Fixed-dose combination antihypertensives and risk of medication errors
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ABSTRACT
Objective While fixed-dose combinations (FDC) can improve adherence, they may add complexity to the prescribing/dispensing process, potentially increasing risk of medication errors. This study aimed to determine if prescriptions for antihypertensive FDCs increase the risk of therapeutic duplication and drug-drug interactions (DDI).
Methods This retrospective observational study used administrative pharmacy claims data from the Irish Primary Care Reimbursement Service. Prescriptions dispensed to adults in 2015 were included if they contained an antihypertensive FDC, or the same drugs prescribed separately. The outcomes were therapeutic duplication and potentially serious DDI involving FDC drugs. Relative risk (RR) of these outcomes, adjusted for prescription and patient factors, was determined using generalised linear models with Poisson distributions and propensity score matching.
Results This study included 307,833 FDC prescriptions (67.0%) and 151,632 separate component prescriptions. Half of patients prescribed FDCs were female with a mean age of 67.1 (SD 12.5) years and, compared with separate component prescriptions, FDCs were less often coprescribed with other cardiovascular medications. Therapeutic duplication occurred in 0.8% of prescriptions, most often involving calcium channel blockers, and 10.6% contained a DDI (most often amlodipine and simvastatin). The RR of therapeutic duplication on FDC prescriptions compared with separate component prescriptions was 1.46 (95% CI 1.17 to 1.83) and the adjusted RR was 2.06 (95% CI 1.64 to 2.60). For DDIs, there was no significant difference between FDC and separate component prescriptions after confounder adjustment.
Conclusions This study found FDCs were associated with increased risk of duplication. When considering prescribing FDCs, this safety consideration should be weighed against potential benefits.

INTRODUCTION
Fixed-dose combinations (FDC), single medications or dosage forms that contain a combination of two or more active ingredients, are becoming increasingly common. They are most often used where multiple drugs may be required to treat control a condition, such as HIV/AIDS, diabetes, or hypertension, and polyphills combining more diverse drug combinations (eg, for cardiovascular prevention) also exist. By replacing multiple treatments, they can reduce pill burden for patients and simplify medication regimens. For this reason, FDCs can increase adherence compared with patients taking the equivalent drugs separately, and improve objective measures such as blood pressure. Combination therapy using multiple drugs acting on different therapeutic targets can produce synergistic effects and provide superior efficacy compared with monotherapy. Using multiple agents can also benefit tolerability where a combination allows for each drug to be used at lower doses than would be required if either drug was used alone, reducing the risk of adverse effects. Hypertension is one of the conditions where FDCs are used most commonly. Most patients require multiple antihypertensive drugs to meet blood pressure targets, and hence the greatest number of FDCs is in this therapeutic area. Hypertension is highly prevalent, particularly among older people, and is often comorbid with other conditions in this age group. Hence, FDCs may be particularly beneficial for such patients with high pill burdens for whom adherence to treatment may be challenging. Studies have demonstrated the advantages both in efficacy and safety of utilising multiple antihypertensives instead of a higher dose of a single agent, and there is evidence from a recent Cochrane review that initiating combination antihypertensive therapy rather than monotherapy may be advantageous.

A disadvantage to FDCs is the ‘fixed’ nature of the dosing combinations may make dosage adjustment more difficult, leading to potential underdosing or overdosing. FDCs may reduce the ability to identify the cause of an adverse drug event relating to one of the drug ingredients. FDCs could also contribute to medication errors. They are frequently prescribed by brand name, and presence of multiple ingredients available in varying strengths within a single product adds complexity to the prescribing and dispensing process. Medication errors cause a substantial burden of patient harm, morbidity and mortality; however, the impact of FDCs on medication safety and prescribing quality has not been extensively evaluated to date. Therefore, the aim of this study is to determine if prescriptions for antihypertensive FDCs increase the risk of prescribing errors, namely therapeutic duplications and potentially serious drug-drug interactions (DDI), compared with the free combination (FC) ingredients prescribed separately.

METHODS
Study design, setting and participants
The Strengthening the Reporting of Observational Studies in Epidemiology statement has been used in the planning and reporting of this research.
This is a retrospective cohort study using the Health Service Executive-Primary Care Reimbursement Service (HSE-PCRS) administrative pharmacy claims database. The analysis includes prescriptions dispensed to adults (aged 18 years and over) under the General Medical Service (GMS) scheme in Ireland in 2015. The GMS scheme is public health cover that provides free medical care and prescribed medications to about one-third of the general Irish population whose household income is below the eligibility threshold. It also covers the vast majority (approximately 95%) of people aged 70 years and over, where a higher income threshold applies.

The unit of analysis was each prescription dispensing claim, and these were included if there was a dispensing for either of the following:

- An FDC of antihypertensive drugs where the components are also available to be prescribed separately.
- The same drugs as an FDC prescribed as separate components (or FC) in solid oral dosage form.

All such prescriptions dispensed to an adult on the GMS scheme during 2015 were included in the analysis. The relevant combinations available on the market, all of which were included in this study, are listed in online supplementary table S1. Permission was obtained from the HSE-PCRS to conduct this analysis. As the data were anonymised and results presented at group level, ethical approval was not required.

Outcomes

The primary outcome was therapeutic duplication involving a component of an included antihypertensive FDC, defined as two drugs from a therapeutic class (ACE inhibitors, angiotensin II receptor blockers (ARB), calcium channel blockers or beta blockers) on the same pharmacy claim (ie, dispensed from the one prescription). Products containing the same drug were not considered therapeutic duplication. The secondary outcome was the presence of a potentially serious DDI involving a component of an included antihypertensive FDC and another coprescribed medication. Interactions where the sole adverse effect relates to hypotension were excluded, as prescribers may have accounted for this interaction in the dose they prescribe and thus these are less likely to constitute medication errors. Interactions were considered potentially serious if they carry a ‘black dot’ in the British National Formulary (online supplementary table S2).

Exposure and potential confounders

The exposure of interest was prescribing of antihypertensives as an FDC compared with prescribing of individual antihypertensives separately.

To adjust for potential differences between prescriptions containing FDCs and separate components, the following potential confounders were included: the age and sex of the patient, and the type of antihypertensive (ACE inhibitor, ARB or beta blocker) and total antihypertensive dosage dispensed (expressed using the WHO classification of defined daily dosages or DDD). We categorised based on drug class for adjustment due to the large number of individual drug combinations. To account for potential differences in cardiovascular comorbidities, the analysis adjusted for the total numbers of items on the same prescription claim from each of the following classes (defined by WHO Anatomical Therapeutic Classification codes):

- Other antihypertensives (C02, C03, C07, C08, C09).
- Lipid-lowering agents (C10).
- Anticoagulants/antiplatelets (B01).
- Antidiabetic agents (A10).

Other cardiovascular agents (C01, C04, C05).

Lastly, the number of other items (excluding the above categories) on the prescription claim was also adjusted for. Previous research on the relationship between FDCs and adherence has similarly adjusted for coprescribing of other medicines. 16 17

Statistical methods

Analyses were all conducted at the level of the pharmacy claim (ie, prescription). Descriptive statistics are presented for included dispensed prescriptions and separately for FDC and FC prescriptions. Differences between the FDC and FC groups were assessed by calculating standardised mean differences (SMD) for each variable, which are independent of sample size.

Regression models were fitted for therapeutic duplication as the binary outcome variable, and combination status (FDC vs FC) as the exposure variable of interest. This analytical approach was then repeated for the secondary outcome of presence of a potentially serious DDI. The non-independence of repeated dispensions to individuals was accounted for by estimating robust standard errors. Generalised linear models using the Poisson distribution were fitted to produce unadjusted and adjusted estimates of the relative risk (RR) of therapeutic duplication, with 95% CIs. Age, sex, antihypertensive type and DDDs in the FDC/FC, and the numbers of other prescription items mentioned above were adjusted for.

A propensity score (representing the probability of an FDC being prescribed) was generated by fitting a logistic regression model including all of the prescription and patient characteristics as covariates. This was used to match FDC and FC prescriptions using a calliper of 0.2 of the SD of the log of the propensity score. 18 This allowed for the absolute risk difference (ARD) between the FDC and FC prescriptions for therapeutic duplication and DDI to be calculated in both crude and propensity score-matched analyses. By taking the reciprocal of these, we also determined the numbers needed to treat to cause harm (NNTH; ie, the number of patients who need to be prescribed an FDC rather than an FC to cause one additional case of therapeutic duplication/DDI). To assess the impact of residual covariate imbalance, the propensity score-matched regression was repeated with double adjustment for covariates with an SMD of >0.10 after matching. 19 Different approaches to propensity score adjustment were also conducted as a sensitivity analysis, that is, adjusting for propensity score (crude, trimmed, quintiles) in the regression alone or with other covariates.

To assess the robustness of the results and impact of potential residual confounding, sensitivity analysis was conducted to assess the magnitude of effect of residual confounding that would fully explain the observed results. 20

RESULTS

Descriptive statistics

A total of 459,465 prescriptions, issued to 49,283 patients, were included in this study, 307,833 (67%) containing an FDC and the remaining 151,632 (33%) containing an equivalent FC. Descriptive statistics for included prescriptions are provided in table 1. Fifty per cent of FDC prescriptions were for women, with a mean age of 67.1 (SD 12.5) years, while for FCs, 48.1% of prescriptions were for women and the mean age was 70.1 (12) years. Prescriptions for FDCs involved an ARB more frequently and an ACE inhibitor or beta blocker less frequently compared with FC prescriptions. FDCs had higher doses of antihypertensives than FCs, although these prescriptions were less likely to contain another coprescribed
medication to treat cardiovascular disease and contained fewer other prescription items.

**Therapeutic duplication and DDDs**

Of all included prescriptions, 0.8% had an instance of therapeutic duplication on the same prescription claim, most often relating to calcium channel blockers, and 10.6% contained a potentially serious DDI relating to a combination ingredient (see tables 2 and 3). Calcium channel blockers were the most commonly implicated of the antihypertensive agents in both duplications and interactions, with amlopidine and simvastatin being the most frequently occurring individual interaction (in 40.5% of all prescriptions with an interaction, online supplementary table S3).

The crude RR of drug duplication on FDC prescriptions compared with FC prescription was 1.46 (95% CI 1.17 to 1.83, ARD 0.28%; NNTH 358), and the RR was higher after adjusting for prescription and patient characteristics (table 2). A propensity score match was successful for 97% of FC prescriptions (online supplementary figure S1 and table S4) and in propensity score-matched regression, the RR of duplication was 2.29 (95% CI 1.81 to 2.90; ARD 0.75%; NNTH 133). The magnitude did not vary substantially regardless

**Table 1** Descriptive characteristics of included prescription claims*

| Characteristics                              | FC (n=151632) | FDC (n=307833) | Standardised mean difference |
|----------------------------------------------|---------------|---------------|-----------------------------|
| Age of prescription recipient (years)        |               |               |                             |
| Mean (SD)                                    | 70.1 (12.0)   | 67.1 (12.5)   | 0.021                       |
| Female prescription recipient, n (%)         |                |               |                             |
| 72968 (48.1)                                 | 154037 (50.0) | 0.077         |
| Antihypertensive type†, n (%)                |                |               |                             |
| Beta blocker                                 | 4630 (3.1)    | 1294 (0.4)    | 1.246                       |
| ACE inhibitor (±beta blocker)                | 69671 (45.9)  | 108671 (35.3) | 0.553                       |
| ARB (±beta blocker or ACE inhibitor)         | 77331 (51.0)  | 197868 (64.3) | 0.446                       |
| Total number of antihypertensive DDDs prescribed |            |               |                             |
| Mean (SD)                                    | 87.3 (31.1)   | 88.7 (26.1)   | 0.017                       |
| Any other BP drugs, n (%)                    | 67356 (44.4)  | 104454 (33.9) | 0.294                       |
| Any other CV drug, n (%)                     | 9020 (5.9)    | 12625 (4.1)   | 0.308                       |
| Any antiplatelet/anticoagulant, n (%)        | 72333 (47.7)  | 105838 (34.4) | 0.450                       |
| Any cholesterol drug, n (%)                  | 82553 (54.4)  | 138484 (45.0) | 0.359                       |
| Any diabetic drug, n (%)                     | 18036 (11.9)  | 25090 (8.2)   | 0.248                       |
| Number of other items on prescription        | 2 (1–4)       | 2 (0–3)       | 0.064                       |

*Issued to 49283 patients.
†Prescriptions containing ≥1 antihypertensive type were categorised in a hierarchy as follows: 1090 ARB prescriptions also contained a combination involving an ACE inhibitor and 34 involving a beta blocker. Ninety-six ACE inhibitor prescriptions also contained a combination involving a beta blocker.

**Table 2** Prevalence of therapeutic duplication and regression analyses for risk of duplication

| Characteristic                              | FC (n=151632) | FDC (n=307833) | Relative risk (95% CI) | P values |
|---------------------------------------------|---------------|---------------|------------------------|----------|
| Therapeutic duplication, n (%)              | 918 (0.61)    | 2723 (0.88)   | 1.46 (1.17 to 1.83)    | 0.001    |
| ARB                                         | 57 (0.04)     | 404 (0.13)    | 2.10 (1.67 to 2.65)    | <0.001   |
| ACE inhibitor                               | 103 (0.07)    | 201 (0.07)    | 2.29 (1.81 to 2.90)    | <0.001   |
| Beta blocker                                | 129 (0.09)    | 128 (0.04)    | 2.24 (1.77 to 2.83)    | <0.001   |
| Calcium channel blocker                     | 629 (0.41)    | 2014 (0.65)   | 2.10 (1.47 to 2.98)    | <0.001   |

*Adjusted for patient age and gender, type of combination product (ARB, ACE inhibitor or beta blocker), and total number of antihypertensive defined daily dosages (DDD) in the FC/FDC, number of other antihypertensive prescription items, number of other cardiovascular drugs, number of antiplatelet/anticoagulant drugs, number of cholesterol drugs, number of diabetes drugs and number of other prescribed items.
†Propensity score generated from logit model including all covariates adjusted for in ".

**Table 3** Prevalence of potentially serious drug–drug interactions and regression analyses for risk of interaction

| Characteristic                              | FC (n=151632) | FDC (n=307833) | Relative risk (95% CI) | P values |
|---------------------------------------------|---------------|---------------|------------------------|----------|
| Drug–drug interaction, n (%)                | 20206 (13.33) | 28477 (9.25)  | 0.69 (0.66 to 0.73)    | <0.001   |
| ARB                                         | 4905 (3.23)   | 8706 (2.83)   | 1.00 (0.94 to 1.05)    | 0.934    |
| ACE inhibitor                               | 5114 (3.37)   | 7623 (2.48)   | 1.09 (1.03 to 1.15)    | 0.005    |
| Beta blocker                                | 78 (0.05)     | 43 (0.01)     | 1.07 (1.01 to 1.13)    | 0.030    |
| Calcium channel blocker                     | 12775 (8.43)  | 16378 (5.32)  | 2.24 (1.77 to 2.83)    | <0.001   |

*Adjusted for patient age and gender, type of combination product (ARB, ACE inhibitor or beta blocker), and total number of antihypertensive defined daily dosages (DDD) in the FC/FDC, number of other antihypertensive prescription items, number of other cardiovascular drugs, number of antiplatelet/anticoagulant drugs, number of cholesterol drugs, number of diabetes drugs and number of other prescribed items.
†Propensity score generated from logit model including all covariates adjusted for in ".

ARB, angiotensin II receptor blockers; FC, free combination; FDC, fixed-dose combination; SMD, standardised mean differences.
of how the propensity score was used for adjustment (see online supplementary table S5).

For DDIs (table 3), the risk was lower for FDC prescriptions relative to FC prescriptions in unadjusted analysis (RR 0.69, 95%CI 0.66 to 0.73, ARD −4.07%; NNTH −25). Adjusting for covariates, the RR was 1.00 (95% CI 0.94 to 1.05). Propensity score matching yielded an RR of 1.09 (95% CI 1.03 to 1.15; ARD 0.98%; NNTH 101); however, most other methods of propensity score adjustment produced RR estimates that were not statistically significant (online supplementary table S5).

Sensitivity analysis
Considering the largest effect an unmeasured confounder would need to explain the observed association between FDC prescriptions and therapeutic duplication, a factor occurring in 5% of FDC prescription would need to have an RR of therapeutic duplication and DDIs of 5 or 10%. These action-based errors, that is, discordance between the intended product to be prescribed/dispensed and the actual action, could not be identified using our data source. Instead, these pharmacy claims were used to evaluate the knowledge-based errors of duplication and DDIs, for which there are a number of plausible mechanisms. As marketing of FDCs often results in patent extension of off-patent drugs, brand names are more likely to be used for FDCs. Brand names are more often confused with another at the prescribing/dispensing stage than generic or international non-proprietary names (INN). Moreover, the information provided by the INN suffix on a drug’s therapeutic class (ie, -sartan indicating an ARB) is lost when prescribing a brand name. Hence, healthcare professionals may be less likely to identify a drug interaction or duplication if they do not recognise the type of drug an FDC contains.

Knowledge-based errors such as therapeutic duplication or drug interactions may be mitigated through the use of computer-based clinical decision support systems (CDSS). The majority of prescribing/dispensing systems incorporate CDSS capable of detecting instances of therapeutic duplication and DDIs. It is possible that implementation of duplication/interaction checking may be less comprehensive for combination products if software is only capable of cross-referencing one active ingredient per medication. A lack of reference to the calcium channel blocker component of combination products in the software drug product file may explain the increased risk of therapeutic duplication. However, due to the proprietary nature of the prescribing/dispensing software systems used in Ireland, we are unable to determine their capability for cross-referencing products with multiple ingredients. Even when detection is effective, CDSS alerts ought to be implemented appropriately to minimise alert fatigue and ensure such medication issues are acted on where necessary. This is an important consideration in the development and implementation of electronic health records, particularly given the increasing use of combination products across therapeutic domains. In addition, increased generic prescribing and dispensing (ie, using INN) may also reduce medication errors. In a simulated before and after study of generic labelling of medications, FDCs were one of just two circumstances where errors decreased. When patients and doctors are considering an FDC, it is important to assess the potential risks and benefits. Although use of FDCs can reduce pill burden, the potential impact on medication adherence is complex. A lower pill burden can reduce regimen complexity; however, this is only one of over 700 potential factors found to be associated with non-adherence, and so any potential benefit of FDCs is dependent on the factors contributing to non-adherence in each individual patient’s case. FDCs could have a negative impact on some aspects of adherence, for example, unnecessarily high doses due to inflexible combinations could result in treatment discontinuation (or non-persistence) due to adverse effects. FDCs can also provide economic benefits. These benefits should however be weighed against the potential for iatrogenic harm due to medication errors. Even if the risk is low, medication errors can cause a substantial burden of patient harm, morbidity and mortality.

This study has a number of strengths and limitations. This is a large analysis which used the PCRS database, the most comprehensive source of medication prescribing and dispensing information in Ireland, capturing approximately 40% of the population. As this is an observational study, there may be residual confounding due to unmeasured factors which predict both whether antihypertensive medications

Figure 1  Effect of an unmeasured confounder present in 0.05 of fixed-dose combination (FDC) prescription claims required to explain observed association between FDC prescriptions and duplication.
are prescribed in combination and therapeutic duplication/ 
drug interactions, such as whether a prescriber uses CDSS. 
Due to the retrospective nature of this study we could not 
collect data on these additional factors. However, the results 
were robust to various methods of adjustment for measured 
confounders, and we quantified the magnitude of confounding 
due to unmeasured factors that would alter the findings. 
Other potential action-based medication errors (ie, selecting 
a different product than intended) could not be evaluated. In 
addition, these data include only medications dispensed on 
the GMS scheme.\textsuperscript{52} The scheme population is not representa-
tive of the general population (tending to be older and more 
socioeconomically deprived), and so the observed association 
may differ in other populations. We were unable to adjust for 
clustering of prescriptions at the prescriber level, and so the 
width of the CIs may be underestimated. However, some of 
the prescriber-level effects are likely to be accounted for in 
our adjustment for patient-level clustering. There may be clinical 
awareness and rationale for the duplications and interactions 
detected in this study, but regardless of whether these were 
tentional, FDCs appear to be associated with marginally higher 
therapeutic duplication. The definition of therapeutic 
duplication used did not include cases where the same active 
ingredient was prescribed in two different medications as this 
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