. The limitation is that only 2 students were specifically designed for the elderly and these had small sample sizes.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
			edoxaban in one study. The follow up ranged from 60 days to 2.06 years. 5 RCTs reported data according to age group (aged > 75 or < 75 years). The percentage of patients aged > 75 years ranged from 31.3 to 43.3% and follow-up periods ranged from 1.8 to 2.8 years among RCTs.		stroke/systemic embolism (RR 0.82, 0.67-0.96, I^2= 51.7% and ICH (RR 0.47, 0.31-0.63, I^2=42%) and had no clear effect on major bleeding (RR 0.89, 0.66-1.12, I^2=87.3%), GI bleeding (RR 1.34, 0.91-1.77, I^2=86.1%) and all causes of mortality (RR 0.94, 0.87-1.00, I^2=0.0%) when compared with VKAs. None of the RCT reported DOAC data on MI.	
287	N. N. Shen et al. (2020). Direct Oral Anticoagulants vs. Vitamin-K Antagonists in the Elderly With Atrial Fibrillation: A Systematic Review Comparing Benefits and Harms Between Observational Studies and Randomized Controlled Trials. *Front Cardiovasc Med,* 7: 132	Systematic Review and Metanalysis of VKA vs DOAC in Older people. 5 RCT 27 Observational studies	Study mainly looked at subgroup analyses from papers where data on older people were specifically recorded added to two studies specifically performed in older people. Dichotomised to >75 and <75 years. Further analysis done for people >80, >85 and >90 years and Geographical Location but probably underpowered for this. Dabigatran, Rivaroxaban, Apixaban and Edoxaban	Stroke /SE ICH Major Bleeding GI Bleeding Mortality MI	Significantly reduced ISSE and ICH in the DOAC Groups. Reduced Major bleeding and GI Bleeding in the Apixaban and Edoxaban Groups.	+ Acceptable/Good. DOACs associated with reduced hazard and better efficacy against ISSE. Limited data from RCTs. No specific consideration of secondary prevention.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
288	N. Wang et al. (2020). Comparison of effectiveness and safety of direct oral anticoagulants versus vitamin-k antagonists in elderly patients with atrial fibrillation: a systematic review and cost-effectiveness analysis protocol. *Ann Transl Med,* 8:6 391	Systematic review Used data from real world studies and RCTs. For real world studies only studies that reported adjusted data using authorized method to minimize confounding were included.	To compare the effectiveness, safety and cost of DOACS versus VKAs in the elderly patients with AF.	Outcomes: Efficacy, safety and cost-effectiveness in DOACs vs VKAs	No data on this publication were presented. This is publication is about the analysis of the protocol that the authors propose to use to perform	- Low
288	N. Wang et al. (2020). Comparison of effectiveness and safety of direct oral anticoagulants versus vitamin-k antagonists in elderly patients with atrial fibrillation: a systematic review and cost-effectiveness analysis protocol. *Ann Transl Med,* 8:6 391	No data, just a protocol description	Compare VKA vs DOAC in Older population	Planned analyses only, no data	No data only a protocol description and rationale.	- Low/None
289	W. Xu et al. (2021). Severe Bleeding Risk of Direct Oral Anticoagulants Versus Vitamin K Antagonists for Stroke Prevention and Treatment in Patients with Atrial Fibrillation: A Systematic Review and Network Meta-Analysis. *Cardiovasc Drugs Ther,* :	Systematic review and network meta-analysis: 23 RCTs and a total of 87,616 patients enrolled	DOAC vs VKAs for stroke prevention and treatment in patients with AF	Outcomes: Severe bleeding risk	Based on the surface under the cumulative ranking curves (SUCRA), the relative ranking probability for each group was generated; the bleeding safety was ranked from highest to lowest as follows: fatal bleeding: edoxaban (SUCRA, 80.2), rivaroxaban (SUCRA, 68.3), apixaban (SUCRA, 48.5), dabigatran (SUCRA, 40.0), and VKAs (SUCRA, 12.9);	++ All DOACs had lower bleeding risks than VKAs in this large systematic review and network meta-analysis The most safe DOAC is edoxaban in terms of fatal bleeding, dabigatran in terms of major bleeding and intracranial bleeding and apixaban in terms of GI bleeding.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					Major bleeding: Dabigatran (SUCRA, 74.0), apixaban (SUCRA, 71.5), edoxaban (SUCRA, 66.5), rivaroxaban (SUCRA, 22.7), VKAs (SUCRA, 15.4); GI bleeding: apixaban (SUCRA, 55.9), VKAS (SUCRA 53.7), edoxaban (SUCRA, 50.5), rivaroxaban (SUCRA, 50.4), dabigatran (SUCRA, 39.5); Intracranial haemorrhage: Dabigatran (SUCRA, 84.6), edoxaban (SUCRA, 74.1), apixaban (SUCRA, 65.8), rivaroxaban (SUCRA, 24.4), VKAs (SUCRA, 1.1).	
289	W. Xu et al. (2021). Severe Bleeding Risk of Direct Oral Anticoagulants Versus Vitamin K Antagonists for Stroke Prevention and Treatment in Patients with Atrial Fibrillation: A Systematic Review and Network Meta-Analysis. *Cardiovasc Drugs Ther,* :	Meta-analysis. 4 RCT and 6 observational studies; total of 6405 patients (2142 in DOAC group and 4263 in VKAs group) In the RCTs the VKAs dose was adjusted to maintain a target INR of 2.0 to 3.0. In RCTs the DOAC regimen included 110 mg of dabigatran twice a day, 60 mg of edoxaban daily, 5mg of apixaban twice a day, or 20 mg of rivaroxaban daily.	DOAC vs VKAs in patients with atrial fibrillation and bioprosthetic valves	Outcomes: all causes of death, major bleeding, stroke, and systemic embolism	Pooled analysis: similar rates of all-cause death (HR 0.90, 95% CI 0.77-1.05; p=0.18; I^2=0%) in DOAC vs VKAs group. The rate of major bleeding was significantly lower in DOAC group (0.66, 0.48-0.89, p=0.006; I^2=0%) Rate of stroke or systemic embolism was similar in the DOACs and VKAs (HR 0.72, 0.44-1.77; p=0.18, I^2=39%). All the outcomes were consistent between RCTs and observational studies (P for the interaction=0.77, I^2=0 for all-cause deaths; P for the interaction =0.78, I^2=0 for major bleeding; and P for interaction =0.36, I^2=0 for stroke).	**+** This publication is relevant only for subgroup of patients with bioprosthetic valves and AF

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					Publication bias was assessed using funnel plots which showed no evidence of publication bias.	
290	Y. Yokoyama et al. (2021). Direct oral anticoagulants versus vitamin K antagonists in patients with atrial fibrillation and bioprosthetic valves: A meta-analysis. *J Thorac Cardiovasc Surg,* :	Meta-analysis. 4 RCT and 6 observational studies; total of 6405 patients (2142 in DOAC group and 4263 in VKAs group) In the RCTs the VKAs dose was adjusted to maintain a target INR of 2.0 to 3.0. In RCTs the DOAC regimen included 110 mg of dabigatran twice a day, 60 mg of edoxaban daily, 5mg of apixaban twice a day, or 20 mg of rivaroxaban daily.	DOAC vs VKAs in patients with atrial fibrillation and bioprosthetic valves	Outcomes: all causes of death, major bleeding, stroke and systemic embolism	Pooled analysis: similar rates of all-cause death (HR 0.90, 95% CI 0.77-1.05; p=0.18; I^2=0%) in DOAC vs VKAs group. The rate of major bleeding was significantly lower in DOAC group (0.66, 0.48-0.89, p=0.006; I^2=0%) Rate of stroke or systemic embolism was similar in the DOACs and VKAs (HR 0.72, 0.44-1.77; p=0.18, I^2=39%). All the outcomes were consistent between RCTs and observational studies (P for the interaction=0.77, I^2=0 for all-cause deaths; P for the interaction =0.78, I^2=0 for major bleeding; and P for interaction =0.36, I^2=0 for stroke). Publication bias was assessed using funnel plots which showed no evidence of publication bias.	**+** This publication is relevant only for subgroup of patients with bioprosthetic valves and AF.
290	Y. Yokoyama et al. (2021). Direct oral anticoagulants versus vitamin K antagonists in patients with atrial fibrillation and bioprosthetic valves: A	Meta analysis of 10 studies of population with both AF and bioprosthetic valves. DOAC vs VKA	DOAC vs VKA in patients with Atrial Fibrillation and Bioprosthetic valves. No specific reference to history of Stroke or TIA.	Mortality ISSE Major Bleeding	Equivalent efficacy in preventing ISSE. DOACs safer with significantly less bleeding	**-** Low. Only relevant to patients with A. fib and Bioprosthetic valves. No specific reference to secondary prevention of Stroke /TIA

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	meta-analysis. *J Thorac Cardiovasc Surg,* :					
700	Oldgren et al. Early Versus Delayed Non–Vitamin K Antagonist Oral Anticoagulant Therapy After Acute Ischemic Stroke in Atrial Fibrillation (TIMING): A Registry-Based Randomized Controlled Noninferiority Study *Circulation*. 2022;146:00–00. DOI: 10.1161/CIRCULATIONAHA.122.060666	RCT of early (≤4 days versus ≥ 5 days) anticoagulation with a NOAC in AF related stroke	Initiation of a NOAC per physician choice early or late post stroke	Composite outcome of ischaemic stroke and intracerebral haemorrhage	Early initiation with NOAC Non inferior (P < .004) to delayed initiation and no excess of intracerebral haemorrhage noted. Lower risk of ischaemic stroke and all cause mortality was seen in the early initiation group BUT early initiation not superior to delayed initiation . NIHSS score was low in both groups (mean < 6 and median 4 (range 2-9)	**+** Good quality evidence No haemorrhage observed in either group? Strokes too mild
700	J. Oldgren et al. (2022) Early Versus Delayed Non–Vitamin K Antagonist Oral Anticoagulant Therapy After Acute Ischemic Stroke in Atrial Fibrillation (TIMING): A Registry-Based Randomized Controlled Noninferiority Study. Circulation. 6.	Multi-centre registry-based, randomized, noninferiority, open-label, blinded end-point study in Sweden N=888 patients (450 vs. 438) with AF and recent ischaemic stroke (<72h)	Early (≤4 days) or delayed (5–10 days) NOAC initiation	Primary outcome: recurrent ischemic stroke, symptomatic intracerebral haemorrhage, or all-cause mortality at 90 days. The prespecified noninferiority margin was 3%. Secondary outcomes: individual components of the primary outcome	- Primary outcome: 31 patients (6.89%) assigned to early initiation vs 38 patients (8.68%) assigned to delayed NOAC initiation (absolute risk difference,−1.79% [95% CI, −5.31% to 1.74%]; Pnoninferiority=0.004). - Ischemic stroke rates were 3.11% and 4.57% (risk difference,−1.46% [95% CI, −3.98% to 1.07%]) - All-cause mortality rates were 4.67% and 5.71% (risk difference, −1.04% [95% CI, −3.96% to 1.88%])	**++** High quality although study under-powered (vs. initially planned sample size). Not directly related to PICO question on DOAC vs. VKA. Useful information to add in terms of timing

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					No patient in either group experienced symptomatic intracerebral hemorrhage.	
701	X. Wang et al (2021). Anticoagulants for acute ischaemic stroke. Cochrane Database Syst Rev. 10: 10. Cd000024.	Cochrane systematic review	Review of randomised trials of early initiation of Anticoagulants (within 2 weeks of onset) in acute ischaemic stroke	Death or dependent at > 1 month Death from all causes during treatment Recurrent ischaemic stroke Deep venous thrombosis Pulmonary embolus Intracranial haemorrhage Major extracranial haemorrhage	No difference in death or disability in those treated early (≤ 2 weeks) with anticoagulation in all cause ischemic stroke Reduction in recurrent stroke (moderate GRADE evidence) , DVT (LOW) and pulmonary embolus (HIGH) observed but with increased risk of intracerebral (moderate) and extracranial (moderate) haemorrhage	**++** High quality systematic review
701	X. Wang et al (2021). Anticoagulants for acute ischaemic stroke. Cochrane Database Syst Rev. 10: 10. Cd000024.	Systematic review and meta-analysis including 28 trials involving 24,025 participants	early anticoagulant therapy (started within two weeks of stroke onset) with control in people with acute presumed or confirmed ischaemic stroke.	- death or dependence at the end of follow-up - death from all causes during the treatment period. - - recurrent ischaemic strokes	- death or dependence at the end of follow-up (odds ratio (OR) 0.98, 95% CI 0.92 to 1.03; 12 RCTs, 22,428 participants; high-certainty evidence). - Death from all causes (OR 0.99, 95% CI 0.90 to 1.09; 22 RCTs, 22,602 participants; low-certainty evidence)	**++** High-quality on its own but some studies included were of high risk of bias and a range of anticoagulants were included (standard unfractionated heparin, low-molecular-weight heparins, heparinoids, oral anticoagulants, and thrombin inhibitors) so not directly relevant to Q6

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
				- symptomatic intracranial haemorrhage - symptomatic pulmonary emboli - extracranial haemorrhage	during the treatment period. - recurrent ischaemic strokes (OR 0.75, 95% CI 0.65 to 0.88; 12 RCTs, 21,665 participants; moderate-certainty evidence) - symptomatic intracranial haemorrhage (OR 2.47; 95% CI 1.90 to 3.21; 20 RCTs, 23,221 participants; moderate-certainty evidence). - symptomatic pulmonary emboli (OR 0.60, 95% CI 0.44 to 0.81; 14 RCTs, 22,544 participants; high-certainty evidence), extracranial haemorrhage (OR 2.99, 95% CI 2.24 to 3.99; 18 RCTs, 22,255 participants; moderate-certainty evidence).	
948	S.J. Connolly at el, 2022. Rivaroxaban in Rheumatic Heart Disease-Associated Atrial Fibrillation. N Engl J Med. 387: 11. 978-988.	Africa, Asia and Latin American patients with rheumatic heart disease-associated atrial fibrillation. Mean age 50 years, 72% women. 82% were moderate to severe mitral stenosis. Unblinded.	Warfarin (in 85%) of patients randomised to VKA, with a TTR that rose to about 65% at 3-4 years. Compared to: Rivaroxaban 20mg or 15mg adjusted by renal function	Composite of stroke, systemic embolism, MI, or death from known vascular or unknown causes.	560 primary outcomes with rivaroxaban, and 446 with warfarin (HR 1.25, 1.10-1.41). More stroke with Rivaroxaban. Fewer cardiac deaths with VKA. Rates of major bleeding not different between groups.	**++** High quality

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
		4531 patients in the ITT analysis. Mean follow-up 3.1 years	(estimated creatinine clearance).		The composite outcome of stroke or systemic embolism was not statistically different between groups.	