Supplementary file

eTable 1 – Full search strategy in PubMed

"atrial fibrillation"	Polypharmacy [mh] OR Pharmacoepidemiology OR prescribing pattern* [all] OR Prescription pattern* [all] OR Practice pattern, Physicians' [mh]	Stroke [all] OR Cerebrovascular accident OR Cerebro vascular accident OR CVA OR Hemorrhage [mh] OR Haemorrhag* [all] OR Haemorrhag* [all] OR Bleeding [all] OR Death* OR mortalit* OR Fatal* OR ((cardiac OR cardiovascular OR heart) AND (outcome* OR event*)) OR Hospitalization [mh] OR Hospitalisation [all] OR "hospital admission" OR "hospital admissions" OR Health status [mh] OR "quality of life" OR HRQL OR "life quality" OR "quality adjusted life year" OR qaly OR "quality adjusted life years" OR "short form 12" OR SF-12 OR SF12 OR "short form 20" OR SF-20 OR SF20 OR "short form 36" OR SF-36 OR SF36 OR "short form 8" OR SF-8 OR SF8 OR "symptom burden" OR "Cost of illness" OR "transient ischemic attack" OR "transient ischaemic attack" OR "TIA"

eTable 2: Assessment of risk of bias in included studies

	Study participation	**Study attrition**	**Prognostic factor measurement**	**Outcome measurement**	**Study confounding**	**Statistical analysis and reporting**
ROCKET-AF post hoc analysis	Exclusion and inclusion criteria described in detail 14264 patients from 1178 sites in 45 countries (Nth America, Latin America, Europe, Asia-Pacific from Dec 2006 to June 2009 Population of interest is patients with moderate- high risk of stroke Baseline characteristics adequately described except for concurrent medications	93 patients from one site excluded due to violations in CGP guidelines 32 patients lost to follow-up	All patients included 3 categories of polypharmacy considered (0-4, 5-9, and ≥10 meds) for all patients Types of medications included under polypharmacy is not defined and unclear if data collected uniformly across all sites Polypharmacy determined at a single time point (study enrolment)	Efficacy and safety outcomes defined in protocol Events adjudicated and classified by an independent clinical events committee Anticoagulant discontinuation assessed as an additional safety end-point The same method is used for all patients	Efficacy endpoints adjusted for age, sex, BMI, region, DM, CVA/TIA, vascular disease, CHF, HT, COPD, PAF, diastolic BP, creatinine clearance (C-G), heart rate, alcohol, randomised treatment Safety endpoints adjusted for age, sex, region, CVA/TIA, anaemia, previous GI bleed, COPD, diastolic BP, creatinine clearance (C-G), platelets, albumin previous aspirin, VKA, thienopyridine and randomised treatment 35% of patients took Aspirin at some point during the study (≤100mg per day permitted by protocol) Details on NSAIDs, SSRIs/SNRIs not provided. Patients who	Intention-to-treat population was used for all efficacy analyses Primary outcome was reported Cox proportional hazard models used to assess associations and included covariates found to be predictive of outcomes in full cohort Missing values of covariates were imputed with the use of the median for continuous variables and the most common vale for categorical variables Risk relationships reported as hazard ratios with 95% Cis

					were likely to need chronic treatment with an NSAID excluded from the study.	
Overall rating ROCKET-AF post hoc analysis	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk
ARISTOTLE post hoc analysis	18201 patients at 1034 sites in 39 countries (Nth America, Latin America, Europe, Asia-Pacific) from Dec 2006 to April 2010 Exclusion and inclusion criteria described in detail Population of interest is patients with high risk of stroke Baseline characteristics adequately described, ATC system used to classify concurrent medications	199 patients withdrew consent 69 patients lost to follow-up	All patients included Polypharmacy defined as the use of 5 or more drugs 3 categories of polypharmacy considered (0-5,6-8, and ≥9 meds) for all patients Types of medications included under polypharmacy is not defined and unclear if data collected uniformly across all sites Polypharmacy determined at a single time point (study enrolment)	Efficacy and safety outcomes defined in protocol Events adjudicated and classified by an independent clinical events committee The same method is used for all patients	Efficacy and safety outcomes adjusted only for country, sex and age Other drugs used classified by ATC system Aspirin, NSAIDs or Prednisone used by 13.8% in those taking 0-5 meds, 31.7% taking 6-8, and 49.7% taking ≥9	Population used not defined Primary outcome was reported Adjusted hazard ratio derived using Cox regression models adjusting for sex, age and country One way analysis of variance and Chi squared tests to compare groups No details provided on missing data Risk relationships reported as hazard ratios with 95% Cis
Overall rating ARISTOTLE post hoc analysis	Low risk	Low risk	Low risk	Low risk	Moderate-high risk	Low risk

thrombEVAL post hoc analysis	2011 participants from the regular care cohort from the thrombEVAL study in Germany (telemedicine cohort not included) between 2011 and 2013 Exclusion and inclusion criteria described in detail Population of interest is patients with high risk of venous thromboembolism Baseline characteristics adequately described, ATC system used to classify concurrent medications	Follow up information available for 1558 participants States information unavailable for remaining 453 participants due to study design	Only participants from regular care cohort included 2 categories of polypharmacy considered (5-8 and ≥9 meds) compared to reference group (1-4 meds) for all patients Medications classified according to ATC system Polypharmacy determined at a single time point (study enrolment)	Outcomes defined in rationale and design manuscript Events adjudicated by an independent committee The same method is used for all patients	Outcomes adjusted for sex, age, diabetes, dyslipidaemia, arterial hypertension, obesity, family history of MI or stroke, current smoking and Charlson Comorbidity index	Population studies defined All outcomes reported Adjusted hazard ratio derived using Cox regression model adjusting for sex, age, diabetes, dyslipidaemia, arterial hypertension, obesity, family history of MI or stroke, current smoking and Charlson Comorbidity index No detail reported on missing data
Overall rating thrombEVAL post hoc analysis	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk

Extra references

31. Nobili A, Marengoni A, Tettamanti M, Salerno F, Pasina L, Franchi C, et al. Association between clusters of diseases and polypharmacy in hospitalized elderly patients: results from the REPOSI study. Eur J Intern Med. 2011;22(6):597-602.
32. Jaspers Focks J, Brouwer MA, Wojdyla DM, Thomas L, Lopes RD, Washam JB, et al. Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the ARISTOTLE trial. BMJ. 2016;353:i2868.
33. Piccini JP, Hellkamp AS, Washam JB, Becker RC, Breithardt G, Berkowitz SD, et al. Polypharmacy and the efficacy and safety of rivaroxaban versus warfarin in the prevention of stroke in patients with nonvalvular atrial fibrillation. Circulation. 2016;133(4):352-60.
34. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
35. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(4):692-4.
36. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-6.
37. Eggebrecht L, Nagler M, Gobel S, Lamparter H, Keller K, Wagner B, et al. Relevance of Polypharmacy for Clinical Outcome in Patients Receiving Vitamin K Antagonists. J Am Geriatr Soc. 2019;67(3):463-70.
38. Roalfe AK, Bryant TL, Davies MH, Hackett TG, Saba S, Fletcher K, et al. A cross-sectional study of quality of life in an elderly population (75 years and over) with atrial fibrillation: secondary analysis of data from the Birmingham Atrial Fibrillation Treatment of the Aged study. Europace. 2012;14(10):1420-7.
39. McAvay G, Allore HG, Cohen AB, Gnjidic D, Murphy TE, Tinetti ME. Guideline-Recommended Medications and Physical Function in Older Adults with Multiple Chronic Conditions. J Am Geriatr Soc. 2017;65(12):2619-26.
40. Prochaska JH, Coldewey M, Gobel S, Keller K, Hendelmeier M, Konstantinides S, et al. Evaluation of oral anticoagulation therapy: rationale and design of the thrombEVAL study programme. European journal of preventive cardiology. 2015;22(5):622-8.
41. Mastromarino V, Casenghi M, Testa M, Gabriele E, Coluccia R, Rubattu S, et al. Polypharmacy in heart failure patients. Curr Heart Fail Rep. 2014;11(2):212-9.
42. Wong CY, Chaudhry SI, Desai MM, Krumholz HM. Trends in comorbidity, disability, and polypharmacy in heart failure. Am J Med. 2011;124(2):136-43.
43. Chapman RH, Benner JS, Petrilla AA, Tierce JC, Collins SR, Battleman DS, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. Arch Intern Med. 2005;165(10):1147-52.
44. Gastelurrutia P, Benrimoj SI, Espejo J, Tuneu L, Mangues MA, Bayes-Genis A. Negative clinical outcomes associated with drug-related problems in heart failure (HF) outpatients: impact of a pharmacist in a multidisciplinary HF clinic. J Card Fail. 2011;17(3):217-23.
45. Borne RT, O'Donnell C, Turakhia MP, Varosy PD, Jackevicius CA, Marzec LN, et al. Adherence and outcomes to direct oral anticoagulants among patients with atrial fibrillation: findings from the veterans health administration. BMC Cardiovascular Disorders. 2017;17(1):236.
46. Chang SH, Chou IJ, Yeh YH, Chiou MJ, Wen MS, Kuo CT, et al. Association between use of non-vitamin K oral anticoagulants with and without concurrent

medications and risk of major bleeding in nonvalvular atrial fibrillation. JAMA. 2017;318(13):1250-9.
47. Kent AP, Brueckmann M, Fraessdorf M, Connolly SJ, Yusuf S, Eikelboom JW, et al. Concomitant Oral Anticoagulant and Nonsteroidal Anti-Inflammatory Drug Therapy in Patients With Atrial Fibrillation. J Am Coll Cardiol. 2018;72(3):255-67.
48. Goldberg RM, Mabee J, Chan L, Wong S. Drug-drug and drug-disease interactions in the ED: Analysis of a high-risk population. Am J Emerg Med. 1996;14(5):447-50.
49. Dumbreck S, Flynn A, Nairn M, Wilson M, Treweek S, Mercer SW, et al. Drug-disease and drug-drug interactions: systematic examination of recommendations in 12 UK national clinical guidelines. BMJ. 2015;350:h949.
50. Skov J, Bladbjerg E-M, Sidelmann J, Vamosi M, Jespersen J. Plenty of pills: polypharmacy prevails in patients of a Danish anticoagulant clinic. European journal of clinical pharmacology. 2011;67(11):1169-74.
51. Wong CX, Brooks AG, Leong DP, Roberts-Thomson KC, Sanders P. The increasing burden of atrial fibrillation compared with heart failure and myocardial infarction: A 15-year study of all hospitalizations in Australia. Archives of Internal Medicine. 2012;172(9):739-41.
52. Jackson SL, Tong X, Yin X, George MG, Ritchey MD. Emergency department, hospital inpatient, and mortality burden of atrial fibrillation in the United States, 2006 to 2014. Am J Cardiol. 2017;120(11):1966-73.
53. Hung C-Y, Wu T-J, Wang K-Y, Huang J-L, Loh E-W, Chen Y-M, et al. Falls and atrial fibrillation in elderly patients. Acta Cardiol Sin. 2013;29(5):436-43.
54. Wong CX, Gan SW, Lee SW, Gallagher C, Kinnear NJ, Lau DH, et al. Atrial fibrillation and risk of hip fracture: A population-based analysis of 113,600 individuals. Int J Cardiol. 2017;243:229-32.
55. Rao MP, Vinereanu D, Wojdyla DM, Alexander JH, Atar D, Hylek EM, et al. Clinical outcomes and history of fall in patients with atrial fibrillation treated with oral anticoagulation: insights from the ARISTOTLE trial. Am J Med. 2017.
56. Reeve E, Thompson W, Farrell B. Deprescribing: A narrative review of the evidence and practical recommendations for recognizing opportunities and taking action. Eur J Intern Med. 2017;38:3-11.
57. Marengoni A, Onder G. Guidelines, polypharmacy, and drug-drug interactions in patients with multimorbidity. BMJ. 2015;350:h1059.
58. Tinetti ME, Bogardus STJ, Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. N Engl J Med. 2004;351(27):2870-4.
59. Green JL, Hawley JN, Rask KJ. Is the number of prescribing physicians an independent risk factor for adverse drug events in an elderly outpatient population? Am J Geriatr Pharmacother. 2007;5(1):31-9.