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A Comparative Safety Analysis of Medicines Based on the UK Pharmacovigilance and General Practice Prescribing Data in England

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Abstract. *Background/Aim: Adverse drug reactions (ADRs) represent a major concern leading to significant increases in both morbidity and mortality globally. Providing healthcare professionals (HCPs) and patients with real-world data on drug safety is imperative to facilitate informed decision-making. The study aimed to determine the feasibility of creating comparative safety charts for medicines by mapping ADR reporting onto prescribing data. Materials and Methods: Data on serious and fatal ADR reports from the Yellow Card database was mapped onto general practice prescription data in England. The rate of serious and fatal ADR reports per million items prescribed was calculated for commonly-prescribed medicines. Results: Quantitative comparative analyses for 137 medicines belonging to 26 therapeutic classes were conducted. Significant differences were observed within most therapeutic classes for the rate of serious and fatal ADR reports per prescribing unit. Conclusion: Despite the limitations of ADR reporting and prescribing databases, the study provides a proof-of-concept for the feasibility of mapping ADR reporting onto prescribing data to create comparative safety charts that could support evidence-based decision-making around formulary choices.*

All medicines can cause adverse drug reactions (ADRs) leading to increases in both mortality and morbidity and incurring substantial financial costs and a significant burden on healthcare systems worldwide (1-8). The reported prevalence of ADRs in primary care is 8.3%, one fifth of which are preventable (9). Serious ADRs may be life-threatening, resulting in death or hospitalisation and may cause permanent disability or congenital abnormalities (birth defects) (10). These serious ADRs account for up to 30% of all ADRs with many being identified post-marketing (11-13). It has been shown that 30-70% of ADRs resulting in hospitalisation are considered predictable and thereby potentially preventable (11, 14-17).

The detection and quantification of ADRs is a key component of clinical trials prior to approval. While clinical trials are considered the bedrock for assessing drug efficacy, they are less efficient in detecting ADRs, therefore, findings from clinical trials have limited use in extrapolating risks to clinical practice (18-25). Unlike easily-detectable and well-recognised ADRs that are often identified during pre-marketing in clinical trials, rare and late-onset ADRs remain under-detected until the post-marketing stage, during which medicines are used by a more diverse and larger population than initially intended, and for a longer period in normal clinical practice (26-30). Such ADRs are often undetected during clinical trials due to the relatively small number of participants studied (30-33) and the exclusion criteria, which do not usually allow for the frailest patients to participate (34). The limited trial duration and the focus on main outcomes can also hamper the detection of unpredictable (35-37) and relatively-infrequent events (38) that are rarely considered as primary focus and, therefore, may not be accurately diagnosed or reported.

The main method of post-marketing safety surveillance is spontaneous reporting of ADRs (*i.e.*, pharmacovigilance), which remains the cornerstone of safety signal detection systems (39, 40) as the majority of new medicine-related safety signals are prompted through this path (29, 41). The well-established gateway for reporting ADRs in the UK to the Medicines and Healthcare Regulatory Agency (MHRA) is the Yellow Card Scheme (YCS) (42), through which reports of suspected ADRs are submitted on a voluntary basis by both HCPs and patients (43). Nonetheless, pharmaceutical companies have a legal obligation to submit ADRs reports of their products independently.

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Key Words: Drug safety, adverse drug reactions, side effects, pharmacovigilance, spontaneous reporting, yellow card scheme, primary care, shared decision-making, general practice, data linkage.

While pharmacovigilance databases can be used for hypothesis-free data mining of safety reports (44), their use in pharmaco-epidemiological analyses is limited, mainly due to lack of evidence-based approaches or insufficient accessibility to such data. Hence, performing a retrospective analysis of ADR reports that are available in pharmacovigilance databases can be useful (45-47). However, without adjusting for factors, such as the length of time the medicine has been on the market and the number of people taking it, numerical comparisons and definitive conclusions about the risks of medications made solely on ADR reports can be misleading (48, 49). Therefore, to avoid drawing erroneous conclusions, the number of ADR reports should not be used in isolation to determine the incidence of ADRs. Database linkage between data sourced from pharmacovigilance databases and observational data, including prescribing data is desirable (50, 51), so as to help eliminate the shortcomings of separate databases (52). Significant results have been published from such linkage studies (53). Mapping medicine usage data onto outcomes data has the potential to quantify the relative risk that is associated with the different medicines (54).

To determine the feasibility of creating quantitative comparative safety charts by mapping 'exposure' data of the items prescribed onto an 'outcome' data of ADR reports, we performed this pilot investigation, linking serious and fatal ADR reports in YCS to the number of prescriptions in general practice in England. While the 'outcome' data is the number of ADR reports recorded, the difference in the number of items prescribed over the period of (Jan-2016_ Jan-2021) will be accounted for with the 'exposure' data. This linkage study provides simple and up-to-date quantitative comparative safety charts for medicines belonging to the same therapeutic class in a convenient format. Medicines within a particular therapeutic class are often used for the same indication. This makes comparative figures for medicines within the same therapeutic class of paramount relevance to prescribers seeking to assist patients in making informed decisions about their care. The comparative data generated from this project may also help commissioners make evidence-based decisions on formulary choices.

Materials and Methods

ADR reporting data. All UK fatal and serious ADR reports received by the MHRA were manually retrieved for all listed medicines from January 2016 until January 2021 from the Interactive Drug Analysis Profiles (iDAPs) in the MHRA's Yellow Card database (42). The data was extracted into Microsoft Excel Spreadsheet (55). To simplify the presentation of the results, both serious and fatal ADR reports were combined. Since MHRA continuously screens for duplicate reports at the stage of data entry, systematic de-duplication was not conducted before analysis.

Prescription data. General practice prescribing data was retrieved from the "OpenPrescribing" interface (56). This covers prescriptions that are written in England by General Practitioners (GPs) and non-medical prescribers who are linked to GP practices and that are dispensed in the community in the UK. A prescription item refers to a single supply of a medicine written in one prescription form. Prescribing data were manually extracted for each medicine listed and the number of items prescribed for the period from January 2016 to January 2021 was calculated.

Linking ADR reporting data to prescribing data. All medicines available in the MHRA's Yellow Card database were mapped onto prescribing data using the strategy described below.

For medicines with ADR reports falling within the desired period (Jan-2016 to Jan-2021), the number of serious and fatal ADR reports was calculated when prescribing data were available for this period. If prescribing data existed for a particular timeframe where no ADR reports were available, no ADR reports were assumed to have been submitted during this period, counting them as zero. Related prescription data were simultaneously evaluated and the number of items prescribed for the longest period during (Jan-2016_Jan-2021) were also calculated. Medicines with ADR reports but without prescription data during this period were excluded.

Since the number of ADR reports in iDAPs for a multiple constituent medicine represents the total number of reports submitted for its both single and combination formulations (*e.g.*, Co-Tenidone containing Atenolol and Chlortalidone), we included ADR reports and prescriptions only for single constituent medicines as the inclusion of such combination products in the denominator (prescribing data) might slightly reduce the apparent ADR rate.

As the ADR reports in iDAPs for a particular medicine may include reports that originate from secondary care along with the reports from general practice (*e.g.*, Furosemide is available in both oral and intravenous formulations), we excluded ADR reports that are likely to have originated from the use of medicines *via* routes considered inappropriate for general practice (*e.g.*, intravenous formulation).

Medicines were thereafter manually grouped to the therapeutic classifications defined by the British National Formulary (BNF). Medicines that, following classification, fit in more than one category, were "re-classified" based on their prescribing frequency. Clinical judgement was exercised for medicines that could not be unequivocally classified based on the experience of both the prescribing and the clinical practice, for which two clinical researchers were involved. The scope of analyses was then narrowed by including only the most frequently prescribed medicines during the period of interest. Figure 1 illustrates the methodology employed and the exclusion criteria.

Safety profiles for the included medicines were then analysed as per the total number of serious and fatal ADR reports per million items prescribed. Medicines within their therapeutic classes were compared to one another and their relative safety was determined. The concept of 'high-risk medicines' can be used instead of 'high-alert medications' (57). Collectively, we ensured that the most frequently prescribed therapeutic classes in general practice were mapped.

Statistical analyses. The statistical analyses were performed using the software R package (v 4.1.1) 'meta' (58). As the outcomes of the study are rate data that often follow a Poisson distribution, a random intercept Poisson regression model (59) was fitted using the *metarate* function with the argument "GLMM"(generalised linear mixed-effects model), as previously described (60), to meta-analyse the single rates

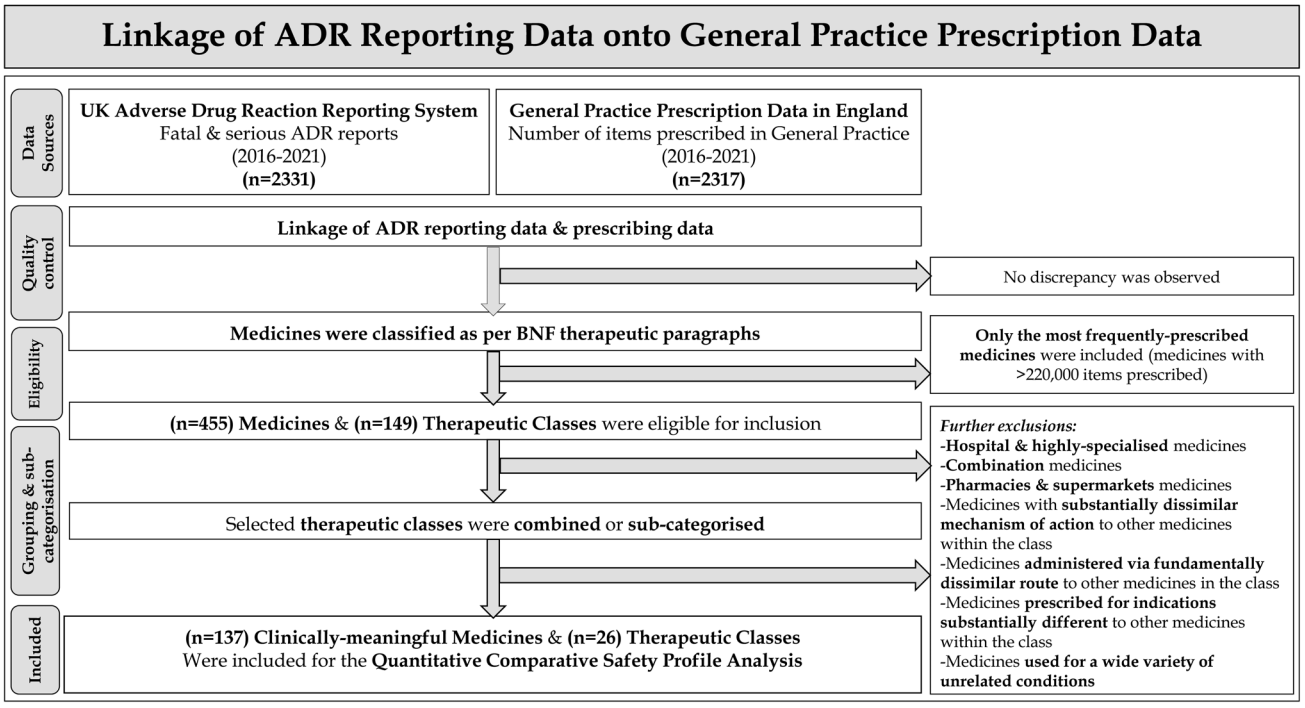


Figure 1. *Study methodology data on serious and fatal ADR reports from the MHRA's Yellow Card database was mapped onto general practice prescription data in England extracted from OpenPrescribing platform for the period January 2016 until January 2021. ADR: Adverse drug reactions; MHRA: Medicines and Healthcare Regulatory Agency.*

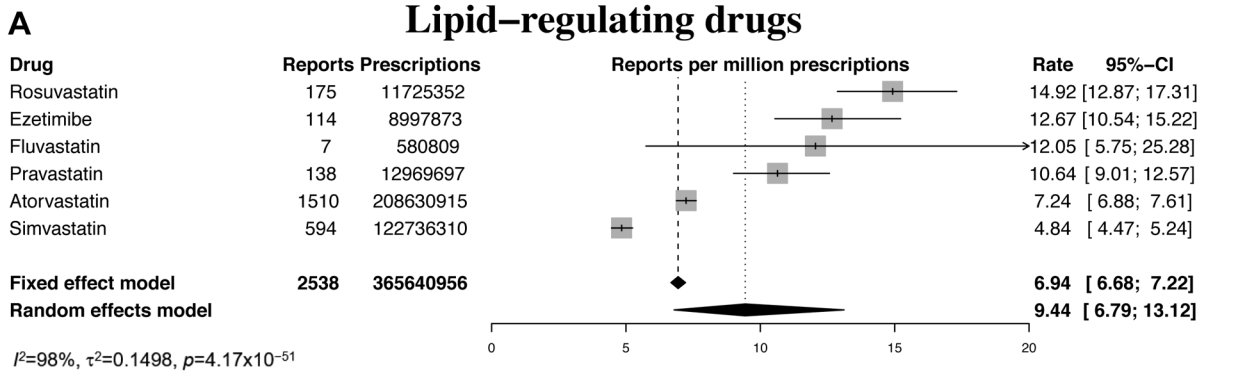
of serious and fatal ADR reports per prescribing unit over the period of interest for the medicines analysed. This approach takes account of the different number prescriptions issued for each medicine over this period. The inclusion of the 'exposure' data of the items prescribed to adjust counts on the 'outcome' data of the ADR reports makes use of the correct probability distributions and, thus, the relative ranking of medicines. Heterogeneity among medicines was evaluated using the I^2 statistic (61), which represents the percentage of total variance across the medicines within a therapeutic class that is explained by between-medicine heterogeneity (based on Q) in terms of the rate of serious and fatal ADR reports per prescribing unit (62). Maximum-likelihood estimator (63) was used for the GLMM to calculate the between-medicines variance τ^2. Forest plots were generated using the same software R package 'meta' to visually summarise the comparative safety profiles for all the medicines included. In the forest plots, we reported I^2, τ^2 and p-value for the Q-statistic.

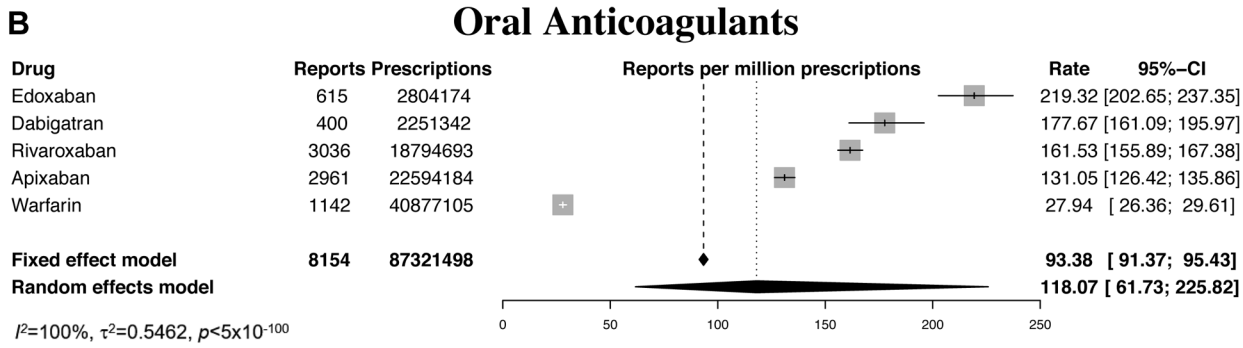
Ethical approval. This is an observational study. The Yellow Card and general practice prescribing databases are non-identifiable and anonymised databases. Institutional review board approval was obtained from the ethics committee of the Medical School of Exeter University (reference 21/01/006).

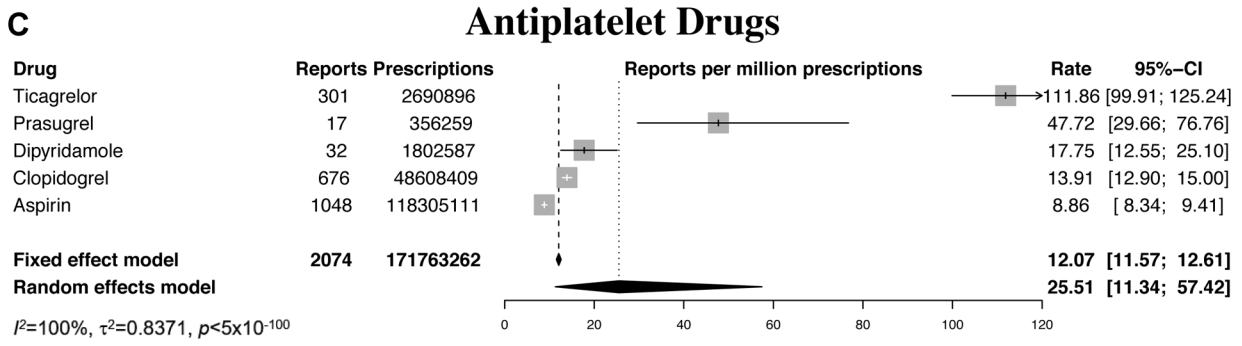
Results

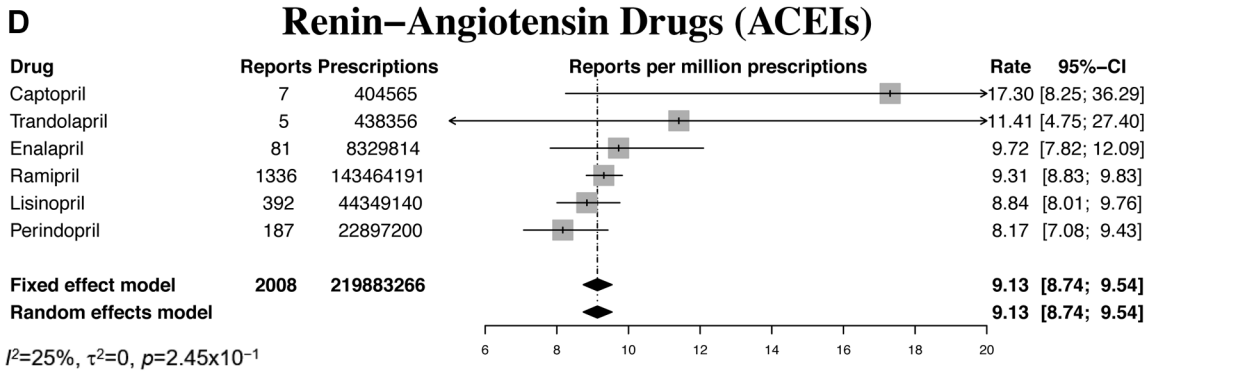
A total of (n=2,331) medicinal products were identified from the iDAPs. A total of 2,317 chemicals belonging to 406 different therapeutic classes, were identified through the OpenPrescribing platform. Having mapped all medicines and narrowed the scope of analyses by including only the most frequently-prescribed medicines during the period January 2016 to January 2021, there were 455 frequently-prescribed medicines belonging to 149 therapeutic classes as per the BNF and with >220,000 items prescribed during this time. After applying other exclusion criteria, the final analysis dataset included 137 medicines belonging to 26 clinically-meaningful therapeutic classes.

Based on the I^2 statistic and the p-value for Q-statistic, the linkage showed significant differences in terms of the rate of serious and fatal ADR reports per million items prescribed among medicines in 23 classes out of the 26 therapeutic classes analysed ($p<0.05$), supporting the use of random-effects model. There were only three classes that showed no significant differences among the medicines analysed, namely: i) angiotensin-converting-enzyme inhibitors, ii) potassium-sparing diuretics and aldosterone antagonists, and iii) drugs for erectile dysfunction. Forest plots summarise the safety profiles for all the medicines included (Figure 2, Figure 3, Figure 4, Figure 5, Figure 6, Figure 7 and Figure 8). Forest plots have the potential to enable informed prescribing decisions by allowing any two medicines within a therapeutic class to be compared directly, by considering whether the confidence intervals overlap. For example, in the lipid-lowering drugs, the









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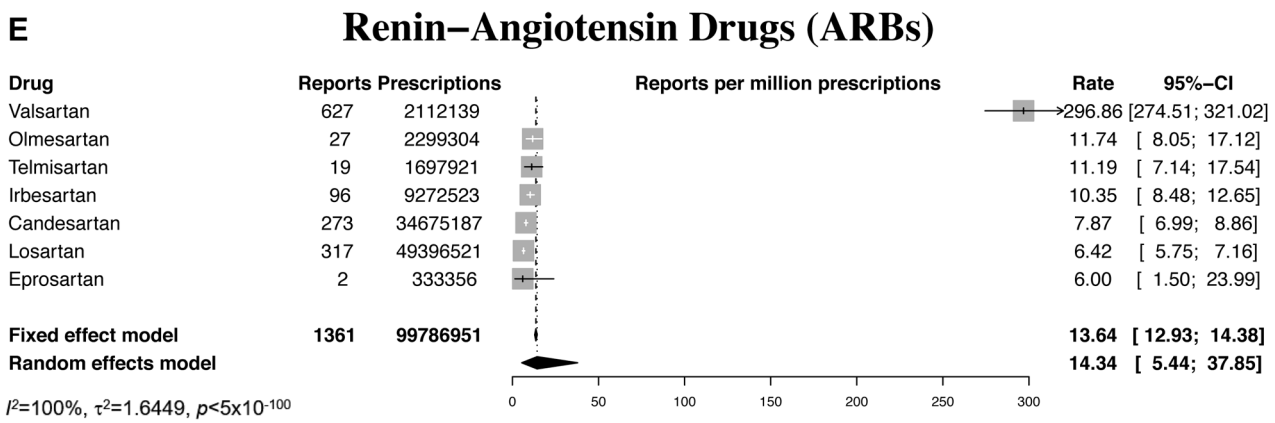

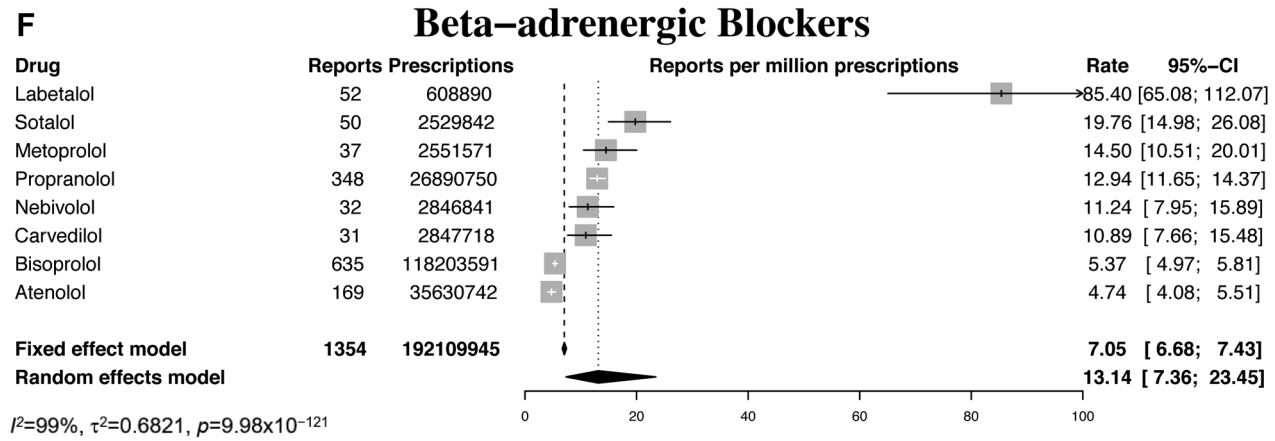

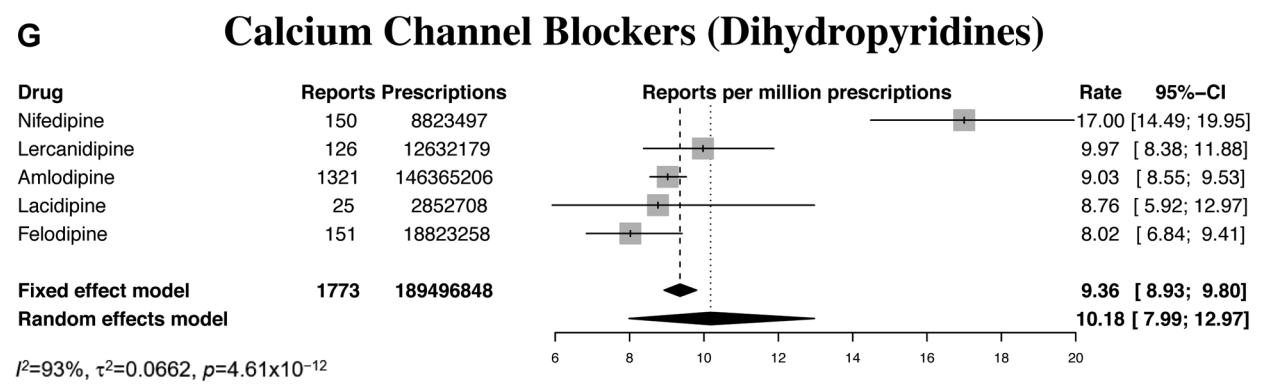

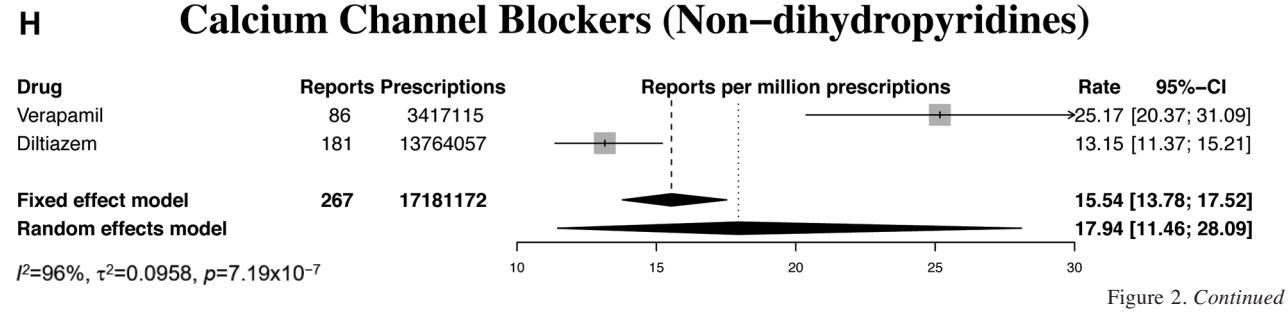

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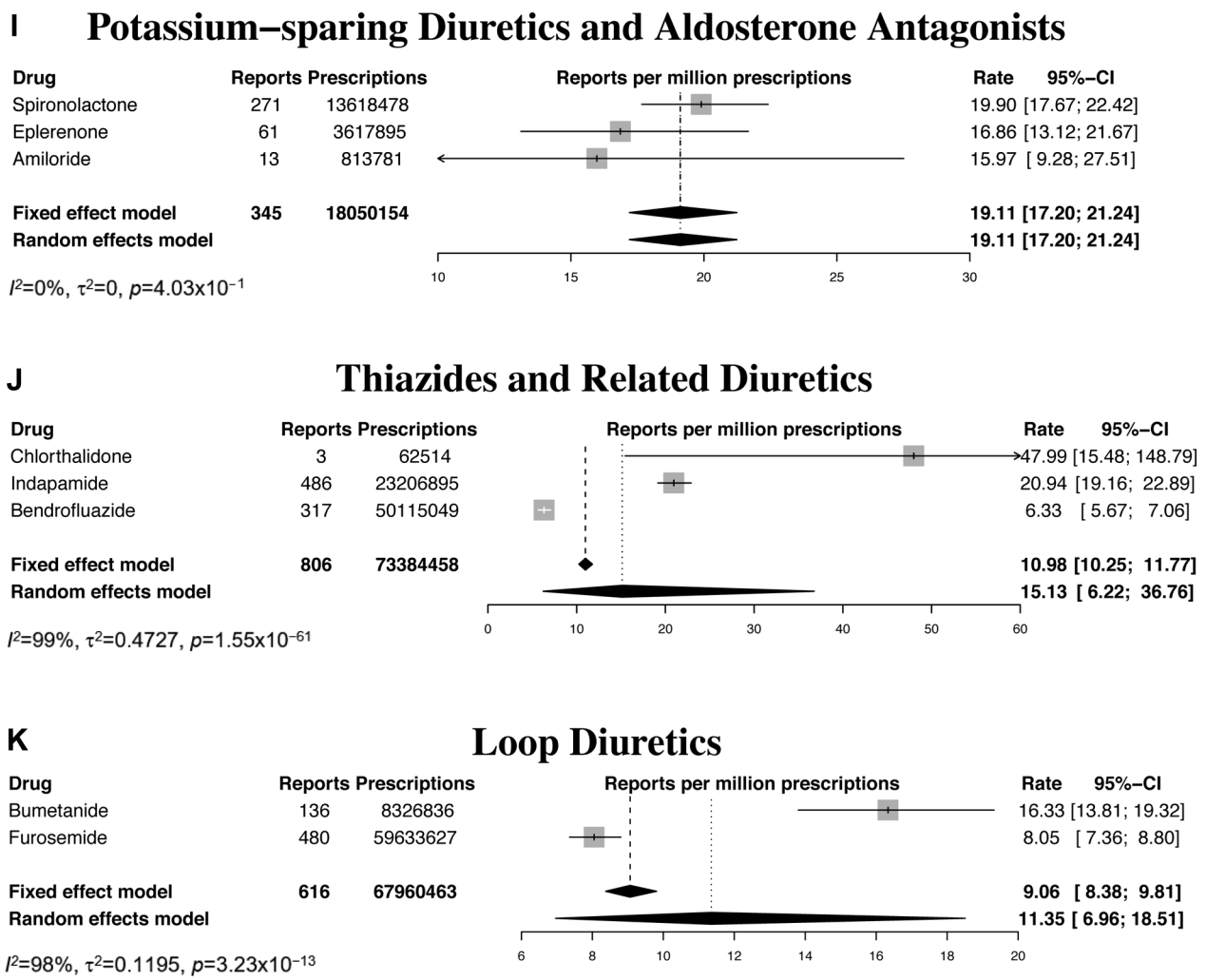


Figure 2. *Cardiovascular system. A) Lipid-regulating drugs, B) Oral anticoagulants, C) Antiplatelet drugs, D) Angiotensin-converting enzyme inhibitors (ACEIs), E) Renin-angiotensin receptor blockers (ARBs), F) Beta-adrenergic Blockers, G) Calcium channel blockers (Dihydropyridines), H) Calcium channel blockers (Non-dihydropyridines), I) Potassium-sparing diuretics and aldosterone antagonists, J) Thiazides and Related Diuretics, K) Loop Diuretics.*

overlapping confidence intervals for Pravastatin and Fluvastatin show that the rates of ADR reports do not significantly differ. In contrast, the confidence intervals for Atorvastatin and Simvastatin do not overlap, thus, demonstrating that Atorvastatin has a significantly higher rate of serious and fatal ADR reports per prescribing unit compared to Simvastatin.

An additional analysis of the time-trends of the number of ADR reports for some commonly prescribed medicines in general practice indicated that older medicines tend to be under-reported as their safety profiles become well-known and predictable (Figure 9).

A separate analysis of the total ADR reports in both the UK's Yellow Card database from inception until September 2020 and the European pharmacovigilance database, known as 'EudraVigilance' from inception until November 2020, was performed. This analysis showed that 72% of all ADR reports in the Yellow Card database and 85% of all ADR reports in EudraVigilance are serious and fatal (Figure 10).

Discussion

The importance of safe and effective prescribing is stressed by both the UK General Medical Council (64) and the General Pharmaceutical Council (65). Access to accurate data on drug safety is crucial for shared decision making in prescriber-patient consultations. Despite this, there are often many similar drug choices for each indication with only a few tools to objectively compare the safety profiles

between different medications. The aim of this study was to determine the feasibility of creating quantitative comparative safety charts for medicines belonging to the same therapeutic class. This was achieved by mapping MHRA's ADRs reporting database onto the NHS England general practice prescribing database. This pilot study successfully generated drug safety ratios for serious and fatal ADR reports of common general practice medicines per million items prescribed.

A previous report analysed ADR reports and prescriptions issued in the UK primary care setting between 2008-2012 (66). However, that report investigated the overall number of prescriptions rather than those of individual medicines and was mainly focused on comparing the proportion of ADRs reported for specific age groups with what is expected from the proportion of primary care prescriptions within each of these groups. The study was also limited by the use of IMS Disease Analyzer to estimate the prescriptions issued in the UK primary care. The IMS Disease Analyzer represents only around 1.7% of the UK general population, and all prescribing figures used there, are, therefore, projected up to estimate the number of prescriptions that reflects the total population of the UK.

Numerous studies and multiple organisations have attempted to identify high-risk medicines (67-71). However, these individual lists of high-risk medicines differ significantly from those in our study as many of them were created with particular focus on medication error reports rather than ADRs (68). Of note, these lists of high-risk medicines were mainly created based on in-patient settings or for particular clinical settings (*e.g.*, acute, ambulatory or long-term care) (70, 72, 73) and, thereby, may differ substantially for different settings (74).

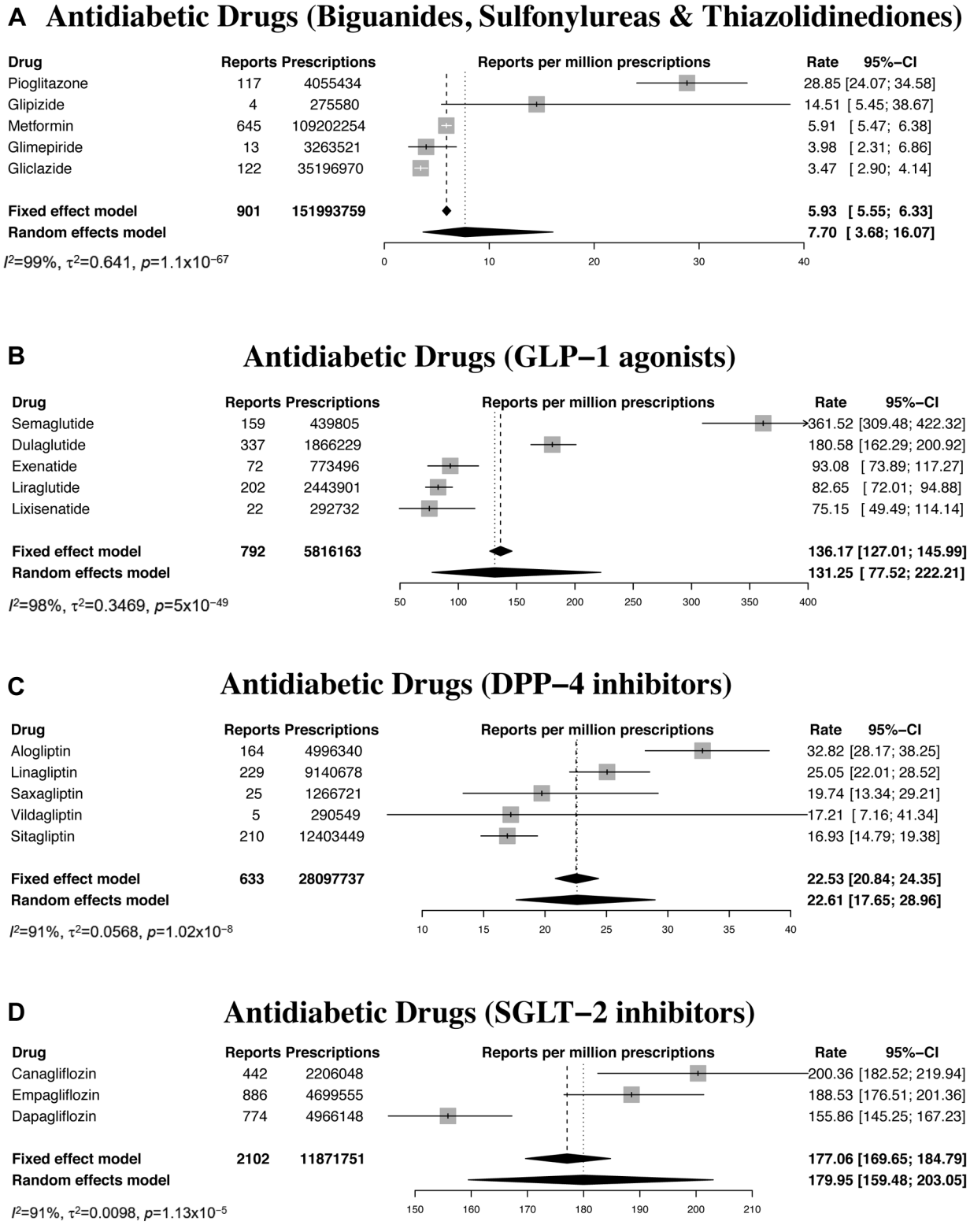
Other tools have been created to identify high-risk medications including Medication Appropriateness Index (MAI) (75, 76), Inappropriate Prescribing in the Elderly Tool (IPET) (77), Screening Tool Alert Doctors to Right Treatment (START) (78), Screening Tool of Older Persons' Prescriptions (STOPP) (79), GerontoNet (80) and Beers criteria. However, these tools were mainly constructed to identify potentially inappropriate medicines (81) and none has the potential to provide clinicians with comparative data for serious ADRs within a therapeutic class. Moreover, most of these tools were developed with a focus on the elderly and in-patient settings, such as including IPET>70 years old patients in hospital, and STOPP and Beers criteria (>65 years old patients) (82, 83). Consequently, most of these tools may not be generalisable to routine clinical practice across different age groups and populations. Furthermore, tools such as STOPP/START tool were primarily created to formalise the process of conducting a medication review (84) from the consensus of experts rather than based on real-time ADR reports (85). There is no robust evidence as yet that these tools can help reduce the incidence of hospitalisations or deaths (86). Other studies investigating medicines most commonly implicated in ADRs and medication errors, have identified similar medicines and therapeutic classes to IPET, STOPP lists and Beers criteria (87-90).

One systematic literature review has attempted to identify medicines involved in serious and fatal medication events (69), but it was focused on medication errors rather than ADRs identified in normal practice within the license for that medicine. A more recent systematic review investigated ADRs in primary care (9), however, its main objectives were to investigate the prevalence and proportion of preventable ADRs rather than identifying high-risk medicines. Although the review identified therapeutic classes most frequently involved in ADRs in primary care, the classes were involved in all types of ADRs rather than the serious ones. Another review of 100 deaths caused by or related to medicines has identified high risk therapeutic classes of drugs (91), however, it has not specified individual medicines or quantified usage as a denominator. These studies are also prone to a publication bias, as serious events are more frequently reported and published in case reports compared to non-serious ones.

Although this data integration study is sufficient to draw robust preliminary conclusions, the comparative charts should be interpreted with caution taking into account the linkage issues and inherent limitations that largely reflect the nature of the ADR reporting and prescribing data used. However, although the study databases have flaws and limitations, they reflect real world data rather than the product of a controlled clinical trial from which findings have limited use in extrapolating risks to normal clinical practice, particularly for late-onset and rare ADRs.

Linkage issues. Although this study demonstrates that linkage of ADR reporting data to prescribing data is feasible, this is not expected to be complete. First, linkage at the individual patient level was not possible as neither pharmacovigilance nor prescribing databases contain unique patient identifiers. This prevented the detailed investigation of circumstances around individual ADRs.

The second linkage issue is that low volume medicines, based on their prescribing frequency, were excluded so as to reduce the dataset size to a manageable level for this pilot project. This might have under-represented some less frequently prescribed yet clinically important general practice medicines that may still have significant ADRs rates. Finally, although we excluded ADR reports related to medicinal forms deemed inappropriate for general practice (*e.g.*, intravenous formulation), we were unable to completely differentiate between ADR reports originated from general practice and secondary care for formulations considered to be appropriate for prescribing in both settings



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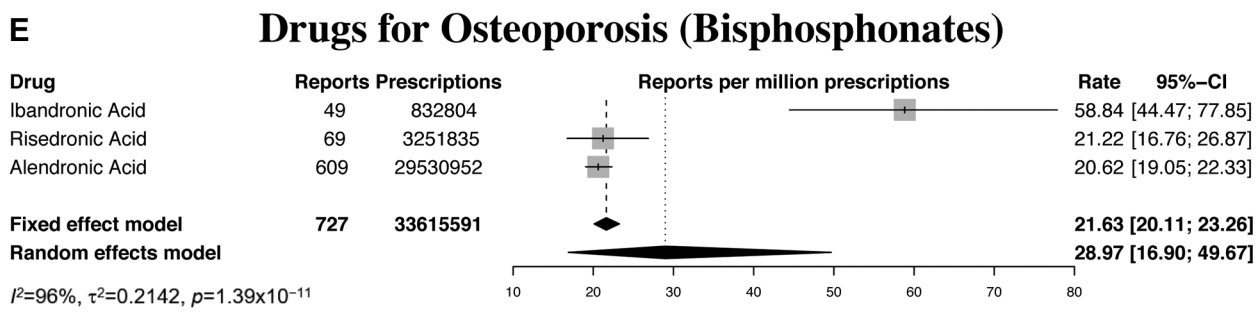


Figure 3. *Endocrine system. A) Antidiabetic drugs (Biguanides, Sulfonylureas and Thiazolidinediones), B) Antidiabetic drugs (GLP-1 agonists), C) Antidiabetic drugs (DPP-4 inhibitors), D) Antidiabetic drugs (SGLT-2 inhibitors), E) Drugs for osteoporosis (Bisphosphonates),*

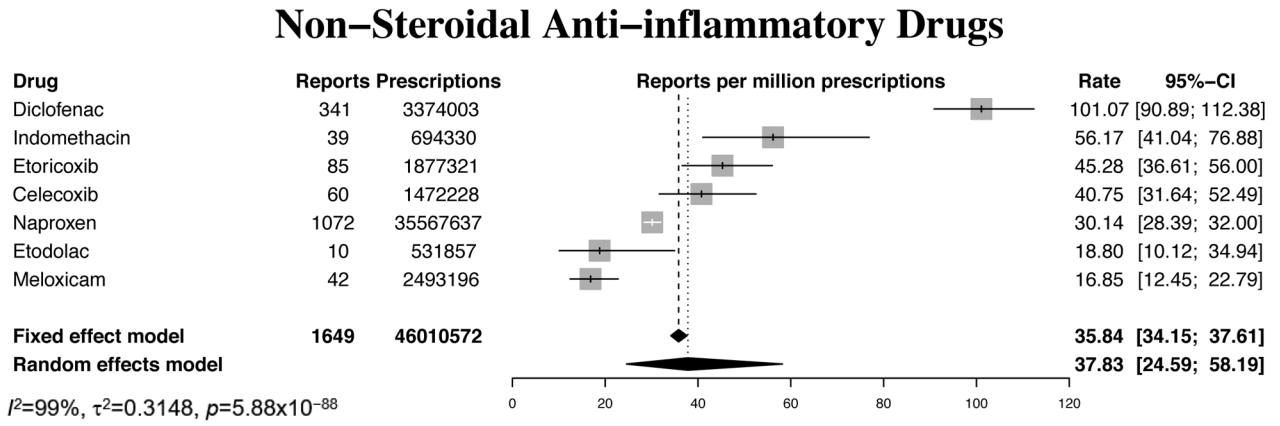


Figure 4. *Musculoskeletal and joint diseases – Non-steroidal anti-inflammatory drugs.*

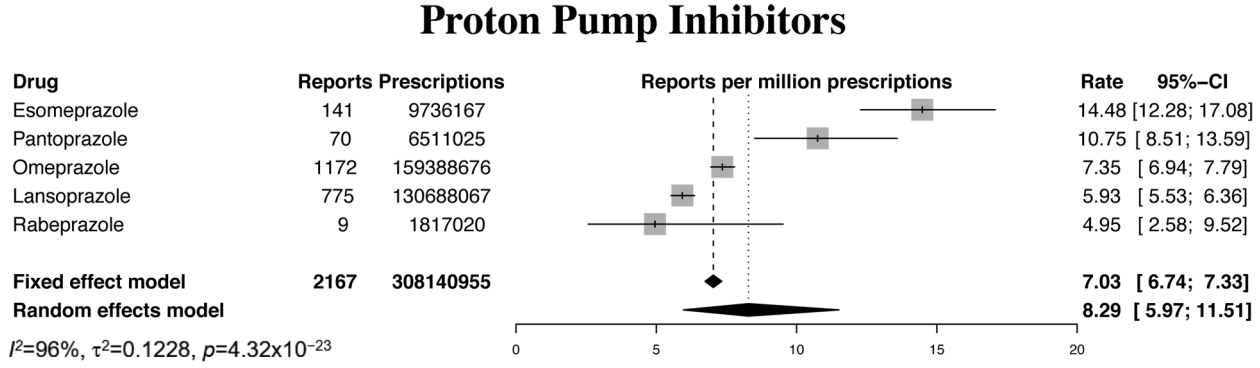
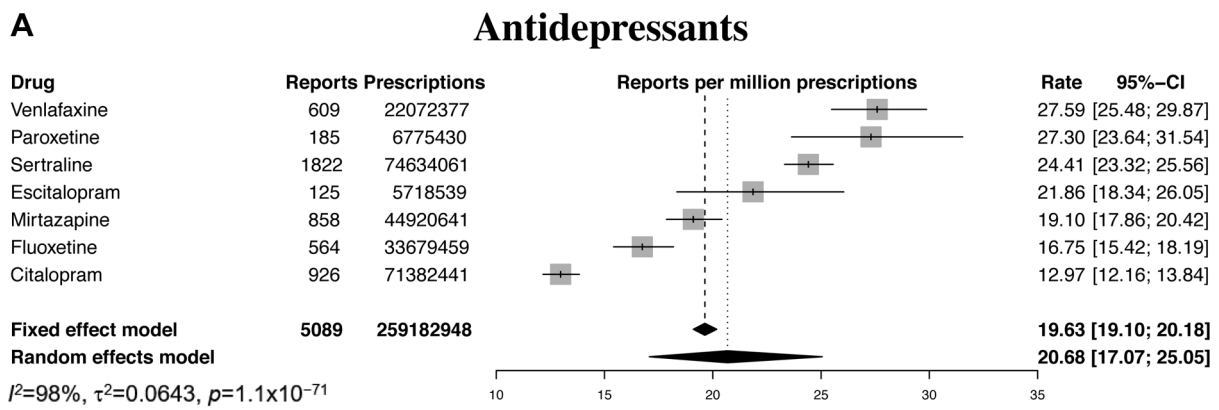
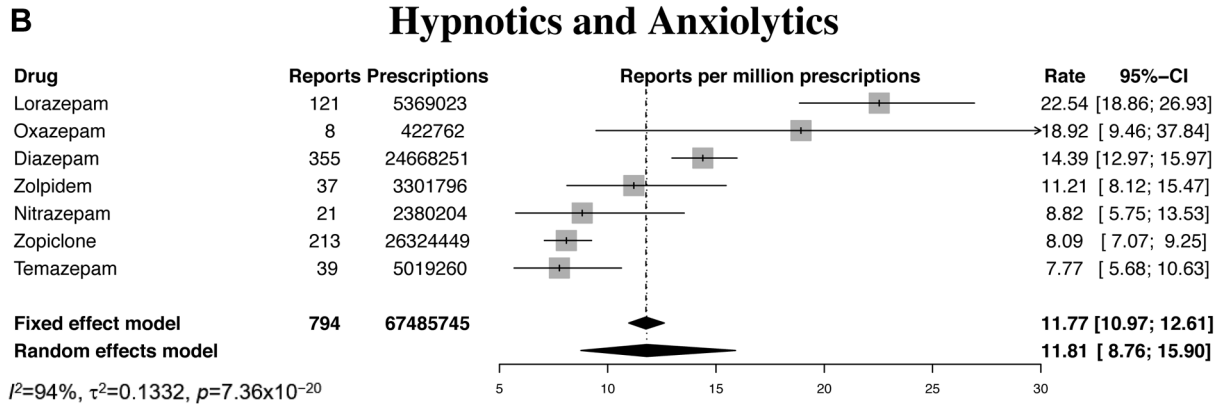


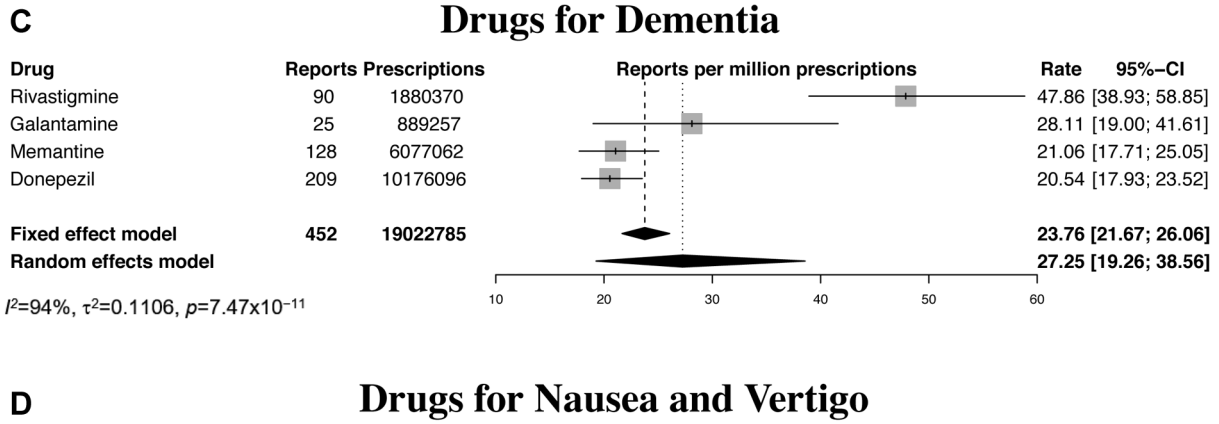
Figure 5. *Gastro-intestinal system – Proton pump inhibitors.*

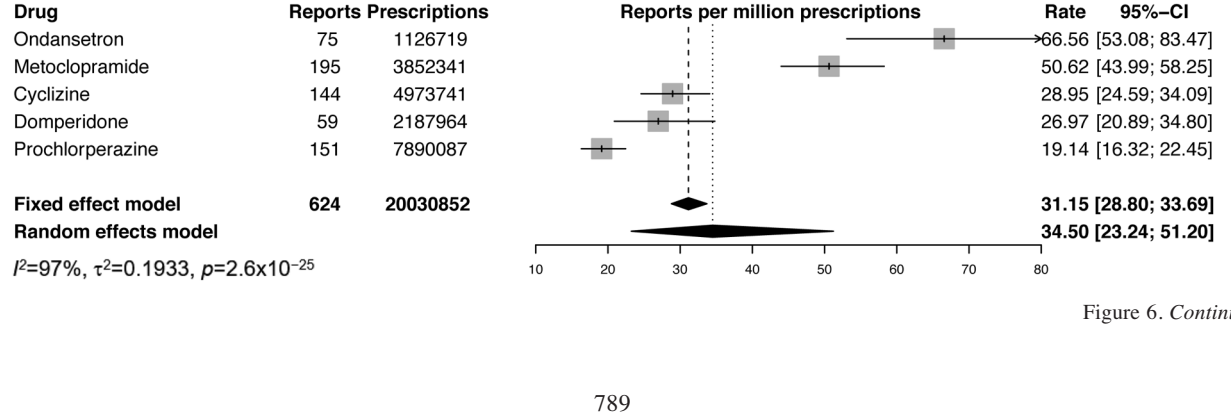
(*e.g.*, oral formulation). This can potentially confound data on ADR reports for some medicines, by increasing the number of ADR reports while only including general practice prescribing data.

Prescribing data issues. There are some key issues with the use of general practice prescribing data as the denominator value for calculating the rate of ADR reports per prescribing unit. First, the prescribing data used were obtained from









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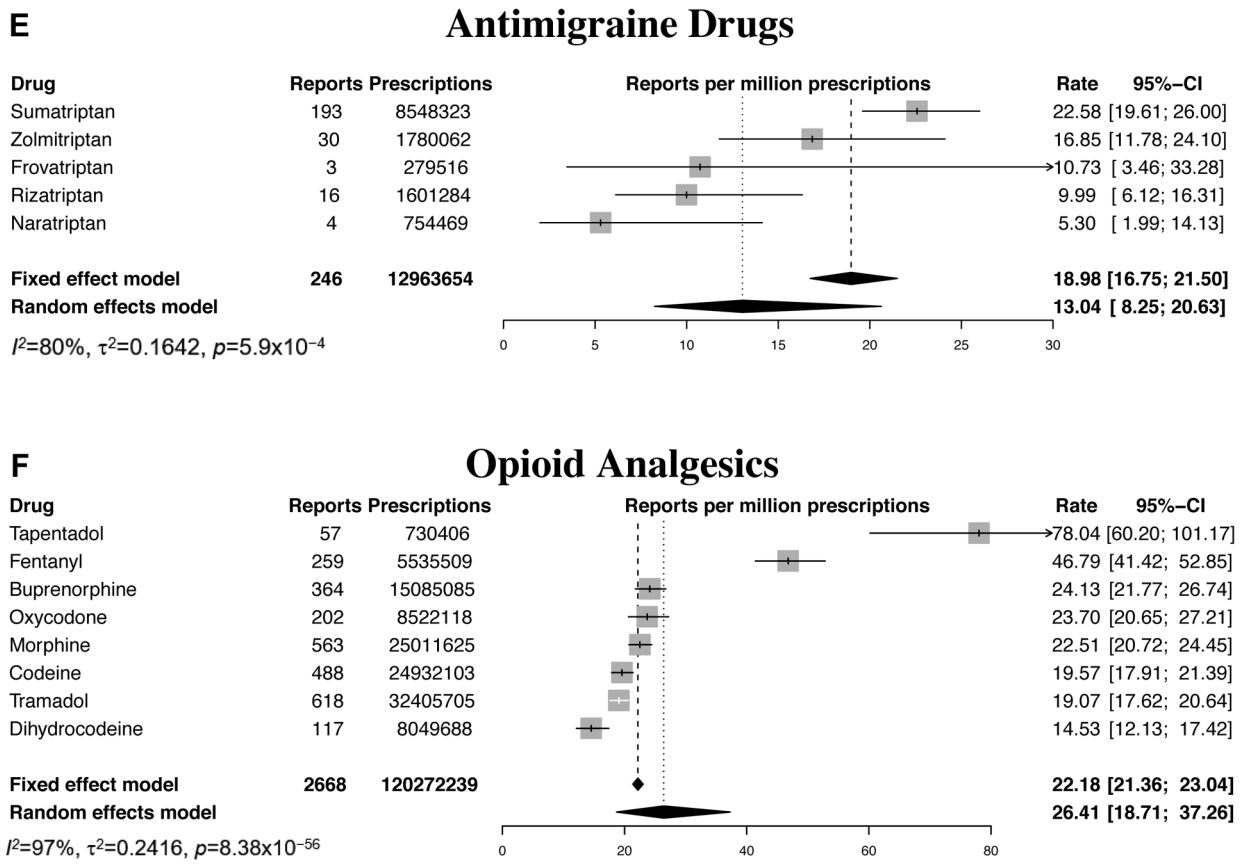


Figure 6. *Central nervous system. A) Antidepressants, B) Hypnotics and anxiolytics, C) Drugs for dementia, D) Drugs for nausea and vertigo, E) Antimigraine drugs, F) Opioid analgesics.*

prescriptions written only in England. As 84.3% of the UK population lives in England, England has the vast majority of prescriptions and, therefore, analysing these data reflects the majority of UK general practice prescribing. Whilst it can be assumed that the drug prescribing patterns in the other nations of the UK generate similar ADR reports to the ones used here, this was not tested in this study.

The second issue concerning prescribing data is that their limited scope from general practice alone does not provide a complete overview of prescribing information. In contrast, the Yellow Card database is derived from all UK healthcare settings, including secondary care, Over-the-counter (OTC), Pharmacy medicines (P-medicines) and General Sales List (GSL) medicines purchased in pharmacies or supermarkets that do not require a prescription. Therefore, the use of general practice prescribing data is not representative of the total usage of medicines, and reporting rates for some OTC and GSL as well as P-medicines may have been over-represented in the yellow card data compared to the prescription data. A limitation of this study is the lack of a systematic process for recording secondary care prescribing data, which has possibly led to missing prescriptions that did not originate from GP practices. However, the majority of prescriptions for medicines are generated in GP practices, as GPs prescribe ongoing supplies for almost all oral medications used in the UK. Although this study may have missed around 20% of the total UK prescriptions, the majority of them would have been initiated by medical specialists but subsequently repeated by GPs during follow-up. Therefore, the relative numbers of prescriptions from secondary care are small compared to the ones from general practice and the effect of not including them is likely to be marginal and affect medicines across all therapeutic classes similarly. Moreover, the medicines covered by secondary care prescribing data have little utility for the purposes of our project and this study sought to minimise potential confounding information by excluding medicines prescribed exclusively in the secondary care setting and medicines extensively available as OTC or GSL. While general practice prescribing is robust and collected automatically, there is no

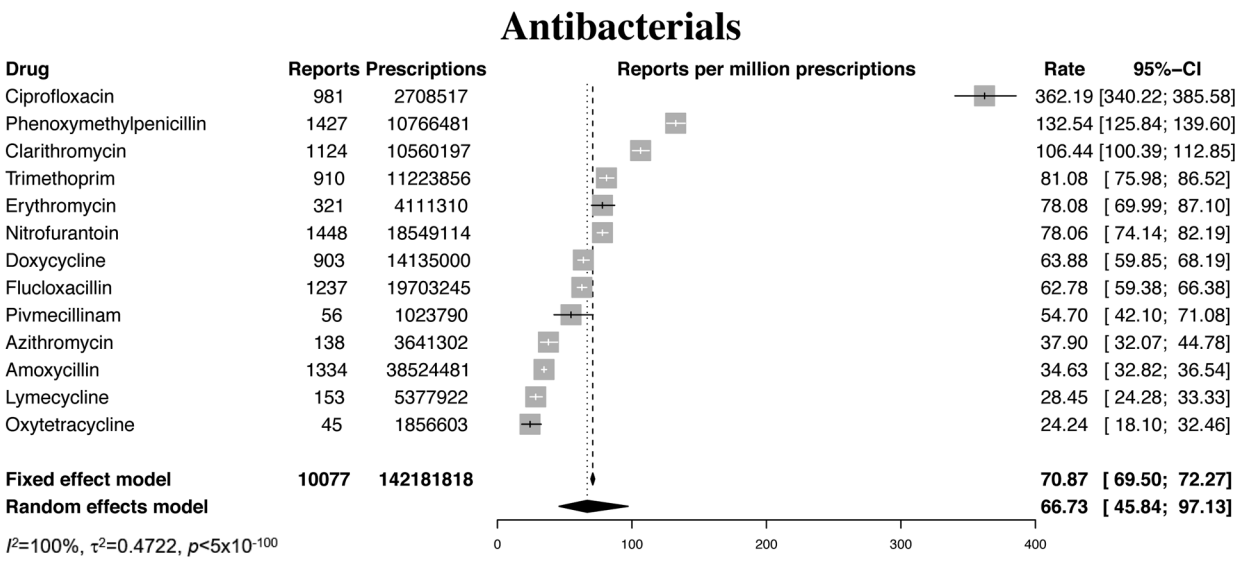


Figure 7. *Infections– Antibacterials.*

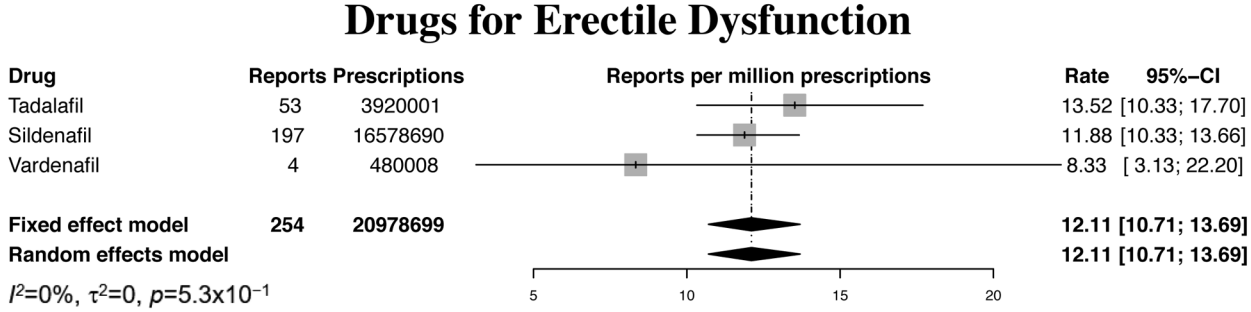


Figure 8. *Obstetrics, gynaecology and urinary-tract disorders – drugs for erectile dysfunction.*

similar process for exclusively accessing secondary care data. In ideal circumstances and when a comprehensive national database of all secondary care prescriptions becomes available, this work could be extended to include all drugs licensed in the UK and the hospital prescribing data could be combined with the general practice prescribing data.

A third issue is that the prescribing unit used represents the number of times a medicine has been written on a prescription form without providing information on the quantity of medicine prescribed or the length of treatment. While many prescriptions are for one month's supply, some will be for different lengths of treatment. Individual prescriptions may, therefore, contain a range of quantities, from one month's to several months' supply. Nevertheless, the majority of the UK GPs are encouraged to prescribe one month's supply at a time, which may minimise confounding due to this effect.

A fourth issue concerning prescription data, is that they do not necessarily indicate exposure to the medicines as some dispensed prescriptions may not have been taken by patients. Nonetheless, this study used prescriptions that are dispensed as a proxy for actual medicine use, and it is, therefore, likely to be more representative of exposure compared to simple prescribing data. It is estimated that only 87.0-94.7% of prescriptions generated in primary care are subsequently dispensed (92, 93).

Although these issues may affect the precision of the prescribing data used in this study, they are likely to affect all medicines equally, and thus will not affect the relative rates of ADRs.

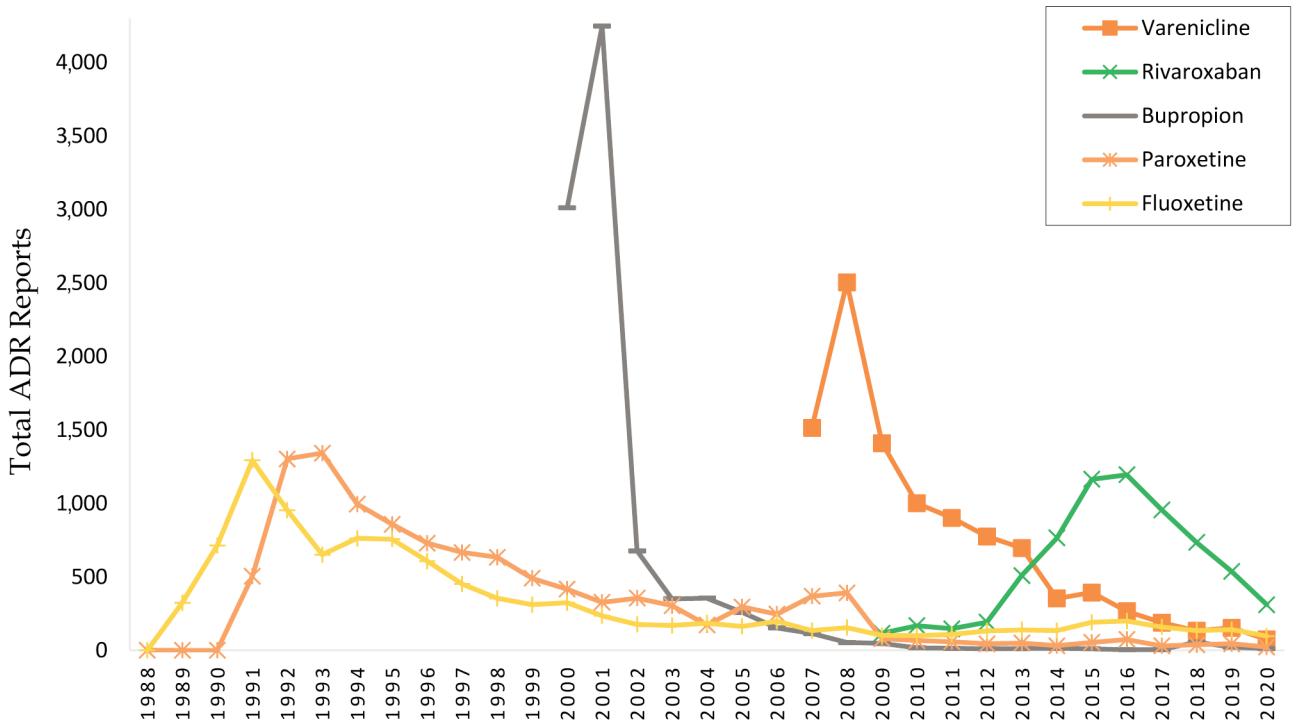


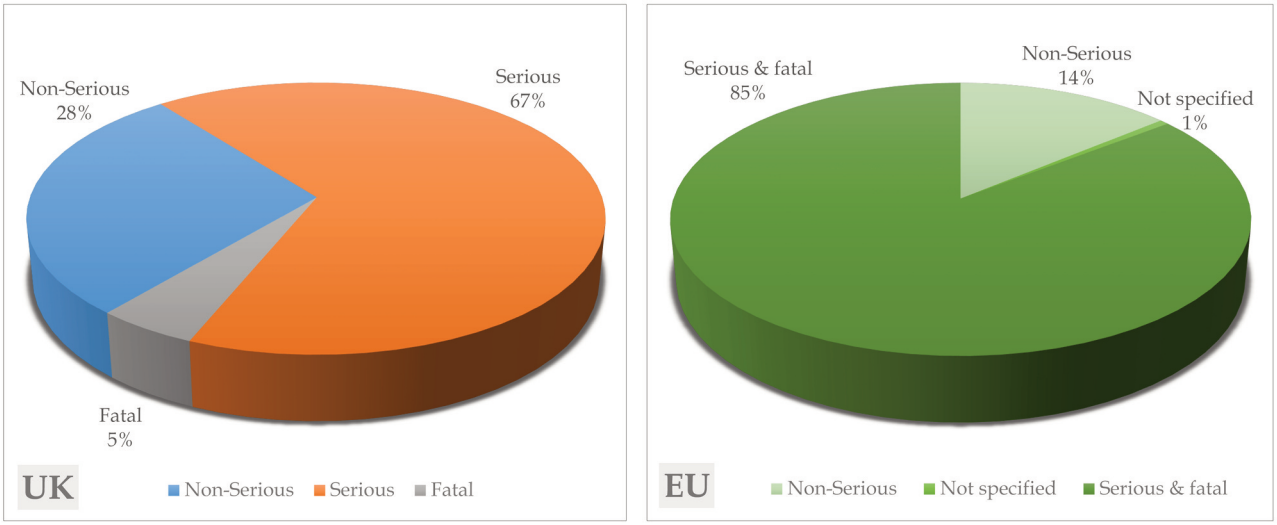
Figure 9. *Time trends of the number of ADR reports for some commonly prescribed drugs in general practice from 1988 to 2020.*

Adverse drug reaction reporting data issues. Data sourced from pharmacovigilance databases are subject to bias and the use of ADR reporting rates to quantify the risk is to an extent confounded by issues, such as under-reporting, reporting bias, false positives, missing information and duplicate reports. However, Yellow Card database is the only currently available comprehensive resource for ADR reporting at a national level.

First issue concerning the reporting of ADRs is that, except for Marketing Authorisation Holders (MAHs), who have legal obligations to report ADRs associated with the use of their medicines (94-96), reporting is entirely voluntary (43). Studies suggest only a minority of ADRs are reported (47, 97-101). It has been estimated that that only 2%-4% of non-serious ADRs are reported *via* YCS and approximately 90% of serious ADRs remain unreported (102-105). The rate of ADR reporting by HCPs is falling (106, 107), and there has been a 37% decline in reports over a 9-year period up to 2013 (107). While it has been recently possible to report ADRs through an app on smartphones, occasional anecdotal reports suggest this facility is not widely known (108).

The low proportion of reported ADRs is a global phenomenon that may delay signal detection and underestimate the extent of ADRs (109-113). Incentive payment schemes, legally-required reporting or use of reporting as a quality indicator in the GPs' contracts have been suggested so as to improve ADR reporting rates (114), however, none of them have succeeded to do so in many countries (43). Several studies suggest active training and educational interventions for HCPs on pharmacovigilance may improve their attitude and knowledge of ADR identification and reporting (115-117). Pharmacists are well-positioned to identify and report ADRs (43, 118-120) and the quality of ADR reports submitted by both community and hospital pharmacists have been found to be comparable to reports from hospital doctors (121-124). While continuous education programs can result in short to medium-term improvement in hospital-based settings (125), it is yet to be determined whether such improvements can be sustained in long-term and community-based settings. It has been advocated that ADR reporting and pharmacovigilance education should be vital competencies in undergraduate and postgraduate education (126, 127).

Several other factors contribute to under-reporting of ADRs, such as the seriousness of the ADR and the familiarity with it or the medication causing it (128). Although there is undoubtedly extensive under-reporting of minor ADRs that have no significant disadvantageous effects on the patient, serious and fatal ADR reports are more notable and more likely to be reported. Patients with serious ADRs are also expected to be hospitalised or treated under hospital care, and, consequently, more likely to be reported. In addition, it is mandatory for



Pharmacovigilance database	Number of medicinal products	Non-Serious reports	Not specified reports	Serious reports	Fatal reports	Serious & fatal reports	Total reports
UK 'Yellow Card'	2,331	301,449	-	707,661	52,255	759,916	1,061,365
EU 'EudraVigilance'	2,521	1,159,770	48,954	-	-	7,139,343	8,348,067

Figure 10. *Analyses of the ADR reports in both the UK's Yellow Card database from inception until September 2020 and the European pharmacovigilance database 'EudraVigilance' from inception until November 2020.*

MAHs to report all serious ADRs related to their medication to MHRA and therefore less prone to under-reporting. Our analysis of the ADR reports in both the UK's Yellow Card and the European pharmacovigilance databases has shown that 72-85% of all ADR reports were serious and fatal, with similar findings in other databases (129). This suggests that the extent to which underreporting is likely to significantly skew our findings across different medicines is small. Exceptions may include very old medicines and medicines with familiar ADRs, as a significant trigger for reporting is likely to be the novelty of drugs or novelty of ADRs.

Second issue concerning the reporting of ADRs is that the number of ADR reports for a medicine can be biasedly subject to higher or lower levels of reporting compared to other medicines. Public awareness and media coverage on a safety issue related to a particular medicine, or assigning a certain medicine to a patient support program, can affect the number of ADR reports for this medicine. Moreover, ADRs to the first drug of a new therapeutic class, such as statins, will be novel and more likely to be reported, but as more drugs within that class are released, similar ADRs may be assumed to be class-related effects and thus not reported. Reporting rates for newly-licensed medicines or medicines on the Black Triangle Additional Monitoring list (▼) are likely to be higher than older medicines in the few years following authorisation, however, they gradually decline over time even if the medicine is progressively used more broadly (130).

Therefore, the relatively higher reporting rate for newly licensed medicines and medicines on the Black Triangle scheme may be due to this time-trend effect, rather than inherent safety issues. Analysing all ADRs within the first five years from the introduction of each medicine to the market may reduce this effect. Unless all medicines within a class are introduced into the market around the same time, comparative figures based on reporting rates within a restricted timeframe can be misleading. However, this is less likely to considerably skew our results as the number of newly-licensed medicines and medicines with Black Triangle status that are included in our analysis is very small (Table I).

Third issue concerning the reporting of ADRs, is that the MHRA encourages HCPs and patients to submit a report on a given medicine, even though they are not certain that it caused this ADR. This may result in false positive reports, and, therefore, further analyses may need to be undertaken to confirm possible associations. Establishing causality is a challenge, particularly when other medicines have been administered simultaneously or there is a long delay between initiation of medicine and the appearance of the ADR (131). The incidence of erroneous reports by pharmacists and physicians is high, often with difficulty in accurately determining the causality of ADRs (132). Cases of misuse,

Table I. *The newly-licensed medicines of the past 10 years & medicines on the Black Triangle Additional Monitoring list (▼) included in our analyses.*

Medicine	Year of approval or Black Triangle status
Rivaroxaban	▼
Semaglutide	▼
Edoxaban	2016
Dulaglutide	2015
Canagliflozin	2014
Empagliflozin	2014
Alogliptin	2014
Lixisenatide	2013
Dapagliflozin	2013
Linagliptin	2011
Ticagrelor	2011
Tapentadol	2011

abuse, medication errors, occupational exposure and administration, or dispensing errors may also affect the number of reports submitted.

Fourth, the quality of reports submitted by patients compared to HCPs can be unreliable (133). While patients can provide many distinct ADR types from a different perspective, resulting in broader information that should not be dismissed (102, 134-141), often patients' inability to accurately describe the seriousness of incidents may impact the data (134, 142). Medical seriousness as per CIOMS official criteria may differ from patients' perception of what represents a "serious" ADR (143). Studies have shown mixed results on whether HCPs compared to patients are less or more prone to submit serious and life-threatening ADR reports (133, 136, 142, 144-148). Analysis of the Danish ADR database has demonstrated that the share of 'serious' ADRs submitted by patients is similar to that of GPs, yet lower than that of other HCPs (148), which may help detect safety signals earlier than if ADR reports from HCPs alone were relied on (149-151).

In conclusion, to the best of our knowledge, this is the first and largest assessment of the suitability of mapping ADR reporting data from the Yellow Card database onto the general practice prescribing data. This proof-of-concept study created generally applicable rules to execute this linkage and demonstrated the feasibility of using real-time real-world prescribing data in conjunction with ADR reporting data to compare the safety profiles of medicines. To allow for more precise and accurate data integration, future work should focus on improving ADR reporting data and incorporating prescriptions for secondary care and private prescriptions.

In addition to predicting medicine safety, the comparative safety charts provide a potential resource for policy makers and represent a benchmark against which to compare findings from pharmaco-epidemiological studies investigating high-risk medicines. Even with the acknowledged limitations that might considerably affect the quality of the data, dissemination of these charts has the potential to support informed decision-making regarding a patient's treatment regimen and can, therefore, be useful for prescribers and pharmacists counselling patients on medications. Nevertheless, a comprehensive benefit-risk assessment based on the patient's overall risks and other patient-specific data in conjunction with the product information should be considered. A follow-up step to validate these comparative charts and test of their suitability for clinical practice is also warranted.

Conflicts of Interest

All Authors declare that they have no conflicts of interest that are directly relevant to the content of this study.

Authors' Contributions

KM, RD and LJ conceptualised the study and designed the research. KM conducted the research and graphical overviews. MNW performed the statistical analysis and generated the graphs.

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