Use of modified intention to treat analysis in studies of direct oral anticoagulants and risk of selection bias.

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Intention to treat (ITT) principle

- Analysis includes all randomised
- Regardless of the treatment or outcome
- “once randomized, always analyzed”

Intention to treat (ITT) principle

- Maintains randomisation
- Consolidated Standards of Reporting Trials (CONSORT) recommends ITT
- As opposed to *per protocol*

Modified Intention to Treat (mITT)

- Deviations from ITT
- Many definitions
  - Post-randomisation exclusions above 20% may seriously impair results validity
- Increasingly published (Abraha & Montedori, 2010)

Modified Intention to treat (mITT)

- Increased risk of selection bias
- Confusing or inaccurate results
- Associated with inferior methodological quality compared to ITT
- Trials with exclusions tended to be more beneficial

Direct oral anticoagulants (DOACs)

- Rivaroxaban, apixaban, dabigatran, edoxaban
- Common Indications: AF, venous thromboembolism, thromboprophylaxis
- Multiple phase 3 trials
- Do these trials use ITT?

Objective

- Review of DOACs phase III trials
- Evaluate the extent of post-randomization exclusions in DOACs randomized controlled trials

Methods

- Systematically searched PubMed, EMBASE and the Cochrane library

- Keywords: edoxaban, rivaroxaban, dabigatran, apixaban, VTE, AF, prophylaxis, and clinical trial

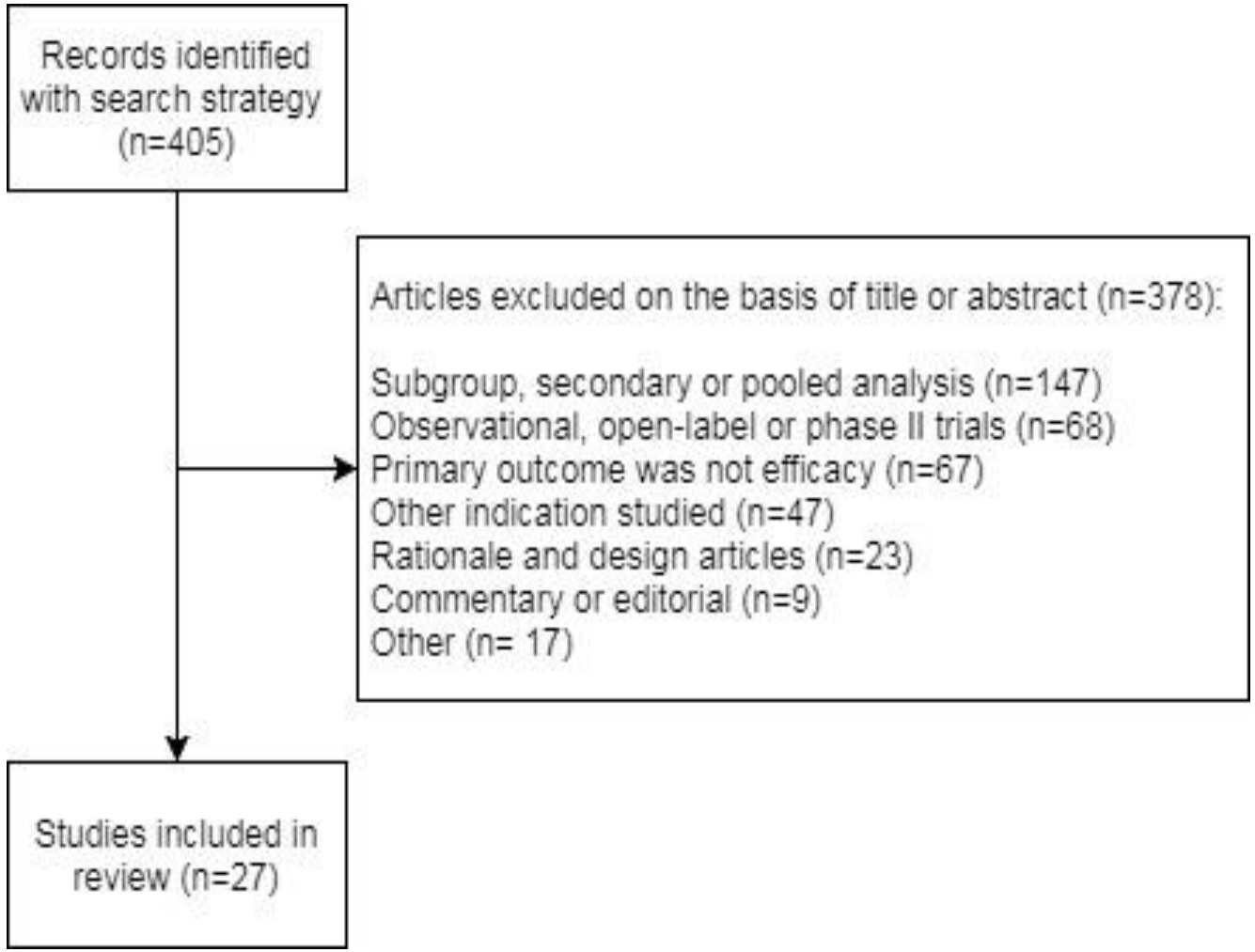

Figure 1. Study selection process

Results

- 29 studies included

(18)

(4)

(1)

Results

	AF	VTE	Thromboprophylaxis	Total
mITT	1	5	7	13
ITT	4	5	2	11
Not specified	0	0	5	5

Table 1. Phase III RCTs for direct oral anticoagulants by indication

	Population	Study drug	Comparator	Primary outcome	Conclusion
VENOUS THROMBOEMBOLISM					
RE-COVER	DVT or PE	Dabigatran	Warfarin	Symptomatic recurrent VTE or related death	Non-inferior
EINSTEIN-DVT	DVT without PE	Ruvaroxaban	Enoxaparin then Warfarin	Symptomatic recurrent VTE or related death	Non-inferior
EINSTEIN-EXT	DVT or PE treated for 6-12 months	Rivaroxaban	Placebo	Symptomatic recurrent VTE or related death	Superior
EINSTEIN-PE	PE	Rivaroxaban	Enoxaparin then Warfarin	Symptomatic recurrent VTE or related death	Non-inferior
AMPLIFY	DVT or PE	Apixaban	Enoxaparin then Warfarin	Symptomatic recurrent VTE or related death	Non-inferior
AMPLIFY-EXT	DVT or PE treated for 6 to 12 months	Apixaban	Placebo	Symptomatic recurrent VTE or death from any cause	Superior
Hokusai-VTE	DVT or PE	Edoxaban	Warfarin	Symptomatic recurrent VTE or related death	Non-inferior
RE-MEDY	DVT or PE treated 3 to 12 months	Dabigatran	Warfarin	Symptomatic recurrent VTE or related death	Non-inferior
RE-SONATE	DVT or PE treated 6 to 18 months	Dabigatran	Placebo	Symptomatic recurrent VTE, related or unexplained death	Superior
RE-COVER II	DVT or PE	Dabigatran	Warfarin	Symptomatic recurrent VTE or related death	Non-inferior
ATRIAL FIBRILLATION					
RE-LY	AF and increased risk of stroke	Dabigatran	Warfarin	Stroke or systemic embolism	Superior
AVERROES	AF with increased risk for stroke for (vitamin K antagonist therapy was unsuitable)	Apixaban	Aspirin	Stroke or systemic embolism	Superior
ARISTOTLE	AF and increased risk of stroke	Apixaban	Warfarin	Stroke or systemic embolism	Superior
ROCKET AF	Nonvalvular AF with CHADS score ≥ 2	Rivaroxaban	Warfarin	Stroke or systemic embolism	Non-inferior
ENGAGE AF-TIMI 48	AF with CHADS score ≥ 2	Edoxaban	Warfarin	Stroke or systemic embolism	Non-inferior

SURGICAL THROMBOPROPHYLAXIS					
RE-MODEL	Primary elective unilateral total knee replacement	Dabigatran	Enoxaparin	VTE (venographic or symptomatic) or death	Non-inferior
RE-NOVATE	Primary elective unilateral total hip replacement	Dabigatran	Enoxaparin	VTE (venographic or symptomatic DVT or symptomatic PE) and mortality	Non-inferior
RECORD1	Elective total hip arthroplasty	Rivaroxaban	Enoxaparin	VTE (venographic or symptomatic DVT or symptomatic PE) and mortality	Superior
RECORD2	Elective total hip arthroplasty	Rivaroxaban	Enoxaparin	VTE (venographic or symptomatic DVT or symptomatic PE) and mortality	Superior
RECORD3	Total knee arthroplasty	Rivaroxaban	Enoxaparin	VTE (venographic or symptomatic DVT or symptomatic PE) and mortality	Superior
RECORD4	Total knee arthroplasty	Rivaroxaban	Enoxaparin	VTE (venographic or symptomatic DVT or symptomatic PE) and mortality	Superior
RE-MOBILIZE	Unilateral total knee arthroplasty	Dabigatran	Enoxaparin	VTE (venographic or symptomatic DVT or symptomatic PE) and mortality	Non-inferiority criteria not met
ADVANCE-1	Total knee replacement	Apixaban	Enoxaparin	VTE (venographic or symptomatic DVT or symptomatic PE) and mortality	Non-inferiority criteria not met
ADVANCE-2	Total knee replacement	Apixaban	Enoxaparin	VTE (venographic or symptomatic DVT or symptomatic PE) and mortality	Superior
ADVANCE-3	Elective total hip replacement	Apixaban	Enoxaparin	VTE (venographic or symptomatic DVT or symptomatic PE) and mortality	Superior
RE-NOVATE II	Primary, unilateral, elective total hip arthroplasty	Dabigatran	Enoxaparin	VTE (venographic or symptomatic DVT or symptomatic PE) and mortality	Non-inferior
STARS E-3	Unilateral total knee arthroplasty (Japan and Taiwan)	Edoxaban	Enoxaparin	Asymptomatic or symptomatic DVT or symptomatic PE	Superior
MEDICAL THROMBOPROPHYLAXIS					
ADOPT	Medically ill with high risk of VTE	Apixaban	Enoxaparin	VTE (venographic or symptomatic DVT or symptomatic PE) or related death	Not superior
MAGELLAN	Hospitalized for acute medical illness and reduced mobility	Rivaroxaban	Enoxaparin	Asymptomatic DVT or symptomatic VTE	Superior

Table 2a. Reporting of analysis and reasons for patient exclusion for atrial fibrillation and VTE studies

Name	Author reported analysis type	Randomized participants	Analyzed participants	**Percentage used in analysis**	Reasons for exclusions
VENOUS THROMBOEMBOLISM					
RE-COVER	mITT	2564	2539	**99.02**	Did not receive any study medication
EINSTEIN-DVT	ITT	3449	3449	**100**	
EINSTEIN-EXT	ITT	1197	1196	**99.92**	Invalid Informed consent
EINSTEIN-PE	ITT	4833	4832	**99.98**	
AMPLIFY	ITT	5400	5244	**97.11**	Did not receive study medication, withdrew consent, loss to follow-up, absent source documentation
AMPLIFY-EXT	ITT	2486	2482	**99.84**	Lacking source documentation
Hokusai-VTE	mITT	8292	8240	**99.37**	Did not receive any study medication
RE-MEDY	mITT	2866	2855	**99.62**	
RE-SONATE	mITT	1353	1343	**99.26**	
RE-COVER II	mITT	2589	2568	**99.18**	
Total:		**35029**	**34748**	**99.20**	
ATRIAL FIBRILLATION					
RE-LY	ITT	18,113	18,113	**100**	None
AVERROES	ITT	5599	5599	**100**	
ARISTOTLE	ITT	18,201	18,201	**100**	
ROCKET AF	ITT	14264	14171	**99.35**	Violations in Good Clinical Practice guidelines at one site
ENGAGE AF-TIMI 48	mITT	21,105	21,026	**99.63**	Did not receive any study medication
Total:		**77,282**	**77,110**	**99.78**	

Table 2b. Reporting of analysis and reasons for patient exclusion for surgical and medical thromboprophylaxis studies

Name	Author reported analysis type	Randomized participants	Analyzed participants	**Percentage used in analysis**	Reasons for exclusions
SURGICAL THROMPOPROPHYLAXIS					
RE-MODEL	Not mentioned	2101	1541	**73.35**	Venography not performed/inadequate, surgery not performed, and participant did not receive any study medication
RE-NOVATE	mITT	3494	2651	**75.87**	
RECORD1	mITT	4541	3153	**69.43**	Venography not performed/inadequate, inadequate evaluation of efficacy, surgery not performed, participant did not receive study medication
RECORD2	mITT	2509	1733	**69.07**	
RECORD3	mITT	2531	1702	**67.25**	Venography not performed/inadequate, surgery not performed, participant did not receive study medication
RECORD4	mITT	3148	1924	**61.12**	
RE-MOBILIZE	ITT	2615	1896	**72.50**	
ADVANCE-1	Not mentioned	3195	2287	**71.58**	Venography not performed/inadequate, participant did not receive study medication
ADVANCE-2	ITT	3057	1973	**64.54**	
ADVANCE-3	Not mentioned	5407	3866	**71.50**	
RE-NOVATE II	mITT	2055	1577	**76.74**	Venography not performed/inadequate, surgery not performed, participant did not receive study medication
STARS E-3	Full analysis set	716	594	**82.96**	Venography not performed/inadequate, participant did not receive study medication
Total:		**35369**	**21744**	**70.39**	
MEDICAL THROMBOPROPHYLAXIS					
ADOPT	Not specified	6528	4495	**68.86**	Missing or non-analyzable ultrasound, inadequate assessment for symptomatic VTE, and participant did not receive any study medication
MAGELLAN	mITT	8101	6024	**74.36**	Inadequate assessment of VTE, violations of good clinical practice standards
Total :		**14629**	**10519**	**71.91**	

Summary

- **Trials of direct oral anticoagulants in AF and VTE respected the ITT principle.**
- **In thromboprophylaxis trials, around 30% of participants were excluded, associated with non-clinical outcomes**
- **Thromboprophylaxis trials are at risk of selection bias.**
- **Reporting of the analysis strategy in phase III trials of DOACs was often misleading.**

References

- Abraha, I., & Montedori, A. (2010). Modified intention to treat reporting in randomised controlled trials: systematic review. *Bmj, 340*, c2697. doi:10.1136/bmj.c2697
- Eriksson, B. I., Borris, L. C., Friedman, R. J., Haas, S., Huisman, M. V., Kakkar, A. K., . . . Geerts, W. (2008). Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med, 358*(26), 2765-2775. doi:10.1056/NEJMoa0800374
- Hollis, S., & Campbell, F. (1999). What is meant by intention to treat analysis? Survey of published randomised controlled trials. *Bmj, 319*(7211), 670-674.
- Ioannidis, J. P., Evans, S. J., Gotzsche, P. C., O'Neill, R. T., Altman, D. G., Schulz, K., & Moher, D. (2004). Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med, 141*(10), 781-788. Retrieved from Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gotzsche, P. C., Devereaux, P. J., . . . Altman, D. G. (2010). CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol, 63*(8), e1-37. doi:10.1016/j.jclinepi.2010.03.004
- Montedori, A., Bonacini, M. I., Casazza, G., Luchetta, M. L., Duca, P., Cozzolino, F., & Abraha, I. (2011). Modified versus standard intention-to-treat reporting: are there differences in methodological quality, sponsorship, and findings in randomized trials? A cross-sectional study. *Trials, 12*, 58. doi:10.1186/1745-6215-12-58
- Nuesch, E., Trelle, S., Reichenbach, S., Rutjes, A. W., Burgi, E., Scherer, M., . . . Juni, P. (2009). The effects of excluding patients from the analysis in randomised controlled trials: meta-epidemiological study. *Bmj, 339*, b3244. doi:10.1136/bmj.b3244
- Tierney, J. F., & Stewart, L. A. (2005). Investigating patient exclusion bias in meta-analysis. *Int J Epidemiol, 34*(1), 79-87. doi:10.1093/ije/dyh300