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REVIEW ARTICLE

Towards better reporting of the proportion of days covered method in cardiovascular medication adherence: A scoping review and new tool TEN-SPIDERS

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Although medication adherence is commonly measured in electronic datasets using the proportion of days covered (PDC), no standardized approach is used to calculate and report this measure. We conducted a scoping review to understand the approaches taken to calculate and report the PDC for cardiovascular medicines to develop improved guidance for researchers using this measure. After prespecifying methods in a registered protocol, we searched Ovid Medline, Embase, Scopus, CINAHL Plus and grey literature (1 July 2012 to 14 December 2020) for articles containing the terms "proportion of days covered" and "cardiovascular medicine", or synonyms and subject headings. Of the 523 articles identified, 316 were reviewed in full and 76 were included (93% observational studies; 47% from the USA; 2 grey literature articles). In 45 articles (59%), the PDC was measured from the first dispensing/

claim date. Good adherence was defined as 80% PDC in 61 articles, 56% of which contained a rationale for selecting this threshold. The following parameters, important for deriving the PDC, were often not reported/unclear: switching (53%), early refills (45%), in-hospital supplies (45%), presupply (28%) and survival (7%). Of the 46 articles where dosing information was unavailable, 59% reported how doses were imputed. To improve the transparent and systematic reporting of the PDC, we propose the TEN-SPIDERS tool, covering the following PDC parameters: **T**hreshold, **E**ligibility criteria, **N**umerator and denominator, **S**urvival, **P**resupply, **I**n-hospital supplies, **D**osing, **E**arly **R**efills, and **S**witching. Use of this tool will standardize reporting of the PDC to facilitate reliable comparisons of medication adherence estimates between studies.

KEYWORDS
cardiovascular disease, drug utilization, medication adherence, methods, pharmacoepidemiology, scoping review

1 | INTRODUCTION

Suboptimal adherence to cardiovascular medicines is reported to contribute to increased readmissions for vascular events, greater healthcare costs and mortality.[1,2] However, health professionals often report difficulty in recognizing suboptimal medication adherence in everyday practice,[3] highlighting the need for enhanced methods for monitoring medication adherence in patients. The recent expansion in the availability of administrative data on patient-level prescription/dispensing of medicines has provided opportunities to measure medication adherence from a population-level more objectively than traditional self-reported methods.[4] However, differences in the measurement approaches used to assess adherence to cardiovascular medicines from a population-level has led to widespread variability in adherence estimates reported in the literature.[5–7]

The proportion of days covered (PDC) is widely used to assess medication adherence using administrative data during the implementation phase (i.e. between medication initiation and discontinuation).[8] The PDC is defined broadly as the proportion (or percentage) of days that an individual has access to medication during a specified observation period, based on the fill dates and days' supply for each dispensing.[7] In the conventional approach of the PDC, the denominator is the number of days between the first prescription fill date and a defined end date, while the numerator is the number of days covered by the prescription fills during the denominator period.[9] This adherence measure is reported to be more precise than the medication possession ratio because overlapping supplies of medications are excluded.[7] Hence, the PDC is endorsed by various organizations and authors as the preferred method to measure adherence using administrative drug data.[10–12]

Currently, there remains no agreed-upon or standardized method for calculating and reporting the PDC, including how to approach more complex medication-related issues such as medication presupply (i.e. existing medication supplies), early refills (i.e. stockpiling) and switching (i.e. changing drugs within the same pharmacological class). Guidelines such as EMERGE[13] and RECORD-PE[14] have been developed to improve the consistency and systematic reporting of studies of pharmacoepidemiology. The TEOS framework[15] also proposes practical guidelines including operational definitions for computing adherence. Within these guidelines, specific recommendations for calculating and reporting the PDC are lacking. We conducted a scoping review to understand the approaches taken to calculate and report the PDC for cardiovascular medicines to develop improved guidance for researchers using this measure in the future.

2 | METHODS

2.1 | Working group establishment

In October 2020, a collaborative working group was established comprising doctors, pharmacists, pharmacoepidemiologists, statisticians and researchers involved in medication adherence research across 6 countries (Australia, Canada, UK, USA, Singapore, Switzerland). This working group met on 4 occasions (via teleconference and email) throughout the project to develop the protocol, finalize the search strategy, interpret the results and develop the reporting tool.

2.2 | Protocol development

The methods used for this scoping review were specified in advance in a protocol registered in the Open Science Framework on 7 December 2020.[16] The protocol was developed with input from members of the working group and was based on published guidelines on preparing scoping review protocols.[17] The subsequent conduct and reporting of this scoping review adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) extension for Scoping Reviews.[18]

2.3 | Search Strategy

A comprehensive search strategy was formulated using the terms "proportion of days covered" (or "percentage of days covered") and "cardiovascular medicine" (including specific drug classes and names) in the title or abstract. Search terms were mapped to Medical Subject Headings (MeSH) or analogous thesaurus subject headings (e.g. Emtree) where possible in each database (the exact search strategy is outlined in Table S1). The search strategy was executed in Ovid Medline, Ovid Embase Classic + Embase, Scopus and CINAHL Plus on 14 December 2020. Articles published before 1 July 2012 were excluded to ensure that our review reflected current research published after the landmark study by Vrijens and colleagues on the ABC taxonomy of medication adherence.[8,13] In this taxonomy, the PDC was first conceptualized as a measure of medication adherence in the *implementation* phase, between medication initiation and discontinuation.

2.3.1 | Inclusion and exclusion criteria

We included all articles meeting the following eligibility criteria:

- Full text published in English between 1 July 2012 and the date of the search
- Study participants were adults who were dispensed ≥1 medicine for long-term prevention/treatment of stroke or cardiovascular disease (i.e. medicine intended for indefinite use and not for acute or short-term treatment)
- Involved the assessment of adherence to cardiovascular medicines using the PDC method
- Included details on how the PDC was calculated

Conference abstracts, case reports, expert opinions, editorials and letters to the editor were excluded as these articles were unlikely to include sufficient details on the PDC method. No other exclusions were made based on study design, sample size, duration of follow-up or country of publication.

2.4 | Article screening

Using the search strategy, 1 reviewer (L.L.D.) independently searched the electronic databases and subsequently imported the retrieved articles into an online review software (Covidence, Melbourne, Australia). Duplicate articles were removed at this stage. Two reviewers (L.L.D. and M.F.K.) screened the titles and abstracts to assess the eligibility of the articles against the inclusion criteria. For abstracts that appeared to meet the inclusion criteria, full-text articles were retrieved and independently assessed by 2 reviewers (L.L.D. and M.F.K.) for suitability of inclusion. A checklist was used by both authors to ensure that the included articles had sufficient details on the PDC method to justify inclusion (Table S2). Disagreements were resolved through discussion and outstanding conflicts resolved with a third author (J.K.). Finally, 1 reviewer (L.L.D.) searched the grey literature to identify additional relevant articles for inclusion. Similar to other authors,[19] this involved snowballing of reference lists and targeted website searches.

2.5 | Data extraction

One reviewer (L.L.D.) extracted data from each article on the article characteristics (year, country, study design, sample size, participant characteristics, medicine[s] investigated and data source), the PDC method (PDC observation period, numerator, denominator and threshold) and the approaches to account for the following PDC parameters: survival, presupply, in-hospital supplies, dosing information, early refill and switching. *Survival* refers to the strategy used to account for individuals who died during the observation period. *Presupply* refers to the strategy used to account for medicines available before the start of the observation period. *In-hospital supplies* refers to the strategy used to account for medications supplied to hospitalized patients. *Dosing information* refers to the strategy used to obtain data on the prescribed daily dose (i.e. the intended medication dose to be taken by patients each day, as prescribed by their provider). This information is required to derive the PDC numerator but is often unavailable in administrative data.[5] *Early refills* refers to the strategy used to account for early refills of the same medication (i.e. medication stockpiling). *Switching* refers to the strategy used to account for switching of medicines within the same therapeutic class (e.g. from simvastatin to atorvastatin). Extracted data were finally checked for accuracy by a researcher external to the authorship group (A.S.; see acknowledgements).

2.6 | Quality assessment

One reviewer (L.L.D.) appraised articles using the Quality Assessment Tool for Quantitative Articles from the Effective Public Healthcare Panacea Project.[20] Each article was assigned a rating between 1 (weak) and 3 (strong) across 6 components: selection bias, article design, confounders, blinding, data collection methods, and withdrawals and dropouts. A global rating of strong was assigned to articles with no weak ratings; moderate to articles with 1 weak rating; and weak to articles with 2 or more weak ratings. A second author (J.K.) audited a random 10% sample of articles to ensure reliability in the assigned quality ratings. Interrater reliability was assessed using the weighted kappa coefficient (κ_w), with values of 0.61–0.80 considered good and values >0.80 very good.[21]

2.7 | Synthesis of results

Due to the high variability of PDC methods reported in the different articles, data from each article were tabulated and narratively

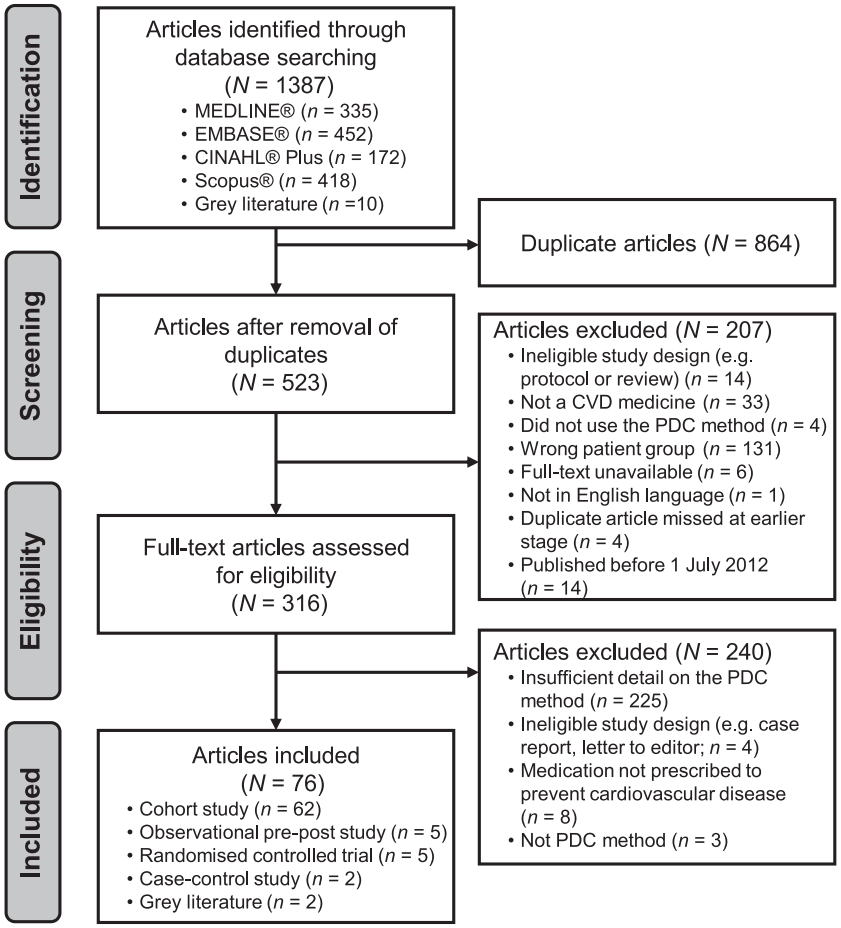

FIGURE 1 PRISMA flow diagram. PDC, proportion of days covered

synthesized. Articles with missing information on PDC parameters were categorized as *not reported* for the given parameter, whereas *no adjustment* was assigned to articles in which authors specifically reported the PDC was calculated without adjustment for the parameter (e.g. due to data being unavailable). Sensitivity analyses were undertaken to determine whether the reporting of PDC parameters differed between articles based on their assigned quality rating. We also assessed whether the reporting of PDC parameters improved following publication of the EMERGE medication adherence reporting guideline in 2018.[13] Differences were assessed using χ^2 tests, with a 2-sided *P*-value of <.05 considered statistically significant. Data were managed and analysed using Microsoft Excel and Stata SE 16.0 (StataCorp, College Station, USA).

2.8 | Development of the PDC reporting tool

To address the second part of our aim, we developed a reporting tool containing a list of important parameters to be disclosed in future medication adherence studies based on the PDC method. This tool was initially based on elements from the checklist used for article screening (Table S2) but was refined further through an iterative review process with members of the working group until a consensus was achieved.

3 | RESULTS

The initial search strategy yielded 523 unique articles (including 10 grey literature articles), of which 316 were assessed in full and 76 (including 2 grey literature articles) were included (Figure 1). Of the 74 scientific articles, 46 (62%) were related to primary prevention.[7,22–66] and 26 (35%) were related to secondary prevention (Table 1).[6,67–93] Lipid-lowering medicines were the most commonly investigated cardiovascular medicine (36%). The majority of the scientific articles were observational studies (93%), conducted in Europe (31%) or the USA (47%), and included ≥10 000 individuals (52%). Additional characteristics of articles is provided in Table S3. The 2 grey literature articles represented technical reports on PDC methods published by USA organizations (Pharmacy Quality Alliance and Centers for Medicare and Medicaid Services). Differences in the PDC approaches and parameters identified in these articles are discussed below.

3.1 | Eligibility criteria for inclusion in sample

The PDC was calculated for individuals who filled 1 or more prescriptions during the observation period in 54 articles (71%), or 2 or more prescriptions in 21 articles (28%). In 1 article, both approaches were

TABLE 1 Characteristics of the included studies

	N = 74[a] *n* (%)
Region of study	
Australia	7 (9)
Asia	4 (5)
Canada	5 (7)
Europe	23 (31)
USA	35 (47)
Year of publication	
2012–2013	5 (7)
2014–2015	17 (23)
2016–2017	21 (28)
2018–2019	18 (24)
2020–2021	13 (18)
Patient population	
Primary prevention (*N* = 46)	
General population	26 (57)
Atrial fibrillation	8 (17)
Hypertension	6 (13)
Diabetes	3 (7)
Dyslipidaemia	1 (2)
Hypertensive subjects with diabetes	1 (2)
Hypertensive subjects with diabetes and dyslipidaemia	1 (2)
Secondary prevention (*N* = 26)	
Acute coronary syndrome	10 (38)
Heart failure	9 (35)
Stroke or transient ischemic attack	5 (19)
Any cardiovascular disease	2 (8)
Primary and secondary prevention (*N* = 2)	2 (100)
Data source	
Administrative data	
Health insurance claims	35 (47)
Government-held dispensing data	33 (45)
Pharmacy-held dispensing data	4 (5)
Structured interviews of individuals or pharmacists	2 (3)
Study design	
Longitudinal observational study	62 (84)
Randomized controlled trial	5 (7)
Pre–post, observational study	5 (7)
Case control study	2 (3)
Medicine(s) investigated	
Lipid-lowering	27 (36)
Combination of cardiovascular medicines[b]	22 (30)
Antihypertensive	12 (16)
Antithrombotic	12 (16)
Anticoagulant	10 (14)
Antiplatelet	2 (3)
Heart failure	1 (1)

(Continues)

TABLE 1 (Continued)

	N = 74[a] *n* (%)
Sample size, median (Q1, Q3)	10 446.5 (2967, 40 632)
<1000	9 (12)
1000–9999	27 (36)
10 000–100 000	30 (41)
100 000+	8 (11)

Q1, 25th percentile; Q3, 75th percentile.
[a]Excludes 2 technical reports identified from the grey literature search as these articles did not contain information on the characteristics of participants.
[b]Combination of antihypertensive, antithrombotic, lipid-lowering, heart failure, heart-rate lowering or vasodilating drug.

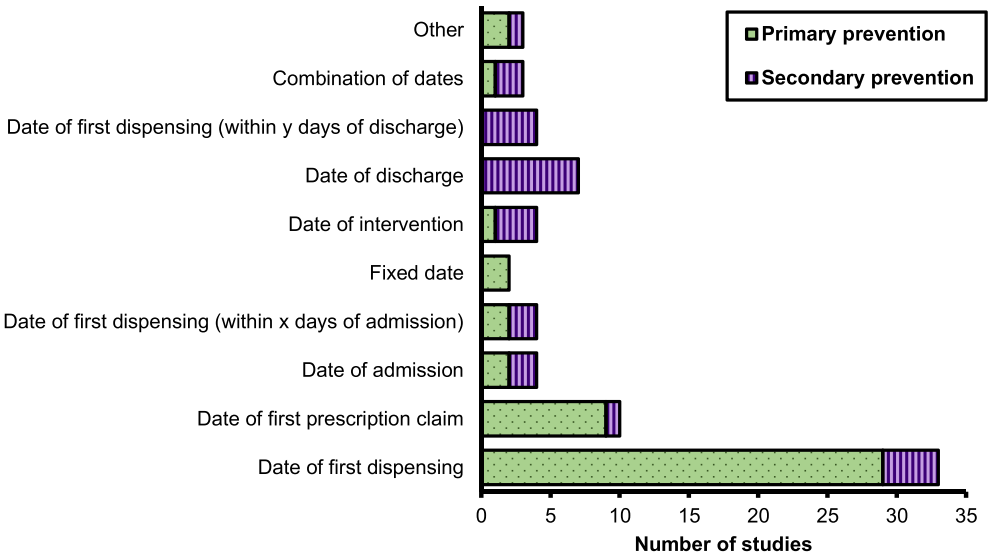

FIGURE 2 Start of the observation period to calculate the proportion of days covered in scientific articles involving the assessment of medication adherence for primary prevention (A) and secondary prevention (B) of cardiovascular disease. Note: x ranged from 30 to 180 days and y from 60 to 90 days. Date of intervention was the date of randomization in randomized controlled trials. Excludes 2 grey literature articles and 2 scientific articles where a primary and secondary prevention cohort was included.

used.[43] Additional criteria were used in 33% of articles (Table S4), such as being prescribed at hospital discharge ($n = 2$), or within 30 ($n = 3$), 60 ($n = 1$), 90 ($n = 4$), 180 ($n = 1$), 270 ($n = 2$), or 365 ($n = 1$) days of the hospitalization. In 5 articles, individuals were only included if 2 supplies of medication were dispensed at least 7–180 days apart.[11,29,44,59,60]

3.2 | Numerator and denominator

The PDC denominator was 1 year in 37 (49%) articles, and between 3 and 11 months in 18 (24%) articles. For an additional 17 (22%) articles, a longer observation period of between 2 and 10 years was used. Whereas, in 4 (5%) articles, the PDC was derived using denominators of 1 year and also <1 year (Table S5). The PDC was most commonly calculated from the first dispensing date in articles of primary prevention, or from the date of hospital discharge in articles of secondary prevention (Figure 2). Other start dates included the intervention date ($n = 4$) or an arbitrary fixed date ($n = 3$).

3.3 | Survival

In 28% of the articles, the PDC was measured in individuals who were insured for the entire observation period as a way of ensuring only survivors were included. Individuals who died during the observation period were excluded from PDC calculations in 24% of the articles (Table 2). Whereas, in 41% of articles, PDC calculations were censored at an individual's date of death.

3.4 | Presupply

Adjustment for presupply was not necessary in 39 articles (51%), which were focused on new users of medication. Of the remaining 37 articles, 21 (28% of all articles) lacked information on whether medication presupply was considered in the PDC numerator. The use of a look-back period to account for medication presupply was used in 9 articles (90-d look-back in 4 articles; 180-d look-back in 1 article; 365-d look-back in 1 article; unknown look-back in 3 articles). Using

TABLE 2 Differences in the reporting and application of proportion of days covered (PDC) methods to determine adherence to cardiovascular medicines among the included scientific and grey literature articles

Parameter of the PDC, approach used by authors	*N* = 76 *n* (%)
Survival (*N* = 76)	
PDC denominator right-censored at the date of death	31 (41)
Limited sample to those with continuous insurance enrolment, a proxy method to exclude deaths	21 (28)
Deaths excluded	18 (24)
No adjustment	1 (1)
Not reported	5 (7)
Presupply (*N* = 76)	
Limited sample to new users	37 (49)
All users initially, but sensitivity analysis among new users	2 (3)
Limited sample to prevalent users	1 (1)
Washout period used to minimize the influence of any presupply	1 (1)
Available presupply carried into the observation period	9 (12)
No adjustment	5 (7)
Not reported	21 (28)
In-hospital supplies (*N* = 76)	
Days spent in hospital excluded from calculation	19 (25)
Days spent in hospital added to numerator	9 (12)
Excluded individuals who were in supported care	3 (4)
PDC denominator right-censored at the first date of re-hospitalization	2 (3)
Excluded individuals who were readmitted	1 (1)
Combination of these methods	4 (5)
No adjustment	4 (5)
Not reported	34 (45)
Dosing information (*N* = 76)	
Available in data	30 (39)
Imputed	
1 unit/d	16 (21)
75th–80th percentile of time taken to refill medications	2 (3)
World Health Organization Defined Daily Dose	1 (1)
Typical dosages	1 (1)
Dose based on the average daily strength per person compared to the entire sample	1 (1)
Combination of these methods	6 (8)
Not reported	19 (25)
Early refills, i.e. stockpiling (*N* = 76)	
Carry-over granted	34 (45)
Carry-over granted, up to a maximum length of time	4 (5)
Combination of these methods	1 (1)
Unclear	6 (8)
No adjustment	3 (4)
Not reported	28 (37)
Switching (*N* = 76)	
Examined a single medicine only	3 (4)
For multiple medicines within a single therapeutic class:	
Carry-over not granted for therapeutic switches	15 (20)
Carry-over granted for therapeutic switches	6 (8)

(Continues)

TABLE 2 (Continued)

Parameter of the PDC, approach used by authors	N = 76 n (%)
PDC denominator right-censored at the date of first therapeutic switch	6 (8)
PDC calculated by drug class and then averaged	3 (4)
Combination of these methods	3 (4)
Unclear	22 (29)
Not reported	18 (24)

PDC, proportion of days covered.

this approach, any unused medication supplies at the start of the observation period contributed to the PDC numerator.

3.5 | In-hospital supplies

Methods to account for in-hospital supplies were not reported in 45% of articles. In the other 55% of articles, exclusion of hospitalized days from both the PDC numerator and denominator was the most common method used to account for in-hospital supplies (25%), whereas, hospitalized days were added to the PDC numerator in 12% of articles, assuming that patients received separate medications while in hospital. Other approaches involved censoring PDC calculations at the first date of hospitalization (3%) or excluding individuals who were readmitted or in supported care (5%).

3.6 | Dosing information

The prescribed daily dose was reported to be available in only 30 (39%) articles. Among the remaining 46 articles, 27 (59%) contained information on the approach used to impute dosing information. In 16 (21%) articles, authors assumed that all medicines were prescribed at a dose of 1 unit per day. Other approaches included using the World Health Organization defined daily dose system (1 article), developing a standardized daily dose using either the average medication strength in the sample (1 article), or percentile of time taken for individuals to return for refills (2 articles).

3.7 | Early refills

Methods to account for early refills of the same medication were reported in 48 (63%) articles. In 34 (45%) articles, overlapping days of supply were carried forward as individuals were assumed to finish any existing medication supply before commencing use of a refill of the same medication. A similar approach was used in 4 articles, whereby a limited number of days were allowed to be carried over. The authors of 3 articles declared that no adjustment was performed for early refills, whereas in another 6 articles, adjustment for early refills was unclear/not reported.

3.8 | Switching

The assessment of adherence to multiple medicines within a single therapeutic class was mentioned in 73 articles. Of these, 15 articles reported that overlapping days of supply for different medicines within the same therapeutic class were disregarded (i.e. carry over was not granted for therapeutic switches). Further, the approach used to account for therapeutic switching was unclear in 22 articles or was not reported in 18 articles.

3.9 | Thresholds

In 3 articles (4%), authors performed analyses to identify the most appropriate threshold(s) to define good adherence based on associations with health outcomes.[66,74,82] Various PDC thresholds between 60 and 84% were shown to be optimally related to all-cause mortality.[66,74,82] Among the remaining 73 articles, 61 (84%) used a threshold of ≥80% PDC to define high adherence and 56% of them included the rationale for selecting this threshold (Figure 3). Reasons for selecting an 80% threshold included that it was consistent with earlier research (27%), reported to improve health outcome(s) (18%) or was recommended by organization(s) (11%). In 8 articles, PDC was treated as a continuous variable, avoiding the use of an arbitrary threshold to define high adherence.

3.10 | Quality assessment

Quality assessment was performed for the 74 scientific articles, of which 24% had a strong global quality rating and 62% had a moderate global quality rating (Table S6).[20] The agreement in quality ratings between the main reviewer and second independent reviewer was good ($\kappa_w = 0.75$; 89% agreement). Articles of strong quality were more likely to contain information on the approach used to handle in-hospital stays in the PDC calculation than articles of lower quality (63 *vs.* 17%; $p = .001$). There were no other differences in the reporting of other PDC parameters by the global quality rating. We were also unable to detect an improvement in the reporting of PDC parameters for articles published after the 2018 EMERGE Reporting Guideline on Medication Adherence.[13]

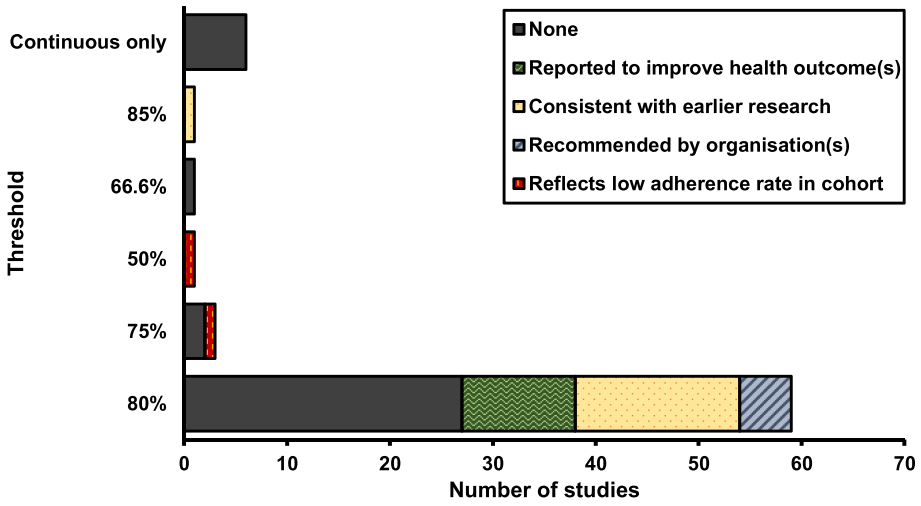

FIGURE 3 Proportion of days covered threshold used to define high adherence to cardiovascular medicine(s) and the corresponding rationale for selecting this threshold. Note: Excludes 2 grey literature articles and 3 scientific articles where data-driven approaches were used to identify the threshold optimally associated with outcome

3.11 | TEN-SPIDERS reporting tool for PDC

After discussing the results with members of the working group, the following parameters were considered as important for calculating and reporting the PDC: **T**hreshold, **E**ligibility criteria, **N**umerator and denominator, **S**urvival, **P**resupply, **I**n-hospital supplies, **D**osing information, **E**arly **R**efills, and **S**witching. Therefore, the TEN-SPIDERS reporting tool (Table 3), an acronym of these parameters with corresponding definitions, was developed to provide authors of future studies with a framework to more comprehensively and systematically report parameters of the PDC.

4 | DISCUSSION

In this comprehensive scoping review, we systematically assessed the various approaches used by researchers to calculate and report the PDC and developed improved guidance for reporting this measure. Despite the PDC being endorsed by authors and organisations,[10–12] we identified widespread variation in the approaches used to calculate this measure in the literature. Inconsistencies were observed in the approaches to account for participant eligibility, survival, presupply, in-hospital supplies, dosing, early refills and switching. Our results highlight the need for standardization of the methods used to calculate and report these PDC parameters to enhance the quality and reliability of this measure when used in pharmacoepidemiology research. We propose the TEN-SPIDERS tool to provide authors of future studies with a structured framework to more comprehensively and systematically report parameters of the PDC. This tool is complimentary to existing reporting guidelines (e.g. EMERGE,[13] RECORD-PE[14] and TEOS[15]) and provides additional guidance for reporting parameters specific to the PDC. By adequately describing these parameters, comparisons of medication adherence will be possible between studies that use equivalent methods of estimating the PDC.

Over the past 15 years, there have been concerted efforts to standardize the methods and terminology for assessing medication adherence using administrative data. One of the earliest proposals for standardization was published in 2007 by members of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Special Interest Group.[94] In this earlier paper, the authors presented a checklist to improve the reporting of studies of medication adherence, but no guidance was provided on reporting parameters underpinning the PDC calculation. In 2012, the European Society for Patient Adherence, Compliance and Persistence (ESPACOMP) published the taxonomy for describing medication adherence across 3 distinct phases: initiation, implementation and discontinuation.[8] Subsequently in 2016, Arnet and colleagues proposed a list of issues that should be clearly addressed in studies of medication adherence including: how the dosing information was obtained, how hospitalizations were considered, how therapeutic switching was handled, why an adherence threshold was selected and whether participants were selected based on a minimum number of filled prescriptions, among others.[95] These parameters are needed for calculating adherence in general and the TEN-SPIDERS tool provides a more specific and structured framework to facilitate better reporting of these essential PDC parameters. More recently, *AdhereR*, a user-written statistical package in *R*, has been developed to allow researchers to derive measures of continuous medication adherence from electronic healthcare databases.[96] A major advantage of using *AdhereR* is the ability to easily modify parameters and produce graphs to visualize the effect on medication adherence. Although *AdhereR* simplifies this calculation and visualization process, it does not specifically address the current gap in the reporting of PDC parameters in the literature. In this sense, our TEN-SPIDERS tool can be seen as a preceding instrument to facilitate the operationalization of parameters before calculating and reporting adherence results.

Despite extensive efforts to standardize methods for measuring adherence using administrative data, our review highlights continued variability in the approaches used to derive the PDC and its parameters. Of particular concern, we noted no improvement in the reporting of PDC parameters after publication of the 2018 EMERGE medication

TABLE 3 TEN-SPIDERS tool to assist with the calculation and reporting of the proportion of days covered (PDC)

	Parameter	Recommendation[a]
T	**Threshold**	• State whether the PDC was analysed as a dichotomous or continuous variable. • If the PDC was dichotomized, provide a rationale for selecting this threshold. • Consider conducting a sensitivity analysis with PDC analysed as a continuous variable, or dichotomized at an alternative cut-off informed from the data, literature or other method.
E	**Eligibility criteria for inclusion in sample**	• Define the eligibility criteria for assessing the PDC, e.g. minimum number of scripts required to be filled within a period.
N	**Numerator and denominator**	• Define the numerator and denominator for the PDC, e.g. The PDC was defined as the total number of days with at least 1 medication available (numerator) in the 1-year period following hospital discharge (denominator).
S	**Survival**	• State whether the PDC was assessed among individuals surviving the entire measurement period or whether the PDC was measured until the date of death for those who died during the observation period.
P	**Presupply**	• State whether analyses were limited to new users or how presupply was handled if previous users of medication were included.
I	**In-hospital supply**	• State whether information on in-hospital medication dispensing was available. • If unavailable, describe how periods of time spent in hospital were handled, e.g. periods where an individual was admitted to hospital were excluded from both the PDC numerator and denominator.
D	**Dosing information**	• State whether dosing information was available in the data or imputed. • If applicable, describe the approach used to impute doses and the validity and/or limitations of this method.
ER	**Early refills**	• Describe how overlapping supplies due to early refills of the same medication (i.e. stockpiling) were handled, e.g. carry-over was granted for early refills of the same drug.
S	**Switching**	• Describe how overlapping supplies of different medications within the same therapeutic class were handled (i.e. therapeutic switches), e.g. carry-over was not granted for therapeutic switches (e.g. switching from simvastatin to atorvastatin).

[a]Authors should describe in the methods and discussion if 1 or more parameters are unavailable (or require imputation).

adherence guideline. While the approaches used to account for survival were reported in most articles, the methods used to account for early refills, switching and in-hospital supplies were reported variably. Differences in these parameters can have significant effects on PDC estimates, highlighting the need for consistent PDC methodology.[6] In particular, authors of only 30% of articles reported they calculated the PDC using actual information on the prescribed daily dose. Unfortunately, the prescribed daily dose may not be available depending on the data source (e.g. unavailable in specific databases in Australia, Ireland and Germany).[97] Thus, researchers often replace it with the defined daily dose published by the World Health Organization or other proxy estimates of dose.[98] A common approach involves imputing a dose of 1 unit per day, which has been shown to be reliable for certain antihypertensive medications.[91] However, this approach is less reliable for drugs with variable dosages such as β blockers and warfarin and induces variability in the calculation with these agents.[99] Given that information on the prescribed daily dose is fundamental for accurately assessing the duration of medication exposure, custodians of administrative databases should consider collecting this information to better support research on medication use and associated outcomes.

In our review, the most common approach used to account for early refills involved allowing carry-over of overlapping supplies of the same medication. This approach has been previously recommended as it is likely to replicate the behaviours of patients in the real-world setting whereby existing medication supplies are finished before commencing use of any refills.[95] For medication switching, the most common method involved disregarding overlapping supplies resulting from use of different medicines within the same therapeutic class during the observation period. This is because therapeutic switching is thought to occur in response to side effects, intolerance, or lack of effectiveness associated with use of the initial medication.[95] The approaches used to account for a lack of information on in-hospital medication dispensing were reported in only half of the articles. Of these, the most common method involved excluding hospitalized days from the PDC numerator and denominator. Evidence from an observational study conducted in Taiwanese patients with myocardial infarction suggests that hospitalizations have a negligible effect on PDC estimates for individuals who spend <28 days of the observation period in the hospital.[72] Alternatively, it can be assumed that patients will continue to receive their usual medications whilst an inpatient, and therefore the time spent in hospital could be added to the numerator in the PDC calculation. Further research is needed to reach an internationally agreed-upon approach for deriving these parameters that underpin the PDC.

Although a PDC threshold of 80% was the most commonly used threshold to define high adherence in our review, few articles included any clinical or empirical rationale for selecting this threshold. In a recent study of 8363 survivors of stroke in Australia, optimal survival benefits were observed at 100% PDC, rather than the commonly cited threshold of 80% PDC.[100] This study involved landmark analysis methods to minimize the potential for reverse causality and immortal time bias.[101] However, it is possible that the observed associations may have been influenced by healthy adherer effects (i.e. people with greater medication adherence may have adopted other healthy behaviours that also improved their survival, such as smoking cessation and a healthy diet). Similarly, in an earlier systematic review on the relationship between adherence measures and clinical outcomes,[102] only 1 study provided evidence in support of the 80% threshold, whilst others suggested that an optimum threshold existed between 46 and 92%. Nevertheless, the cut-off point of adherence is undoubtedly influenced by the disease (e.g. severity and time since the acute event), type of medicine, length of observation and individual characteristics of the patient (e.g. comorbidities and health literacy). Reaching an agreement on standard thresholds for different treatments or diseases would be of great interest and pragmatic.

Similar to the results of an earlier systematic review conducted in patients with heart failure by Krueger *et al*.,[5] we also found differences in the parameters used by authors to calculate medication adherence using the PDC. Although the review by Krueger *et al*. was not specifically focused on the PDC, the authors identified similar inconsistencies in the published approaches for handling early refills, switching, in-hospital supplies and survival. The authors proposed that the following parameters be considered and reported when measuring medication adherence in administrative data: measurement method, observation period, medications, dosing information, switches, early refills, statistical analyses, thresholds, and censoring at death or hospital stays.[5] In addition to these previously reported parameters, we also suggest additional PDC parameters in our TEN-SPIDERS tool including: numerator and denominator, participant eligibility criteria, and medication presupply.

4.1 | Strengths and limitations

There were several strengths of this review including an interdisciplinary working group that provided regular advice to support the interpretations of our results. Second, the search strategy was developed with input from an experienced librarian and was executed in 4 scientific databases to capture a large and diverse range of relevant articles. Third, bias was minimized by enlisting a second reviewer to independently screen the articles, check the extracted data and perform a 10% random audit of the quality assessment. Fourth, although quality assessments are not a mandatory component of scoping reviews, we opted to collect this information to facilitate comparisons of PDC methods based on article quality. Fifth, we also searched the grey literature to maximize the scope of our review and included 2 grey literature articles. Finally, we set the start of the search as 2012 to ensure that the included studies were published after the landmark publication by Vrijens *et al*., which has changed adherence research and adherence reporting.[8,13]

We must, however, acknowledge some limitations of our review. First, as we focused on adherence to cardiovascular medicines in chronic cardiovascular diseases, our findings may not be generalizable to other diseases where medicines are only intended for short-term or intermittent use. However, we expect the findings to be generalizable

to the majority of other chronic diseases that require long-term use of medications similar to cardiovascular diseases. Second, we searched only the English literature and may have missed articles published in other languages. Third and related to language selection, approximately half of the articles were from the USA, where the PDC is commonly used as a quality measure in pharmacies and electronic health records, which may represent a selection bias. Fourth, since executing our search strategy in December 2021, 18 additional articles have been published. However, similar gaps in the reporting of PDC parameters were observed in a brief assessment of these articles. Fifth, we were unable to determine the operationalization of the parameters to derive the most appropriate and accurate PDC estimate. Instead, we provided a summary of the various approaches to the PDC parameters. These parameters may have been purposefully selected by authors based on differences in the study design, research question or data sources available. Further research is required to investigate this area in greater detail.

5 | CONCLUSION

In this systematically performed scoping review, we identified widespread variation in the approaches used to derive and report adherence to cardiovascular medicines using the PDC measure. Specifically, the assumptions underpinning important parameters of the PDC were often inconsistent or unclear between studies, highlighting the urgent need to standardize and operationalize the calculation and reporting of this measure. To assist with this standardization process, we propose the TEN-SPIDERS tool to improve the transparent and systematic reporting of the PDC and its parameters. Adoption of this tool will facilitate more reliable and accurate comparisons of medication adherence between different studies, regions and health systems.

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CONTRIBUTORS

L.L.D. led the review and was responsible for the search strategy, article screening, data extraction, quality assessment and writing the first draft of the manuscript. M.F.K. was responsible for article screening and supervision of the analyses. J.K. was responsible for resolving disagreements during the article screening and for auditing the quality assessment. D.A.C. was responsible for supervision of the review. All authors contributed to the working group, protocol development, interpretation of findings and editing of the manuscript for intellectual content.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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