Discrepancies between the collection periods for harm and efficacy outcomes within antithrombotic randomized controlled trials: an example of missing outcome data

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Background

- Selecting an inappropriate collection period for harm outcomes may affect the benefit versus risk analysis, particularly if the collection period for efficacy and harm outcomes differs
- Reporting of major bleeding events in the ARISTOTLE trial exemplifies the basis for specifying outcome collection periods. The US Food and Drug Administration's (FDA) review of apixaban illustrates that major bleed events occurred at different time points during the study period **(see Table 1)**. However, only events during the on-treatment period (i.e., 327 events) were reported in the principal journal publication
- Results of a systematic review may be inaccurate if different harm outcome collection periods exist across the included studies. There are currently no recommendations provided regarding the management of these differences
- In trials involving direct oral anticoagulants (DOAC), we noted heterogeneity among the collection periods for capturing harm, which are usually defined as a set number of days after administering the last dose of study drug

Outcomes of Interest

- Randomized controlled trial (RCT) data:
  1) Differences in collection periods for efficacy & harm outcomes
  2) Reporting of collection periods for harm outcomes
- Systematic review (SR) data:
  1) Identification of differences in collection periods between trials
  2) Handling of differences in collection periods between trials

Methods

Design	Qualitative analysis
Databases	MEDLINE, EMBASE, PubMed
Inclusion	- Systematic review evaluating at least one DOAC available in North America - Published in top 10 ranked medical journals by impact factor
Exclusion	- Duplications - Bleeding events not reported as outcome - Review articles - Meta-analyses without a SR component - Systematic review of SRs
Data collection	- Independent duplicate data extraction by two reviewers (50% of SRs, 17% of RCTs) - Discrepancies referred to a 3rd reviewer

	Treatment	Study Period				
		On treatment	PST 3-30 d	PST 31-60 d	PST >60 d	Total
First bleed	Apixaban	327	44	4	21	397
	Warfarin	462	29	8	12	511
Total bleeds	Apixaban	355 (+28)	51 (+7)	9 (+5)	26 (+5)	442 (+48)
	Warfarin	493 (+31)	37 (+8)	10 (+2)	13 (+1)	553 (+42)

Table 1. FDA summary of major bleeding events within the ARISTOTLE study period.
PST = Post treatment period

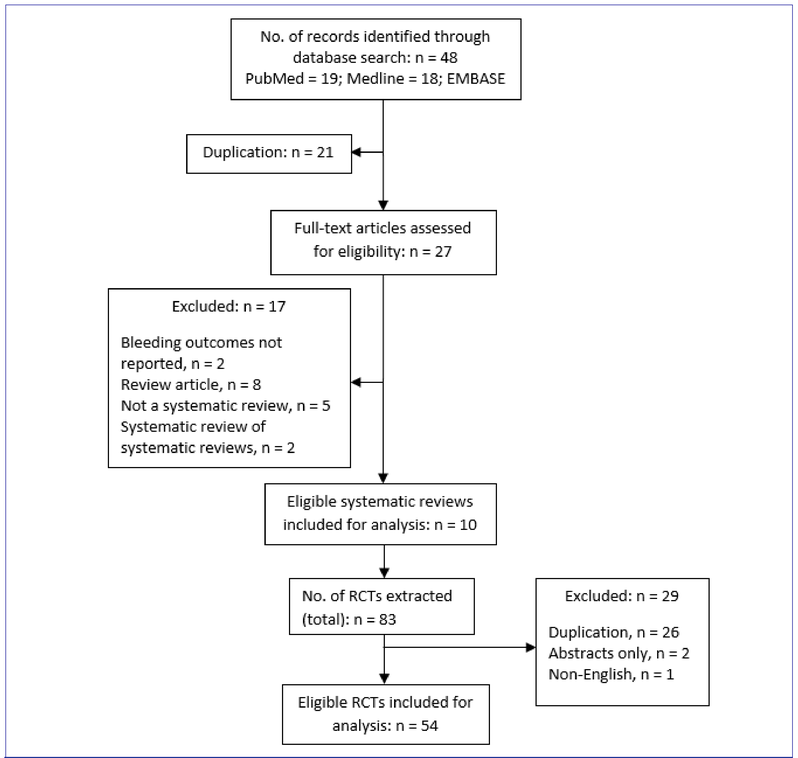


Figure 2. Flow diagram of the study selection process

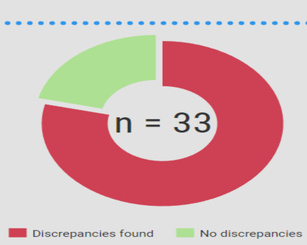
Table 2: Characteristics of Included RCTs

Journal	NEJM 52%, J Thromb Haemost 13%, Thromb Haemost 9%, Circulation 6%, Circulation Journal (Japan) 6%, Other 14%
Intervention	Rivaroxaban 28%, Apixaban 19%, Edoxaban 15%, Dabigatran 11%, Other DOAC 9%, Warfarin/Antiplatelet 18%
Indication	Surgical prophylaxis 35%, VTE prophylaxis 20%, Atrial Fibrillation 19%, VTE treatment 17%, ACS 9%
Funding	Industry funded 89%

Results

We reviewed a total of **54 RCTs & 10 SRs**

74% of RCTs reported safety outcome collection periods



Differences in efficacy and harm collection were identified in **85%** of RCTs

2 in **10** SRs identified differences in collection periods between trials

None discussed the implications of heterogeneous collection periods across trials

Discussion

- We noticed significant variability with respect to the definitions of harm outcome collection periods across trials (e.g., collection window ranged from including events from the first dose of study drug until 1 to 10 days after administration of the last dose)
- Our sample consisting principally of industry funded studies, there may be an opportunity for sponsors to influence the reporting of adverse events by selecting a specific collection period
- Among the sampled SRs, the identification and discussion regarding data collection periods was largely nonexistent. The meta-analysis of major bleeding events captured at various time points introduces heterogeneity and, at a minimum, the implications of this should be discussed
- At the present time, we are unsure if these findings may impact results in a quantitative manner, but we strongly encourage:
  1) Revision of guidelines to standardize collection of trial outcomes
  2) Future SR authors to follow recommendations for reporting harm outcomes to facilitate transparency and provide more confident estimations of risks and benefits for the interventions in question

Conclusions

- Definition of harms collection period is highly variable, generally unexplained, and often differs from the efficacy outcome collection period
- Our findings call for larger, quantitative studies to investigate the degree of impact on overall results by selecting different data collection periods for both efficacy and harm outcomes, and examine the significance of introducing bias to publications

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