

**Anticoagulation in nonvalvular atrial
fibrillation:
update searches and screening
for
Universitätsklinikum Schleswig-Holstein/Campus Kiel**



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1. PROJECT OBJECTIVES

A key aim of the research project “Making SDM a reality” is to inform patients as part of shared decision making (SDM).

Kleijnen Systematic Reviews (KSR) Ltd has prepared an evidence report with a synthesis of the evidence of anticoagulation in nonvalvular atrial fibrillation.

2. METHODS

LITERATURE SEARCHES

Literature searches were conducted to identify systematic reviews and evidence-based guidelines about atrial fibrillation to update the 2019 evidence report.

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were limited by date range to update earlier searches: 2019-2021. Searches were not limited by language or publication status.

SEARCH SOURCES

Systematic reviews and guidelines

The following systematic review and health technology assessment specific databases were searched:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): issue 9 of 12, September 2021
- KSR Evidence (Internet) (<https://ksrevidence.com/>): 2019-2021
- Epistemonikos (Internet) (<https://www.epistemonikos.org/>): 2019-2021
- International HTA Database (INAHTA) (<https://database.inahta.org/>): 2019-2021

The following guidelines resources were searched:

- Guidelines International Network (GIN) (Internet) (<https://www.g-i-n.net/home>): 2019-2021
- NICE Evidence (Internet) (www.evidence.nhs.uk/): 2019-2021
- NICE Guidance (Internet) (<https://www.nice.org.uk/guidance>): 2019-2021
- ECRI Guidelines Trust (Internet) (<https://guidelines.ecri.org/>): 2019-2021
- Trip Database (<https://www.tripdatabase.com/>): 2019-2021
- Canadian Agency for Drugs and Technologies in Health (CADTH) (www.cadth.ca): 2019-2021

Full details of all search strategies are presented in Appendix 1.

Handling of citations

References identified from the searches were downloaded into EndNote bibliographic management software for further assessment and handling.

Supplementary searches

The bibliographies of included studies and review articles were also checked for additional relevant articles.

PRIORITISATION

During formal screening of titles and abstracts, studies were subject to a prioritisation process whereby the recency e.g., to most up-to-date clinical practice guidelines (CPG), methodological quality e.g., Cochrane systematic review (CSR), quality of the analyses per outcome (e.g., ratio of RCTs to observational studies), the number of included RCTs, the breadth of the timepoints reported etc. were considered to further prioritise which studies would be used to inform analyses. Studies were categorised into the following three categories: '1' = German, American, European or similar CPG; '2' = CSR or similar quality SR; '3' = potentially lower/other quality SR.

3. RESULTS

The original KSR searches were conducted on January 18, 2019; and of the 394 references screened, 20 studies were deemed eligible. In the current update, a total of 1,682 records were retrieved from the electronic literature searches (Appendix 1). After the removal of duplicate records 936 titles and abstracts were screened by two reviewers. One hundred and sixty-five records were found to be potentially eligible and were longlisted after a consensus. Of those, five were short-listed and included in the analyses (Table 1).¹⁻⁵ See also Table 2 for an overview of primary studies included in the identified SRs/CPGs.

UPDATE – Concluding assessment by SHARE-TO-CARE Evidence Team (31/10/22)

Based on the update searches conducted by KSR Ltd in September 2021, we want to highlight the following aspects: evidence syntheses of clinical guidelines confirm that direct acting oral anticoagulants (DOACs) were at least as efficacious as vitamin K antagonists. Current guidelines recommend using DOAC over vitamin K antagonists in patients with atrial fibrillation, but head-to-head trial data do not exist to guide the choice of DOAC. A network meta-analysis of real-world data (Hirschl et al., 2019) – including less selected patient groups than in RCTs – supports the results on efficacy and safety outcomes, showing some differences between the three analysed DOACs. Although the methodological quality and strength of that meta-analysis is not strong enough to replace numerical data of the existing decision aid, network meta-analysis confirms recommendations of clinical guidelines stressing treatments should be individualized and based on net clinical benefit. Therefore, balancing the results of bleeding scores with risk scores and considering patient preferences are crucial parts in the decision-making process as well (Hirschl et al., 2019).

Conclusion regarding the evidence report: The former evidence report (January 15, 2019) remains valid but will be supplemented with this update report.

Table 1 Evidence sources

Study/year	Evidence type	Primary studies	Number of studies	Intervention(s)	Comparator(s)	Outcome(s)	Date searched	Conclusions	Notes S2C
National Institute for Health and Care Excellence ¹	CPG	RCT	26	Anticoagulants	Multiple	Multiple	10 Sept 2020	For anticoagulants see section 1.5.6. of document G1 of the CPG.	Evidence synthesis confirm that direct acting oral anti-coagulants were at least as efficacious as vit K antagonists, and might have slightly better safety (bleeding) outcomes. DOACs are recommended over warfarin (considering special issues, e.g. contraindications, special populations, patient preferences...)
January 2019 ²	CPG	SR,RCT, non-RCT, OS	26*	Anticoagulants	Multiple	Multiple	August 2018	Please refer to the synopsis and sections 4.1-4.3 of the CPG	Recommendations are in line with European guidelines.
Andrade 2020 ³	CPG	RCT	19**	Anticoagulants	Multiple	Multiple	N/M	<i>Please also refer to sections 7,8 of the supplementary material of the CPG</i>	Evidence synthesis and recommendations are in line with European guidelines.
Hindricks 2021 ⁴	CPG	RCT	13***	Vitamin K antagonists, non-vitamin K antagonist oral anticoagulants,	Multiple	Multiple	N/M	See sections 9,10,11 of the CPG.	<i>For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs</i>

Study/year	Evidence type	Primary studies	Number of studies	Intervention(s)	Comparator(s)	Outcome(s)	Date searched	Conclusions	Notes S2C
				other antithrombotic drugs					<i>(excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis). Treatment should be individualized based on net clinical benefit and consideration of patient values and preferences. (see exceptions and recommendations for special populations)</i>
Hirschl 2019 ⁵	SR	SR, RWD	88	Direct acting oral anticoagulants	Vitamin K antagonists	Stroke, systemic embolism, major bleeding, intracranial bleeding	September 2017	“Direct acting oral anticoagulants (factor II inhibitors (dabigatran) and factor Xa inhibitors (apixaban, rivaroxaban)) were at least as efficacious as vitamin K antagonists. In terms of safety endpoints, direct acting oral anticoagulants performed better under real-world conditions than in RCTs”	

Study/year	Evidence type	Primary studies	Number of studies	Intervention(s)	Comparator(s)	Outcome(s)	Date searched	Conclusions	Notes S2C
* = pertains to the number of studies published after 2016; ** = pertains to the number of studies published in 2020; *** = pertains to the number of studies published after 2015. CPG = clinical practice guideline; N/M = not mentioned; RCT = randomised controlled trial; OS = observational study; RWD = real world data; SR = systematic review.									

Table 2 Overview of primary studies included in the identified SRs/CPGs

Study/year	Primary study(ies)	Reference (first author & journal)
National Institute for Health and Care Excellence ¹	RCT*	1. Ke HH, He Y, Lv XW, Zhang EH, Wei Z, Li JY. Efficacy and safety of rivaroxaban on the resolution of left atrial/left atrial appendage thrombus in nonvalvular atrial fibrillation patients. <i>Journal of Thrombosis and Haemostasis</i>. 2019; 48(2):270-276 2. Kikuchi S, Tsukahara K, Sakamaki K, Morita Y, Takamura T, Fukui K et al. Comparison of anti-inflammatory effects of rivaroxaban vs. dabigatran in patients with non-valvular atrial fibrillation (RIVAL-AF study): multicenter randomized study. <i>Heart and Vessels</i>. 2019; 34(6):1002-1013 3. Shosha RI, Ibrahim OM, Setiha ME, Abdelwahab AA. The efficacy and safety of rivaroxaban as an alternative to warfarin for the prevention of thromboembolism in patients with atrial fibrillation. <i>International Journal of Pharmaceutical Sciences Review and Research</i>. 2017; 43(2):38-48
January 2019 ²	SR,RCT**	1. Siontis KC, Zhang X, Eckard A, et al. Outcomes associated with apixaban use in end-stage kidney disease patients with atrial fibrillation in the United States. <i>Circulation</i>. 2018;138:1519–29 2. Nielsen PB, Skjøth F, Overvad TF, et al. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA2DS2-VA score rather than CHA2DS2-VASc? <i>Circulation</i>. 2018;137:832–40 3. Reed D, Palkimas S, Hockman R, et al. Safety and effectiveness of apixaban compared to warfarin in dialysis patients. <i>Res Pract Thromb Haemost</i>. 2018;2:291–8. 4. Kent AP, Brueckmann M, Fraessdorf M, et al. Concomitant oral anticoagulant and nonsteroidal anti-inflammatory drug therapy in patients with atrial fibrillation. <i>J Am Coll Cardiol</i>. 2018;72:255–67 5. Friedman DJ, Piccini JP, Wang T, et al. Association between left atrial appendage occlusion and readmission for thromboembolism among patients with atrial fibrillation undergoing concomitant cardiac surgery. <i>JAMA</i>. 2018;319:365–74. 6. Ezekowitz MD, Pollack CV Jr, Halperin JL, et al. Apixaban compared to heparin/vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: the EMANATE trial. <i>Eur Heart J</i>. 2018;39:2959–71.

Study/year	Primary study(ies)	Reference (first author & journal)
		7. Lopes RD, Rordorf R, De Ferrari GM, et al. Digoxin and mortality in patients with atrial fibrillation. <i>J Am Coll Cardiol</i>. 2018;71:1063–74 8. Pan K-L, Singer DE, Ovbiagele B, et al. Effects of non-vitamin K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and valvular heart disease: a systematic review and metaanalysis. <i>J Am Heart Assoc</i>. 2017;6:e005835. 9. Floyd CN, Ferro A. Indications for anticoagulant and antiplatelet combined therapy. <i>BMJ</i>. 2017;359:j3782. 10. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. <i>Circulation</i>. 2017;135:e1159–95 11. Quinn GR, Severdija ON, Chang Y, et al. Wide variation in reported rates of stroke across cohorts of patients with atrial fibrillation. <i>Circulation</i>. 2017;135:208–19. 12. Rivera-Caravaca JM, Roldán V, Esteve-Pastor MA, et al. Prediction of long-term net clinical outcomes using the TIMI-AF score: comparison with CHA2DS2-VASc and HAS-BLED. <i>Am Heart J</i>. 2018;197:27–34. 13. Fanola CL, Giugliano RP, Ruff CT, et al. A novel risk prediction score in atrial fibrillation for a net clinical outcome from the ENGAGE AF-TIMI 48 randomized clinical trial. <i>Eur Heart J</i>. 2017;38:888–96. 14. Philippart R, Brunet-Bernard A, Clementy N, et al. CHA2DS2-VASc score for predicting stroke and thromboembolism in patients with AF and biological valve prosthesis. <i>J Am Coll Cardiol</i>. 2016;67:343–4. 15. Carnicelli AP, De Caterina R, Halperin JL, et al. Edoxaban for the prevention of thromboembolism in patients with atrial fibrillation and bioprosthetic valves. <i>Circulation</i>. 2017;135:1273–5. 16. Stanton BE, Barasch NS, Tellor KB. Comparison of the safety and effectiveness of apixaban versus warfarin in patients with severe renal impairment. <i>Pharmacotherapy</i>. 2017;37:412–9. 17. Mavrakanas TA, Samer CF, Nessim SJ, et al. Apixaban pharmacokinetics at steady state in hemodialysis patients. <i>J Am Soc Nephrol</i>. 2017;28:2241–8. 18. Reed D, Palkimas S, Hockman R, et al. Safety and effectiveness of apixaban compared to warfarin in dialysis patients. <i>Res Pract Thromb Haemost</i>. 2018;2:291–8. 19. Fauchier L, Clementy N, Bisson A, et al. Should atrial fibrillation patients with only 1 nongender-related CHA2DS2-VASc risk factor be anticoagulated? <i>Stroke</i>. 2016;47:1831–6. 20. Dias C, Moore KT, Murphy J, et al. Pharmacokinetics, pharmacodynamics, and safety of single-dose rivaroxaban in chronic hemodialysis. <i>Am J Nephrol</i>. 2016;43:229–36

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		21. Ntaios G, Papavasileiou V, Makaritsis K, et al. Real-world setting comparison of nonvitamin-K antagonist oral anticoagulants versus vitamin-K antagonists for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. <i>Stroke</i>. 2017;48:2494–503. 22. Bai Y, Shi X-B, Ma C-S, et al. Meta-analysis of effectiveness and safety of oral anticoagulants in atrial fibrillation with focus on apixaban. <i>Am J Cardiol</i>. 2017;120:1689–95 23. Yao X, Tangri N, Gersh BJ, et al. Renal outcomes in anticoagulated patients with atrial fibrillation. <i>J Am Coll Cardiol</i>. 2017;70:2621–32. 24. Lau WCY, Chan EW, Cheung C-L, et al. Association between dabigatran vs warfarin and risk of osteoporotic fractures among patients with nonvalvular atrial fibrillation. <i>JAMA</i>. 2017;317:1151–8. 25. Bah A, Nuotio I, Gronberg T, et al. Sex, age, and time to cardioversion. Risk factors for cardioversion of acute atrial fibrillation from the FinCV study. <i>Ann Med</i>. 2017;49:254–9. 26. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. <i>N Engl J Med</i>. 2017;377:1513–24.
Andrade 2020 ³	RCT***	1. Guimarães HP, Lopes RD, de Barros E, Silva PGM, et al. RIVER Trial Investigators. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. <i>N Engl J Med</i> 2020;383: 2117-26. 2. De Vriese AS, Caluwe R, Pyfferoen L, et al. Multicenter randomized controlled trial of vitamin K antagonist replacement by rivaroxaban with or without vitamin K2 in hemodialysis patients with atrial fibrillation: the Valkyrie Study. <i>J Am Soc Nephrol</i> 2020;31:186-96. 3. Thoren E, Wernroth ML, Christersson C, et al. Compared with matched controls, patients with postoperative atrial fibrillation (POAF) have increased long-term AF after CABG, and POAF is further associated with increased ischemic stroke, heart failure and mortality even after adjustment for AF. <i>Clin Res Cardiol</i> 2020;109:1232-42. 4. Andrade JG, Macle L, Verma A, et al. Quality of life and health care utilization in the CIRCA-DOSE study. <i>JACC Clin Electrophysiol</i> 2020;6:935-44. 5. Stiell IG, Sivilotti MLA, Taljaard M, et al. Electrical versus pharmacological cardioversion for emergency department patients with acute atrial fibrillation (RAFF2): a partial factorial randomised trial. <i>Lancet</i> 2020;395:339-49. 6. Hawkins NM, Scheuermeyer FX, Youngson E, et al. Impact of cardiology follow-up care on treatment and outcomes of patients with new atrial fibrillation discharged from the emergency department. <i>Europace</i> 2020;22:695-703. 7. Atzema CL, Fang J, Cox JL, et al. Assessment of an algorithm for prescription of oral anticoagulation for patients with atrial fibrillation in emergency departments. <i>JAMA Netw Open</i> 2020;3:e200306. 8. Kirchhof P, Camm AJ, Goette A, et al. Early rhythm-control therapy in patients with atrial fibrillation. <i>N Engl J Med</i> 2020;383:1305-16.

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		9. Glikson M, Wolff R, Hindricks G, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion - an update. <i>EuroIntervention</i> 2020;15:1133-80. 10. Malik AH, Yandrapalli S, Shetty S, et al. Impact of weight on the efficacy and safety of direct-acting oral anticoagulants in patients with non-valvular atrial fibrillation: a meta-analysis. <i>Europace</i> 2020;22: 361-7. 11. Okumura K, Akao M, Yoshida T, et al. Low-dose edoxaban in very elderly patients with atrial fibrillation. <i>N Engl J Med</i> 2020;383: 1735-45 12. Cheung CC, Roston TM, Andrade JG, Bennett MT, Davis MK. Arrhythmias in cardiac amyloidosis: challenges in risk stratification and treatment. <i>Can J Cardiol</i> 2020;36:416-23. 13. Yang H, Bouma BJ, Dimopoulos K, et al. Non-vitamin K antagonist oral anticoagulants (NOACs) for thromboembolic prevention, are they safe in congenital heart disease? Results of a worldwide study. <i>Int J Cardiol</i> 2020;299:123-30. 14. Lee AYY. Anticoagulant therapy for venous thromboembolism in cancer. <i>N Engl J Med</i> 2020;382:1650-2. 15. Stanifer JW, Pokorney SD, Chertow GM, et al. Apixaban versus warfarin in patients with atrial fibrillation and advanced chronic kidney disease. <i>Circulation</i> 2020;141:1384-92. 16. Randhawa MS, Vishwanath R, Rai MP, et al. Association between use of warfarin for atrial fibrillation and outcomes among patients with endstage renal disease: a systematic review and meta-analysis. <i>JAMA Netw Open</i> 2020;3:e202175. 17. Pokorney SD, Black-Maier E, Hellkamp AS, et al. Oral anticoagulation and cardiovascular outcomes in patients with atrial fibrillation and endstage renal disease. <i>J Am Coll Cardiol</i> 2020;75:1299-308. 18. Miura K, Ikemura N, Kimura T, et al. Treatment strategies and subsequent changes in the patient-reported quality-of-life among elderly patients with atrial fibrillation. <i>Am Heart J</i> 2020;222:83-92. 19. Wijnvliet E, Tieleman RG, van Gelder IC, et al. Nurse-led vs usual-care for atrial fibrillation. <i>Eur Heart J</i> 2020;41:634-41.
Hindricks 2021 ⁴	SR,RCT*	1. Sjalander S, Sjogren V, Renlund H, Norrving B, Sjalander A. Dabigatran, rivaroxaban and apixaban vs. high TTR warfarin in atrial fibrillation. <i>Thromb Res</i> 2018;167:113118. 2. Carmo J, Moscoso Costa F, Ferreira J, Mendes M. Dabigatran in real-world atrial fibrillation. Meta-analysis of observational comparison studies with vitamin K antagonists. <i>Thromb Haemost</i> 2016;116:754763 3. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, Halperin JL, Ma CS, Zint K, Elsaesser A, Lu S, Bartels DB, Lip GYH; GLORIAAF Investigators. Two-year follow-up of patients treated with dabigatran for stroke prevention in atrial fibrillation: Global Registry on Long-Term Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) registry. <i>Am Heart J</i> 2018;198:5563.

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		4. Camm AJ, Amarenco P, Haas S, Hess S, Kirchhof P, Kuhls S, van Eickels M, Turpie AG; XANTUS Investigators. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. <i>Eur Heart J</i> 2016;37:11451153. 5. Martinez CAA, Lanas F, Radaideh G, Kharabsheh SM, Lambelet M, Viaud MAL, Ziadeh NS, Turpie AGG; XANTUS Investigators. XANTUS-EL: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation in Eastern Europe, Middle East, Africa and Latin America. <i>Egypt Heart J</i> 2018;70:307313. 6. Li XS, Deitelzweig S, Keshishian A, Hamilton M, Horblyuk R, Gupta K, Luo X, Mardekian J, Friend K, Nadkarni A, Pan X, Lip GYH. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in 'real-world' clinical practice. A propensity-matched analysis of 76,940 patients. <i>Thromb Haemost</i> 2017;117:10721082. 7. Lee SR, Choi EK, Han KD, Jung JH, Oh S, Lip GYH. Edoxaban in Asian patients with atrial fibrillation: effectiveness and safety. <i>J Am Coll Cardiol</i> 2018;72:838853. 8. Ingrasciotta Y, Crisafulli S, Pizzimenti V, Marciano I, Mancuso A, Ando G, Corrao S, Capranzano P, Trifiro G. Pharmacokinetics of new oral anticoagulants: implications for use in routine care. <i>Expert Opin Drug Metab Toxicol</i> 2018;14:10571069. 9. Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, Lip GYH, Chen SA. Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study. <i>Circulation</i> 2018;138:3747. 10. Stanton BE, Barasch NS, Tellor KB. Comparison of the safety and effectiveness of apixaban versus warfarin in patients with severe renal impairment. <i>Pharmacotherapy</i> 2017;37:412419. 11. Siontis KC, Zhang X, Eckard A, Bhave N, Schaubel DE, He K, Tilea A, Stack AG, Balkrishnan R, Yao X, Noseworthy PA, Shah ND, Saran R, Nallamothu BK. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. <i>Circulation</i> 2018;138:15191529. 12. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, Kowey PR, Mahaffey KW, Naccarelli G, Reiffel J, Singer DE, Peterson ED, Piccini JP; ORBIT-AF Investigators and Patients. Off-label dosing of non-vitamin K antagonist oral anticoagulants and adverse outcomes: the ORBIT-AF II registry. <i>J Am Coll Cardiol</i> 2016;68:25972604. 13. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. <i>J Am Coll Cardiol</i> 2017;69:27792790.
Hirschl 2019 ⁵	SR,RWD*	1. Proietti M, Laroche C, Opolski G, Maggioni AP, Boriani G, Lip GYH. 'Real-world' atrial fibrillation management in Europe: Observations from the 2-year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase. <i>Europace</i>. 2017;19(5):722–33.

Study/year	Primary study(ies)	Reference (first author & journal)
		2. Almutairi AR, Zhou L, Gellad WF, Lee JK, Slack MK, Martin JR, et al. Effectiveness and Safety of Non-vitamin K Antagonist Oral Anticoagulants for Atrial Fibrillation and Venous Thromboembolism: A Systematic Review and Meta-analyses. <i>Clin Ther.</i> 2017;39(7):1456–78.e36. 3. Bai Y, Shi XB, Ma CS, Lip GYH. Meta-Analysis of Effectiveness and Safety of Oral Anticoagulants in Atrial Fibrillation With Focus on Apixaban. <i>Am J Cardiol.</i> 2017;120(9):1689–95. 4. Beyer-Westendorf J, Camm AJ, Coleman CI, Tamayo S. Rivaroxaban real-world evidence: Validating safety and effectiveness in clinical practice. <i>Thromb Haemost.</i> 2016;116(Suppl. 2):S13–s23. 5. Deitelzweig S, Farmer C, Luo X, Vo L, Li X, Hamilton M, et al. Risk of major bleeding in patients with non-valvular atrial fi - brillation treated with oral anticoagulants: a systematic review of real-world observational studies. <i>Curr Med Res Opin.</i> 2017;33(9):1583–94. 6. Gong X, Tang S, Li J, Zhang X, Tian X, Ma S. Antithrombotic therapy strategies for atrial fibrillation patients undergoing percutaneous coronary intervention: A systematic review and network meta-analysis. <i>PLoS One.</i> 2017;12(10):e0186449. 7. Lip GY, Mitchell SA, Liu X, Liu LZ, Phatak H, Kachroo S, et al. Relative efficacy and safety of non-Vitamin K oral anticoagulants for non-valvular atrial fi brillation: Network meta-analysis comparing apixaban, dabigatran, rivaroxaban and edoxaban in three patient subgroups. <i>Int J Cardiol.</i> 2016;204:88–94. 8. Lopez-Lopez JA, Sterne JAC, Thom HHZ, Higgins JPT, Hingorani AD, Okoli GN, et al. Oral anticoagulants for prevention of stroke in atrial fi brillation: systematic review, network meta-analysis, and cost effectiveness analysis. <i>BMJ.</i> 2017;359:j5058. 9. Ntaios G, Papavasileiou V, Makaritsis K, Vemmos K, Michel P, Lip GYH. Real-World Setting Comparison of Nonvitamin-K Antagonist Oral Anticoagulants Versus Vitamin-K Antagonists for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Meta-Analysis. <i>Stroke.</i> 2017;48(9):2494–503. 10. Pan KL, Singer DE, Ovbiagele B, Wu YL, Ahmed MA, Lee M. Effects of Non-Vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: A Systematic Review and Meta-Analysis. <i>J Am Heart Assoc.</i> 2017;6(7). 11. Patel P, Pandya J, Goldberg M. NOACs vs. Warfarin for Stroke Prevention in Nonvalvular Atrial Fibrillation. <i>Cureus.</i> 2017; 9(6):e1395. 12. Sun MT, Wood MK, Chan W, Selva D, Sanders P, Casson RJ, et al. Risk of Intraocular Bleeding With Novel Oral Anticoagulants Compared With Warfarin: A Systematic Review and Meta-analysis. <i>JAMA Ophthalmol.</i> 2017;135(8):864–70.

Study/year	Primary study(ies)	Reference (first author & journal)
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Study/year	Primary study(ies)	Reference (first author & journal)
		24. Coleman CI, Antz M, Bowrin K, Evers T, Simard EP, Bonnemeier H, et al. Real-world evidence of stroke prevention in patients with nonvalvular atrial fi brillation in the United States: the REVISIT-US study. <i>Curr Med Res Opin.</i> 2016;32(12):2047–53. 25. Coleman CI, Antz M, Ehlken B, Evers T. REal-Life Evidence of stroke prevention in patients with atrial Fibrillation – The RELIEF study. <i>Int J Cardiol.</i> 2016;203:882–4. 26. Ellis MH, Neuman T, Bitterman H, Dotan SG, Hammerman A, Battat E, et al. Bleeding in patients with atrial fi brillation treated with dabigatran, rivaroxaban or warfarin: A retrospective population-based cohort study. <i>Eur J Intern Med.</i> 2016;33:55–9. 27. Gorst-Rasmussen A, Lip GY, Bjerregaard Larsen T. Rivaroxaban versus warfarin and dabigatran in atrial fi brillation: comparative effectiveness and safety in Danish routine care. <i>Pharmacoepidemiol Drug Saf.</i> 2016;25(11):1236–44. 28. Graham DJ, Reichman ME, Wernecke M, Hsueh YH, Izem R, Southworth MR, et al. Stroke, Bleeding, and Mortality Risks in Elderly Medicare Benefi ciaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation. <i>JAMA Intern Med.</i> 2016;176(11):1662–71. 29. Hecker J, Marten S, Keller L, Helmert S, Michalski F, Werth S, et al. Effectiveness and safety of rivaroxaban therapy in daily-care patients with atrial fibrillation. Results from the Dresden NOAC Registry. <i>Thromb Haemost.</i> 2016;115(5):939–49. 30. Korenstra J, Wijtvliet EP, Veeger NJ, Geluk CA, Bartels GL, Posma JL, et al. Effectiveness and safety of dabigatran versus acenocoumarol in ‘real-world’ patients with atrial fi brillation. <i>Europace.</i> 2016;18(9):1319–27. 31. Kwon CH, Kim M, Kim J, Nam GB, Choi KJ, Kim YH. Real-world comparison of non-vitamin K antagonist oral anticoagulants and warfarin in Asian octogenarian patients with atrial fi brillation. <i>Journal of Geriatric Cardiology.</i> 2016;13(7):566–72. 32. Larsen TB, Skjoth F, Nielsen PB, Kjaeldgaard JN, Lip GY. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fi brillation: propensity weighted nationwide cohort study. <i>BMJ.</i> 2016;353:i3189. 33. Lip GY, Keshishian A, Kamble S, Pan X, Mardekian J, Horblyuk R, et al. Real-world comparison of major bleeding risk among non-valvular atrial fi brillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. <i>Thromb Haemost.</i> 2016;116(5):975–86. 34. Lip GYH. How to REVISIT the increasing “real world” evidence for stroke prevention in non-valvular atrial fibrillation? <i>Curr Med Res Opin.</i> 2016;32(12):2055–7. 35. Nishtala PS, Gnjdic D, Jamieson HA, Hanger HC, Kaluarachchi C, Hilmer SN. ‘Real-world’ haemorrhagic rates for warfarin and dabigatran using population-level data in New Zealand. <i>Int J Cardiol.</i> 2016;203:746–52.

Study/year	Primary study(ies)	Reference (first author & journal)
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Study/year	Primary study(ies)	Reference (first author & journal)
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Study/year	Primary study(ies)	Reference (first author & journal)
		59. Li WH, Huang D, Chiang CE, Lau CP, Tse HF, Chan EW, et al. Efficacy and safety of dabigatran, rivaroxaban, and warfarin for stroke prevention in Chinese patients with atrial fibrillation: the Hong Kong Atrial Fibrillation Project. <i>Clin Cardiol.</i> 2017;40(4):222–9. 60. Li X, Deitelzweig S, Keshishian A, Hamilton M, Horblyuk R, Gupta K, et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in “realworld” clinical practice: A propensity-matched analysis of 76,940 patients. <i>Thromb Haemost.</i> 2017;117(6):1072–82. 61. Lin J, Trocio J, Gupta K, Mardekian J, Lingohr-Smith M, Menges B, et al. Major bleeding risk and healthcare economic outcomes of non-valvular atrial fibrillation patients newly-initiated with oral anticoagulant therapy in the real-world setting. <i>J Med Econ.</i> 2017;20(9):952–61. 62. Naganuma M, Shiga T, Nagao T, Suzuki A, Murasaki K, Hagiwara N. Effectiveness and safety of dabigatran versus warfarin in “real-world” Japanese patients with atrial fibrillation: A single-center observational study. <i>J Arrhythm.</i> 2017;33(2): 107–10. 63. Nielsen PB, Skjoth F, Sogaard M, Kjaeldgaard JN, Lip GY, Larsen TB. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. <i>BMJ.</i> 2017;356:j510. 64. Norby FL, Bengtson LGS, Lutsey PL, Chen LY, MacLehose RF, Chamberlain AM, et al. Comparative effectiveness of rivaroxaban versus warfarin or dabigatran for the treatment of patients with non-valvular atrial fibrillation. <i>BMC Cardiovasc Disord.</i> 2017;17(1). 65. Noseworthy PA, Yao X, Gersh BJ, Hargraves I, Shah ND, Montori VM. Long-term stroke and bleeding risk in patients with atrial fibrillation treated with oral anticoagulants in contemporary practice: Providing evidence for shared decision-making. <i>Int J Cardiol.</i> 2017;245:174–7. 66. Peacock WF, Tamayo S, Sicignano N, Hopf KP, Yuan Z, Patel M. Comparison of the Incidence of Major Bleeding With Rivaroxaban Use Among Nonvalvular Atrial Fibrillation Patients With Versus Without Diabetes Mellitus. <i>Am J Cardiol.</i> 2017;119(5):753–9. 67. Russo-Alvarez G, Martinez KA, Valente M, Bena J, Hu B, Luxenburg J, et al. Thromboembolic and Major Bleeding Events With Rivaroxaban Versus Warfarin Use in a Real-World Setting. <i>Ann Pharmacother.</i> 2017;1060028017727290 68. Staerk L, Fosbol EL, Lip GYH, Lamberts M, Bonde AN, Torp-Pedersen C, et al. Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study. <i>Eur Heart J.</i> 2017;38(12): 907–15.

Study/year	Primary study(ies)	Reference (first author & journal)
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CPG = clinical practice guideline; OS = observational study; RCT = randomised controlled trial; RWD = real world data; SR = systematic review. * = only studies published after 2015 were extracted; ** = only studies published after 2016 were extracted; *** = only studies published in 2020 were extracted.		

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APPENDIX 1: SEARCH STRATEGIES

Shared Decision Making: atrial fibrillation update (EBSCO)

Table 3. Systematic reviews and guideline search results

Database	Dates	Results
CDSR	2019 - Issue 9, September 2021	17
KSR Evidence	2019-2021	674
Epistemonikos	2019-2021	892
INAHTA	2019-2021	10
NICE Evidence	01/01/2019 - 30/09/2021	58
NICE Guidance	2019-2021	11
GIN	2019-2021	0
ECRI	2019-2021	4
Trip	2019-2021	14
CADTH	2019-2021	2
Total		1682
Total after de-duplication		936

Search strategies

Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 9 of 12, September 2021
Searched: 30.9.21

#1 MeSH descriptor: [Atrial Fibrillation] explode all trees 4908
#2 ((atrial or auricular or atrium) near/3 (fibrillat* or arrhythmi*)):ti,ab,kw 14123
#3 #1 or #2 with Cochrane Library publication date Between Jan 2019 and Dec 2021, in Cochrane Reviews, Cochrane Protocols 17

KSR Evidence (Internet): Database last updated 30 September 2021

<https://ksrevidence.com/>

Searched: 30.9.21

1 (atrial or auricular or atrium) near/2 (fibrillat* or arrhythmi*) in Title Date published: 2019 - 2021 666 results
2 (atrial or auricular or atrium) near/2 (fibrillat* or arrhythmi*) in Bottom line 100 results
3 #1 or #2 in All text Date published: 2019 - 2021 674 results
Search run Thu Sep 30 2021

Epistemonikos (Internet): up to 30 September 2021

<https://www.epistemonikos.org/en/>

Searched: 30.9.21

title(("atrial fibrillation" OR "auricular fibrillation" OR "atrium fibrillation")); Publication year: Custom year range: From 2019 To 2021; Publication Type: Systematic Review
Records retrieved 892

International HTA Database (INAHTA): up to 30 September 2021

<https://database.inahta.org/>

Searched: 30.9.21

```
1      "Atrial Fibrillation"[mh]          107
2      "atrial fibrillation" OR "auricular fibrillation" OR "atrium fibrillation"      143
3      #2 OR #1      YEAR 2019 TO 2021      10
```

NICE Evidence Search (Internet): up to 30 September 2021

<https://www.evidence.nhs.uk/>

Searched: 30.9.21

Search terms	Results (Guidance): 01/01/2019-30/09/2021
"atrial fibrillation"	136
"auricular fibrillation"	0
"atrium fibrillation"	0
Total retrieved	136
Sifted for relevance	58

National Institute for Health and Care Excellence (NICE): Guidelines

<https://www.nice.org.uk/>

Searched: 30.9.21

NICE Guidance; Conditions and diseases; Cardiovascular conditions; Heart rhythm conditions

2019-2021

Guidance 5

Advice 5

Quality standards 0

Pathways 1

Total 11

Guidelines International Network (GIN). International Guidelines Library (Internet): up to 30 September 2021

<https://g-i-n.net/international-guidelines-library/>

Searched: 30.9.21

atrial fibrillation

auricular fibrillation

atrium fibrillation

2019-2021

0 records retrieved

ECRI Institute Guidelines Trust (Internet): up to 30 September 2021

<https://guidelines.ecri.org/>

Searched: 30.9.21

atrial fibrillation

auricular fibrillation

atrium fibrillation

2019-2021

4 records retrieved

Trip Database: up to 30 September 2021

<https://www.tripdatabase.com/>

Searched: 30.9.21

"atrial fibrillation" OR "auricular fibrillation" OR "atrium fibrillation"; in the Title; 2019, 2021

Guidelines: 14 records retrieved

Canadian Agency for Drugs and Technologies in Health (CADTH): up to 30 September 2021

<https://www.cadth.ca/>

Searched: 30.9.21

"atrial fibrillation"

"auricular fibrillation"

"atrium fibrillation"

Advanced Search; Project Line; Health Technology Assessment; 2019-2021

2 records retrieved