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Adoption of new medicines in primary care: a comparison between the uptake of new oral anticoagulants and diabetes medicines

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Submitted

ABSTRACT

Aim

To gain insight in the uptake and practice variation in the prescription of two new medicine groups for common conditions in primary care (direct-acting oral anticoagulants (DOACs) and incretin-based therapies) from introduction, around 2007, to 2019 and the correlation between the adoption of those medicines in primary care.

Methods

Prescription data from general practices in the Dutch Nivel Primary Care Database from 2007 – 2019 were used. The percentage of patients with prescriptions for DOACs of all patients with prescriptions for DOACs and vitamin K antagonists (VKAs) was calculated per practice per year, as was the percentage of patients prescribed incretin-based therapies as a proportion of all patients with diabetes medication. Multilevel models were used to estimate practice variation for DOACs and incretin-based therapies, expressed as intraclass correlation coefficients (ICC). Linear regression analysis was used to study the association between the prescription of DOACs and incretin-based therapies.

Results

Per year, 46 to 424 general practices and 179,933 to 1,654,376 patients were included. In 2019, the mean percentage of patients per practice using DOACs or incretin-based therapies was 54.9% and 9.7%, respectively. The ICC decreased from 0.75 to 0.024 for DOACs and from 0.33 to 0.074 for incretin-based medicines during the study period. No clear correlation was found between the prescription of DOACs and incretin-based therapies.

Conclusion

DOACs and incretin based therapies have different adoption profiles and practice variation is large, especially in the years before guidelines. Early adopters of both medicine classes differ.

INTRODUCTION

New medicines have been associated with increased longevity and can therefore be beneficial for patients [1]. On the other hand, the benefit-risk ratio of new medicines has not been fully elucidated and new medicines are often more expensive than established treatments [2,3]. Therefore, monitoring and understanding the uptake patterns of new medicines is important, to maintain quality of care, to identify patients who would benefit most from new treatments and to prevent unnecessary healthcare costs [4].

The uptake of new medicines in primary care is often not equally distributed among physicians [5]. For example, in studies among British general practitioners, 42% of prescriptions for new medicines were initiated by 10% of the physicians [6]. The adoption of new medicines is likely to be dependent on patient factors (e.g. sex, age and body weight) as well as physician characteristics (e.g. practice location, degree of scientific commitment) [2,4,5,7]. In most cases, the number of adopters of new medicines increases quickly after introduction and thereafter reaches a plateau [8], leading to extensive practice variation in the first years after introduction. Whether this general pattern of innovation is applicable to all kinds of new medicines in primary care is unknown. In addition, it is not known whether early adoption of new medicines, independent of medicine group, is practice related.

The introduction of new treatments for thrombo-embolic diseases and type 2 diabetes mellitus (T2DM) offers opportunities to study and compare the uptake of new medicines in primary care. Direct-acting oral anticoagulants (DOACs) were introduced in 2008 for the treatment of thrombo-embolic diseases. Dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, both incretin-based therapies, were introduced in 2007 and (late) 2006 respectively, for the treatment of T2DM [9]. Both new medicine classes share some important characteristics. For example, they were introduced about the same period and both DOACs and incretin-based therapies are indicated for common conditions that are mainly treated in primary care. In addition, both new classes were not recommended as first-line treatments in the clinical guidelines – which are known to have a profound impact on prescription behaviour in the Netherlands [10,11] – for primary care practitioners, until 2016 (DOACs) and 2018 (T2DM) [12,13]. Because of the impact of guidelines on prescription behaviour, it is of particular interest to shed light on the prescription patterns in the period before and shortly after those medicines were recommended in the guidelines. Although former studies have focused on the uptake patterns of both new medicine classes [14,15], uptake of both medicine classes in primary care has not been compared. In addition, it is not known whether early adoption of DOACs is associated with the early adoption of incretin-based therapies and vice versa.

To gain more insight in the similarities and differences in the uptake of new medicines in primary care, we studied the uptake and practice variation in the prescription of DOACs and incretin-based therapies from 2007 to 2019 and determined the correlation between the adoption of those new medicines.

METHODS

Study setting and subjects

Data from the Nivel Primary Care Database (Nivel-PCD) was used. Nivel-PCD collects data from routine electronic health records from a dynamic sample of general practices in the Netherlands and covers currently approximately 10% of the Dutch population [7]. Data includes information on patient characteristics (e.g. sex, age, consultations, morbidity, prescriptions and laboratory test results) and practices (e.g. number of listed patients and location). The age and sex distribution of listed patients is representative of the general Dutch population.

We selected all patients who were prescribed one or more anticoagulants or blood glucose lowering medicines (excluding insulins) from 2007 up to and including 2019, the year after the uptake of the incretin-based medicines in the T2DM guideline and before the outbreak of COVID-19 which could have influenced prescription behaviour. Corresponding Anatomical Therapeutic Chemical Classification system (ATC) codes included B01AA (vitamin K antagonists [VKAs]), B01AE (direct thrombin inhibitors), B01AF and B01AX06 (direct factor Xa inhibitors) and A10B (blood glucose lowering medicines, excluding insulins).

Data analysis

For each year, the number of practices, enlisted patients and number, sex and age of patients with prescriptions for anticoagulants or blood glucose lowering medicines were extracted. All eligible practices and patients were included, irrespective of their inclusion in former years.

Among patients with anticoagulants, we selected the last prescription per patient per year. Thus, if a patient switched between anticoagulants during the year, the last prescribed anticoagulant was included. The percentage of patients with prescriptions for DOACs (B01AE, B01AF and B01AX06) as a proportion of all patients with prescriptions for DOACs and VKAs (B01AA) was calculated per practice per year, for the period 2008, the year of introduction of DOACs, to 2019.

Since T2DM patients often use multiple blood glucose lowering medicines simultaneously, we first selected all patients with prescriptions for blood glucose lowering medicines excluding insulins (A10B). We then selected all patients with a prescription for a DPP-4 inhibitor (A10BH, A10BD07, A10BD08, A10BD10, A10BD11) or GLP-1 receptor agonist (A10BJ, A10BX04, A10BX07, A10BX10, A10BX13, A10BX14). Patients with the incomplete ATC-code A10BX were excluded from further analysis, since this could refer to incretin-based therapies as well as other blood glucose lowering medicines ($n = 2$ in both 2007 and 2015). We subsequently calculated the percentage of patients with prescriptions for incretin-based therapies (DPP-4 inhibitors or GLP-1 receptor agonists) as a proportion of all patients with prescriptions for blood glucose lowering medicines excluding insulins per practice per year, for the period 2007 to 2019.

To examine practice variation, we constructed multilevel models with patients (level 1) clustered within general practices (level 2) per year, using random effects models. For DOACs, the analysis were conducted for 2009 and further, because prescription rates in former years were too low to perform multilevel modelling. For incretin-based therapies, results were available from 2008. We used grand mean centering for both age and sex and included those as independent variables in these models, to adjust for population differences between practices. For every year, the intercept and corresponding standard errors were calculated. These were transformed into probabilities and corresponding 95% confidence intervals (95% CIs) and plotted per practice. Intraclass correlation coefficients (ICC) were calculated to indicate the relative contribution of variation at practice level (level 2) to the total variation.

From 2008 and further, scatter plots were constructed with the percentage of patients with DOACs among all patients with DOACs or VKAs per practice and percentage of patients with incretin-based therapies among T2DM patients per practice per year. The association between both variables was determined by linear regression analysis, both univariate and multivariate including mean age and sex of patients per practice. As sensitivity analysis, the linear regression analysis was also performed with sodium-glucose co-transporter 2 (SGLT2) inhibitors (A10BK, A10BD15, A10BD16, A10BD20, A10BD23, A10BX09, A10BX11 and A10BX12) added to the incretin-based therapies. This was done to investigate whether the introduction of SGLT2 inhibitors, introduced in 2013 for the treatment of T2DM [9], affected the correlation with the prescription of DOACs. In the second sensitivity analysis, the analysis was restricted to single-handed practices only, to investigate whether the prescription of new medicines was related to prescribers rather than to practices.

Results were considered statistically significant if $p < 0.05$. Stata SE version 16.1 was used for all analyses.

RESULTS

Baseline characteristics

The number of included practices and total number of enlisted patients per year are shown in Table 1. The percentage of patients with prescriptions for anticoagulants (VKA or DOAC) among the total population increased from 1.6% in 2007 to 3.4% in 2019. The number of patients with prescriptions for T2DM medicines increased from 2.8% in 2007 to 4.2% in 2016 and thereafter remained almost stable and was 4.1% in 2019.

Table 1: Number of included practices and patients and the number of patients with prescriptions for anticoagulants and T2DM medication (excluding insulin) from 2007 to 2019.

	Number of practices	Anticoagulants				T2DM medication			
		Number of patients	Number of patients (%)	Sex (% female)	Age, mean (SD)	Number of patients (%)	Sex (% female)	Age, mean (SD)	
2007	46	179,933	2,912 (1.62)	44	70 (14)	4,991 (2.77)	50	66 (13)	
2008	61	235,975	3,923 (1.66)	44	71 (13)	7,093 (3.01)	50	66 (13)	
2009	61	246,159	4,337 (1.76)	44	71 (14)	7,757 (3.15)	49	66 (13)	
2010	169	665,030	13,171 (1.98)	45	71 (13)	23,245 (3.50)	49	66 (12)	
2011	288	1,114,966	24,581 (2.20)	45	72 (13)	41,412 (3.71)	48	66 (12)	
2012	327	1,285,864	28,875 (2.25)	45	72 (13)	48,323 (3.76)	48	66 (12)	
2013	414	1,654,376	39,687 (2.40)	45	72 (13)	64,350 (3.89)	48	66 (12)	
2014	422	1,642,396	41,940 (2.55)	45	72 (13)	64,959 (3.96)	47	67 (12)	
2015	405	1,471,700	41,574 (2.82)	45	73 (12)	59,825 (4.07)	46	67 (12)	
2016	319	1,190,602	36,598 (3.07)	44	73 (12)	50,233 (4.22)	46	67 (12)	
2017	424	1,579,988	48,615 (3.08)	44	73 (12)	65,845 (4.17)	46	67 (12)	
2018	399	1,495,697	47,962 (3.21)	44	73 (12)	61,908 (4.14)	45	67 (12)	
2019	363	1,390,321	47,342 (3.41)	44	73 (12)	57,223 (4.12)	45	68 (12)	

SD = standard deviation, T2DM = type 2 diabetes mellitus.

Uptake of DOACs and newer T2DM medicines

The mean percentage of patients per practice using DOACs among all users of anticoagulants increased from 0.047% in 2008, their first year of introduction to 54.9% in 2019 (Figure 1). The percentage of patients with prescriptions for incretin-based therapies per practice increased in the period 2007 to 2019 from 0.029% to 9.7%. After a slight increase from 2007 to 2013 (+7.3%) the percentage stabilized until 2017. In 2018 and 2019, the proportion of patients with prescriptions for DPP-4 inhibitors or GLP-1 receptor agonists started to increase again.

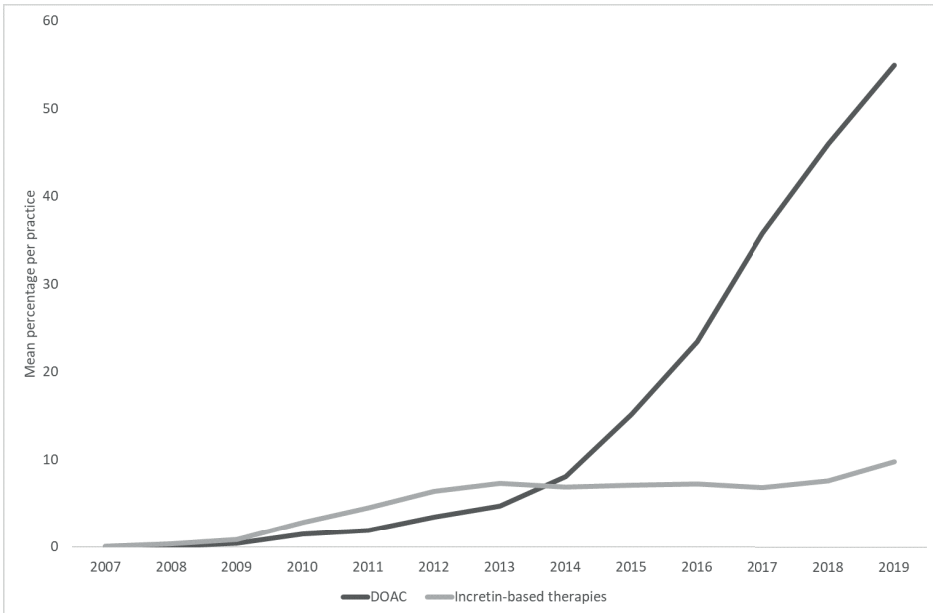


Figure 1: Mean percentage of patients per practice with prescriptions for DOACs and incretin-based therapies compared to all patients with anticoagulants and T2DM medication, respectively.

Practice variation

Figures 2 and 3 represent the variation in the prescription of new medicines, corrected for age and sex of patients for all practices per year.

In the first years after the introduction of both the DOACs and incretin-based therapies, the overall prescribing was low and both the variation within a practice (indicated by the length of each bar individually) as between practices (indicated by the range of y-values per practice) was large. This is also represented in Table 2, which shows the ICC as indication of the relative importance of the variation between practices to the total variation. For DOACs, the ICC started at 0.75 in 2009 and was as low as 0.024 in 2019. A sudden decline was seen in 2015, when the ICC decreased from 0.19 to 0.073. For the incretin-based therapies, the decline in ICC showed much more of a gradient. In the first years after their introduction, the ICC was not as high as for the DOACs (between 0.15 and 0.33). From 2010, the ICC showed a steadily decrease every year to 0.074 in 2019. To sum up, as the uptake of the new medicines increased, the variation between practices decreased, which was more outspoken for the DOACs than for the incretin-based therapies.

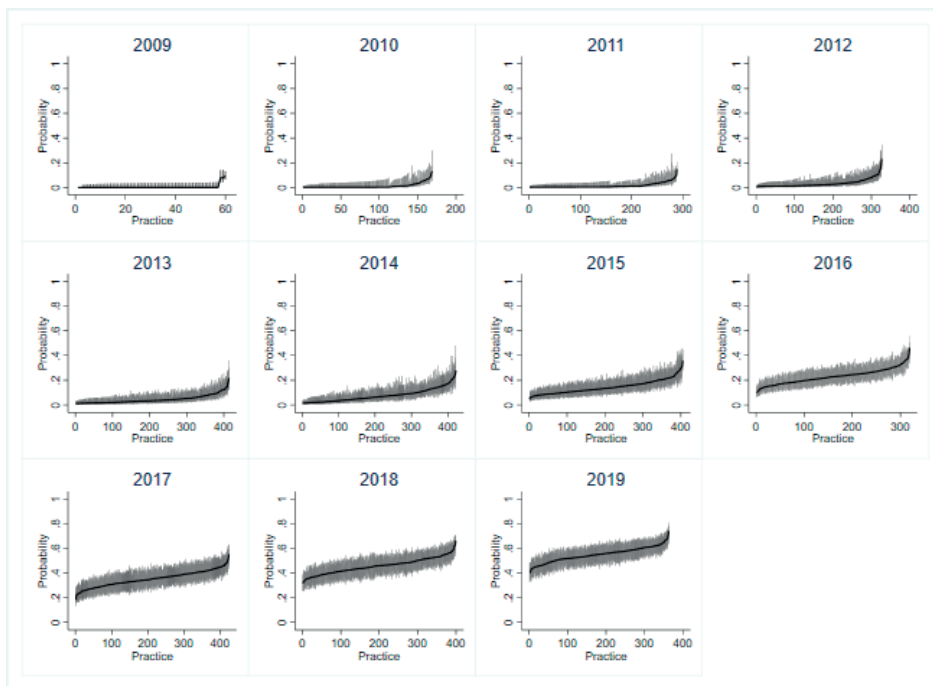


Figure 2: Variation in the prescription of DOACs from 2009 – 2019 (2008 not available due to too few values). The figure shows the variation within a practice (indicated by the length of each bar individually) as well as the variation between practices (indicated by the range of y-values per practice).

Table 2: ICC for DOACs and incretin-based therapies per year.

	DOACs		Incretin-based therapies	
	ICC	95%CI	ICC	95%CI
2008	N/A	N/A	0.15	0.025 – 0.54
2009	0.75	0.39 – 0.94	0.33	0.17 – 0.54
2010	0.52	0.40 – 0.63	0.20	0.15 – 0.26
2011	0.38	0.30 – 0.46	0.18	0.15 – 0.22
2012	0.27	0.22 – 0.32	0.16	0.14 – 0.19
2013	0.19	0.16 – 0.23	0.14	0.12 – 0.17
2014	0.19	0.16 – 0.23	0.13	0.11 – 0.16
2015	0.073	0.060 – 0.088	0.12	0.10 – 0.14
2016	0.047	0.038 – 0.059	0.12	0.098 – 0.14
2017	0.032	0.026 – 0.039	0.10	0.088 – 0.12
2018	0.027	0.022 – 0.033	0.097	0.081 – 0.12
2019	0.024	0.020 – 0.030	0.074	0.061 – 0.090

95%CI = 95% Confidence Interval, ICC = Intraclass Correlation Coefficient, N/A = not applicable.

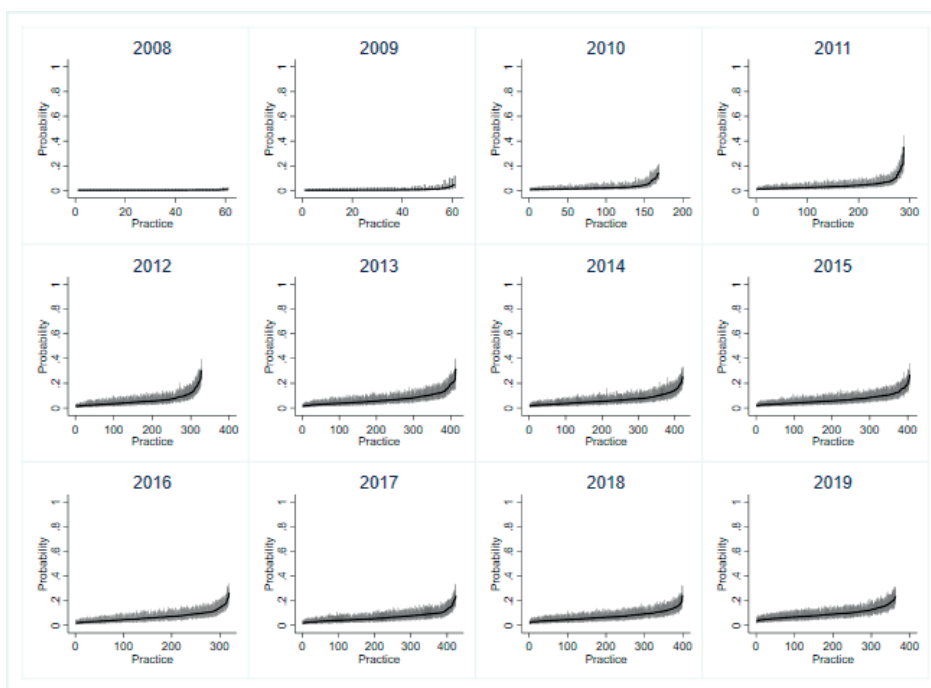


Figure 3: Variation in the prescription of incretin-based therapies from 2008 – 2019 (2007 not available due to too few values). The figure shows the variation within a practice (indicated by the length of each bar individually) as well as the variation between practices (indicated by the range of y-values per practice).

Correlation between uptake of DOACs and incretin-based therapies

No clear correlation was found between the uptake of DOACs on one hand and incretin-based therapies on the other hand (Figure 4). From the linear regression analysis, it can be concluded that – although a statistically significant correlation was found in 2014 – the relationship between the prescription of DOACs and incretin-based therapies within practices was very weak or absent across the study period. Correction for patient age and sex, using multivariate linear regression analysis, had no relevant effect on the regression coefficients (Table S1).

Both sensitivity analyses yielded comparable results. No distinct correlations were observed between the prescription of DOACs and the newer T2DM medicines, including SGLT2 inhibitors and for single-handed practices only (Figures S1 and S2).

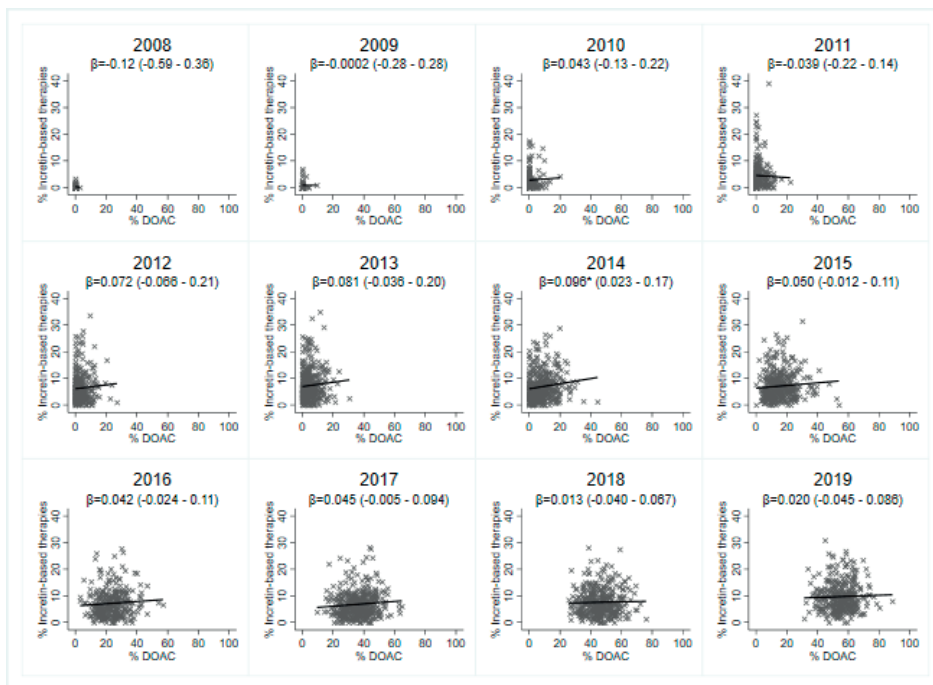


Figure 4: Correlation between prescription of DOACs and incretin-based therapies. The x-axis shows the percentage of patients with prescriptions for DOACs (among all anticoagulant users), the y-axis the percentage of patients with prescriptions for incretin-based therapies (among the total number of patients using T2DM medication, excluding insulins). Each dot represents one practice. Regression lines were fitted with univariate linear regression analysis and regression coefficients are mentioned in the figures.

* $P < 0.05$.

DISCUSSION

Since the introduction of DOACs, DPP-4 inhibitors and GLP-1 receptor agonists in the Netherlands, the prescription rates in primary care increased annually, although with different patterns. As for the DOACs, the uptake remained limited in the first years after their introduction, but substantially increased from 2014 and further on, eventually overpowering the prescription of VKAs. As for the incretin-based therapies, the percentage of prescriptions compared to all T2DM medicines increased to nearly 10% in the first years after their introduction and then remained stable during many years. The variation between practices was more pronounced for the DOACs in the first years after their introduction, but declined to a minimum in 2019. For incretin-based therapies, the variation remained more stable throughout the study period. No correlation was found between the prescription of both new classes of medicines.

The uptake patterns of both DOACs and incretin based-therapies found in our study are comparable to the results of previous drug utilization research [12,16-18]. The uptake of those medicines in the Netherlands seems slower compared to other countries [12,15,19,20], which can be explained by, among others, differences in population (for example in age and body weight), changes in country-specific clinical guidelines, national medicines policies, and reimbursement decisions [21]. We found considerable differences between the uptake patterns and practice variation of DOACs and incretin-based therapies. The high ICC in the first years after the introduction of the DOACs implies that most variability can be attributed to differences between general practices while no consensus on the use of these medicines was reached yet. From 2012 and further on, different initiatives were cultivated to ensure a well-dosed and conservative introduction of the DOACs [12]. This most probably accounted for the low overall prescription volume, automatically resulting in large practice variation caused by individual prescribers choosing to initiate the DOACs. The publication of a position paper by the Dutch College of General Practitioners in 2016, stating the equivalence of DOACs and VKAs, is likely to have had a major effect on the increase in uptake and the harmonization of prescription behaviour [12]. Indeed, adherence to treatment recommendations from the Dutch College of General Practitioners is generally high [10,11].

For incretin-based therapies, the uptake went faster than for DOACs in the first years after their introduction, but then remained stable for many years. Differences between practices had a less profound impact on the prescription of those medicines in the early years after their introduction, indicated by the lower ICC compared to the DOACs. The modest decline in ICC however implies that less consensus was reached about those medicines in the last years in comparison with DOACs. The DPP-4 inhibitors and GLP-1 receptor agonists were not recommended in the T2DM guideline in primary care until 2018 and were explicitly recommended against in the 2013 guideline [13], most probably explaining the slow-down in uptake from 2013 to 2019. The difference in uptake between incretin-based therapies and DOACs in the first years after introduction might be explained by an important difference between both medicine classes. For anticoagulants, a physician has to choose to prescribe one anticoagulant or another. For T2DM patients, a stepped-care approach is recommended [13]. This means that the treatment should be intensified when a patient does not meet his treatment goals. Therefore, a physician can add a new incretin-based therapy to the blood glucose lowering medicines the patient already uses. The addition of a newer medicine might be less troublesome to physicians than the switch of a familiar medicine to a new one. Previous research showed that failure to an existing treatment was the main reason for physicians to prescribe a new medicine [22,23]. The progressive nature of T2DM compared to most thrombo-embolic conditions could therefore account for the faster

adoption of new T2DM medicines compared to DOACs in the first years after their introduction. In the later years, the publication of guidelines is likely to have had the most profound effect on prescription behaviour.

At practice level, early adoption of DOACs was not related to the early adoption of new T2DM medicines, irrespective of the inclusion of SGLT2 inhibitors. There are some possible explanations for this lack of correlation. First, obviously, it could mean that no correlation exists between early prescription of new medicines and early adoption of new medicines in general is not a personal trait. Former research has also failed to demonstrate that early adoption of one type of new medicine could predict the early adoption of other new medicines [24], although an association between the prescription of new medicine classes for the same condition has also been described [7]. It is however conceivable that the association is absent when it concerns medicines for different conditions, also because of the differences between both classes as described before. Another explanation for the lack of correlation might be the focus on practices and not prescribers in our study. Different prescribers in one general practice and prescriptions from secondary care providers could disguise a possible correlation at prescribers' level. However, since no correlation was found in solo practices only, an effect of multiple prescribers in one general practice seems unlikely to have played a relevant role in shaping the global results. It could however not be ruled out that prescriptions from secondary care providers may have affected the results.

The differences in uptake patterns and lack of correlation between the prescription of new medicines indicate that no singular explanation is present to understand the dynamics of physicians prescribing new medicines, especially in the years before clinical guidelines with recommendations about the new medicines are published. The distribution of new medicines in primary care is a complex phenomenon that is likely to be dependent on characteristics of physicians, medicines, diseases and patients [2,4,5,23]. Furthermore, medicine prescription patterns are known to be affected both by regional and cultural factors [25]. More research on the perspectives of healthcare professionals on newer medicines and their prescription behaviour is warranted to gain more insight in the considerations that lead to the prescription of new medicines.

The main strength of this study is the use of a large and representative database with a maximum of 424 general practices and 1,654,376 patients per year, contributing to stable and robust analysis. In addition, the 13-years study period led to a clear overview of prescription patterns. There were, however, also some limitations. First, it was not known whether the prescriptions were initiated by the general practitioner or a secondary care provider. Therefore, it is not known to what extent medical specialists contributed to the

initiation of new medicines over the study period. Second, no selection has been made on diagnosis. For the analysis of anticoagulants, only VKAs and DOACs were included because of their comparable indications. Other anticoagulants and antiaggregants, like acetylsalicylic acid and heparin were not included, because they can also be used for indications DOACs are not authorised for. Because of the exclusion of these treatments, we might have overestimated the share of DOACs, especially in the first studied years, since acetylsalicylic acid had a minor place in former Dutch guidelines for the treatment of atrial fibrillation [26]. For the analysis of incretin-based medicines, fixed combinations of GLP-1 receptor agonists and insulins were not included. Since these medicines are rarely prescribed in the Netherlands, it is unlikely that this has significantly altered the results.

Despite these limitations, this study provides a clear overview of uptake patterns, practice variation and lack of correlation in the prescription of two different classes of new medicines in primary care. Clinical guidelines are likely to have the most profound effect on prescription behaviour and this can be seen as an encouraging result. However, large practice variation, especially in the years before guidelines advise about new treatments, also shows how important it is to regularly revise current guidelines and to develop customized interventions so that new knowledge is timely integrated, which might be rapidly taken up in everyday primary care clinical practice.

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SUPPLEMENT

Table S1: Regression coefficients for the correlation between prescriptions of DOACs and incretin-based therapies, derived from univariate linear regression analysis and multivariate linear regression (including age and sex).

	Regression coefficients (95%CI)	
	Univariate analysis	Multivariate analysis
2008	-0.12 (-0.59 – 0.36)	-0.089 (-0.58 – 0.40)
2009	-0.0002 (-0.28 – 0.28)	0.008 (-0.27 – 0.29)
2010	0.043 (-0.13 – 0.22)	0.053 (-0.12 – 0.23)
2011	-0.039 (-0.22 – 0.14)	-0.033 (-0.21 – 0.15)
2012	0.072 (-0.066 – 0.21)	0.077 (-0.061 – 0.21)
2013	0.081 (-0.036 – 0.20)	0.077 (-0.041 – 0.19)
2014	0.096 (0.023 – 0.17)*	0.091 (0.019 – 0.16)*
2015	0.050 (-0.012 – 0.11)	0.045 (-0.018 – 0.11)
2016	0.042 (-0.024 – 0.11)	0.039 (-0.027 – 0.10)
2017	0.045 (-0.005 – 0.094)	0.039 (-0.011 – 0.090)
2018	0.013 (-0.040 – 0.067)	0.015 (-0.039 – 0.068)
2019	0.020 (-0.045 – 0.086)	0.026 (-0.040 – 0.091)

95%CI = 95% Confidence Interval.

* $P < 0.05$.

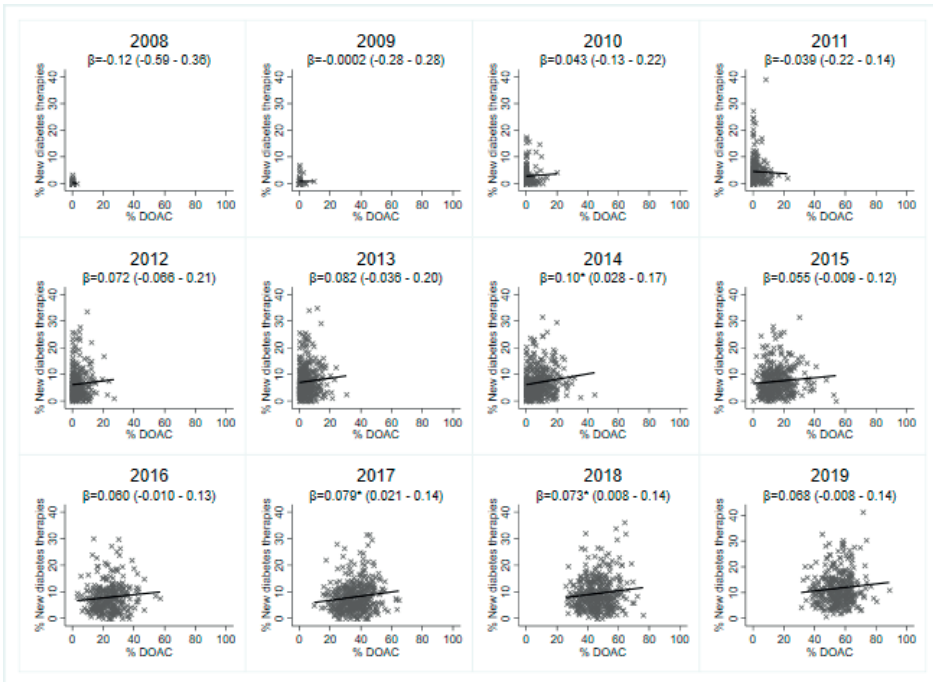


Figure S1: Correlation between prescription of DOACs and new diabetes therapies (DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors). The x-axis shows the percentage of patients with prescriptions for DOACs (among all anticoagulant users), the y-axis the percentage of patients with prescriptions for incretin-based therapies and SGLT2 inhibitors (among the total number of patients using T2DM medication, excluding insulins). Each dot represents one practice. Regression lines were fitted with univariate linear regression analysis and regression coefficients are mentioned in the figures.

* $P < 0.05$.

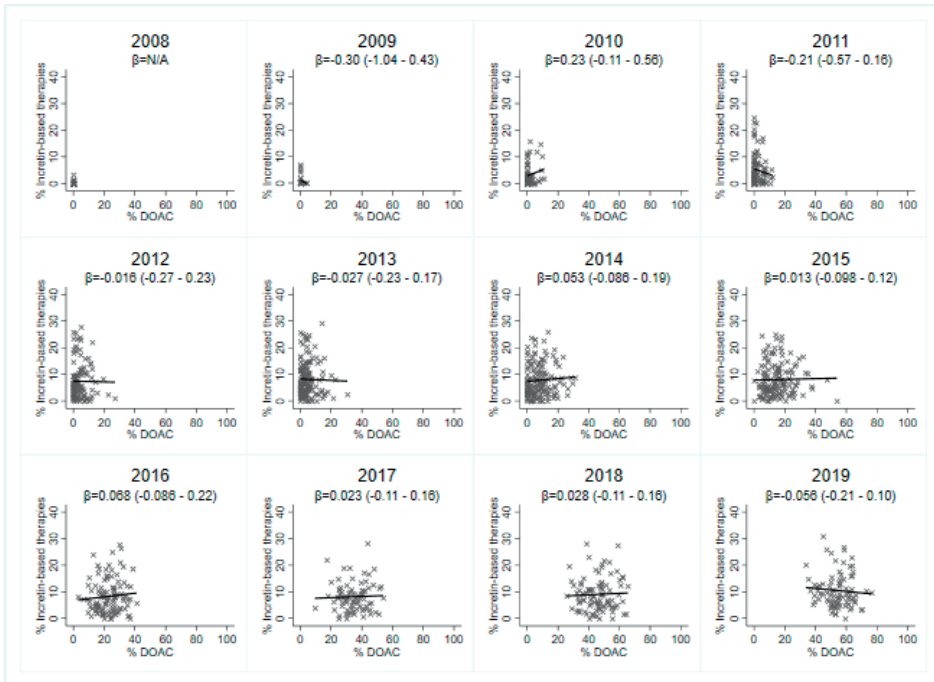


Figure S2: Correlation between prescription of DOACs and incretin-based therapies for solo practices only. The x-axis shows the percentage of patients with prescriptions for DOACs (among all anticoagulant users), the y-axis the percentage of patients with prescriptions for incretin-based therapies (among the total number of patients using T2DM medication, excluding insulins). Each dot represents one practice. Regression lines were fitted with univariate linear regression analysis and regression coefficients are mentioned in the figures.

* $P < 0.05$.

