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Systematic identification of confounders and co-interventions for three non-randomized studies of interventions (NRSI)

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Abstract

Objectives: To identify potential confounders and co-interventions systematically to optimise control for confounding for three non-randomized studies of interventions (NRSI) designed to quantify bleeding in populations exposed to different dual antiplatelet therapies (DAPT).

Study Design and Setting: Systematic review, interviews and surveys with clinicians. We searched Ovid Medline, Ovid Embase and the Cochrane Library to identify randomised controlled trials and cohort studies of DAPT interventions. Two researchers independently screened citations, identified eligible studies and extracted data. We conducted individual semi structured interviews with 6 cardiologists and 6 cardiac surgeons to elicit factors clinicians consider when they prescribe DAPT. We administered two online surveys to members of professional cardiology and cardiac surgery organisations.

Results: We screened 2544 records, identified 322 eligible studies and extracted data from 47. We identified 10 co-interventions and 70 potential confounders: review 31 (91%); interviews 19 (56%); surveys 31 (91%). 16/34 (47%) were identified by all three methods while 3/34 (9%) were picked up by one method only.

Conclusion: The review identified the majority of factors, but the interviews identified hard-to-measure factors such as perceived patient adherence and local prescribing culture. The methods could, in principle, be widely applied when designing or reviewing NRSI.

Key words: Non-randomized studies of interventions (NRSI), target trial, confounders, dual antiplatelet therapy (DAPT); acute coronary syndrome (ACS); percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG); bleeding; Clinical Practice Research Datalink (CPRD); Hospital Episode Statistics (HES).

What is new?

Key findings

We report a comprehensive approach – systematic review, interviews and surveys with clinicians – to identify potential confounders for three non-randomized studies of interventions (NRSI).

The majority of potential confounders can be identified by systematic review, but some may need to be identified by other methods (e.g. interviews or surveys with clinicians).

A systematic review of confounders may be challenging due to the large number of informative studies and uncertainty about how data should be extracted from different designs.

What this adds to what is known

Systematic methods are required to identify confounders comprehensively when designing NRSI.

Most NRSI do not report on the methods they use to identify confounders that they adjust for in the statistical analysis.

What is the implication and what should change now?

The methods used in this study should be applied more widely when designing NRSI.

Further research is needed to develop guidance for how to extract data on confounders from different study designs and how confounders should be organised into confounding domains.

The relative benefits of this approach compared to data-driven approaches for confounder adjustment (for example, generating empirically-derived covariates using the high-dimnensional propensity score) needs to be carefully considered in NRSI using administrative healthcare databases.

1. Introduction

Confounding is the main criticism of non-randomized studies of interventions (NRSI). It is an important source of bias because it can distort the estimated measure of association between an exposure of interest and an outcome. Although there is guidance available to researchers about how to *select* confounding variables for adjustment, e.g. the use of causal diagrams to define underlying causal relations, statistical confounder selection, etc. [1], there is little guidance about how to *identify* confounders.

We conducted three retrospective, NRSI designed to emulate randomized controlled trials (RCTs), referred to as target trials, to quantify rates and hazard ratios for bleeding in populations prescribed different dual antiplatelet therapy (DAPT) regimens [2]. The populations were: patients undergoing percutaneous coronary intervention (PCI); coronary artery bypass grafting (CABG) and conservatively-managed patients with acute coronary syndrome (ACS). The three target trials were assembled using Clinical Practice Research Datalink (CPRD), a database of primary care electronic health record data, linked with Hospital Episode Statistics (HES), which covers all hospital admissions for all English patients whose treatment is funded by the UK National Health Service (NHS).

We conducted a sub-study, which we report here, to identify potential confounders and co-interventions comprehensively and systematically. We used guidance from the Cochrane Non-Randomized Studies Methods Group [3], which recommends specifying confounders a priori "*independently* " and "*systematically*", "*based on evidence and expert opinion from members of the review team and advisors*". This

recommendation was also endorsed by in the ROBINS-I tool for assessing risk of bias in non-randomized studies of interventions [4,5]

To our knowledge, this is the first attempt to identify and pre-specify potential confounders for a NRSI using systematic methods. In this paper, we report our findings, the challenges of the process and suggest how to improve and refine this process when designing future NRSI.

2. METHODS

2.1. Systematic review

We reasoned that potential confounders were likely to be repeated across multiple studies and study designs, but considered that higher quality study designs would be more likely to report relevant information more comprehensively. We therefore restricted eligibility to cohort studies and randomized controlled trials (RCTs). We included RCTs because authors usually report baseline characteristics of participants from concern that they may be a predictor of the intervention and prognostic for the outcome (but not on the causal pathway from intervention to outcome).

2.1.1. Search methods for identification of studies

The search strategy is shown in the online supplementary material (S1). Search terms included the population (e.g. acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass grafting, etc.), the intervention (e.g. dual antiplatelet therapy, triple therapy, P2Y12 inhibitor, etc.) and a filter for study design (RCT and cohort study). We searched the following electronic databases:

Medline (Ovid) 1950 to 24/08/2016; the Cochrane Library (Issue 7, 2016) and Embase (Ovid) 1970 to 24/08/2016.

2.1.2. Study selection

We included all RCTs/cohort studies (prospective or retrospective) that compared different antiplatelet interventions (or combinations of antiplatelets and anticoagulants) in the three study populations, regardless of intervention duration. One review author (MP) triaged the titles and abstracts identified by the search and obtained the full text of studies identified as relevant to the review. Due to the large number of relevant studies identified, we only included the studies for which full text was available to download electronically (no attempt was made to obtain the full text of studies without online access or unpublished studies). We only considered studies published in English.

2.1.3. Quality assessment

We did not perform a risk of bias assessment because the output of the review is descriptive (i.e. a list of potential confounders and co-interventions) and there are no established criteria for assessing the validity with which primary researchers consider potential confounders and cointerventions. It would have been inappropriate to apply a risk-of-bias tool for studies intended for a different purpose, e.g. estimating a treatment effect.

2.1.4. Data extraction and checking

Data on potential confounders and cointerventions were extracted by two researchers (MP and KM) independently using a data extraction form specifically designed for the study. Variables extracted included study characteristics, population

characteristics (reported in the tables of baseline characteristics), study design (RCT or cohort study), interventions considered, and factors adjusted for in the statistical analyses. We took a broad approach to data extraction and included every factor considered by the authors in the baseline characteristics table of RCTs and all factors adjusted for in the regression models, regardless of whether they were significant or not, for cohort studies.

We used “saturation” as a criterion for discontinuing data extraction, defined as review of full text of 10 consecutive studies without identifying an additional confounder/cointervention. All identified potential confounders were grouped into: demographic factors; medical history; comorbidity; presentation risk factors, biomarkers; procedural risk factors; and other factors (for those that did not fit into these categories).

2.2. Semi-structured interviews with cardiologists and cardiac surgeons

2.2.1. Recruitment and sampling

Six cardiologists and eight cardiac surgeons based in one of four UK regions – Bristol (University Hospitals Bristol NHS Foundation Trust); Gloucestershire (Gloucestershire Hospitals NHS Foundation Trust); Oxford (Oxford Health NHS Foundation Trust); and Cardiff (Cardiff and Vale University Health Board) – were invited to take part in individual, face-to-face or over-the-phone semi-structured interviews. Potential participants were identified using purposive sampling. The participants selected regularly prescribed different DAPT in their professional practice, and practised over a wide geographical area. We aimed to recruit six cardiologists and six cardiac surgeons; this number was considered adequate to reach saturation with regards to the factors likely to be elicited from similar

professionals [6,7]. Potential participants who expressed an interest in the study when approached by study team members were contacted by a qualitative researcher (CP) via email and were provided with a participant information sheet. A suitable date for the interview was arranged if the clinician was still able to participate within the study period. Five interviews were conducted face-to-face and the rest were over the phone. Interviews lasted between 26 and 45 minutes.

2.2.2. Qualitative data collection

Face-to-face or telephone interviews were conducted between June and October 2017. Before each interview, participants signed a consent form (face-to-face), provided oral informed consent or signed and returned the form by post or electronically (telephone). All interviews were audio-recorded.

A clinical vignette-based topic guide was used to guide discussions and elicit clinician prescribing judgements and the range of prescribing decisions when considering different antiplatelet regimens, including if an anticoagulant was also required [8,9]. Four vignettes presenting different clinical scenarios were generated for the interviews (online supplementary material, S2). Participants were asked to comment on whether they would prescribe DAPT for the particular scenario, their choice of antiplatelet regimen and the factors which would influence their decisions. The scenarios did not ask specifically about any co-interventions clinicians would choose to administer with DAPT.

2.2.3. Qualitative data analysis

Interview audio recordings were transcribed verbatim by a professional transcription service. All transcripts were checked for accuracy against the original audio-recordings, anonymized and imported into QSR NVivo 11 data management software to aid data coding and management. Data were analysed using a framework approach [10]. The analysis aimed to identify a detailed list of factors reported by participants to influence their decision to prescribe different antiplatelet agents. Framework matrices were created in NVivo 11 to address specific research questions, e.g. when and why clinicians prescribe DAPT or single antiplatelet agents, and allow for comparisons to be made between and within the two clinician groups in their responses on codes of interest. The factors identified were then matched to the factors identified by the systematic review by two members of the research team independently (MP and CP).

2.3. Surveys with clinicians

2.3.1. Survey development

We developed two online surveys, one for cardiologists and one for cardiac surgeons, based on factors that influence prescribing decisions identified through the systematic review and clinician interviews. Survey respondents were asked to rank the top five factors they take into account when prescribing DAPT. The survey questions were uploaded to SurveyMonkey® and piloted among a small group of cardiologists and cardiac surgeons to ensure ease of use and to test face and content validity. All members of the Society for Cardiothoracic Surgery (cardiac surgeons) and British Cardiovascular Intervention Society (cardiologists) were then invited to complete the survey through their respective societies.

2.3.2. Survey analysis

The data analysis tool in SurveyMonkey and Microsoft Excel (Microsoft, Redmond, WA. USA) were used to calculate descriptive statistics.

2.3.3. Ethical approval

The qualitative study and surveys with clinicians were approved by the South West-Cornwall & Plymouth Research Ethics Committee (17/SW/0092).

2.3.4. Classification of potential confounders

We used the clinical expertise available in the research team to classify the potential confounders identified by all three methods into: predictors of intervention and outcome; predictor of intervention only; predictor of outcome only; and neither predictor of intervention nor outcome. We also specified the expected direction of effect (based on clinical expertise) of each factor on risk of bleeding, i.e. whether the factor increases or decreases risk of bleeding.

3. Results

3.1. Systematic review

We screened 2544 records and identified 322 studies eligible for inclusion. Because of the large number of studies identified we selected a random sample of 70 for initial data extraction. The saturation criterion (no further new factors identified in 10 consecutive studies) was reached after data extraction from 47 studies (16 RCTs and 31 cohort studies) (**Figure 1**). We identified 59 potential confounders (7 demography, 5 medical history, 16 comorbidities, 6 presentation risk (symptoms patients present with at the hospital), 4 risk scores, 7 biochemical markers, 14

procedural risk), shown in **Table 1.** The systematic review also identified 10 co-interventions (medications administered concurrently with DAPT).

3.2. Qualitative study with clinicians

We conducted 12 interviews, six with cardiologists and six with cardiac surgeons (demographic characteristics are shown in Supplementary Table 1). We identified 39 factors that clinicians consider important when prescribing DAPT; 28/39 (72%) were also identified by the systematic review but 11/39 (28%) were not (**Table 1**). This brought the total number of factors identified by both methods to 70. Factors identified through clinician interviews but not identified by the systematic review included commissioning considerations i.e. cost of antiplatelet agents, the use of local/international prescribing guidelines, adherence issues in patients, clinician professional opinion and resistance to antiplatelet agents.

3.3. Survey of clinicians

Seventy-nine cardiologists and 31 cardiac surgeons from across all regions of the UK completed the survey (see online supplementary material). The majority were consultant grade and had practised for more than 5 years. Of the 70 factors identified by systematic review (59) and clinician interviews (11), 59 (84%) were listed in the top five factors by one or more respondents in the clinician surveys (**Table 1**).

3.4. Classification of potential confounders

The classification of the 70 potential confounders is shown in **Table 1.** 34/70 (48.5%) of the factors were classified as factors that influence both DAPT prescribing risk of

bleeding. The systematic review identified most of these, 31/34 (91%), the clinician interviews identified 19/34 (56%) and the clinician surveys identified 31/34 (91%). The systematic review identified 2 factors (6%) not identified by the clinician interviews, while the clinician interviews identified 1 factor (3%) not identified by the literature review or surveys. The overlap between the three methods is shown in **Figure 2**.

Table 1. Classification of 70 potential confounders and 10 co-interventions identified through literature review, clinician interviews and clinician surveys into predictor of intervention and outcome, predictor of intervention, predictor of outcome, or none of these

Factors identified	Source	Predictor of intervention (I) or outcome (O)	Direction of effect for underlying risk of bleeding
Demography (n=7)			
Older age	SR, CI, CS	I, O	↑
Female sex	SR, CS	I, O	↑
Lower body mass index	SR, CI, CS	I, O	↑
South Asian ethnicity	SR	I, O	↑
Smoker	SR, CS	I	-
Lower educational level	SR	None	-
Family history of IHD	SR	None	-
Medical history (n=5)			
Previous MI	SR, CI, CS	I	-
Previous CABG or PCI	SR, CI, CS	I	-
Previous bleeding	SR, CI, CS	I, O	↑
Dyspnoea	SR, CI	None	-
Recent surgery	SR, CS	I, O	↑
Comorbidity (n=16)			
Ischaemic heart disease	SR, CI, CS	I	-
Diabetes	SR, CI, CS	I, O	-
Hypertension	SR, CI, CS	I, O	↑
Hypercholesterolaemia	SR	I	-
Peripheral vascular disease	SR, CI, CS	I	-
Stroke or TIA	SR, CI, CS	I, O	↑
Heart failure	SR, CS	I, O	↑
Peptic ulcer disease	SR, CS	I, O	↑
Chronic kidney disease	SR, CI, CS	I, O	↑
Cancer	SR, CS	I, O	↑
Haematological disorder	SR, CS	I, O	↑
AF/thrombosis/valve disease requiring warfarin or NOAC	SR, CI, CS	I, O	↑
Anaemia	SR, CI, CS	I, O	↑
Lung disease (e.g. COPD, asthma)	SR	None	-
Liver disease (e.g. cirrhosis)	SR, CI, CS	I, O	↑
Gout	SR	None	-
Presentation risk (n=6)*			
ACS risk scores	SR, CI, CS	I, O	↑
LV impairment	SR, CI, CS	I, O	↑
Cardiogenic shock	SR, CS	I, O	↑
Killip class	SR, CS	I, O	↑
ECG	SR, CI	I	-
Median HR	SR	None	-
Ischaemic/bleeding risk scores (n=4)*			
SYNTAX	SR, CI, CS	I	-
CRUSADE	SR, CI, CS	I, O	↑

Factors identified	Source	Predictor of intervention (I) or outcome (O)	Direction of effect for underlying risk of bleeding
HASBLED	SR, CI, CS	I, O	↑
CHADS2VASC	SR, CI	None	-
Biochemical marker (proxies of disease) (n=7)*			
Troponin (ACS)	SR, CI, CS	I, O	↑
Glucose or HbA1c (diabetes)	SR, CS	I, O	↑
Creatinine or GFR (kidney disease)	SR, CS	I, O	↑
Hb or haematocrit (anaemia)	SR, CS	I, O	↑
Platelet count	SR, CI, CS	I, O	↑
CRP or ESR (inflammation)	SR, CS	O	↑
Leucocytes (infection, malignancy)	SR	None	-
Procedural risk (PCI) (n=14)*			
IABP use	SR, CS	I, O	↑
Total ischaemic time	SR	None	-
Clopidogrel loading dose	SR	O	↑
GpII/IIIa inhibitor use	SR	I, O	↑
Radial access site	SR	O	↑
Method of arterial haemostasis	SR, CS	I	-
Type of stent used (BMS vs Stent)	SR, CI	None	-
Length of stented segment	SR, CI, CS	I	
Stent failure	SR, CI, CS	I	-
TIMI flow pre/post procedure	SR	None	-
Multivessel PCI	SR, CI, CS	I	-
Native vs graft PCI	SR, CS	I	-
Infarct related characteristics (no reflow/reduced TIMI flow/MVO)	SR, CS	I	-
Coronary complication (perforation, dissection)	SR, CS	I, O	↑
Other (n=11)*			
Drug potency	CI	I, O	↑
Drug allergies	CI, CS	I	-
Resistance to antiplatelet agents**	CI, CS	I, O	↓
Adherence to clinical guidelines	CI, CS	None	-
Commissioning and organisation budget policy	CI	I	-
Local DAPT prescribing culture	CI	I	-
Multidisciplinary team (MDT) opinion	CI	I	
Adherence-related factors	CI, CS	I, O	↓
Patient views and preferences	CI	I	-
Individual clinician professional opinion	CI	I	-
Conflicts of interest and pharmaceutical company influence	CI	I	
Co-interventions (n=10)			
Statin	SR	None	-
Beta-blocker	SR	None	-
ACE-I	SR	None	-
Calcium channel blocker	SR	None	-

Factors identified	Source	Predictor of intervention (I) or outcome (O)	Direction of effect for underlying risk of bleeding
Diuretic	SR	None	-
RAS-acting agents	SR	None	-
NSAIDS	SR	I, O	↑
Steroids	SR	I, O	↑
Anti-arrhythmic medications	SR	None	-
Proton pump inhibitors	SR	I, O	↑

ACE: angiotensin converting enzyme inhibitors; ACS: acute coronary syndrome; BMS: bare metal stent; CABG: coronary artery bypass grafting; $CHAD_2DS_2$-VASc: Congestive heart failure, Hypertension, Age, Diabetes, previous Stroke/transient ischemic attack, Vascular disease history; CI: clinician interviews; COPD: chronic obstructive pulmonary disease; CI: clinician interviews; CS: clinician survey; CRP: C reactive protein; CRUSADE: ; CS: clinician survey; DAPT: dual antiplatelet therapy; ECG: electrocardiogram; ESR: erythrocyte sedimentation rate; GFR: glomerular filtration rate; Gp: glycoprotein; HAS-BLED: Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage; HbA1C: haemoglobin A1C; HR: heart rate; IABP: intra-aortic balloon pump; IHD: ischaemic heart disease; LV: left ventricular; MDT: multi-disciplinary team; MI: myocardial infarction; MVO: microvascular obstruction; NOAC: novel oral anticoagulant; NSAIDS: non-steroidal anti-inflammatory drugs; PCI: percutaneous coronary intervention PPI: proton pump inhibitors; RAS: renin angiotensin system; SYNTAX: SYNergy between PCI with TAXus and Cardiac Surgery; SR: systematic literature review; TIA: transient ischaemic attack; TIMI: thrombolysis in myocardial infarction.

* No data available in either Clinical Practice Research Datalink (CPRD) or Hospital Episode Statistics (HES) to characterise the factors.

** Failure of the antiplatelet (most commonly clopidogrel) to achieve its effect because the patient's genetic make-up prevents them from metabolising the drug.

4. Discussion

We identified 70 potential confounders and 10 co-interventions by systematic review, clinician interview and clinician survey. Of these, we classified just under half (34) as factors influencing both DAPT prescribing and risk of bleeding. The systematic review identified most of these (31). Our study highlights that in populations for which a large body of evidence exists a literature review alone may be sufficient to identify potential confounders. The clinician interviews identified hard-to-measure factors such as patient adherence and resistance to certain antiplatelet agents; these factors are unlikely to be characterised in routinely collected data and would therefore represent unmeasured confounding. Some of these factors may also influence eligibility criteria in RCTs and lead to the exclusion of certain patients (e.g. those deemed unlikely to comply with medication regimen, those with drug allergies or resistance to antiplatelets). We were unable to weigh up whether identification of such factors justifies the additional research effort required for the interviews, particularly since such factors might be identified within a research team which includes clinicians with the relevant expertise.

We used standard propensity score methods (inverse probability treatment weights) [11] in our analysis to adjust for confounding in our analysis of the target trials. Most of the potential confounders are captured with reasonable accuracy in our datasets (CPRD and HES), for example, comorbidities identified using clinical codes have been subject to extensive validation by other researchers.[12] We did not attempt to select true confounders on the basis of a causal understanding of underlying mechanisms or considerations of clinician behaviour, mainly because we do not have full knowledge of the structure of the causal diagram that relates all covariates

to each other and to the DAPT prescription and risk of bleeding. Therefore, we cannot be certain that the 34 covariates selected as influencing both DAPT prescribing and risk of bleeding would be sufficient to control for bias due to confounding [13] in our target trials.

We did not attempt to classify the factors into confounding domains [4,14] i.e. domains that can be characterised by measuring one or more of a range of our identified variables. Such an approach is logical and could reduce the number of covariates used for statistical adjustment, given that many of these will be highly correlated. For example, bleeding risk could, in theory, be identified from several factors: previous bleed; increasing age; presence of anaemia; biomarkers such as haemoglobin, haematocrit and platelet count, etc. Similarly, co-morbidities can be captured as such, e.g. presence/absence of diabetes or kidney disease) or inferred from biomarkers (e.g. glucose or haemoglobin A1c reflect diabetes status; creatinine and glomerular filtration rate reflect kidney disease, etc.). However, the relative importance of each variable within the bleeding risk domain with respect to bias due to confounding and the extent to which each variable is a valid and reliable measure of bleeding risk is unknown.

Reliance on the literature only to identify potential confounders may be problematic for target trials with safety endpoints (such as bleeding in our study). In our review, most of the studies used for data extraction had DAPT efficacy endpoints as the primary outcome (e.g. major adverse cardiovascular events, or MACE) and very few studies (<5%) were designed with bleeding as the primary outcome. In this instance, the inclusion of clinician interviews and surveys alongside the literature reviews confirmed that similar risk factors influenced both ischaemic and bleeding risk.

However, it may not always be the case that the same factors influence efficacy and safety endpoints. This highlights the likely importance of identifying potential confounders from multiple sources.

There is currently no guidance for how to extract data on potential confounders using literature review, given the variety of study designs potentially eligible for inclusion (e.g. RCTs, prospective/retrospective cohort studies/registries, some descriptive and some NRSI, prognostic/risk prediction studies, etc.). Non-randomized studies often do not justify their rationale for statistical adjustment [15]. Given these issues and the lack of guidance, we took a broad approach to data extraction and included all factors considered by the authors in their study reports. We also included only RCTs and cohort studies published in the English language, chose a random sample from the retrieved articles for data extraction and used a saturation criterion. We did not apply the saturation criterion separately for RCTs and cohort studies. It is unclear whether this represents the best methodology for identifying potential confounders from a literature review given that there are no studies with which we can compare ours to in the literature. Another limitation of our review is that the search was conducted in 2016, therefore it is possible that a more recent search would have identified additional potential confounders given the large body of literature in this area.

All the studies from which we extracted data included only cardiology populations. There are few RCTs or cohort studies investigating DAPT regimens in cardiac surgery populations; none of these were included in our randomly generated list for data extraction. Cardiac surgery patients have the same underlying disease and

therefore should have the same risk factors for bleeding. The clinician interviews showed that the factors influencing the decision-making process identified by the clinician interviews were similar between cardiac surgeons and cardiologists.

Identifying potential confounders in the way that we did is resource-intensive. The research team requires broad expertise, including clinical, epidemiological, qualitative methods, and survey design. Resources are an important consideration when deciding whether to use the methods we adopted given that the main output is a judgement about the risk of bias from unmeasured confounding (i.e. too much effort for little return, since it does not change the conclusion of the study). In our study, we had no data to characterise half of all potential confounders identified.

The potential confounders we identified could be used in future observational studies in the same populations, for example, studies planning prospective data collection and studies assembling retrospective datasets. It also provides reliable information as to the variables we would need to collect to allow us to perform a formal quantitative bias analysis [16]. Nevertheless, our approach for identifying and controlling for confounding needs to be carefully weighed against other methods of controlling for confounding. Automated data-driven approaches such as high-dimensional propensity score (hdPS) methods are gaining popularity and are increasingly being used in pharmacoepidemiology research using administrative healthcare databases [17]. The hdPS algorithms are widely available and relatively easy to use. Such data-driven approaches, although not perfect, have greater efficiency and allow more rapid analysis of large administrative databases and may therefore be more appropriate for studies using routinely collected data.

5. Conclusion

In summary, we present an example of an approach to systematically identify a comprehensive list of potential confounders and co-interventions that influence DAPT prescribing and/or bleeding outcome for potential inclusion in propensity score models. The factors identified from the literature and interviews may vary by research question but these methods could be applied more widely when designing NRSI. The challenges to conducting the review included the large number of studies identified and uncertainty about the data to extract from different designs. Researchers should weigh out the relative advantages of using resource-intensive methods such as the one we present in this study against more efficient automated data-driven approaches which may be more suitable for studies using routinely collected data.

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Supplementary data

Supplementary data to this article can be found online.

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Conflict of interest

Tom Johnson has received honoraria or consultation fees from Abbott, Bayer AG, Biosensors, Boston Scientific, Medtronic, Terumo and Vascular Perspectives; received grants/research support from AstraZeneca and Bayer; and participates in a company sponsored speaker's bureau for Abbott. The other authors have no conflicts of interest to declare.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Figure 1. PRISMA flow diagram

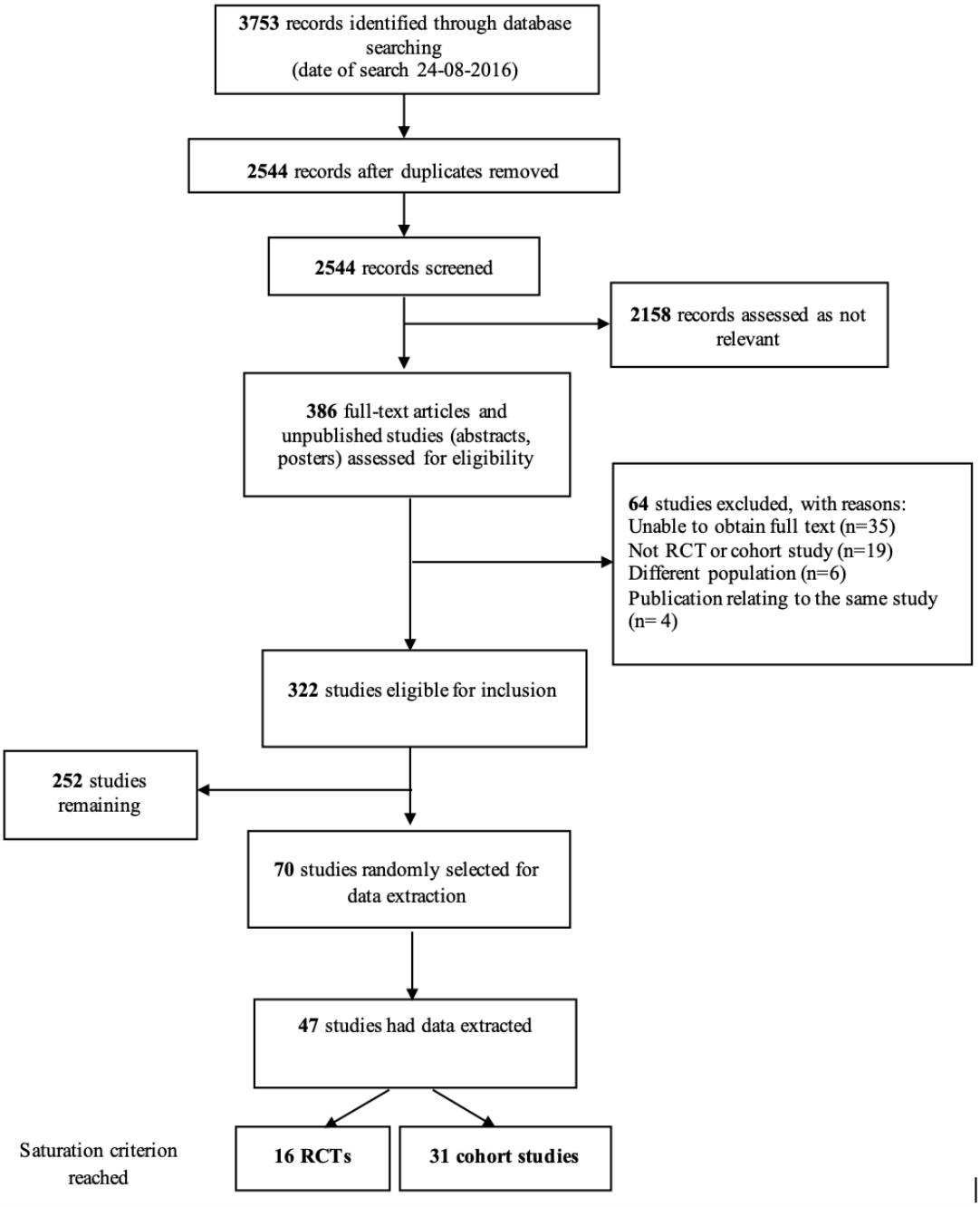

Figure 2. Overlap of 34 factors (not including co-interventions) that influence both intervention and outcome between those identified by systematic review (SR), clinician survey (CS) and clinician interviews (CI).