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Comparative effectiveness and prescribing trends of modified release versus immediate release indapamide in patients with hypertension: cohort study

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ABSTRACT

OBJECTIVE To investigate the prescribing trends of indapamide, a thiazide-like diuretic, and the long term comparative effectiveness of modified release versus immediate release indapamide.

DESIGN Cohort study.

SETTING IQVIA Medical Research Data UK database, incorporating data from The Health Improvement Network database, 1 January 2005 to 31 December 2020.

PARTICIPANTS Of 1 904 289 patients with hypertension, 86 388 started indapamide treatment during the study period. 30 021 patients received modified release and 56 367 immediate release indapamide.

MAIN OUTCOME MEASURES Monthly prescribing trends of modified release and immediate release indapamide are described. A pragmatic trial was emulated to compare the five year risks of composite cardiovascular events (myocardial infarction and stroke) and death between modified release and immediate release indapamide. Intention-to-treat and per protocol effects of treatment were estimated with pooled logistic regression models. Confounding and selection bias were accounted for by multivariable adjustments and inverse probability weights.

RESULTS 138 414 patients who used indapamide were identified among 1 904 289 patients with hypertension. A greater increase was seen in the proportion of users of immediate release indapamide (from 0.43% in 2005 to 2.31% in 2020) than in users of modified release indapamide (from 0.71% to 0.79%). 86 388 patients (30 021 and 56 367 who started modified release and immediate release indapamide, respectively) were eligible for the trial emulation. In the intention-to-treat analysis, no difference was found in the risk of cardiovascular events (hazard ratio 0.99, 95% confidence interval (CI) 0.90 to 1.08) or death (hazard ratio 0.97, 0.92 to 1.02) between modified release and immediate release indapamide. In the per protocol analysis, a lower risk of cardiovascular events was found with modified release indapamide than with immediate release indapamide (risk difference −0.39%, 95% CI −0.71% to −0.06%; hazard ratio 0.81, 95% CI 0.68 to 0.98), which was mainly driven by myocardial infarction (risk difference −0.36%, 95% CI −0.64% to −0.08%; hazard ratio 0.80, 95% CI 0.64 to 1.01). Similar risks of death (hazard ratio 1.03, 95% CI 0.90 to 1.17) were found for the two formulations.

CONCLUSIONS In patients treated with indapamide for hypertension, starting treatment with modified release or immediate release indapamide had similar risks for cardiovascular events or all cause mortality. In an exploratory secondary analysis, sustained treatment with modified release preparations was associated with a lower the risk of cardiovascular events but not all cause mortality compared with immediate release preparations. These findings need to be confirmed in prospective studies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Indapamide is a thiazide-like diuretic that is available in modified release or immediate release formulations

⇒ A previous trial showed that the modified release formulation had preferable pharmacokinetic properties, but no study has directly compared the long term effectiveness of modified release versus immediate release formulations

⇒ No study has investigated the current prescribing practice for modified release and immediate release indapamide in the UK

WHAT THIS STUDY ADDS

⇒ In the UK, a substantial increase was seen in the prescribing of immediate release, but not modified release, indapamide after changes to the National Institute for Health and Care Excellence guideline in 2011

⇒ No significant differences in the risk of cardiovascular events or overall mortality were seen in patients with hypertension starting treatment with modified release or immediate release indapamide

⇒ Secondary analysis found that those who consistently used modified release indapamide had a 0.39% lower absolute risk (19% lower relative risk) of cardiovascular events over five years than those who consistently used immediate release indapamide, with no difference in all cause mortality

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Further prospective studies are required to confirm the findings of the comparative effect between modified release and immediate release indapamide

⇒ Formal cost effectiveness studies are needed to help clinicians weigh the economic factors and patient specific characteristics affecting real world effectiveness, enabling more personalised prescribing of indapamide formulations

Introduction

Thiazide-like diuretics are now considered to be the first line diuretic for the management of hypertension, particularly in older patients, as recommended by current European and

American guidelines.[1 2] Despite the endorsement of thiazide-like diuretics as first line antihypertensive agents in Europe and the US, the UK's National Institute for Health and Care Excellence (NICE) guideline NG136 does not recommend any diuretics, including thiazide and thiazide-like diuretics, as the first line treatment for hypertension.[3] Instead, NICE suggests thiazide-like diuretics in preference to conventional thiazide diuretics only when diuretic treatment is indicated, in step two or three in the treatment of hypertension, in addition to an angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, or calcium channel blocker, or as an alternative to these drug treatments if they are not tolerated as step one treatment.[3] Indapamide is a thiazide-like diuretic with two distinct formulations available in the UK, immediate release (2.5 mg immediate release tablets) and modified release (1.5 mg sustained release tablets).[4] The immediate release and modified release formulations have distinctive pharmacokinetic properties, with peak concentrations reached within 1-2 hours for the immediate release and 12 hours for the modified release formulation.[5]

Randomised trials have shown that modified release indapamide, compared with placebo or other antihypertensive drugs, reduces cardiovascular events, mortality, and target organ damage.[6–8] Recent evidence also indicates that indapamide is increasingly commonly prescribed in the UK.[9] No study, however, has investigated the prescribing practice of modified release and immediate release indapamide specifically and, so far, no study has compared the clinical outcomes of the two formulations. Although both formulations provide equivalent levels of average reduction in blood pressure,[10] differences in their pharmacokinetic properties could affect their overall effectiveness as an antihypertensive agent given that daytime and night-time blood pressure measurements have different associations with increased risks of cardiovascular and total mortality.[11] For example, the immediate release formulation has a faster absorption rate whereas the modified release formulation allows lower peak-to-trough fluctuations.[5] In this study, our aim was to evaluate current prescribing practice and the comparative effectiveness of modified release versus immediate release indapamide treatment in preventing cardiovascular events (fatal and non-fatal myocardial infarction and stroke) and all cause mortality. Our findings will, therefore, help confirm or refute the claims of a difference in effectiveness between the preparations based on their different pharmacokinetic characteristics.

Methods

Data source

We conducted a population based longitudinal cohort study based on the IQVIA Medical Research Data UK database, which incorporates data from The Health Improvement Network, a Cegedim Database.[12] De-identified data provided by patients as part of their routine primary care were used. The IQVIA Medical Research Data UK database is a nationwide database of primary care records in the UK that includes about 6% of the total UK population. Previous studies have shown the validity of the database for pharmacoepidemiological studies and generalisability to the UK population,[13–15] and this database has been used to successfully develop and validate cardiovascular risk prediction models.[16–18] The IQVIA Medical Research Data UK database includes data on personal characteristics, lifestyle information, medical diagnosis and procedures (recorded in read codes), laboratory test values, and prescribing information that are recorded in primary care settings. In the UK primary care setting, all prescription records are automatically computerised and hence the database can capture complete records of prescriptions.[19]

Study design

This cohort study emulated a target pragmatic trial with observational data. We first designed a hypothetical target trial aiming to evaluate the comparative effectiveness of modified release versus immediate release indapamide for the prevention of cardiovascular events and death in patients with hypertension, and then emulated the trial with observational data from the IQVIA Medical Research Data UK database. Online supplemental table S1 summarises the brief protocols of the hypothetical target trial we wanted to emulate and the actual trial emulation with observational data.

Eligibility criteria

Eligible patients for this study were those who started modified release or immediate release indapamide treatment after receiving a diagnosis of hypertension between 1 January 2005 and 31 December 2020. We excluded patients at baseline (the first record of an indapamide prescription) who were aged <18 years, had <1 year of up-to-standard record history, had a history of myocardial infarction, stroke, or heart failure, were concurrently prescribed modified release and immediate release indapamide on the same day, or had no records of the required clinical parameters (body mass index, systolic blood pressure, and diastolic blood pressure).

Treatment strategy

We compared the modified release and immediate release indapamide treatment strategies (ie, starting and continuous use of modified release indapamide

versus starting and continuous use of immediate release indapamide) after a diagnosis of hypertension. Indapamide prescription records were identified with Multilex product codes to differentiate between the formulations prescribed.

Outcome

The primary outcome was a cardiovascular event, defined as a composite of fatal and non-fatal myocardial infarction and stroke. Secondary outcomes were myocardial infarction, stroke, and all cause mortality separately. The diagnosis of myocardial infarction or stroke was identified with Read codes. All cause mortality records were identified from the IQVIA Medical Research Data death records.

Our intention was to emulate the three point major adverse cardiovascular events endpoint commonly used in randomised controlled trials.[20] Because the cause of death is not available in the IQVIA Medical Research Data UK database, we excluded cardiovascular death from the composite primary endpoint and included all cause mortality as a secondary endpoint.

Follow-up

The date of the first modified release or immediate release indapamide prescription during the study period was defined as the index date. All included patients were followed from the index date until the occurrence of the outcome of interest, death, switching or discontinuing indapamide formulations (for the per protocol analysis), transfer-out from the registered practice, end of data collection from that general practice, or the last day of the study period (31 December 2021), whichever occurred first. Discontinuing treatment was defined as having a 60 day prescription free period. If a patient did not receive a new prescription for indapamide within 60 days after the theoretical end date of their last filled prescription, the patient was considered to have discontinued treatment, as of the theoretical end date of that last prescription (for the per protocol analysis).

Covariates

The covariates measured at baseline were age, sex, smoking status (current smoker, ex-smoker, or non-smoker), ethnic group (white, black, Asian, mixed, or other), Townsend deprivation score (levels 1-5, with level 5 being the most deprived and level 1 the least deprived), time between the first diagnosis of hypertension to the first indapamide prescription, calendar year, comorbidities (atrial fibrillation, peripheral vascular disease, asthma, chronic obstructive pulmonary disease, chronic kidney disease, dementia, depression, type 1 or 2 diabetes mellitus, migraine, and rheumatoid arthritis), drug treatment use in the past three months before the index date (aspirin, β blockers, calcium channel blockers, renin-angiotensin system inhibitors, other diuretics, oral anticoagulants, statins, antidiabetic drugs, antipsychotic drugs, corticosteroids, insulin, non-steroidal anti-inflammatory drugs (other than aspirin), and proton pump inhibitors), and clinical parameters (body mass index, systolic blood pressure, and diastolic blood pressure). The diagnoses of all comorbidities were identified with validated algorithms available on the CALIBER platform.[21] The same variables, except for age, sex, ethnic group, Townsend deprivation score, time since the first diagnosis of hypertension, and calendar year, were updated at monthly intervals for the inverse probability weight calculation for the per protocol analysis.

Statistical analyses

Data are summarised as mean and standard deviation (SD) for continuous variables, and number (%) of patients for categorical variables. Missing data for smoking status and Townsend deprivation score were analysed as a different data category, and missing ethnic group was assumed to be white.[22] Standardised mean difference was used to evaluate differences in baseline variables between groups. A standardised mean difference <0.1 was considered to be a good balance between the groups.

We described the trends in the prescribing of modified release and immediate release indapamide for each month, from January 2005 to December 2020. The prescribing trends were indexed with the proportion of patients with hypertension receiving a prescription of modified release or immediate release indapamide each month.

We estimated the observational analogues of the intention-to-treat effect (effect of starting treatment with modified release or immediate release indapamide) and per protocol effect (effect of starting and continuous use of modified release and immediate release indapamide, whichever was started first). Switching between or combined use of modified release and immediate release indapamide was not allowed. The intention-to-treat analysis was the primary analysis because the estimate of treatment effect is conservative and therefore used in trials evaluating effectiveness of treatment.[23]

In the intention-to-treat analysis, all baseline covariates were directly adjusted in multivariable pooled logistic regression models with patient information updated at monthly intervals. This approach approximates Cox regression models for the estimation of hazard ratios when the outcome of interest is rare during each time interval.[24] To account for informative censoring from transfer-out, we estimated the time varying inverse probability of censoring weightings with the marginal structural model. Online supplemental methods S1 has

details of the weight calculation. In brief, we used logistic regression models incorporating the baseline covariates and time varying covariates measured at each monthly interval to estimate stabilised inverse probability of censoring weightings for being uncensored (remained in general practice).[25] The numerator of the weights was estimated with the time dependent intercept (in linear and quadratic terms) and baseline covariates only; the denominator was estimated with the time dependent intercept (in linear and quadratic terms), baseline covariates, and time varying covariates.[25] The inverse probability of censoring weighting models were fitted separately for each treatment arm. The stabilised inverse probability of censoring weightings were truncated at the 1st and 99th centiles to avoid the undue influence of extreme weights. The outcome models included a treatment indicator, all baseline covariates, and time since baseline (in its linear and quadratic terms), and were weighed by the stabilised inverse probability of censoring weighting. Robust variance estimators were used to estimate 95% confidence intervals (CIs) for hazard ratios.

In the per protocol analysis, we also censored patients if treatment was discontinued or switched. Because artificial censoring caused by changes in treatment might introduce selection bias, we estimated a stabilised inverse probability of censoring weighting for changes in treatment based on a similar procedure for the inverse probability of censoring weighting for transfer-out in the intention-to-treat analysis. The final weight was calculated as a product between inverse probability of censoring weighting for transfer-out and inverse probability of censoring weighting for variations in treatment. Finally, the same pooled logistic regression models in the intention-to-treat analysis were used as the outcome models.

We further estimated the absolute risks of each study outcome with pooled logistic regression models. The models also included the product terms between treatment and follow-up time. The model estimates the discrete time hazards at each time interval, and five year absolute risks and risk differences were calculated based on the discrete time hazards.[26] Non-parametric bootstrapping with 300 full samples was used to obtain 95% CIs for the predicted absolute risks (2.5th and 97.5th centiles of the survival differences across the bootstrap samples). Findings were considered to be significant when the 95% CIs for risk on a relative scale did not cross 1 or when the 95% CI for risk difference on an absolute scale did not cross 0. All statistical analyses were performed with R Studio version 3.6.3.

Subgroup analysis and sensitivity analysis

We conducted several prespecified subgroup analyses, grouped by baseline age (≥65 years or <65 years), sex, calendar year (before or after 2012), baseline diabetes status, baseline chronic kidney disease status, and number of concurrent classes of antihypertensive drugs (0-1 or ≥2). We conducted several sensitivity analyses to confirm the robustness of our findings. Firstly, we used the Prescription Cost Analysis England data[27] and Office for National Statistics population data to confirm the prescribing trends. The Prescription Cost Analysis data were used to obtain the yearly prescription rates of modified release and immediate release indapamide, which were calculated as the number of prescribed items/1000 population. Secondly, we used a baseline stabilised inverse probability of treatment weight to account for baseline exchangeability between users of modified release and immediate release indapamide. Thirdly, we varied the definition of treatment discontinued from 60 to 180 days in the per protocol analysis. Fourthly, we dealt with missing data in smoking status and Townsend deprivation score by conducting a complete case analysis, where patients with any missing data were excluded. Fifthly, we repeated the analysis with untruncated weights. Lastly, we separately categorised white ethnic group and unknown ethnic group as two classes and repeated the analysis.

Patient and public involvement

The conception of this study was motivated by existing scientific literature and established research questions. No patients were directly involved in conceptualising the research question. This study mainly involved analyses of de-identified electronic health records which are retrospective and data driven in nature, and thus had no direct patient involvement during the design and implementation phases. We plan to transparently disseminate our findings to patients, healthcare providers, and other members of the public.

Results

Prescribing trends

We included 1 904 289 patients with hypertension in the study. Of these, 138 414 patients were ever prescribed indapamide in any formulation with a total record of 1 568 927 modified release indapamide prescriptions and 2 195 643 immediate release indapamide prescriptions between 2005 and 2020. The proportions of users of modified release and immediate release indapamide among all patients with hypertension were 0.71% and 0.43% in January 2005, respectively. The proportion of users of immediate release indapamide increased steadily from late 2011 to 2.31% in December 2020. The proportion of users of modified release indapamide remained relatively constant (0.79% in December 2020). Figure 1 shows the trends in the use of modified

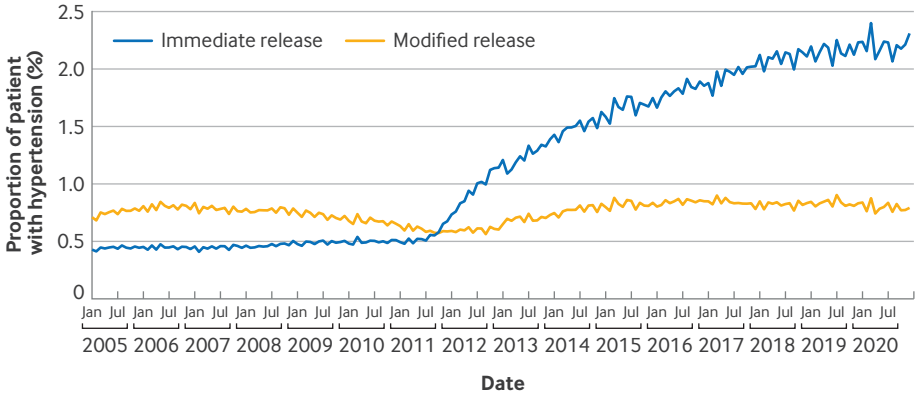

Figure 1 | Trends in the proportion of users of modified release and immediate release indapamide in patients with hypertension, in the IQVIA Medical Research Data UK database, 2005-20

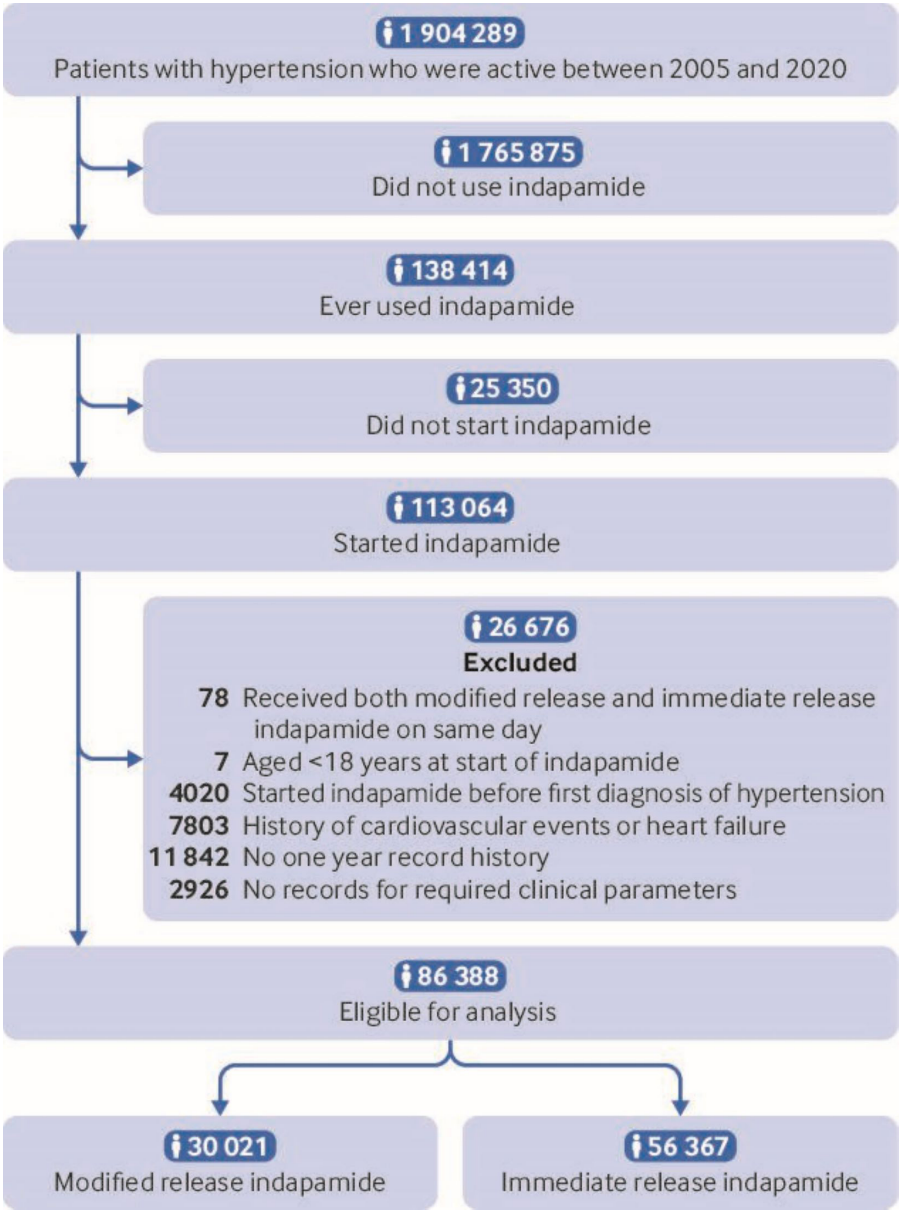

Figure 2 | Selection of eligible patients from IQVIA Medical Research Data UK database between 2005 and 2020 for emulation of the target trial

release and immediate release indapamide in patients with hypertension.

Selection of eligible patients for trial emulation

From the 138 414 patients who were ever prescribed indapamide during the study period, 113 064 started on indapamide treatment during the study period. After applying the eligibility criteria, 86 388 patients were included in the analysis for trial emulation: 30 021 patients started modified release indapamide and 56 367 immediate release indapamide. Figure 2 shows the process for selection and exclusion of patients. Most of the baseline characteristics were comparable between users of modified release and immediate release indapamide without requiring any adjustment (table 1 and online supplemental table S2). The only difference (standardised mean difference ≥0.1) seen between users was calendar year, where patients were more likely to start immediate release indapamide after 2012 (online supplemental table S2). Mean age was 66.9 (SD 12.6) years for users of modified release indapamide and 66.8 (12.4) years for users of immediate release indapamide users, consistent with previous guidelines. The proportions of men were 42.9% and 43.4% in the modified release and immediate release indapamide groups, respectively. Mean time since the first diagnosis of hypertension was 9.1 (SD 9.0) years and 9.6 (8.8) years for the modified release and immediate release groups, respectively. Online supplemental table S2 has a full descriptions of the baseline characteristics of the patients.After applying the stabilised inverse probability of treatment weight (as a sensitivity analysis), all baseline characteristics were well balanced, with a standardised mean difference <0.1 (online supplemental table S2).

Intention-to-treat analysis

In the intention-to-treat analysis, over a median follow-up of period of 53 months for users of modified release indapamide and 44 months for users of immediate release indapamide, 2544 patients had a diagnosis of a cardiovascular event. Among them, 1021 patients started modified release indapamide and 1523 started immediate release indapamide. Figure 3 presents the intention-to-treat cumulative incidence for each treatment arm. The five year cumulative incidence of cardiovascular events was 3.18% (95% CI 2.95% to 3.39%) with modified release indapamide treatment versus 3.21% (3.06% to 3.39%) with immediate release indapamide treatment. Compared with immediate release indapamide, modified release indapamide was not associated with a significantly different risk of cardiovascular events. The absolute risk difference was −0.03% (95% CI −0.34% to 0.19%), corresponding to a hazard ratio of 0.99 (95% CI 0.90 to 1.08) (table 2). The effect estimates for myocardial infarction and stroke separately were similar for the modified release and immediate release groups (online supplemental tables S3,S4 and online supplemental figure S3).

We found no significant difference in the risk of all cause mortality with modified release versus immediate release indapamide treatment. The five year cumulative incidence of all cause mortality was 8.23% (95% CI 7.89% to 8.60%) and 8.44% (8.19% to 8.70%) for modified release and immediate release indapamide treatment, respectively. The absolute risk difference was −0.21% (95% CI −0.61% to 0.22%) and the hazard ratio was 0.97 (95% CI 0.92 to 1.02) (online supplemental table S5 and online supplemental figure S3).

Per protocol analysis

In the per protocol analysis, 76.5% of users of modified release and 77.1% of users of immediate release indapamide deviated from their assigned treatment during the first five years of follow-up. Online supplemental figure S2 shows the cumulative proportion of patients that deviated from the assigned treatment strategies. Over a median follow-up of 13 months for users of modified release indapamide and 12 months for users of immediate release indapamide, 637 patients received a diagnosis of a cardiovascular event. Among them, 223 patients were receiving modified release indapamide treatment and 414 immediate release indapamide treatment. Figure 3 shows the per protocol cumulative incidence in each treatment arm. The five year cumulative incidence of cardiovascular events was 1.54% (95% CI 1.31% to 1.81%) for modified release indapamide treatment versus 1.93% (1.70% to 2.17%) for immediate release indapamide treatment. In the per protocol analysis, we found a lower risk of cardiovascular events with modified release indapamide treatment than with immediate release indapamide. The absolute risk difference was −0.39% (95% CI −0.71% to −0.06%), corresponding to a hazard ratio of 0.81 (95% CI 0.68 to 0.98) (table 2). The associations between modified release and immediate release indapamide and myocardial infarction and stroke individually were consistent with the results for the composite cardiovascular events (online supplemental tables S3,S4 and online supplemental figure S3).

We found no significant difference in the risk of all cause mortality with modified release versus immediate release indapamide treatment. The five year cumulative incidence of all cause mortality was 4.64% (95% CI 4.14% to 5.28%) for modified release indapamide treatment and 4.42% (4.11% to 4.83%) for immediate release indapamide treatment. The absolute risk difference was 0.22% (95% CI −0.36% to 0.96%) and the hazard ratio was 1.03 (95% CI 0.90 to 1.17)

Table 1 | Selected baseline characteristics of patients with hypertension started on modified release and immediate release indapamide treatment, before and after baseline weight

	Before			After		
	Modified release (n=30 021)	Immediate release (n=56 367)	SMD	Modified release (n=30 008.6)	Immediate release (n=56 377.7)	SMD
Mean (SD) age (years)	66.9 (12.6)	66.8 (12.4)	0.007	66.9 (12.6)	66.9 (12.4)	0.004
Men	12 891 (42.9)	24 470 (43.4)	0.010	12 945.4 (43.1)	24 332.1 (43.2)	<0.001
Smoking status:*						
Current smoker	4632 (15.4)	9069 (16.1)		13 474.9 (44.9)	25 319.3 (44.9)	
Ex-smoker	11 508 (38.3)	22 209 (39.4)		11 739.1 (39.1)	22 048.8 (39.1)	
Non-smoker	13 820 (46.0)	25 020 (44.4)		4752.5 (15.8)	8928.5 (15.8)	
Unknown	61 (0.2)	69 (0.1)		42.0 (0.1)	81.1 (0.1)	
Ethnic group:†						
White or unknown	28 455 (94.8)	53 719(95.3)		28 548.1 (95.1)	53 629.5 (95.1)	
Black	460 (1.5)	697 (1.3)		635 (2.1)	1196.1 (2.1)	
Asian	658 (2.2)	1160 (2.1)		401.5 (1.3)	755.7 (1.3)	
Mixed or other	448 (1.5)	791 (1.4)		424.1 (1.4)	796.4 (1.4)	
Mean (SD) time since hypertension diagnosis (years)	9.1 (9.0)	9.6 (8.8)	0.060	9.46 (8.98)	9.46 (8.76)	0.001
Comorbidities:						
Atrial fibrillation	1648 (5.5)	2860 (5.1)	0.019	5598.0 (18.7)	10 532.1 (18.7)	0.001
Dyslipidaemia	5606 (18.7)	10 582 (18.8)	0.003	5662.9 (18.9)	10 603.1 (18.8)	0.002
Peripheral vascular disease	880 (2.9)	1634 (2.9)	0.002	1586.3 (5.3)	2968.1 (5.3)	0.001
Asthma	3980 (13.3)	7923 (14.1)	0.023	874.9 (2.9)	1642.2 (2.9)	<0.001
Chronic obstructive pulmonary disease	1436 (4.8)	2937 (5.2)	0.020	1552.2 (5.2)	2890.7 (5.1)	0.002
Chronic kidney disease	7508 (25.0)	13 675 (24.3)	0.017	4165.3 (13.9)	7799.2 (13.8)	0.001
Dementia	283 (0.9)	503 (0.9)	0.005	554.9 (1.8)	1041.6 (1.8)	<0.001
Depression	6207 (20.7)	12 843 (22.8)	0.051	278.2 (0.9)	516.1 (0.9)	0.001
Diabetes mellitus	5778 (19.2)	10 427 (18.5)	0.019	6628.9 (22.1)	12 439.2 (22.1)	0.001
Migraine	2170 (7.2)	4741 (8.4)	0.044	2379.0 (7.9)	4497.6 (8.0)	0.002
Rheumatoid arthritis	586 (2.0)	1005 (1.8)	0.012	7372.9 (24.6)	13 853.7 (24.6)	<0.001
Drug treatment use in the past 3 months:						
Aspirin	5646 (18.8)	9176 (16.3)	0.066	5257.5 (17.5)	9787.4 (17.4)	0.004
β blockers	6638 (22.1)	10 984 (19.5)	0.065	1176.8 (3.9)	2224.8 (3.9)	0.001
Calcium channel blockers	15 270 (50.9)	31 370 (55.7)	0.096	11 973.5 (39.9)	22 444.2 (39.8)	0.002
Renin-angiotensin system inhibitors	19 419 (64.7)	36 533 (64.8)	0.003	1080.4 (3.6)	2013.1 (3.6)	0.002
Other diuretics	7173 (23.9)	12 647 (22.4)	0.035	3899.4 (13.0)	7305.3 (13.0)	0.001
Oral anticoagulants	1162 (3.9)	2237 (4.0)	0.005	19 419.2 (64.7)	36 517.1 (64.8)	0.001
Statins	11 688 (38.9)	22 665 (40.2)	0.026	6207.1 (20.7)	11 604.8 (20.6)	0.002
Antidiabetic drugs	4025 (13.4)	7208 (12.8)	0.018	16 178.3 (53.9)	30 423.0 (54.0)	0.001
Antipsychotic agents	1650 (5.5)	3418 (6.1)	0.024	6864.2 (22.9)	12 926.8 (22.9)	0.001
Corticosteroids	1249 (4.2)	2576 (4.6)	0.020	1343.0 (4.5)	2518.8 (4.5)	<0.001
Insulin	1151 (3.8)	1940 (3.4)	0.021	2886.0 (9.6)	5429.5 (9.6)	<0.001
Other NSAIDs	3101 (10.3)	5274 (9.4)	0.033	1752.3 (5.8)	3295.7 (5.8)	<0.001
Proton pump inhibitors	7470 (24.9)	15 450 (27.4)	0.058	7989.0 (26.6)	14 983.7 (26.6)	0.001
Clinical parameters:						
Mean (SD) body mass index	29.6 (6.2)	30.0 (6.4)	0.064	29.87 (6.33)	29.88 (6.30)	0.001
Mean (SD) systolic blood pressure (mm Hg)	144.1 (17.8)	142.6 (17.3)	0.086	143.14 (17.34)	143.08 (17.60)	0.003
Mean (SD) diastolic blood pressure (mm Hg)	80.9 (11.1)	80.5 (11.0)	0.041	80.60 (11.08)	80.60 (11.00)	0.001

Data are number (%) unless indicated otherwise.

*Standardised mean difference was 0.040 and 0.001 before and after baseline weight, respectively.
†Standardised mean difference was 0.034 and 0.002 before and after baseline weight, respectively.
NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; SMD, standardised mean difference .

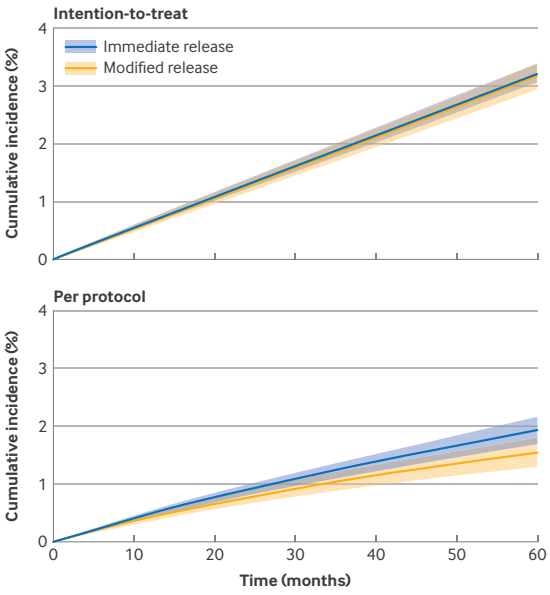

Figure 3 | Standardised, weighted, cumulative incidence curves for composite cardiovascular events (myocardial infarction and stroke) after treatment with modified release versus immediate release indapamide in patients with hypertension

(online supplemental table S5 and online supplemental figure S3)

Subgroup and sensitivity analysis

Figure 4 presents the point estimates for composite cardiovascular events and all cause mortality. The estimates were similar for all subgroup analyses, except for some items in the per protocol analysis. We found a lower risk of cardiovascular events for modified release indapamide versus immediate release indapamide in patients with no diabetes mellitus (hazard ratio 0.76, 95% CI 0.61 to 0.94) or patients receiving 0-1 other antihypertensive agents (0.62, 0.46 to 0.83), but not in patients with diabetes mellitus (1.00, 0.73 to 1.39) or patients receiving two or more antihypertensive drugs (0.97, 0.77 to 1.22) (figure 4).

The results in the sensitivity analyses were consistent with those in the main analysis. The prescribing trends seen in the Prescription Cost Analysis England data were largely consistent with those identified in the IQVIA Medical Research Data UK database (online supplemental figure S1). Online supplemental tables S6–S10 show other results from sensitivity analyses of the trial emulation. Online supplemental table S11 shows the distribution of ethnic groups, with white and unknown ethnic groups separated, for patients with hypertension started on modified release and immediate release indapamide treatment. Online supplemental table S12 presents the balancing of covariates after applying inverse probability of treatment weight and inverse probability of censoring weightings at baseline and 12 months after baseline in the intention-to-treat and per protocol analysis on the primary outcome. All covariates were well balanced in both analyses at baseline and 12 months after baseline.

Discussion

Principal findings

In this study, based on electronic health records from primary care in the UK, we found a substantial increase in the prescribing of immediate release, but not modified release, indapamide since 2011. Prescribing of modified release indapamide was stable over the same time period. We saw similar risks of cardiovascular events and mortality in the analysis of the effect of starting treatment (observational analogue of intention-to-treat effect) whereas in the secondary analysis of the effect of sustained treatment (observational analogue of per protocol effect), we found a lower risk of cardiovascular events for treatment with modified release indapamide than with immediate release indapamide (which was mainly driven by a lower risk of myocardial infarction), but no difference in mortality.

In the UK, indapamide and other thiazide-like diuretics are the recommended diuretics for patients with hypertension.[3] Despite recent increases in

Table 2 | Five year absolute risks, risk differences, risk ratios, and hazard ratios for composite cardiovascular events (myocardial infarction and stroke) after treatment with modified release versus immediate release indapamide in patients with hypertension

Indapamide treatment strategy	No of patients	No of outcomes	Five year absolute risk (%) (95% CI)	Risk difference (%) (95% CI)	Risk ratio (95% CI)	Hazard ratio (95% CI)
Intention-to-treat analysis:						
Modified release	30 021	1021	3.18 (2.95 to 3.39)	−0.03 (−0.34 to 0.19)	0.99 (0.90 to 1.06)	0.99 (0.90 to 1.08)
Immediate release	56 367	1523	3.21 (3.06 to 3.39)	Reference	Reference	Reference
Per protocol analysis:						
Modified release	30 021	223	1.54 (1.31 to 1.81)	−0.39 (−0.71 to −0.06)	0.81 (0.66 to 0.97)	0.81 (0.68 to 0.98)
Immediate release	56 367	414	1.93 (1.70 to 2.17)	Reference	Reference	Reference

CI, confidence interval.

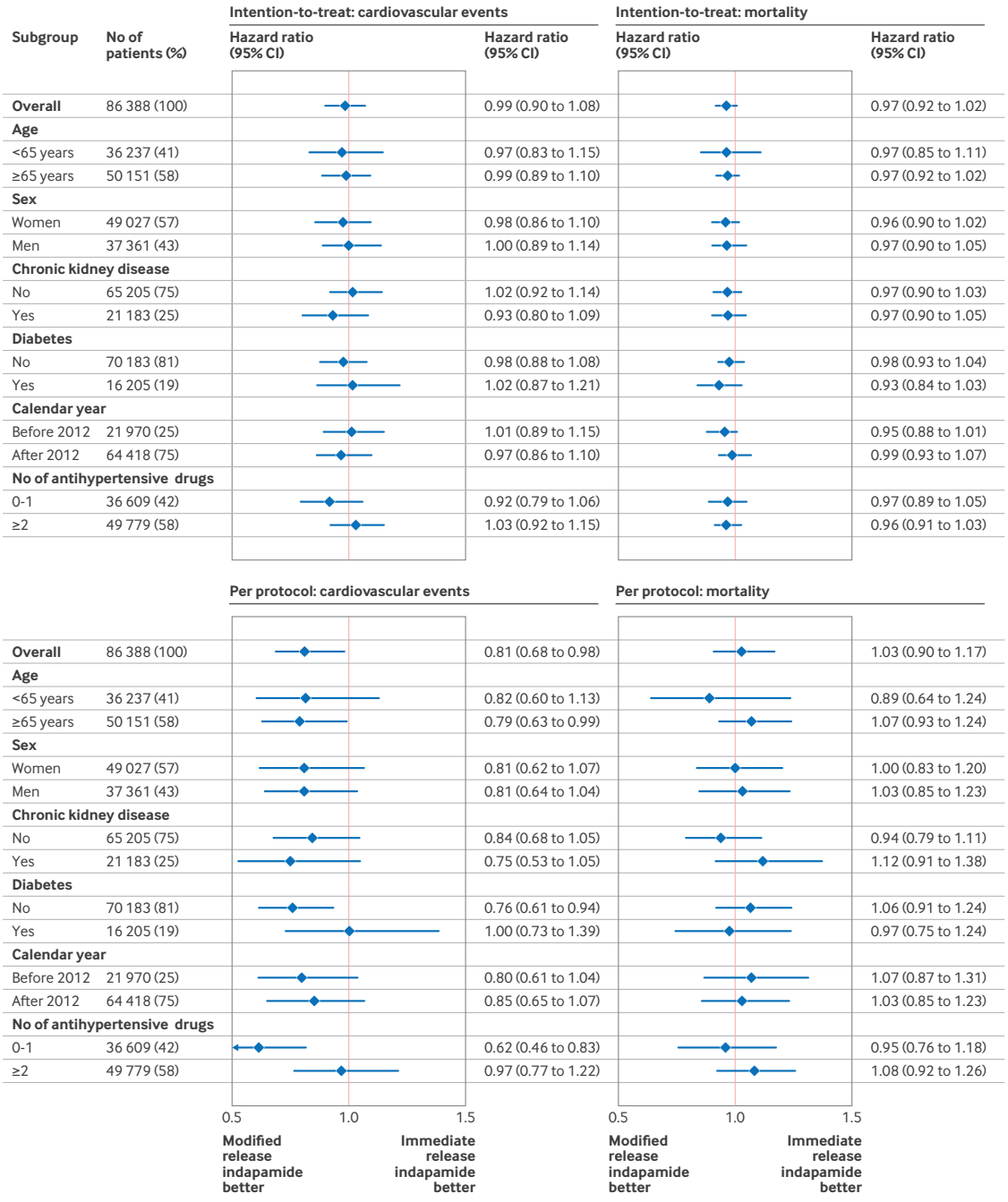

Figure 4 | Subgroup analysis. Hazard ratios for composite cardiovascular events (myocardial infarction and stroke) and all cause mortality for treatment with modified release versus immediate release indapamide in the intention-to-treat and per protocol analyses. CI=confidence interval

prescribing, however, thiazide-like diuretics are underused compared with thiazide diuretics or other antihypertensive agents.[9 28] Our data showed that modified release indapamide has been prescribed less than immediate release indapamide since 2012.[3] Prescribing of modified release indapamide before 2012 might have been influenced by HYVET (Hypertension in the Very Elderly Trial). With a higher drug acquisition cost associated with the modified release formulations (about four times more expensive)[27] and in the absence of evidence on the long term comparative effectiveness of modified release and immediate release preparations, initiatives to change the prescribing practice from modified release to immediate release indapamide during this study period might have occurred at the level of general practice or clinical commissioning group. Our study might therefore provide new insights on the choice of treatment strategy when multiple formulations of the same active substance are available. Formal comparisons between different formulations should be conducted to determine comparative

cost effectiveness and safety outcomes.[29 30] From our data, we found similar effectiveness for starting modified release and immediate release indapamide, and the cardiovascular benefits of modified release over immediate release preparations were only seen with sustained treatment. These findings need to be confirmed in other settings, including in a formal cost effectiveness analysis.

In our data, more than half of users of indapamide discontinued or switched formulations during the first two years of follow-up, reaching three quarters of users by the fifth year of follow-up. These rates are consistent with previously reported real world discontinuation rates for diuretics (42% persistence after two years),[31] but are much higher than those seen in HYVET where >90% of patients remained on indapamide treatment after two years.[6] This finding is expected because patients in real world practice usually have more real life constraints in adhering to treatment.[32] Previous studies have suggested a suboptimal adherence rate for antihypertensive treatment in general, and diuretics were associated with a lower adherence rate than other classes of antihypertensive drug treatments.[28 31 33 34] Poor adherence to diuretics might be related to its distinct side effects, such as hyponatraemia, urinary frequency, and erectile dysfunction.[34] The side effects could further affect the perceived benefits and tolerability of the drugs by prescribers and patients, which is a key determinant of adherence to treatment.[35]

For indapamide specifically, a national shortage in the supply of indapamide preparations during the study period might have further contributed to the pattern of changes in treatment.[36] Furthermore, patients often require diuretics to be switched (eg, to spironolactone at a later stage of hypertension control),[3] also contributing to the high rate of discontinued indapamide treatment during the follow-up period. For these reasons, treatment effects from randomised controlled trials might not be generalisable to real world settings.[37] Thus our study, explicitly emulating a pragmatic trial with observational data, evaluated the real world effect of modified release versus immediate release indapamide on observed cardiovascular event rates. We estimated the effects of starting treatment and sustained treatment, and found similar effectiveness with starting modified release or immediate release indapamide, and potential benefits of sustained treatment with modified release forms over immediate release forms in preventing cardiovascular events. Because of the observed low persistence rate to indapamide treatment, however, we cannot recommend the use of modified release over immediate release indapamide based on our results. Further research on factors influencing adherence to indapamide treatment would help to better understand when and who can benefit from sustained treatment with modified release indapamide.

Within the per protocol analysis on cardiovascular events, we saw signs of heterogeneity in treatment effects of modified release and immediate release indapamide that might be verified in future studies. We found that sustained treatment with modified release indapamide had more marked effects in reducing the incidence of myocardial infarction than stroke. Also, the treatment effects seemed to be more pronounced in some patient subgroups: patients without diabetes had greater benefits from modified release indapamide in reducing myocardial infarction, as did patients who were on fewer concurrent classes of antihypertensive drugs. These analyses are exploratory, however, and the findings need to be interpreted with caution because of the risk of multiple testing and selection bias.[38 39]

Our data should prompt further research into the relative efficacy of indapamide compared with other primary antihypertensive treatments. In the UK, in contrast with other healthcare systems, diuretics have been largely replaced by calcium channel blockers and renin-angiotensin system inhibitors as the first line antihypertensive agents.[28] Previous clinical trials comparing modified release indapamide versus enalapril have shown the non-inferiority of modified release indapamide in reducing blood pressure,[7] and the superiority in reducing left ventricular mass index.[8] Further studies might investigate the effects of modified release indapamide versus other commonly used antihypertensive drugs on cardiovascular outcomes to confirm their comparative benefits.

Strengths and limitations of this study

This study described the prescribing trends of indapamide and directly compared the effectiveness of two different commonly used formulations. We used a database of electronic health records from the UK, which has granular healthcare data allowing us to emulate a pragmatic trial.[40] Specifically, we extracted and adjusted for a large set of potential confounders for indapamide treatment and cardiovascular events or death outcomes. Moreover, we updated these variables longitudinally to account for potential time varying selection bias. Our study was in the target trial emulation framework with an active comparator new user design, which minimised the risk of self-inflicted bias and reduced the risk of confounding.[41 42] Finally, we evaluated the treatment effects in both relative and absolute terms under multiple causal contrasts, which allows more granular interpretation of the data.

Our study had several limitations. Firstly, we emulated assignment of treatment and assessment of adherence based on prescription records; we could not know if the prescriptions were redeemed or consumed by patients. This approach could cause misclassifications of the intervention and bias our results towards null.

Secondly, our study could have measurement errors. We could not obtain data from secondary healthcare settings, and thus we might not have captured all cardiovascular events. Although a previous study showed a high positive predictive value of using primary care data in identifying diagnoses of cardiovascular events, we might have underestimated absolute risks.[43] This misclassification would be expected to be the same for modified release or immediate release indapamide, however, and therefore does not affect the relative risks. Also, a large portion of data were missing on the ethnic group of patients, which prevented us from further investigating the generalisability of our findings to under-represented UK populations.

Thirdly, the length of follow-up in the per protocol analysis was noticeably shortened because of the potential non-adherence to indapamide treatment. This short follow-up period reduced the power of our analyses. Also, we found high rates for discontinuing or switching indapamide treatment but we could not investigate the exact reason for the changes in treatment (ie, because of non-adherence or clinically justifiable changes). Furthermore, we are uncertain about the mechanism of per protocol censoring and whether this mechanism is independent of the outcomes, presenting extra challenges in interpreting the results from the per protocol analysis.

Lastly, because our study was an observational analysis without randomisation, and despite the use of an active comparator and adjustment for many confounders, we cannot completely rule out the effect of residual confounding. This residual confounding might arise from unmeasured variables at the level of the individual patient, medical doctor, or group practice, reflecting non-random prescribing practices of modified release and immediate release formulations. We might also have unmeasured confounding for discontinuing or switching treatment, which could increase the risk of bias by confounding in the per protocol analysis despite the use of inverse probability of censoring weighting models.

Conclusions

We found a substantial increase in the prescribing of immediate release, but not modified release, indapamide, for treating hypertension in the UK after 2011. In patients with hypertension, no difference was seen in the risks of cardiovascular events or overall mortality between starting treatment with modified release or immediate release indapamide. Our secondary per protocol analysis, however, showed that patients who continuously used modified release indapamide had a 0.39% lower absolute risk (19% lower relative risk) of cardiovascular events over five years than those who continuously used immediate release indapamide, with no difference in all cause mortality. These findings suggest that immediate release indapamide is a cost effective option in the general population with hypertension. Clinicians should consider the real world effectiveness together with patient adherence, tolerance, and preferences when selecting between modified release and immediate release formulations for long term management of hypertension.

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Data availability statement Data may be obtained from a third party and are not publicly available. This study used third party data made available under licence that the author does not have permission to share. Requests to access the data should be directed to IQVIA. The statistical codes are available at https://github.com/kcyan96/indapamide/.

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