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ORIGINAL ARTICLE

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

Marloes Dankers[1,2] | Karin Hek[3] | Aukje K. Mantel-Teeuwisse[4] | Liset van Dijk[2,3] | Marjorie H. J. M. G. Nelissen-Vrancken[1]

[1]Dutch Institute for Rational Use of Medicine, Utrecht, The Netherlands

[2]Department of PharmacoTherapy, -Epidemiology & -Economics (PTEE), Groningen Research Institute of Pharmacy, Faculty of Science and Engineering, University of Groningen, Groningen, The Netherlands

[3]Nivel, Netherlands Institute for Health Services Research, Utrecht, The Netherlands

[4]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands

Correspondence
Marloes Dankers, Dutch Institute for Rational Use of Medicine, Utrecht, The Netherlands.
Email: m.dankers@ivm.nl

Aims: To gain insight in the uptake and practice variation in the prescription of 2 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 to 2019 were used. The percentage of patients with prescriptions for DOACs of all patients with prescriptions for DOACs and vitamin K antagonists 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. Linear regression analysis was used to study the association between the prescription of DOACs and incretin-based therapies.

Results: Per year, 46–424 general practices and 179 933–1 654 376 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 intraclass correlation coefficient 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 these medicines were introduced in guidelines. Early adopters of both medicine classes differ.

KEYWORDS
anticoagulants, diabetes, pharmacotherapy, prescribing, primary care

1 | INTRODUCTION

Medicines, both old and new, have been associated with increased longevity and can therefore be beneficial for patients.[1] Specifically for new medicines, the benefit–risk ratio has not been fully elucidated. In addition, they 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 and to prevent unnecessary prescriptions and 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 a personal trait of prescribers.

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 and to investigate whether the preference for different new medicines is related to the general practice. Direct-acting oral anticoagulants (DOACs) were introduced in 2008 for the treatment of thrombo-embolic diseases. Dipeptidyl peptidase-4 inhibitors (DPP4-inhibitors) and glucagon-like peptide-1 receptor agonists (GLP1-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 by general practitioners. The reimbursement for both medicine classes was initially for only a subgroup of patients, but expanded in time.[10,11] 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[12,13]—for primary care practitioners, until 2016 (DOACs) and 2018 (T2DM).[14,15] Because of the impact of guidelines on prescription behaviour, it is interesting 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,[16,17] uptake of the 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 into the similarities and differences in the uptake of new medicines in primary care that gained market access in the same period, 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.

What is already known about this subject

- Direct-acting oral anticoagulants (DOACs) and incretin-based therapies were introduced around 2007 for the treatment of thrombo-embolic diseases and type 2 diabetes mellitus, respectively.
- In general, the number of adopters of new medicines increases quickly after introduction with extensive practice variation in the first years after introduction.

What this study adds

- The uptake patterns of DOACs and incretin-based therapies in primary practice differed.
- As the uptake of DOACs and incretin-based therapies increased, practice variation diminished, which was more outspoken for the DOACs than for incretin-based therapies.
- Early prescription of DOACs does not overlap with early prescription of incretin-based therapies.

2 | METHODS

2.1 | 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).

2.2 | 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 DPP4-inhibitor (A10BH, A10BD07, A10BD08, A10BD10, A10BD11) or GLP1-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 (DPP4-inhibitors or GLP1-agonists) as a proportion of all patients with prescriptions for blood glucose-lowering medicines excluding insulins per practice per year, for the period 2007–2019. The percentage of females and the mean age of anticoagulant and incretin-based therapy users were also calculated.

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 centring 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 and plotted per practice. Intraclass correlation coefficients (ICCs) 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-inhibitors (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 $P < .05$. Stata SE version 16.1 was used for all analyses.

3 | RESULTS

3.1 | 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.

3.2 | 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 DPP4-inhibitors or GLP1-agonists started to increase again.

3.3 | 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.

TABLE 1 Number of included practices and patients including sex and age and the number of patients with prescriptions for anticoagulants and type 2 diabetes mellitus (T2DM) medication (excluding insulin) from 2007 to 2019.

			Anticoagulants			T2DM medication		
	Number of practices	Number of patients	Number of patients (%)	Sex (% female)	Age, mean (SD)	Number of patients (%)	Sex (% female)	Age, mean (SD)
2007	46	179 933	2912 (1.62)	44	70 (14)	4991 (2.77)	50	66 (13)
2008	61	235 975	3923 (1.66)	44	71 (13)	7093 (3.01)	50	66 (13)
2009	61	246 159	4337 (1.76)	44	71 (14)	7757 (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)

Abbreviation: SD, standard deviation.

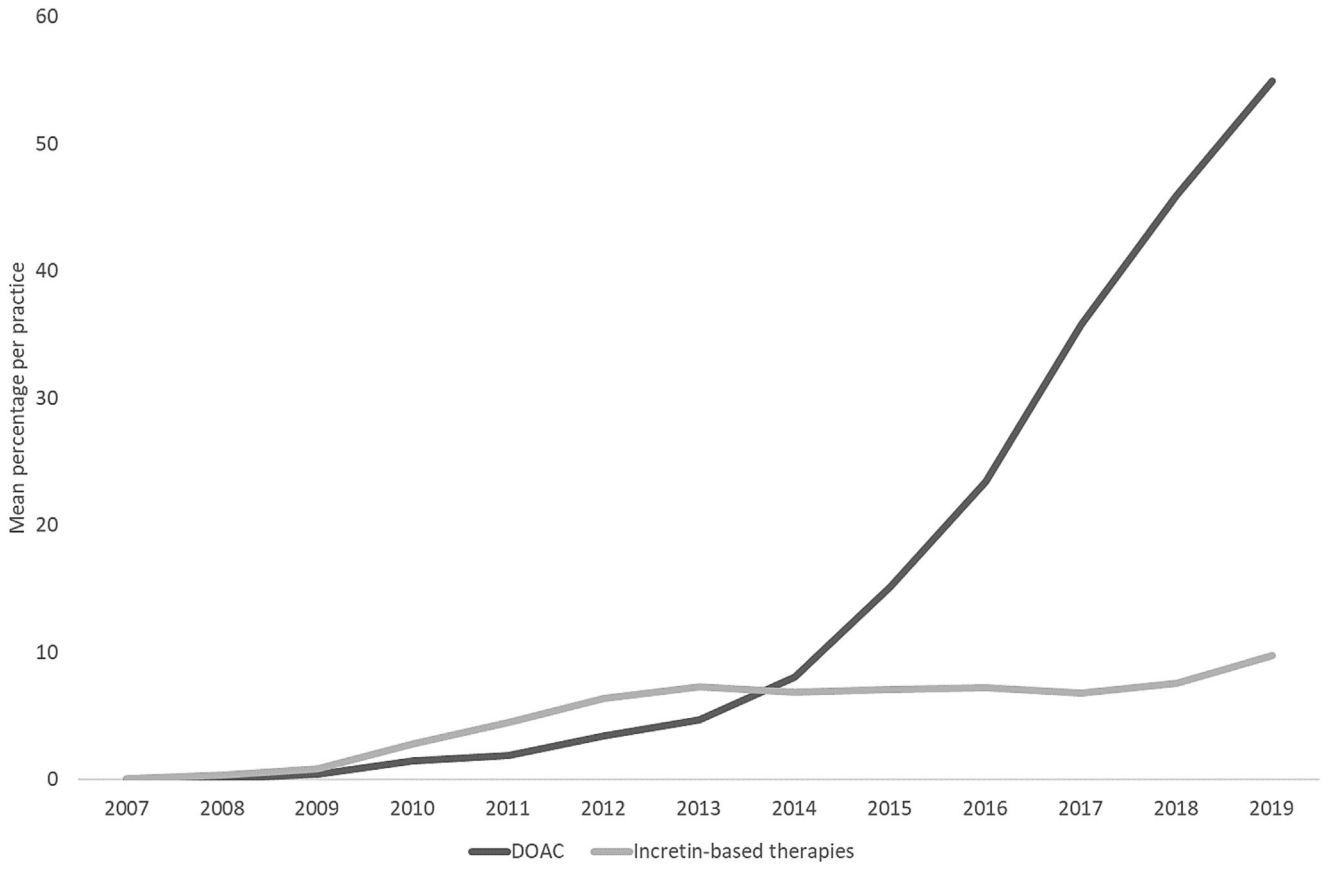

FIGURE 1 Mean percentage of patients per practice with prescriptions for direct-acting oral anticoagulants and incretin-based therapies compared to all patients with anticoagulants and type 2 diabetes mellitus medication, respectively.

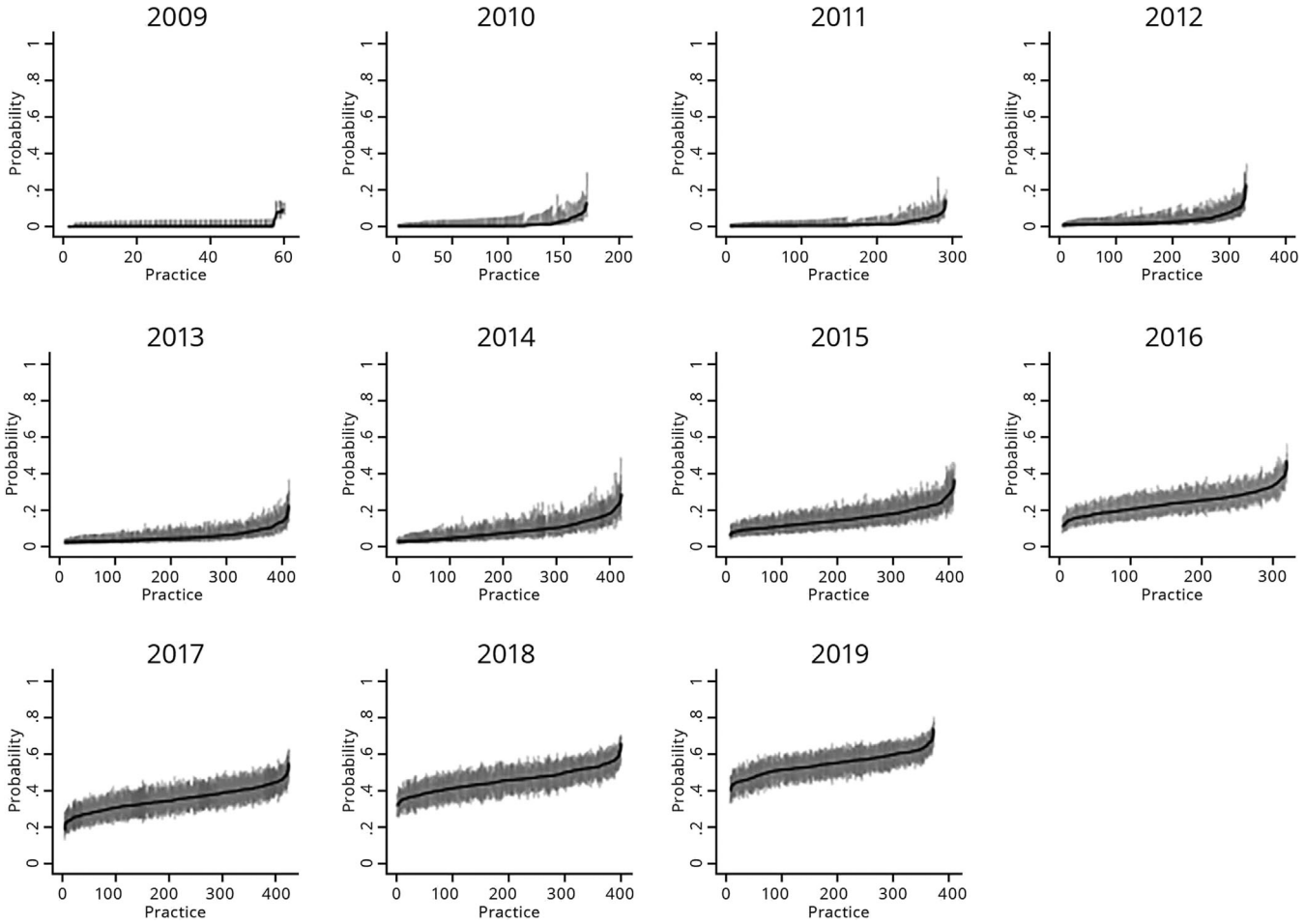

FIGURE 2 Variation in the prescription of direct-acting oral anticoagulants from 2009 to 2019 (2008 not available due to too few values). The figure shows the variation within a practice (indicated by the length of each bar individually) as well as the variation between practices (indicated by the range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

3.4 | Correlation between uptake of DOACs and incretin-based therapies

No clear correlation was found between the uptake of DOACs on the 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).

4 | DISCUSSION

Since the introduction of DOACs, DPP4-inhibitors and GLP1-agonists in the Netherlands, the prescription rates in primary care increased annually, although with different patterns. The uptake of DOACs remained limited in the first years after their introduction, but substantially increased from 2014 and further on, eventually overpowering the prescription of VKAs. 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 for 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.[14,18–20] The uptake of those medicines in the Netherlands seems slower compared to other countries,[14,17,21,22] which can be explained by, among others, differences in population (e.g., in age and body weight), changes in country-specific clinical guidelines, national medicines policies and reimbursement decisions.[23] We found considerable differences between the uptake patterns and practice variation of DOACs and incretin-based therapies. The high

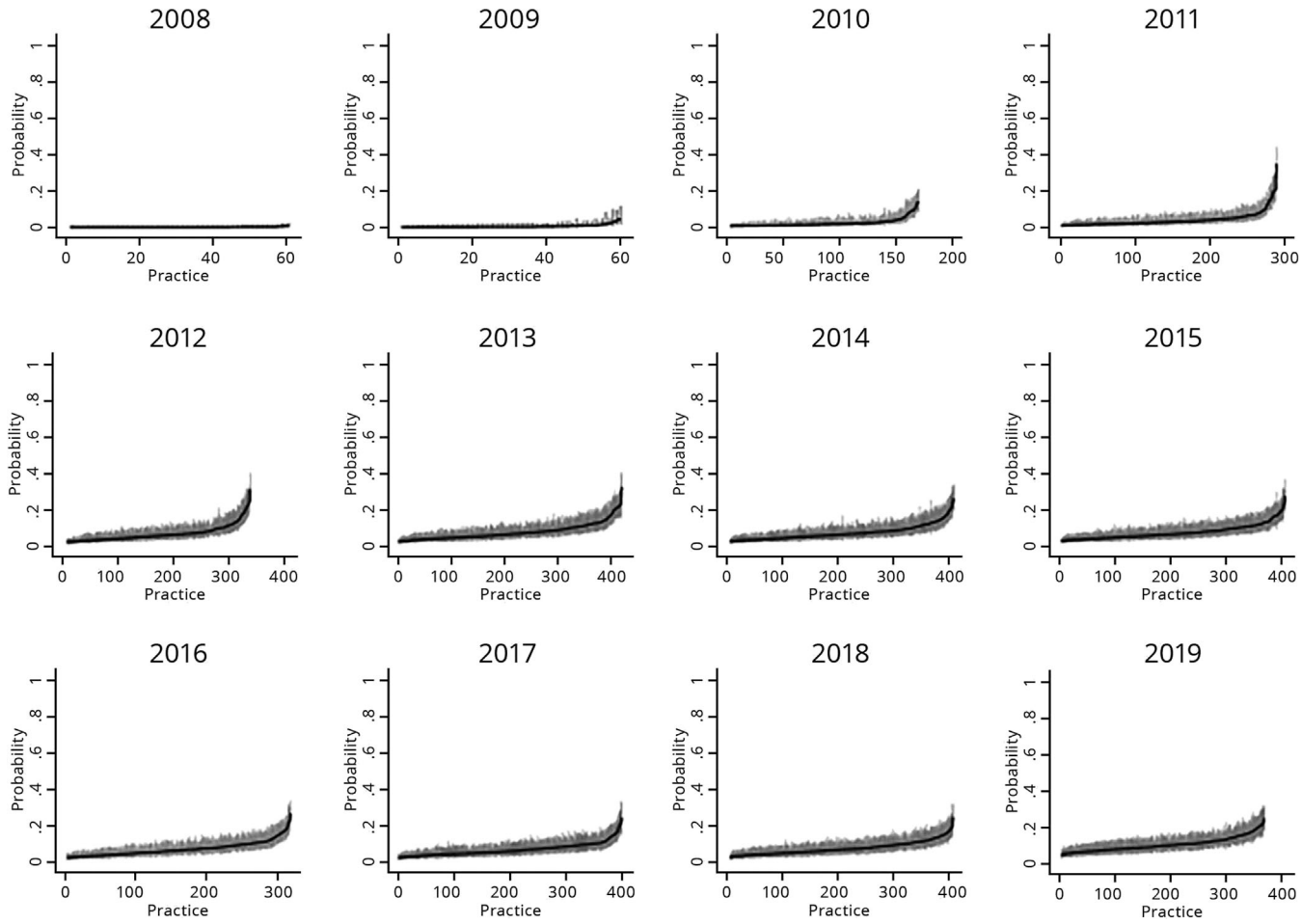

FIGURE 3 Variation in the prescription of incretin-based therapies from 2008 to 2019 (2007 not available due to too few values). The figure shows the variation within a practice (indicated by the length of each bar individually) as well as the variation between practices (indicated by the range of *y*-values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

TABLE 2 Intraclass correlation coefficients (ICCs) for direct-acting oral anticoagulants (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

Abbreviations: 95%CI, 95% confidence interval; N/A, not applicable.

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, different initiatives were cultivated to ensure a guided introduction of the DOACs.[14] This most probably accounted for the low overall prescription volume, potentially explaining the 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.[14] Indeed, adherence to treatment recommendations from the Dutch College of General Practitioners is generally high.[12,13]

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

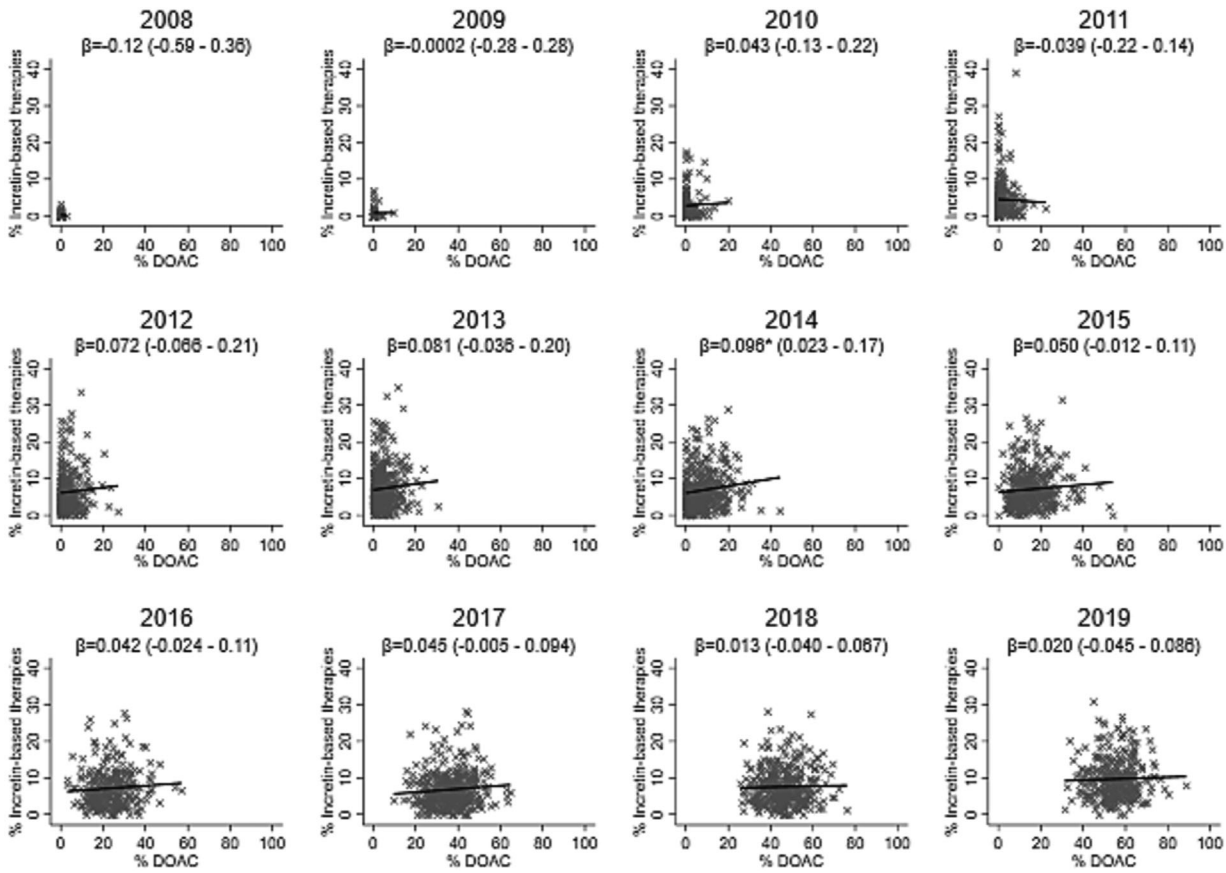

FIGURE 4 Correlation between prescription of direct-acting oral anticoagulants and incretin-based therapies. The *x*-axis shows the percentage of patients with prescriptions for direct-acting oral anticoagulants (among all anticoagulant users), the *y*-axis the percentage of patients with prescriptions for incretin-based therapies (among the total number of patients using type 2 diabetes mellitus 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. *$P < .05$.

consensus was reached about those medicines in the last years in comparison with DOACs. The DPP4-inhibitors and GLP1-agonists were not recommended in the T2DM guideline in primary care until 2018 and were explicitly recommended against in the 2013 guideline,[15] 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.[15] This means that the treatment should be intensified when a patient does not meet their treatment goals. 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.[24,25] 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 general 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 may depend on academic opinion on each new molecule rather than on a personal attitude towards new medicines in general. 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,[26] 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. Another explanation for the lack of correlation might be the focus on general practices and not general practitioners 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 1 general practice seems unlikely to have played a relevant role in shaping the global results. The lack of a general profile of the early adopter can be seen as an encouraging result, indicating that general

practitioners tend to adopt new medicines on a case-by-case basis, rather than being dogmatic or overenthusiastic about new treatments irrespective of their characteristics.

The differences in uptake patterns and lack of correlation between the prescription of new medicines indicate that insights in uptake patterns and early adopters of one new medicine group could not be extrapolated to other new medicine groups. 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.[2,4,5,25] Furthermore, medicine prescription patterns are known to be affected both by regional and cultural factors.[27] More research on the perspectives of healthcare professionals on newer medicines and their prescription behaviour is warranted to gain more insight into 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-year 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 was not made on diagnosis, but just on medicines. For the analysis of anticoagulants, only VKAs and DOACs were included because of their comparable indications. Other anticoagulants and antiaggregants, such as acetylsalicylic acid and heparin, were not included, because they can also be used for indications for which DOACs are not authorized. 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.[28] For the analysis of incretin-based medicines, fixed combinations of GLP1-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. Third, the generalizability of this study might be limited, because we studied the adoption of only 2 medicine groups in one country. However, the lack of correlation in uptake patterns and in early adopter profile support the conclusion that no general uptake pattern or early adopter profile is present, which has also been shown in former studies in different countries and healthcare systems.[2,3,26] The results of our study might be most relevant for countries with a comparable healthcare system, including an important role for the general practitioner in the prescription of medicines.

Despite these limitations, this study provides a clear overview of uptake patterns, practice variation and lack of correlation in the prescription of DOACs and incretin-based medicines in primary care. Although no conclusions can be drawn about the justification of prescription of those new medicines, this study gives insight in the early prescription patterns and early adopters of DOACs and incretin-based therapies and indicates that both prescription profiles and prescribers differ per medicine group. 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.

AUTHOR CONTRIBUTIONS

Marloes Dankers, Aukje K. Mantel-Teeuwisse, Liset van Dijk and Marjorie H. J. M. G. Nelissen-Vrancken developed the research plan. Marloes Dankers and Karin Hek analysed all data. Marloes Dankers wrote the first draft. All authors provided input for interpretation of the results and text suggestions for the first draft. The authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Marloes Dankers, Karin Hek, Aukje K. Mantel-Teeuwisse and Marjorie H.J.M.G. Nelissen-Vrancken declare no conflict of interests. Liset van Dijk received an unrestricted grant from TEVA Pharmaceuticals and Biogen for a research project not related to this study.

DATA AVAILABILITY STATEMENT

Access to data is subject to Nivel PCD governance codes. Requests for access to the data can be directed at directie@nivel.nl. Restrictions involve establishing a data sharing agreement and approval by the appropriate Nivel PCD governance bodies (privacy committee and steering committee). Data were anonymized and are accessible via https://easy.dans.knaw.nl/ui/datasets/id/easy-dataset:326220 (DANS| Centre of expertise & repository for research data; knaw.nl).

ORCID

Marloes Dankers https://orcid.org/0000-0003-0971-8388

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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