

# Metformin-based single pill drug combinations for type 2 diabetes in primary care England: A time trend analysis

Syed Shahzad Hasan<sup>1</sup>, Qasim Aslam<sup>1</sup>, Imarah Islam<sup>1</sup>, Chia Siang Kow<sup>2</sup>, Zaheer Ud Din Babar<sup>1</sup>

<sup>1</sup>Department of Pharmacy, School of Applied Sciences, University of Huddersfield, Huddersfield, United Kingdom

<sup>2</sup>School of Pharmacy, Monash University Malaysia, Bandar Sunway, Selangor, Malaysia

## Correspondence

Syed Shahzad Hasan, PhD  
University of Huddersfield,  
Huddersfield, United Kingdom  
Email: [s.hasan@hud.ac.uk](mailto:s.hasan@hud.ac.uk)

## Abstract

*Aims:* There has been an increase in prescribing and costs of oral hypoglycaemic agents in England and other countries. This study aims to investigate the trends in prescriptions, costs, and adverse events of metformin and metformin-based single pill drug combinations from 2015 to 2020 and explore why changes in use or cost are occurring.

*Methods:* Prescriptions and costs data from Prescription Cost Analysis database and Interactive Drug Analysis Profiles presenting all suspected ADRs reported for each drug were examined. Pharmacy level prices were also obtained. Linear regression analysis was used to investigate the trends in prescribing and costs.

*Results:* Prescribing and costs of metformin-based single pill drug combinations (as a percent mean change per year) saw an increase of 8.78% (95% CI: 7.45%, 10.11%,  $p=0.001$ ) and 5.17% (95% CI: 2.13%, 8.22%,  $p=0.009$ ) on average each year, respectively. Metformin was the most prescribed monotherapy drug between 2015 and 2020. The cost of prescribing metformin (as a proportion of total oral hypoglycaemic agents) has been reduced from 30% in 2015 to 17% in 2020. Metformin-dipeptidyl peptidase-4 inhibitor (e.g., metformin-sitagliptin) combination was the most popular metformin-based single pill drug combination. The number of adverse drug reactions per million items dispensed shows that metformin has the lowest adverse drug reactions per million items compared to other oral hypoglycaemic drugs.

*Conclusions:* Overall, an increase in prescription items can be seen for metformin-based single pill drug combinations along with an increase in their costs in primary care in England between 2015 and 2020. There was a declining trend for the number of ADRs reported per million prescription items dispensed for metformin-containing single pill combinations, even though their prescription rate increased.

**Keywords:** Adverse drug reactions, cost, England, metformin, prescribing, primary care, single pill, type 2 diabetes

## List of abbreviations

ADR – Adverse Drug Reactions

DPP4 – DiPeptidyl-Peptidase 4

MHRA – Medicines and Healthcare Product Regulatory Agency

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

PCA – Prescription Cost Analysis

SGLT2 - Sodium-Glucose co-Transporter-2

UK – United Kingdom

## 1. Introduction

Diabetes mellitus is a chronic health condition characterised by hyperglycaemia, resulting from defects in insulin secretion, insulin action, or both. The prevalence of diabetes is on the rise [1]. Worldwide, approximately 415 million people had diabetes in 2019, and this figure is expected to increase to 642 million by 2040 [1]. Women had a lower prevalence of diabetes than men, and the prevalence increased with age, peaking at 70-79 years of age [2]. The prevalence of diabetes in England from 2018 to 2019 was 3.3 million, and in the United Kingdom (UK), this was 3.9 million. In terms of cost, 10% of the National Health Service (NHS) budget is spent on diabetes management in England and Wales, equating to £1.5 million every hour [3]. Each year, an estimated total cost of £14 billion is spent on managing diabetes and its complications. In 2012 alone, about 7.8% (£1.056 billion) of the total cost was spent on antidiabetic agents in the United Kingdom (UK) [3].

There are many classes of oral antidiabetic agents. The biguanides, particularly metformin, are recommended by the National Institute for Health and Care Excellence (NICE) as the first-line oral antidiabetic agent for managing type 2 diabetes [4]. Metformin is especially preferred in patients with type 2 diabetes and concurrent overweight or obesity since it is considered weight neutral [5]. Metformin is often used in single pill drug combinations with other oral antidiabetic agents such as sulphonylureas and thiazolidinediones [5].

There are several advantages that single pill drug combinations, also known as fixed-dose combinations, can offer - from being able to formulate two or more different drugs into the same tablet to increase the efficacy of therapy to reducing pill burden for patients, which in turn could increase patient adherence [6,7]. In addition, pharmacokinetic studies have shown that single pill drug combinations are bioequivalent to their separate tablets [8]. To illustrate, a study by Chang et al. (2015) found that the metformin/dapagliflozin fixed-dose combination was bioequivalent to their separate tablets [9]. A randomised study involving 48 patients by Migoya et al. (2010) also found metformin/sitagliptin fixed-dose combination to be bioequivalent to their separate tablets while also showing good tolerability [10].

The prescription of oral hypoglycaemic agents seems to be increasing, in line with the growing prevalence of diabetes. A study involving 10,875 patients, based on the Diabetes Registry Tyrol, analysed trends in the prescription of antidiabetic agents from 2012 to 2018 [11]. It was found that more than half of the patients (55.6%) were prescribed metformin-based combination therapy. Overall, the study showed that the prescription of newer drug classes such as sodium-glucose co-transporter-2 (SGLT2) inhibitors has become popular in combination with metformin. In contrast, the prescription of sulphonylurea had decreased, in line with the other studies [11]. Costs of oral antidiabetic

agents have risen substantially over the years due to the rising number of prescription items being dispensed and the ever-increasing prevalence rates of diabetes.

Overall, there is a lack of data reporting trends in prescribing and costs of metformin-based single pill oral hypoglycaemic agents in England. Therefore, the present study investigates the trends in prescribing, costs, and adverse drug reactions reporting of metformin and metformin-based single pill drug combinations and explores the potential reasons for the change in prescribing and costs.

## 2. Methods

This study evaluated the trends in prescribing, costs, and the number of adverse drug reactions reported for metformin and metformin-based single pill combinations in England. Data were obtained for metformin and nine single-pill combinations of metformin with other drug classes such as dipeptidyl-peptidase 4 (DPP4) inhibitors, thiazolidinediones, and sodium-glucose transport protein 2 (SGLT2) inhibitors from January 2015 to December 2020 from the Prescription Cost Analysis (PCA) database [12].

### *2.1. Data Source: Prescription Cost Analysis (PCA)*

The PCA database provides details on how many prescription items are dispensed in the community in England and the net ingredient cost of all National Health Service (NHS) prescriptions. The data is now sourced and released by the National Health Service Business Services Authority [12,13]. Pharmacies submit their prescription data every month to the NHSBSA to reimburse prescription items dispensed, where the data is subsequently collected, sourced, and published. The National Health Service (NHS) is the publicly funded and the second largest single-payer healthcare system in the world that is controlled by the UK government through the Department of Health and Social Care (DHSC) in England. Except for certain groups (e.g., pregnant women, under 16, or people with diabetes), most working-age adults have to pay prescription charges in England (standard charge of £9.35 for each prescribed item).

A prescription item is a single drug/medicine prescribed by doctors, dentists, or even non-medical prescribers such as nurses and pharmacists on an FP10 prescription form. For example, if metformin is being prescribed on an FP10 prescription form, it would be counted as one prescription item dispensed, irrespective of how many packets or quantity of tablets is being supplied. However, if different strengths of the same medicine are being prescribed on a single FP10 prescription form, it would be counted as two items dispensed. The net ingredient cost is the basic cost of a drug/medicine usually listed in the drug tariff. It is not usually the cost the NHS pays to purchase the drug. The net ingredient cost can also be the price for which the manufacturer or wholesaler lists the drug. The price

does not include discounts, the costs to dispense the drug, or other fees such as prescription form charges. The net ingredient cost helps standardise costs nationally, allowing for comparison [12].

Prescriptions that doctors in the hospital write are included only if they were dispensed within the community. If prescriptions are written outside of England, such as in other parts of the United Kingdom but dispensed in England, the data would be included. Data that was not included in the PCA database includes prescriptions written in England but are dispensed in a country other than England and prescriptions dispensed in a hospital setting, and medicines written on a private prescription [12]. Table 1 shows the list of drugs being investigated in this study, including the different formulations and strengths used and the basic costs of each drug.

## *2.2. Yellow Card Scheme*

The Medicines and Healthcare Product Regulatory Agency (MHRA) runs the yellow card scheme in the United Kingdom to collect and monitor side effects and adverse drug reactions [14]. Yellow Card scheme maintains a record of Interactive Drug Analysis Profiles presenting all suspected ADRs reported for each drug and vaccine. In addition, healthcare professionals and the public, such as patients, carers, and parents, voluntarily report any adverse drug reactions using the yellow card scheme. The main aim of the yellow card scheme is to ensure that a warning can be issued regarding the safety of a particular medicine prior to a thorough investigation which could take a long time.

## *2.3. Statistical analysis*

After the data was extracted, Microsoft Excel and SPSS version 24 were used to analyse the data. Data from the PCA database was attained for the last five years (specify the year) as a single file for each metformin-containing single-pill combination that was being investigated, as well as metformin alone. The total number of prescription items dispensed and the cost was worked out for each metformin-containing single-pill combination and metformin alone for each year. Pharmacy level prices were also obtained for each single-pill combination and metformin alone. The Bank of England inflation calculator was used to adjust the costs to consider inflation for 2015 to help analyse the trends [15].

The total amount of prescription items dispensed and costs accounted for by all metformin-containing single-pill combinations and metformin alone was obtained from 2015 to 2020. The contributions made by each drug were also recorded. Linear regression analysis was used to find the relationship between variables: a year as the independent variable, prescription items dispensed, and costs as the dependent variable. The percentage mean change per year (with 95% confidence interval [CI]) was worked out by dividing the regression coefficient by baseline number of prescriptions items or costs, respectively [16].

Adverse drug reactions that were serious and fatal were obtained for all metformin-containing single pill combinations and metformin alone. The total number of reports for each drug was recorded to analyse the trends. Again, data from 2015 to 2020 was used.

### 3. Results

**Table 1** shows all the metformin-containing oral formulations investigated in this study, considering all the available brands and the generics. There was a wide variety of different brands available for metformin. In contrast, the metformin-containing single pill combinations were only available as branded products except for metformin/pioglitazone, which was available as a generic product.

Prescribing of oral antidiabetic agents (listed in the BNF) has increased by 16.62% from 2015 to 2020. The number of prescription items with metformin alone (as a proportion of the total number of oral antidiabetic prescription items) had seen only a slight decrease from 53.67% in 2015 to 53.26% in 2020, whilst the cost of prescription items with metformin alone (as a proportion of the total cost of oral antidiabetic prescription items) has seen a significant decrease from 29.28% in 2015 to 17.02% in 2020.

A comparison of the total number of prescription items with metformin-containing single pill combination dispensed between 2015 and 2020 showed that the total number dispensed in 2020 increased to 0.49 million items from 0.34 million items in 2015 (**Table 2 & Figure 1**). The total number of prescription items with metformin-containing single pill combination dispensed (as a proportion of the total oral antidiabetic agents items) increased by 0.20% from 0.93% in 2015 to 1.13% in 2020. All metformin-containing single pill combinations showed an increasing trend in prescription items from 2015 to 2020 except for metformin-vildagliptin (from 71 thousand items to 41 thousand items) metformin-pioglitazone (from 73 thousand items to 25 thousand items), which showed a decreasing trend. The largest increment was found for single pill combinations of metformin-alogliptin (from 10 thousand items to 76 thousand items) and metformin-empagliflozin (from 100 items to 63 thousand items over the last six years (2015-2020)). Single pill combinations of metformin-sitagliptin were most frequently prescribed across the last six years (0.14 million items in 2015 and 0.16 million items in 2020).

The regression analysis shows an 8.78% (95% CI: 7.45, 10.11) increase in the total number of prescription items with metformin-containing single pill combinations per year from 2015 to 2020, as shown in **Table 3**. There is a general increasing trend in the number of prescriptions of metformin and metformin-containing single pill combinations each year, except for metformin-pioglitazone (-13.28%; 95 % CI: -16.34, -10.23), metformin-saxagliptin (-0.94%; 95 % CI: -6.56, 4.68), and metformin-

vildagliptin (-8.67%; 95 % CI: -10.12, -7.23), which all showed a slight decrease each year on average. Metformin- empagliflozin showed a very sharp increase in prescription items.

Regarding the comparison of costs, the costs for all prescription items with metformin-containing single pill combinations increased to £17 million in 2020 from £15 million in 2015, as shown in **Table 2**. The cost of metformin-containing single pill combinations as a proportion of the cost of all oral antidiabetic agents saw a decrease of 0.49%, from 3.21% in 2015 to 2.72% in 2020. Metformin alone (from £136 million to £106 million), and metformin-sitagliptin (from £6.0 million to £5.6 million), had seen a decrease in cost despite an increase in the number of prescription items dispensed; whereas metformin-pioglitazone (from £3.5 million to £0.8 million) and metformin-vildagliptin (from £3.0 million to £1.5 million) had seen a considerable decrease in cost as prescription items dispensed had also seen a considerable fall. On the other hand, the cost for metformin-saxagliptin has decreased (from £0.4 million to £0.1 million), but the number of items dispensed has remained the same.

The cost per prescription item for all the metformin-containing single pill combinations was significantly higher than metformin alone. However, the single pill combinations of metformin-thiazolidinediones significantly decreased cost per prescription item between 2018 and 2019. Single pill combinations of metformin-DPP4 inhibitors had seen an overall reduction in cost per prescription item over the last six years (2015-2020, **Figure 2**). In contrast, single pill combinations of metformin-SGLT2 inhibitors had seen an overall increase in cost per prescription item after taking an initial dip between 2015 and 2016. Nevertheless, when considering all metformin-containing single pill combinations, the cost per prescription item has seen an overall decreasing trend. The regression analysis shows a 5.17% (95% CI: 2.13, 8.22) increase per year for the costs of all metformin-containing single pill combinations from the year 2015 to 2020. As with the trend of prescriptions, the trends for costs of all the drugs are the same except for metformin alone, where an average yearly decrease of 3.13% (95% CI: -10.50, 4.25) in cost was seen despite an increase in the number of prescription items.

**Figure 3** presents the ADRs reported for individual oral hypoglycaemic drugs analysed in this study. The number of adverse drug reactions per million items dispensed shows that metformin has the lowest adverse drug reactions per million items. Newer drugs such as canagliflozin, empagliflozin, and dapagliflozin have a very high number of adverse reactions per million items. Table S1 presenting the ADRs per 1,000 items, found that the highest ADRs were reported for SGLTs.

#### 4. Discussion

This study aimed to investigate the trends in prescriptions, costs, and adverse events of metformin alone and metformin-containing single pill combinations, in primary care England between 2015 to

2020. Overall, there was an increase in the number of prescriptions for metformin alone and most metformin-containing single pill combinations, except for metformin-vildagliptin and metformin-pioglitazone and metformin-saxagliptin. Increasing trends in prescribing were consistent with the increasing prevalence of type 2 diabetes by over 100% between 2000 and 2013, as reported by Sharma et al. (2016) using data from The Health Improvement Network (THIN) primary care database in the UK [2]. In fact, since 1996, the prevalence in the United Kingdom has risen from 1.4 million people to over 3.9 million people in 2019, 90% of whom have type 2 diabetes [1]. In addition, the prescription of metformin as a stand-alone drug has increased as it is currently the first-line treatment according to the NICE's recommendation [17]. Furthermore, metformin has a long-established safety record; clinical data over the past 60 years has shown no significant safety concerns [18,19].

Prescription of metformin-containing single pill combination has seen a 1.4 fold increase from 2015 to 2020. In clinical trials, these single pill combinations are more efficacious than their stand-alone drug counterparts [20-23]. Indeed, a real-world study by Benford et al. (2012) found that being on a DPP4 inhibitor fixed-dose combination instead of its single counterpart saw a mean reduction in HbA<sub>1c</sub> by 0.25% more irrespective of patient compliance [24]. Furthermore, in general, single pill combinations have shown to be advantageous in many other patient-related outcomes, such as increased compliance and tolerability [25]. The study by Blüher et al. (2015) showed that pill count constituted a burden on medication compliance in patients with type 2 diabetes, and the majority of physicians would prefer to prescribe single pill combinations to overcome issues with compliance [7]. In addition, a retrospective controlled cohort study comparing type 2 diabetes patients who switched from monotherapy to either a fixed-dose combination or a loose-dose combination observed a statistically significantly higher change in adherence as well as higher persistence and a smaller change in the number of drug prescriptions over three years in the fixed-dose combination group compared to the loose-dose combination group [26].

Metformin-sitagliptin had been consistently the most frequently prescribed metformin-containing single pill combination in England from 2015 to 2020. Randomized controlled trials have established the safety and efficacy of metformin-sitagliptin in patients with type 2 diabetes as initial combination therapy and as add-on therapy with monotherapy failure. The randomized trial by Goldstein et al. (2007) showed a significant reduction of placebo-subtracted A1C by 2.1% with the highest dose of this single-pill combination (2000 mg/100 mg) as initial therapy in type 2 diabetes [20]. Although the efficacy of the single pill combination of metformin-sitagliptin as add-on therapy was not directly addressed in randomized trials, previous randomized trial of loose-dose combination reported that in patients with type 2 diabetes inadequately controlled with metformin, the addition of sitagliptin improved A1C (-0.6%), fasting glucose, and two-hour postprandial glucose concentrations compared



with placebo [27]. The preference for a single pill combination of metformin-sitagliptin over other metformin-containing single pill combinations may be due to its familiarity among general practitioners; a single pill combination of metformin-sitagliptin has been launched in the UK since 2007.

A decreasing trend was observed for the prescription of single pill combinations containing metformin-pioglitazone. The decline of this single pill combination could be due to the adverse effects of pioglitazone, including weight gain and fluid retention, which can be quite common among its users. In fact, due to the fluid retention effect, it is contraindicated for use in patients with heart failure [28]. Also, another factor that may contribute to the decreased prescription of metformin-pioglitazone is the safety alert that the use of pioglitazone may increase the risk of bladder cancer. The review by European Medicines Agency's Committee for Medicinal Products for Human Use concluded a small increased risk of bladder cancer. Therefore, though the benefits outweigh any risks, it should not be prescribed in patients with a history of bladder cancer [29]. Consistent with our findings, the utilisation of pioglitazone alone had remained minimal in the UK's primary care, suggesting that this drug class has been out of favour for treating type 2 diabetes [2].

Single pill combinations of metformin-SGLT2 inhibitors had seen a significant rise in their prescription with an annual increment of 229.44% from 2015 to 2020. The general increasing trend may be due to their cardiovascular benefits and nephroprotective effects, weight loss benefits, and low risk of hypoglycaemia [30-33]. While the efficacy of fixed-dose combinations of metformin-SGLT2 inhibitors has not been specifically investigated in randomized trials, the efficacy of low-dose combinations has been established. For example, in a 52-week randomized trial, patients with type 2 diabetes were inadequately controlled on multidose insulin, and metformin (mean A1C 8.3 percent), the reduction in A1C were more significant with empagliflozin (-1.18, -1.21, and -0.81 for empagliflozin 10 mg, empagliflozin 25 mg, and placebo, respectively) compared with placebo [34]. Indeed, the sharpest increase was seen in the single pill combination of metformin-empagliflozin. Its preference over other single pill combinations of metformin-SGLT2 inhibitors may be due to the risk of bone fracture and amputation with canagliflozin [35] and the risk of bladder cancer with dapagliflozin [36].

The metformin-containing single pill combinations were only available as branded versions except for metformin-pioglitazone (**Table 1**). Therefore, metformin monotherapy is cheaper by a significant amount when compared to metformin-containing single pill combinations. Despite an annual increment of 1.94% in its prescription, the annual change in costs was -3.13%, suggesting that the inflation-adjusted cost of metformin has decreased over the years. The decrease in the cost of metformin could be due to increased availability of generic versions of the drug over the years, which

are generally cheaper than their branded counterparts (**Table 1**; the price per unit of generic metformin: £0.01; the price per unit of branded metformin [Glucophage]: £0.03). For metformin-containing single pill combinations, the annual change in cost was consistent with the annual change in their prescription rate; annual increment in prescription led to a yearly increment of cost and vice versa. However, except for metformin-canagliflozin, the cost per prescription item for other metformin-containing single pill combinations had decreased over the years, indicating decreasing price per unit for most of these single pill combinations, which should lead to improved affordability.

Metformin had the lowest number of ADRs reported per million prescriptions dispensed, backing up its long-term safety data. There was a declining trend for the number of ADRs reported per million prescription items dispensed for metformin-containing single pill combinations, showing no increased reporting in ADRs even though an upsurge in their prescription rate. The decrement could be due to increased acknowledgment of health care professionals towards the side effects of these agents, and therefore avoidance of their prescribing in vulnerable populations. For example, the avoidance of metformin-SGLT2 inhibitors in patients with frequent bacterial urinary tract infections or genitourinary yeast infections and avoidance of metformin-DPP-4 inhibitors in patients with liver disease.

Several limitations could help future research into the trends in prescribing, cost, and adverse events of oral antidiabetic agents in the UK. The data source for this study, namely the PCA database, only covers prescribing and cost data from the community, excluding drugs dispensed on private prescriptions and in hospitals. Therefore, the data was not representative of the whole English population. Also, the PCA database did not include patient demographics such as age and sex, and thus relevant patient factors influencing the choice of prescribing could not be investigated. Moreover, there were also limitations with the MHRA yellow card scheme because the reporting of ADRs is voluntary and not mandatory. Therefore, under-reporting might be possible where not all ADRs had been documented.

## 5. Conclusion

Overall, the study has found an increasing trend in the number of prescription items and costs of drugs for type 2 diabetes between 2015 and 2020, with prescribing of metformin-based single pill drug combinations increasing significantly. Therefore, linking prescribing, cost, and ADR data with relevant literature would help clinicians interpret safety and efficacy data of single-pill combinations of various oral antidiabetic drugs.

## Author Contributions

SSH conceptualised the study. SSH, QS, and IS participated in the study design, interpretation of the study results, manuscript drafting, and critical revision. CSK and ZUB participated in the critical revisions of the manuscript. All authors approved the final version of the manuscript.

## Conflict of Interests

The authors have no conflict of interest to declare

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## Ethics Approval

This study used anonymized information from the NHSBSA database; therefore, institutional ethics approval was not required.

## Consent to Participate

This study used anonymized information from the NHSBSA database; therefore, informed consent was not required.

## Availability of Data and Material

The data that support the findings of this study are available from the NHS study; please get in touch with NHSBSA (<https://www.nhsbsa.nhs.uk>).

## Supplemental Material

Supplemental material for this article is available online.

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**Table 1:** Drug presentations included in this study as well as the price per unit

Drug Name	Brand	Strength	Dosage Forms	Price Per Unit (per tab or ml in pence)
Metformin	Generic	500mg & 850mg	Tablet	500mg = 0.010 850mg = 0.030
	Generic	500mg/5ml, 850mg/5ml & 1g/5ml	Oral solution (sugar and sugar free formulations included)	500mg/5ml = 0.026
	Generic	500mg, 750mg & 1g	Modified release tablet	500mg = 0.020 750mg= 0.050 1g= 0.068
	Glucophage	500mg & 850mg	Tablet	500mg = 0.034 850mg = 0.057
	Glucophage	500mg, 750mg & 1g	Modified release tablet	500mg = 0.068 750mg & 1g = 0.100
	Bolamyn	500mg & 1g	Modified release tablet	500mg= 0.034 1g= 0.089
	Metabet (Morningside and Actavis)	500mg & 1g	Modified release tablet	500mg Actavis = 0.070 500mg morn = 0.090 1g Actavis= 0.110 1g morn = 0.160
	Glucient	500mg, 750mg & 1g	Modified release tablet	
	Diagemet XL	500mg	Modified release tablet	
	Sukkarto	500mg, 750mg & 1g	Modified release tablet	500mg= 0.039 750mg= 0.051 1g= 0.066
	Meijumet	500mg, 750mg & 1g	Modified release tablet	
	Yaltormin	500mg, 750mg & 1g	Modified release tablet	500mg= 0.043 750mg= 0.051 1g= 0.069
	Metuxtan	500mg	Modified release tablet	0.071
Metformin /Sitagliptin	Janumet	50mg/1g	Tablet	0.493
Metformin/ Linagliptin	Jentadueto	2.5mg/850mg & 2.5mg/1g	Tablet	0.572
Metformin/ Saxagliptin	Komboglyze	2.5mg/850mg & 2.5mg/1g	Tablet	0.519
Metformin/ Alogliptin	Vipdomet	12.5mg/1g	Tablet	0.437
Metformin/ Dapagliflozin	Xigduo	5mg/850mg and 5mg/1g	Tablet	5mg/850mg= 0.518 5mg/1g= 0.494
Metformin/ Canagliflozin	Vokanamet	50mg/850mg & 50mg/1g	Tablet	0.548
Metformin/ Empagliflozin	Synjardy	5mg/1g, 5mg/850mg, 12.5mg/850mg & 12.5mg/1g	Tablet	0.653
Metformin/ Pioglitazone	Generic	15mg/850mg	Tablet	
	Competact	15mg/850mg	Tablet	0.567
Metformin/ Vildagliptin	Eucreas	50mg/850mg 50mg/1g	Tablet	0.595

**Table 2:** Prescription items dispensed and costs of single-pill combinations of metformin 2015 and 2020.

Drug class, n (%)	Thousands of prescription items		Inflation-adjusted costs, £000s	Costs, £000s
	2015	2020	2015	2020
Metformin	19,759.5	22,868	136,036.42	106,240
Metformin-Dapagliflozin	7.1	42	353.48	1,711
Metformin-Canagliflozin	1.9	12	71.08	470
Metformin-Empagliflozin	0.1	63	6.37	2,474
Metformin-Pioglitazone	73.3	25	3453.23	849
Metformin-Sitagliptin	136.4	157	5999.00	5,598
Metformin-Linagliptin	32.1	60	1276.81	2,017
Metformin-Saxagliptin	10.0	10	376.10	305
Metformin-Alogliptin	10.1	76	340.80	2,091
Metformin-Vildagliptin	70.7	41	3031.01	1,471
Metformin-SGLT	9.1	117	430.93	4,655
Metformin-THZ	73.3	25	3453.40	849
Metformin-DPP4	259.2	344	11,023.73	11,482
<b>Total Single-Pill drugs, n</b>	<b>342</b>	<b>486</b>	<b>14,908</b>	<b>16,987</b>
<b>Total oral hypoglycaemic agents</b>	<b>36,819</b>	<b>42,938</b>	<b>464,678</b>	<b>624,237</b>
<b>Metformin as proportion of oral hypoglycaemic agents total, %</b>	<b>53.67</b>	<b>53.26</b>	<b>29.28</b>	<b>17.02</b>
<b>Single pill as proportion of oral hypoglycaemic agents total, %</b>	<b>0.93</b>	<b>1.13</b>	<b>3.21</b>	<b>2.72</b>

Abbreviations: SGLT= sodium-glucose co-transporter-2 inhibitors, THZ= thiazalidinedione, DPP4= dipeptidyl peptidase-4 inhibitor.

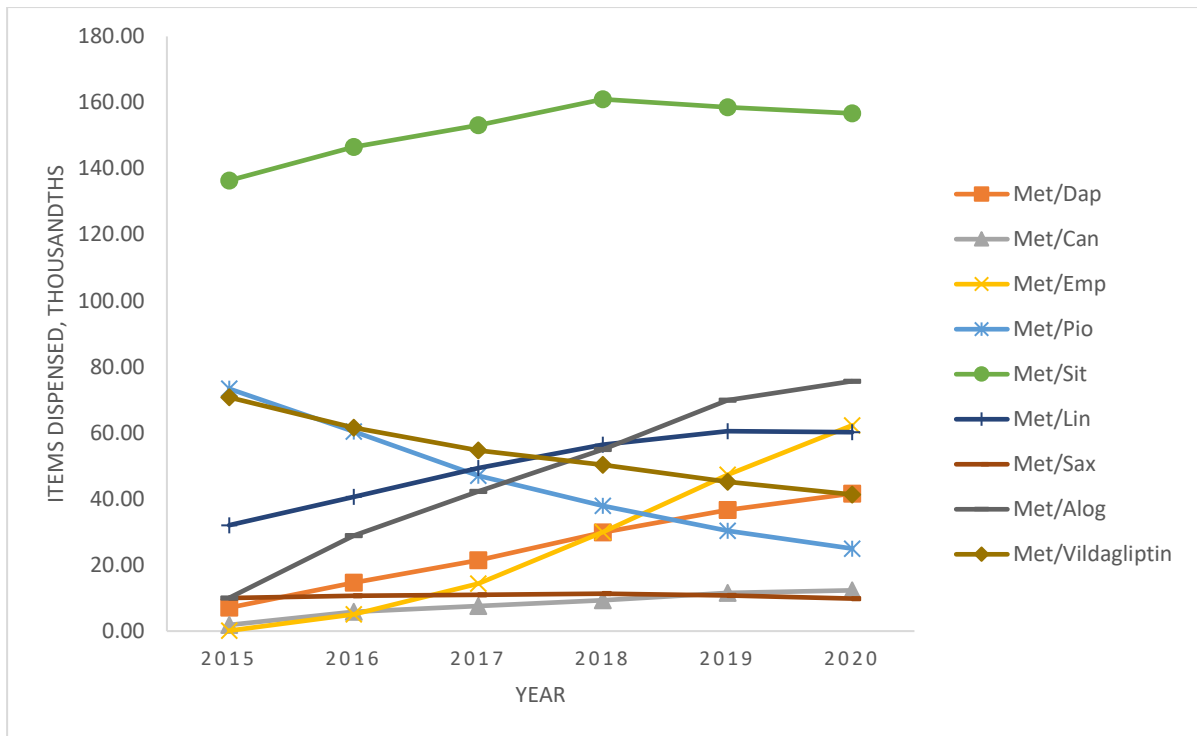


**Table 3:** Regression analysis of yearly trends in prescriptions (items dispensed) and cost

Items	Prescriptions, mean change per year as % of baseline <sup>a</sup> (95% CI)				Costs, mean change per year as % of baseline <sup>a</sup> (95% CI)			
	% change	<i>LCI</i>	<i>UCI</i>	<i>P</i>	% change	<i>LCI</i>	<i>UCI</i>	<i>P</i>
Metformin	1.94	-0.18	4.05	0.064	-3.13	-10.50	4.25	0.305
Metformin-Dapagliflozin	17.89	75.00	112.03	0.001	86.31	71.82	100.80	0.001
Metformin-Canagliflozin	102.35	62.16	142.55	0.002	119.87	78.38	161.37	0.001
Metformin-Empagliflozin	9198.41	7066.25	11330.56	0.001	8654.05	6611.04	10697.06	0.001
Metformin-Pioglitazone	-13.28	-16.34	-10.23	0.001	-14.45	-17.93	-10.97	0.001
Metformin-Sitagliptin	1.88	-2.36	6.12	0.285	0.50	-2.86	3.86	0.700
Metformin-Linagliptin	16.60	6.38	26.83	0.011	15.35	5.92	24.77	0.011
Metformin-Saxagliptin	-0.94	-6.56	4.68	0.668	-1.71	-6.39	2.97	0.367
Metformin-Alogliptin	124.08	88.96	159.19	0.001	114.06	85.83	142.30	0.001
Metformin-Vildagliptin	-8.67	-10.12	-7.23	0.001	-9.22	-11.19	-7.24	0.001
<b>Metformin + SGLT</b>	<b>229.44</b>	<b>198.42</b>	<b>260.47</b>	<b>0.001</b>	<b>218.45</b>	<b>185.45</b>	<b>251.44</b>	<b>0.001</b>
<b>Metformin + THG</b>	<b>-13.28</b>	<b>-16.34</b>	<b>-10.23</b>	<b>0.001</b>	<b>-14.45</b>	<b>-17.94</b>	<b>-10.97</b>	<b>0.001</b>
<b>Metformin + DPP4</b>	<b>5.46</b>	<b>0.61</b>	<b>10.31</b>	<b>0.035</b>	<b>2.98</b>	<b>-0.77</b>	<b>6.74</b>	<b>0.092</b>
<b>Total Single Pill</b>	<b>8.78</b>	<b>7.45</b>	<b>10.11</b>	<b>0.001</b>	<b>5.17</b>	<b>2.13</b>	<b>8.22</b>	<b>0.009</b>
<b>Total oral hypoglycaemic agents</b>	<b>4.25</b>	<b>3.87</b>	<b>4.62</b>	<b>0.001</b>	<b>13.17</b>	<b>8.59</b>	<b>17.76</b>	<b>0.003</b>

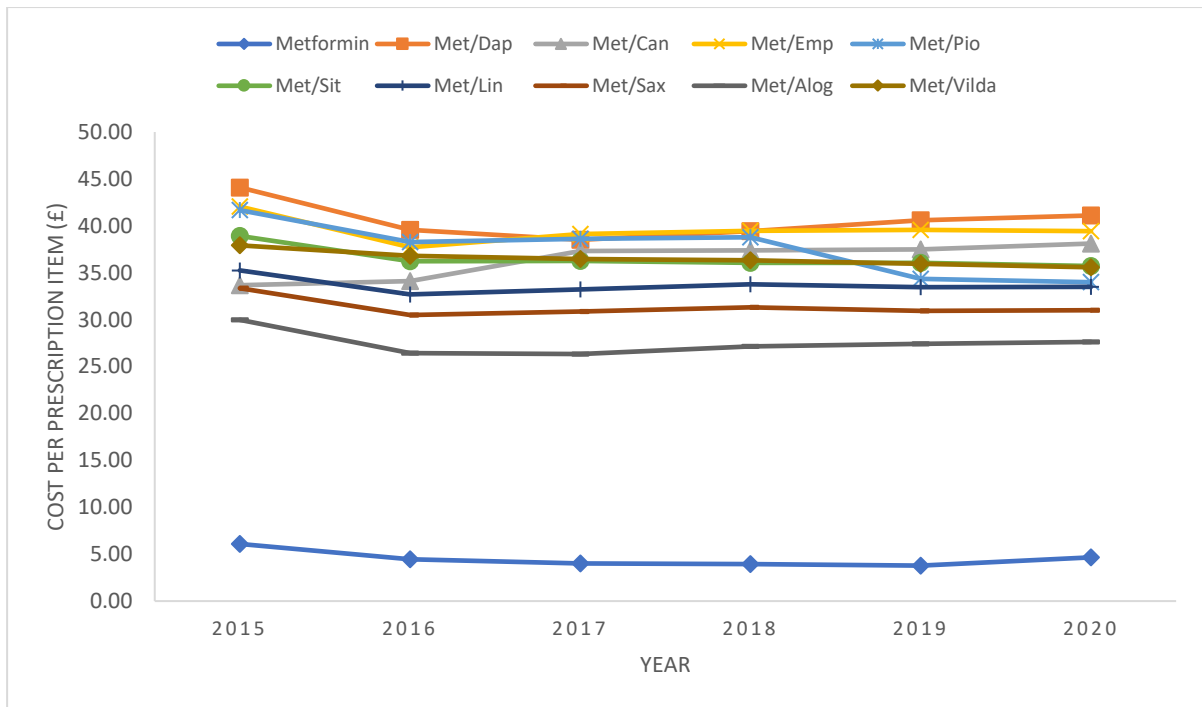
Abbreviations: SGLT= sodium-glucose co-transporter-2 inhibitors, THZ= thiazalidinedione, DPP4= dipeptidyl peptidase-4 inhibitor.

a = % change was calculated by dividing the regression coefficient by baseline prescriptions or costs from 2015 as given in **Table 2**



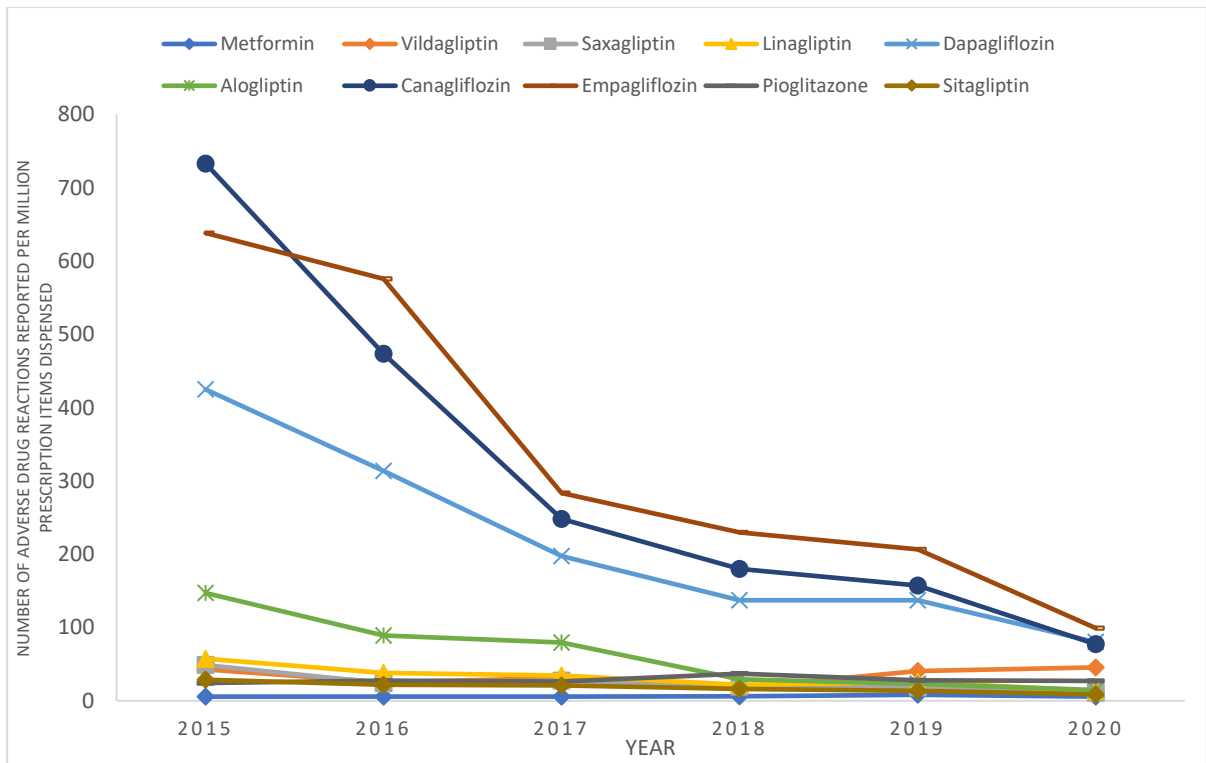
**Figure 1:** The number of items dispensed for metformin-based single pill combination drugs from 2015 to 2020.

Abbreviations: Met/Dap = metformin-dapagliflozin, Met/Can= metformin-canagliflozin, Met/Emp= metformin-empagliflozin, Met/Pio= metformin-pioglitazone, Met/Sit= metformin-sitagliptin, Met/Lin= metformin-linagliptin, Met/Sax= metformin-saxagliptin, Met/Alog= metformin-alogliptin, Met/Vildagliptin= metformin-vildagliptin.



**Figure 2:** Cost per prescription item of each single pill drug formulation from 2015 to 2020.

Abbreviations: Met/Dap = metformin-dapagliflozin, Met/Can= metformin-canagliflozin, Met/Emp= metformin-empagliflozin, Met/Pio= metformin-pioglitazone, Met/Sit= metformin-sitagliptin, Met/Lin= metformin-linagliptin, Met/Sax= metformin-saxagliptin, Met/Alog= metformin-alogliptin, Met/Vilda= metformin-vildagliptin.



**Figure 3:** Graph showing ADR per million items dispensed from 2015 to 2020