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LEADING ARTICLE

Impact on Drug Safety of Variation in Adherence: The Need for Routinely Reporting Measures of Dose Intensity in Medication Safety Studies Using Electronic Health Data

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Abstract Randomized controlled trials always report the dose assessed and usually include a measure of adherence. By comparison, observational studies assessing medication safety often fail to report the dose used and rarely report any measure of adherence to therapy. This limits the ability to control for differences in doses used when undertaking meta-analyses. Non-adherence with therapy is common in the practice setting and varies across countries and settings. Inter-country differences in the registration of medicines may also result in different product strengths being available in different countries. These two factors combined means that observational studies undertaken for the same medicine in different settings may be assessing the same medicine but in circumstances where quite different dosages are used. Given that many adverse drug effects are dose dependent, differences in dosages used could be a factor explaining differences in risk estimates observed across studies. We argue that dose intensity, which can be defined as a product of the dose prescribed and adherence to the dose prescribed over the course of treatment, should be routinely reported in observational studies of medication safety. We illustrate the issue with the example of dabigatran. The randomized controlled trial evidence underpinning dabigatran's marketing authorization resulted in uncertainty about the appropriate dose for efficacy versus safety. As a result, different dosages of dabigatran were registered in the USA and Europe. The USA registered the 150- and 75-mg dabigatran products, while the 150- and 110-mg dabigatran products were registered in Europe. Among five observational studies subsequently undertaken to resolve the safety question concerning dabigatran and risk of bleeding, only one stratified results by dose. None of the US studies stratified results by the 75-mg dabigatran dose, despite this dose not being assessed in the original trial. None of the five studies reported adherence measures, despite three separate observational studies finding between 25 and 40 % of patients were non-adherent to dabigatran. The STROBE and RECORD statements should consider adding the requirement for reporting measures of dose intensity and its component products to improve observational study reports.

Key Points

Medication dose intensity, which provides a measure of the dose given, is a function of the dose prescribed and adherence to dose prescribed within a given period of time.

A difference in dose intensity is one factor that can contribute to differences in risk estimates of medication safety across studies.

Medication dose intensity, including its component parts, should be routinely reported in observational studies assessing medication safety.

Adjusting for dose intensity will enable valid comparisons of risk estimates across studies.

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1 Introduction

1.1 Reporting Medication Doses and Adherence Measures in Clinical and Observational Studies

Randomized controlled trials assessing the safety and efficacy of new medicines always report the doses studied and generally include a measure of patient adherence with therapy during the study period. The adherence measure can be considered a process measure for the trial that enables assessment of the extent to which the intended dosage was administered. Knowledge of the extent of adherence by participants in the trial is needed to minimize the risk of bias that can arise when adherence rates differ significantly between patients in the different arms of the trial.

Similarly to randomized controlled trials, observational studies may also be subject to bias due to non-adherence with therapy. This is recognized in guidelines for reporting observational studies, including the US FDA guideline, 'Best Practices for Conducting and Reporting Pharmacoepidemiologic Studies using Electronic Health Care Data' [1]. This guideline highlights the importance of identifying gaps in therapy and determining when gaps are long enough to be a true interruption to therapy. The guideline also highlights the need to correctly ascertain dose from electronic healthcare data, and indicates the need to clearly define how this is achieved. The 'Strengthening reporting of observational studies in epidemiology' (STROBE) statement [2] also highlights the need to clearly define exposure ascertainment. The FDA guideline and STROBE statement do not include any statement about the need for reporting the doses used or adherence to the medicines. Research undertaken to develop the 'Reporting of studies conducted using observational routinely-collected data' (RECORD) statement also does not highlight the issue of reporting the dose used or adherence to the medicine under study [3]. One of the limitations of not reporting the dose used or adherence to the medicines is the lack of ability to control for drug dose in subsequent meta-analyses and systematic reviews [4].

1.2 Dose Intensity as a Measure for Reporting Dose and Adherence

Dose intensity is a measure commonly used in oncology to enable comparisons of chemotherapy regimens [5]. Dose intensity is measured as the amount of drug given within a specified period of time [5]. A second measure, known as relative dose intensity is a measure of the amount of drug delivered as a ratio of the amount of drug planned to be administered [6]. By adapting these measures to observational studies of medicine use, dose intensity can be described as the product of the dosage prescribed and the adherence with the dosage prescribed during treatment periods. In general, this should be reported as an average dosage per day. In drug safety research, dose intensity may influence the strength of association with the outcome or adverse drug effect under assessment because the majority of adverse drug effects are dose dependent [7]. Thus, studies involving subjects where the average dose intensity is low may be less likely to show an association than studies where the average dose intensity is high [4].

1.3 The Influence of Medication Non-Adherence on Outcomes

There is a significant body of literature showing that there are high levels of non-adherence with medicines in many populations [8–10]. Non-adherence with a medicine can be accidental and minimal, for example, the omission of a single dose, or can range to complete non-adherence, such as when patients do not take any of the prescribed medicine. Within a population, the full spectrum of non-adherence from minimal to full is likely to exist. Hyper-adherence is another form of non-adherence, where patients take more than the prescribed dose. The impact of non-adherence with medicines on clinical outcomes may vary by the amount of non-adherence and whether it is predominantly omission or addition of therapy. A meta-analysis of the effect of adherence with any medical treatment on health outcomes demonstrated a 26 % overall risk difference in outcomes between high and low adherence [odds ratio (OR 2.88, 95 % confidence interval (CI) 2.23–3.73] [11]. When limited to studies on medication use, the risk difference was 21 %. The analysis showed the effect was more apparent for chronic diseases where the risk difference was 31 %; however, a risk difference of 20 % was apparent for acute conditions [11]. For many medicines used for preventive purposes, such as medicines used to treat diabetes, hypertension, and hyperlipidemia, long-term adherence and persistence are factors likely to affect outcomes. However, for other conditions, even small levels of non-adherence, or small interruptions to therapy, can reduce medication effectiveness or cause harms or unintended consequences. Examples include the oral anticoagulants [12, 13], medicines for immunosuppression in transplant recipients [14], oral contraceptives [15], and medicines for treatment of human immunodeficiency virus [16, 17].

The majority of pharmacoepidemiological studies assessing adverse drug effects do not report any adherence measures and many neither stratify results by dosage nor report the mean dosages used. We argue that it is time to consider including the need to report measures of dose

intensity in studies, as well as articulate this requirement in guidelines for reporting pharmacoepidemiological studies. The overall measure should be reported, as should its component parts. Wherever possible, stratification by dose prescribed should be reported; however, in circumstances where this is not appropriate, such as where dose is titrated to a surrogate endpoint, mean dose should be reported. The distribution of adherence scores should be also be reported.

To illustrate the issue, we review the reporting of adherence or dose intensity in the observational studies that have assessed adherence with and safety of the oral anticoagulant dabigatran. We chose an oral anticoagulant as the case study because non-adherence with anticoagulants is associated with increased risk of poor outcomes [18], and there are differences in the dose formulations approved across countries [19]. We compare the outcomes from the observational studies with knowledge generated from the randomized controlled trial that underpinned dabigatran's marketing authorization.

2 The Dabigatran Example

2.1 The Randomized Controlled Trial Evidence for Dabigatran Safety and Efficacy Compared with Warfarin

Dabigatran is a novel oral anticoagulant that directly inhibits thrombin. The initial randomized controlled trial evidence that supported dabigatran's market authorization was the RE-LY trial, a multi-center, non-inferiority, randomized controlled trial assessing the efficacy and safety of dabigatran in comparison with warfarin [20]. Two different doses of dabigatran were trialed, 110 and 150 mg, while warfarin was dose adjusted based on results of prothrombin time. Collectively, the study results demonstrated dabigatran was non-inferior to warfarin at doses of 110 mg [hazard ratio (HR) 0.90, 95 % CI 0.74–1.10] and superior to warfarin at doses of 150 mg (HR 0.65, 95 % CI 0.52–0.81) for the primary endpoint of stroke or systemic embolism. With regards to adverse drug effects, major bleeding risk with dabigatran at a dose of 150 mg was similar to that for warfarin (HR 0.93, 95 % CI 0.81–1.07), while there was a lower risk of major bleeding for dabigatran at the 110 mg dose than for warfarin (HR 0.80, 95 % CI 0.69–0.93) [20]. These results are suggestive of a dose-response effect to the adverse drug effect of major bleeding. This dose-response effect was also observed when limiting the analysis of the adverse drug effect to gastrointestinal bleeding. An equivalent risk of gastrointestinal bleeding was observed between dabigatran 110 mg and warfarin (HR 1.10, 95 % CI 0.86–1.41), and a higher risk of gastrointestinal bleeding was observed with dabigatran 150 mg compared with warfarin (HR 1.36, 95 % CI 1.09–1.70) [20].

2.1.1 *The Randomized Controlled Trial Evidence and the Effect of Adherence*

The potential impact that adherence could have on the risk of major bleeding became apparent when the results of the randomized controlled trial were stratified by time in therapeutic range [21]. Time in therapeutic range was measured for the warfarin arm of the trial [21]. A number of factors can influence time in therapeutic range, including adherence, changes in dietary vitamin K intake, inter-current illness, and co-administration of interacting medicines. The results of the trial were stratified by the quartiles observed in the trial for time in therapeutic range: <57.1, 57.1–65.5, 65.5–72.6, and >76.2 % [21]. For the warfarin patients with time in therapeutic range >72.6 % (a potential measure of high adherence), the randomized controlled trial results showed that dabigatran 150 mg was non-inferior to warfarin with regards to stroke or systemic embolism (i.e., the superiority disadvantage disappeared) (HR 0.95, 95 % CI 0.61–1.48). The reduced risk of major bleeding that had been observed at the 110-mg dose of dabigatran for the collective population was no longer evident compared with the warfarin population that had high periods of time in therapeutic range (>72.6 %) (HR 0.90, 95 % CI 0.67–1.21) [21]. When examining risk of

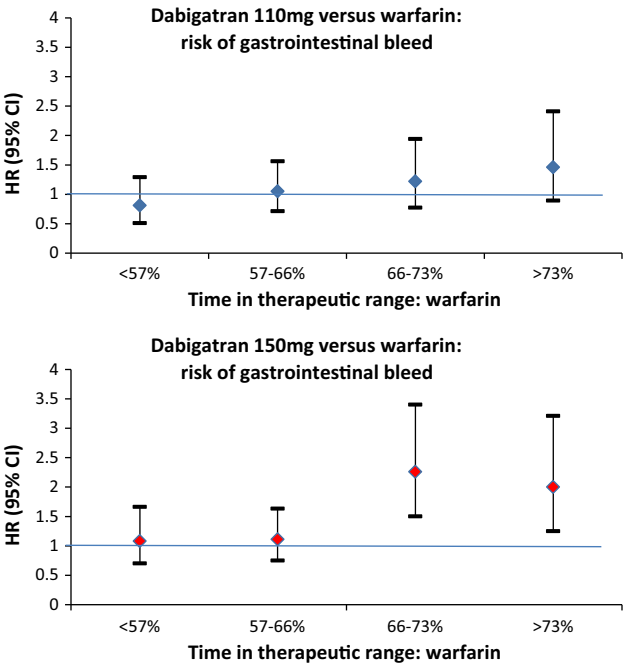

Fig. 1 Risk of gastrointestinal bleed for dabigatran 150 and 110 mg versus warfarin. *CI* confidence interval, *HR* hazard ratio (Source: Wallentin et al. 2010) [21]

gastrointestinal bleeding by time in therapeutic range, the trend in dose response was also apparent (see Fig. 1). One adverse drug effect that remained reduced compared with the warfarin population that had high periods of time in therapeutic range (>72.6 %) was intracranial bleed, the risk of which was reduced with dabigatran 150 mg compared with warfarin (HR 0.39, 95 % CI 0.18–1.54) [21].

2.2 Adherence Differences and the Translation of the Trial Results into Practice

At the time of marketing, concerns were raised about how the RE-LY trial results would translate into practice, as poor adherence to therapy with either dabigatran or warfarin could result in the loss of any therapeutic advantage that one product had over the other [22].

Dabigatran has a dosage schedule of twice daily compared with warfarin's once-daily dosing schedule. Because of the shorter half-life of dabigatran, poor adherence to the twice-daily dabigatran dosage schedule may mitigate any efficacy advantage over warfarin. In addition, a claimed advantage for dabigatran was the lack of a need for monitoring of therapeutic drug levels, a requirement for warfarin that could be a barrier to either initiation or persistence with therapy in some people. However, the requirement for regular monitoring could also provide an opportunity to support adherence to warfarin therapy, and hence the lack of monitoring with dabigatran may result in poorer adherence to dabigatran therapy. Again, if poorer adherence was observed with dabigatran, any efficacy gains would be lost.

Further, the RE-LY trial results demonstrated that the proportion of warfarin patients with time in therapeutic range varied by country, with the mean time in therapeutic range for warfarin as low as 44 % in some countries and up to 77 % in others [21]. Countries where patients on warfarin were in therapeutic range for the majority of time may not realize any therapeutic advantage of dabigatran. Additionally, the trial results demonstrated that patient experience of warfarin use was also a factor in maintaining therapeutic range, with patients naïve to warfarin prior to the study having less time in therapeutic range than patients who had used warfarin previously [21]. Thus, uptake of dabigatran in the warfarin-naïve population compared with the warfarin-experienced population may not yield the same therapeutic advantage.

One additional complicating factor was the response of the USA and European regulators to the trial evidence [19]. Dabigatran was approved at the trial doses of both 110 and 150 mg in Europe; however, in the USA, it was concluded that dabigatran 150 mg was superior to warfarin in all subgroups of patients, thus, the 110-mg dose was not approved [23]. Dabigatran is excreted predominantly via the kidneys, thus, lower dosages are required in patients with renal impairment; for this reason, a dosage of 75 mg was approved in the USA [23]. The 75-mg dose approved in the USA had not been assessed in the clinical trial, thus the clinical efficacy and safety at the 75-mg dose was unknown.

Given the uncertainty about how the clinical trial evidence would translate into practice and the significant potential for patient adherence to influence the results, observational research has focused on assessing adherence to dabigatran or investigating the safety and effectiveness of dabigatran in practice. However, as we highlight in the next section, observational studies of dabigatran's effectiveness and safety do not report adherence levels and do not always report dosages used, all of which have implications for the interpretation of the safety and effectiveness results arising from the observational evidence.

2.3 The Observational Evidence

2.3.1 The Observational Evidence of Adherence with Dabigatran

We identified three retrospective cohort studies that assessed adherence to dabigatran [24–26]. None of these studies included a warfarin arm. Two of the studies demonstrated high rates of adherence to dabigatran, with more than 70 % of patients considered adherent with therapy [25, 26] (Table 1). Consistent with the clinical trial evidence that showed the mean time in therapeutic range for warfarin was as low as 44 % in some countries and varied up to 77 % in others [21], differences in dabigatran adherence rates by site were also evident from the observational evidence [27]. A US study involving 67 sites that had at least 20 patients taking dabigatran reported variation in adherence by site ranging from 42 to 93 % [27]. Median adherence performance by site was 74 %. After adjusting for site and patient characteristics, the variation was still found to be present [27].

Two of the observational studies on adherence with dabigatran reported the proportion of the population receiving the 150-mg dose [25, 26]. The rate was 61 % receiving dabigatran 150 mg in the study from the European country, where both the 110- and the 150-mg doses are available, and higher, at 83.6 % receiving dabigatran 150 mg in the US study, where the 150-mg dosage is recommended for the majority of patients. The higher level of use of dabigatran 150 mg in the USA is consistent with registry data from the USA that found 87 % of dosages of dabigatran were for the 150-mg product [28]. Similarly, the lower level of use of the 150-mg strength in the European study may be reflective of the use of lower doses in countries where the 110-mg strength is available. In

Table 1 Observational studies assessing adherence with dabigatran

Study, country	Study period	Cohort	Measure	Follow-up period	Percent on 150 mg	Mean adherence score (%) (±SD)	Proportion adherent (measure >80 %)
Gorst-Rasmussen et al. 2015 [25], Denmark	August 2011–June 2013	*N* = 2960 Receiving DAB within 30 days of diagnosis of AF	PDC	12 months	61.1	83.9 (±27.7)	76.8 %
Shore et al. 2014 [26], USA	Oct 2010–Sept 2012	*N* = 5376 All pts who filled a DAB prescription of at least 30 days	PDC	12 months	NR	84 (±22)	72.2 % (variation by site 42–93) [27]
Cutler et al. 2014 [24], USA	Jan 2012–Dec 2012	*N* = 159 Pts with AF who filled a DAB prescription	MPR	12 months	83.6 %	63 (±35)	57 %

AF atrial fibrillation, *DAB* dabigatran, *MPR* medication possession ratio, *NR* not reported, *PDC* proportion of days covered, *pts* patients, *SD* standard deviation

Turkey, only 45 % of dabigatran use was for the higher strength [29], and a European survey reported 61 % of dabigatran use in adults was at the 150-mg strength [30].

2.3.2 *The Observational Evidence of Dabigatran Safety and Effectiveness Compared with Warfarin*

We located five observational studies that had assessed risk of gastrointestinal bleeding with dabigatran compared with warfarin in patients who were naïve to both therapies; two of these also reported outcomes for ischemic stroke [31–35]. Uncertainty in the translation of the RE-LY trial to the real-world setting was the rationale underpinning the studies. All of the studies reported outcomes for populations with atrial fibrillation, and these results were extracted for comparison (see Table 2). Four of the studies were based in the USA and one was from Denmark. All studies were retrospective observational studies using electronic health data, and all studies had a new user design. All studies used propensity scores to provide balance across study arms, with two studies using inverse probability of treatment weights (IPTW) and the remaining three studies using matched propensity score designs. All studies provided data to demonstrate how propensity weighting or matching improved covariate balance.

None of the studies reported an average adherence measure or the distribution of adherence scores for participants, despite the observational evidence from separate studies showing between 25 and 40 % could be non-adherent with dabigatran. None of the studies reported time in therapeutic range for subjects receiving warfarin. Only the Danish study stratified results by the dabigatran strength used. None of the US studies reported the proportion of participants receiving the 75-mg dose of dabigatran, nor stratified results by this dose, despite this dose not having been assessed in the clinical trial.

With regards to the outcome of gastrointestinal bleed, two studies reported a significant increased risk of gastrointestinal bleed with dabigatran compared with warfarin, while two studies showed no difference in risk between the two medicines (Table 2). The Danish study, which stratified results by dose, found a lower risk of gastrointestinal bleeding with dabigatran 110 mg than with warfarin and no increased risk with dabigatran 150 mg compared with warfarin (Table 2). With regards to the outcome of ischemic stroke, the Danish study reported no increased effectiveness at dabigatran 150 mg compared with warfarin (HR 1.18, 95 % CI 0.85–1.64) and borderline effectiveness at the 110-mg dose (HR 0.73, 95 % CI 0.53–1) [34]. The mean age of dabigatran users in the Danish study was 67.4 years for the 150-mg dose and 74.7 years for the 110-mg dose. The US study that assessed ischemic stroke found no difference in risk between dabigatran and warfarin users (HR 0.91, 95 % CI 0.81–1.02) [35].

We cannot ascertain the impact of dose intensity, either due to patient non-adherence or due to differential doses prescribed, because these data were not reported in the published studies. However, if there were significant numbers of the population with poor adherence, this would create a bias to the null, and the observational evidence assessing adherence suggests at least a proportion of the population were non-adherent. Similarly, if a significant proportion of the population were receiving the 75-mg dose, this may also create a bias to the null. In the two US studies where increased risk of gastrointestinal bleeding was observed, the dabigatran cohort had higher mean ages than in the US studies where no increased risk was observed (Fig. 2). Given the lack of a 110-mg dose in the

Table 2 Observational studies assessing gastrointestinal bleeding risk with dabigatran compared with warfarin

Study, country	Study period	Cohort	Dose intensity measure	Adherence measure	GI bleeding HR (95 % CI)
Chang et al. 2015 [32], USA New user, propensity weighted	Oct 2010–Mar 2012	4907 DAB 39607 WAR Mean age DAB 62 years	NR	NR	1.21 (0.96–1.53)
Abraham et al. 2015 [31], USA New user, propensity matched	Nov 2010–Sep 2013	7749 matched pairs Mean age DAB 63.1 years	NR	NR	0.79 (0.61–1.03)
Lauffenburger et al. 2015 [35], USA New user, propensity weighted	Oct 2010–Dec 2012	21,070 DAB 43,865 WAR Mean age DAB 67.5 years	NR	NR	1.11 (1.02–1.22)
Hernandez et al. 2015 [33], USA New user, propensity weighted	Oct 2010–Nov 2011	8102 WAR 1302 DAB Mean age DAB 75 years	NR	NR	1.85 (1.64–2.07)
Larsen et al. 2013 [34], Denmark New user, propensity matched	Aug 2009–Dec 2012	2239 DAB 150 mg matched to 3996 WAR 2739 DAB 110 mg matched to 4940 WAR Mean age: DAB 150 mg, 67.4 years; DAB 110 mg, 74.7 years	Stratified by 150 and 110 mg	NR	150 mg: 1.12 (0.67–1.83) 110 mg: 0.60 (0.37–0.93)

CI confidence interval, *DAB* dabigatran, *GI* gastrointestinal, *HR* hazard ratio, *NR* not reported, *WAR* warfarin

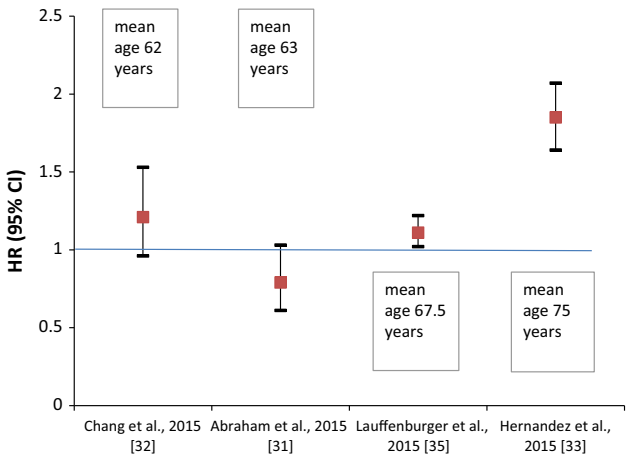

Fig. 2 Risk of gastrointestinal bleeding with dabigatran compared to warfarin users and mean age of study cohort. *CI* confidence interval, *HR* hazard ratio

USA and the higher proportion of use of dabigatran 150 mg in the USA than in Europe, it is possible that the differential effect observed in the US studies is partially attributable to a dose-intensity effect. In the USA, 83 % of people aged ≥80 years are prescribed dabigatran 150 mg [28]; in comparison, only 61 % of the elderly in Europe are prescribed the 150-mg dose [34].

3 The Implications for Medication Safety Research

In this example, we have shown that despite prior knowledge that the dosage of dabigatran used had a differential effect on both safety and efficacy outcomes, none of the published US studies stratified results by the 75-mg dose, a dose that had not been trialed. Only the Danish study stratified results by dosage used. Further, despite prior concerns that patient adherence would be a factor contributing to whether any potential safety or efficacy gains with dabigatran were realized in practice, none of the studies assessing outcomes reported an adherence measure.

There are potential consequences of not reporting dose intensity with observational studies, particularly as the same strength medicines are not necessarily available in all countries. Meta-analyses of medication safety effects without stratification by dose could be biased by the inclusion of studies where dosages differ substantially across studies [4]. For the dabigatran example, pooling data from all studies would provide a result dominated by the US studies, where a higher dose of dabigatran is routinely used compared with Australia and countries in Europe. This may result in over-estimated risks for countries outside the USA where lower doses are more commonly used. International networks to assess drug safety are developing

[36, 37], and it will be increasingly important to report measures of dose and dose intensity so that valid comparisons within and across countries can be made.

Another example of the limitations of not reporting dose in observational studies is found in the observational studies assessing cardiovascular risk with non-steroidal anti-inflammatory agents. Rofecoxib was approved in the USA in a 50-mg formulation; however, countries such as Australia did not register this dose, only registering the 25-mg product. At least 34 observational studies have been undertaken assessing cardiovascular risk from rofecoxib; however, the majority have not reported the dose used [38]. Thus, less than half were able to be pooled in analyses to assess dose response. The dose-response analysis revealed a dose-response effect, with a doubling in risk of adverse cardiovascular outcomes [risk ratio (RR) 2.17, 95 % CI 1.59–2.97] for doses above 25 mg per day compared with a 37 % increased risk for doses of 25 mg per day or less (RR 1.37, 95 % CI 1.20–1.57) [38]. Of the 177 observational studies reported in a meta-analysis assessing cardiovascular risk with non-steroidal anti-inflammatory agents, only one-third were able to be analysed for dose-response effects [38].

4 Conclusion

The lack of reporting of dose intensity in observational studies of medication safety is a lost opportunity for improving medication safety research and limits the ability to control for differential doses when undertaking meta-analyses and systematic reviews. This issue could be easily addressed by requirements to include reporting of dose intensity in guidelines for observational study reporting. In a similar way to the requirement to report the results of propensity adjustment on patient characteristics, which all the studies reviewed in this paper did, the guidelines for reporting medication safety studies from electronic health data should include a requirement to report measures of dose intensity and its component parts. Ideally, the measures would include dose stratification or mean dose, where dose stratification is not possible, and a measure of adherence and the distribution of adherence scores across the study population. As guidelines for reporting results of observational studies from electronic health data are developed, we argue that consideration should be given to including a requirement for reporting dose intensity.

Compliance with Ethical Standards

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Conflict of interest Elizabeth Roughead and Nicole Pratt have no conflicts of interest to declare.

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