New medicines in primary care

Dankers, Marloes

DOI:
10.33612/diss.809910284

New medicines in primary care

Perspectives and practices of healthcare professionals

Marloes Dankers

New medicines in primary care

Perspectives and practices of healthcare professionals

Marloes Dankers

Cover design: Marianne Wijsbeek
Layout and printing by Optima Grafische Communicatie (www.ogc.nl)
ISBN 978-94-6361-930-1

rijksuniversiteit
groningen

New medicines in primary care

Perspectives and practices of healthcare professionals

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. ir. J.M.A. Scherpen
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

dinsdag 14 november 2023 om 16.15 uur

door

Marloes Dankers

geboren op 13 juni 1988
te Hardinxveld-Giessendam

Promotores

Prof. dr. ir. L. van Dijk
Prof. dr. A.K. Mantel-Teeuwisse

Copromotor

Dr. H.J.M.G. Nelissen-Vrancken

Beoordelingscommissie

Prof. dr. P.G.M. Mol
Prof. dr. K. Taxis
Prof. dr. P.J.M. Elders

TABLE OF CONTENTS

General introduction

Medicines are an essential part of modern healthcare and can have a profound effect on quality of life. Every year, new medicines become available for prescription. In 2021, 92 new medicines were recommended for marketing authorisation in Europe, of which 54 had a new chemical substance [1]. New medicines have been associated with decreased morbidity and increased longevity and health related quality of life and can therefore improve treatment outcomes and be beneficial for patients [2,3]. However, the long term safety of new medicines is often not known, and once used by a large and heterogenous population, new risks of these medicines can emerge, which may lead to harmful events [4-6]. In addition, new medicines are often expensive, thereby contributing to increasing healthcare costs [7,8]. Therefore, an urgent need exists for the rational use of new medicines, both in terms of quality of care and healthcare costs [9].

In the Netherlands, the general practitioner functions as gatekeeper of the healthcare system and plays an important role in the prescription of medicines [10]. The adoption of new medicines in primary care differs greatly between practices [11-13]. Variation between practices in itself is not remarkable, since patients characteristics and their preferences can differ. However, these factors comprise only part of the variation in medical treatment, indicating that other, non-medical, factors are also involved [14]. That part of variation indicates room for improvement in the rational use of new medicines in primary care. Insight in the prescription of new medicines by primary healthcare professionals, their considerations and factors that influence their decisions is therefore relevant.

HOW NEW MEDICINES BECOME AVAILABLE FOR PRESCRIPTION

Before a new medicine can be prescribed by a healthcare professional, it has to pass several assessments. Once the initial development phase is completed, a medicine has to be positively evaluated by registration authorities in order to become available on the market. For most new medicines in Europe, this assessment is performed by the European Medicines Agency (EMA). The EMA assessment focuses primarily on the quality and the benefit-risk balance of the new medicine, based on a comprehensive scientific evaluation of data. Only if the benefits of the new medicine outweigh its risks, it will be authorised [1].

Once a new medicine is being authorised, an evaluation of the eligibility for reimbursement is often the next step, which is in the European context usually advised upon by Health Technology Assessment (HTA) bodies. Benefit-risk analysis is again an important part of the evaluation, but the pharmacoeconomic evaluation of the new

medicine is an additional domain for evaluation [15,16]. The final decision whether a medicine is reimbursed, is based on its relative effectiveness and cost effectiveness, particularly compared to current standard of care. Also the total budget impact may be taken into account.

The registration and reimbursement of a new medicine are no guarantee that healthcare professionals will prescribe it. The actual prescription often depends on the guidance and information provided by professional organisations. In the Netherlands, the recommendations by professional organisations are known to have a profound impact on prescription behaviour [17,18]. In the assessment of new medicines by professional organisations, the relative value of the new medicine compared to other already available therapeutic options is taken into account, before it is recommended in professional clinical guidelines [19].

After all these formal evaluations, individual prescribers have to decide whether they are going to prescribe the new medicine, taking into account all former evaluations and adding the question whether the new medicine is the best option for an individual patient.

To summarize, the assessment of new medicines occurs at different moments, by different institutions and within different domains. The base of the evaluation of a new medicine is the assessment of its quality and the benefit-risk balance. Additional evaluation domains are used for the evaluation of reimbursement, clinical guideline recommendations and prescription. This thesis focuses on the final part in this process, the prescription, and considers three different aspects. At first, the assessment of new medicines by prescribers is studied in relation to the assessment of new medicines by official institutions. Second, the internal and external factors influencing the decision-making by prescribers are investigated. Third, the outcome of these processes, i.e. the prescription of new medicines, is quantified.

ASSESSMENT CRITERIA

As stated before, the benefit-risk balance is the base of every assessment of new medicines. In order to determine this balance, the assessment criteria have to be established. Agreement on (importance of) the studied outcomes and improvements on these outcomes that are warranted per disease area is the first step.

Outcomes used for the evaluations of new medicines can be subdivided into different categories. Categories are direct outcomes for clinical efficacy (e.g. mortality), surrogate outcomes for efficacy (e.g. HbA1c in the case of diabetes medicines), safety outcomes (e.g. adverse events) and patient reported outcomes (PROs), like quality of life [20-23]. The relative importance of the outcomes depends on the disease area that is studied, although direct outcomes and PROs are generally valued over surrogate endpoints [23-26]. To determine the relative importance of outcomes, relevant competent authorities often use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. GRADE uses a 9-point scale to define the importance of a specific endpoint [27].

After the definition of relevant endpoints, consensus has to be reached about the improvements a new medicine has to have on these endpoints in order to be considered sufficiently effective. Statistical significance is used to establish the chance of a result being caused by coincidence. Clinical relevance however merely focuses on the real benefit of a new medicine. The assessment of clinical relevance in addition to statistical significance has become increasingly important in the evaluation of new medicines [28,29]. To evaluate clinical relevance, Jaeschke et al. introduced the Minimal Clinically Important Difference (MCID) in 1989 [30]. An MCID is the smallest difference in the domain of interest which patients perceive as beneficial and which would mandate a change in patient treatment [30,31]. MCIDs can be used as cut-off values to decide whether a difference between two treatments is of clinical relevance [32] and therefore to quantify clinical relevance. The use of MCIDs in the evaluation of new medicines has gained more popularity in the last years, although their use differs among diseases and therapeutical areas [33]. For example in the field of chronic obstructive pulmonary disease (COPD), MCIDs are extensively studied and validated and a general consensus exists on which MCIDs should be used in order to evaluate COPD medicines [34]. Therefore, registration authorities, HTA bodies and professional organisations all use the same MCIDs to establish clinical relevance of new COPD medicines [35-37]. In other therapeutical areas, the use of MCIDs is less common. For example, for type 2 diabetes mellitus (T2DM) medicines, no validated MCIDs are available and the use of MCIDs is therefore less common in both registration, reimbursement and recommendation.

To summarize, important developments for a careful evaluation of the benefit-risk balance of new medicines are the definition of evaluation criteria, including the definition of outcomes, use of GRADE scaling to establish the importance of outcomes, calculation of statistical significance to rule out chance, and defining MCIDs to evaluate the clinical relevance of improvements on these outcomes. Although organisations may use additional evaluation domains, many attempts are made to harmonize the

criteria for the assessment of the benefit-risk balance, for example between regulatory authorities and HTA bodies [38,39] and HTA bodies and clinical guideline developers [40]. It is known from previous research that the views of individual healthcare professionals on added value of medicines do not necessarily correspond to the views of official institutions [24,41-43]. It is however not known how healthcare professionals value the evaluation criteria used by regulation authorities, HTAs and clinical guideline developers to establish clinical relevance.

FACTORS IMPACTING DECISION-MAKING

Once available for prescription, the healthcare professional has to decide to prescribe the new medicine or not. The decision to prescribe new medicines is impacted by the context and characteristics of prescribers and patients and by external influences (e.g. other healthcare professionals, organisation of care and pharmaceutical industry) [13]. In order to understand variation in the prescription of new medicines between practices, insight in the factors impacting the decision-making is essential.

The decision of healthcare professionals to prescribe new medicines is not solely based on pharmacological and medical criteria, but also depends on social, situational and psychological variables [44,45]. A systematic review from 2021 found a broad range of factors associated with the early prescription of new medicines, grouped into patient, prescriber, medicine, organisational, and external environment factors [45]. These factors, however, could not explain the extensive variation in the early prescription of new medicines [13]. Behavioural aspects and especially the attitude of healthcare professionals towards new medicines are thought to play an important role in the decision to prescribe new medicines [13,46]. These behavioural aspects remain underexplored and therefore call for further research [45].

One notable external factor that impacts the decision to prescribe new medicines is the pharmaceutical industry. Pharmaceutical companies try to stimulate the use of their specific new medicine by a broad range of marketing activities. The activities vary from direct attempts (e.g. medical representatives visiting the practice, marketing mailings and educations organised by a company) to indirect attempts (e.g. sponsored courses and ghost-writing) [47-49]. Marketing activities by pharmaceutical companies are known to influence the attitude of healthcare professionals towards new medicines [46,50] and impact the prescription of new medicines [47,49,51-53]. The latter effect is often underestimated by healthcare professionals [47,54-57]. Although the contents of marketing activities are widely studied [58-61], the way these activities try to impact

the decision-making by healthcare professionals is less understood. More insight in the factors leading to the decision to prescribe new medicines, and the strategies the pharmaceutical industry uses to impact this decision, is therefore warranted.

PRESCRIPTION OF NEW MEDICINES

Considering the many factors influencing the prescription of new medicines, it is no surprise that the uptake of new medicines in primary care is not equally distributed among physicians [11]. The uptake of new medicines often follows the universal diffusion of innovations, described by Rogers et al. [62]. They distinguish five categories of adopters, ranging from innovators and early adopters to laggards. This diffusion of innovation has also been described for new medicines [12]. A small proportion of general practitioners seems to be accountable for a disproportionate share of all early prescriptions for new medicines [13,63]. Among general practitioners, a distinction can be made between practitioners with a 'wait and see' policy to practitioners who are more willing to experiment [46]. The differences in adoption of new medicines lead to extensive practice variation in the prescription of new medicines, especially in the first years after their introduction [13,64].

Practice variation in itself is not problematic. Differences between patients and practices can call for different approaches and treatments [14]. However, the variation previously found in the prescription of new medicines could often not be explained by different patient or practice characteristics [13,46]. This non-explainable part of practice variation indicates room for improvement in the rational use of new medicine. After all, rational use of medicine would imply that the same patients are treated with the same medicines, irrespective of the healthcare professional they encounter [14]. The last part of this thesis therefore focuses on practice variation in the prescription of new medicines, in order to gain more insight in the rationality of prescription behaviour.

OBJECTIVES OF THIS THESIS

This thesis aimed to gain insight into the perspectives and practices of healthcare professionals in primary care towards new medicines. To achieve this aim, the following objectives were posed:

- To compare the preferences for evaluation criteria of new medicines by individual healthcare professionals with those of registration authorities and professional organisations.

- To establish the factors that are associated with the decision of individual healthcare professionals to prescribe new medicines, also focusing on the strategies pharmaceutical companies use to influence this decision-making.
- To assess the practice variation in the prescription of new medicines in primary care and investigate the association of prescription of new medicines with specific patient characteristics, practice characteristics and prescription of other new medicines.

OUTLINE OF THE THESIS

This thesis consists of three parts divided into individual chapters. The first part of this thesis focuses on healthcare professionals' preferences for outcomes and MCIDs used in the evaluation of new medicines in relation to the standards used by registration authorities and professional organisations (**Chapter 2**). The study in **chapter 2.1** compares the preferred endpoints and MCIDs of healthcare professionals for the evaluation of new COPD medicines and compares those outcomes to the endpoints and MCIDs used by registration authorities. **Chapter 2.2** describes a comparable study in the field of T2DM. The views and perspectives of healthcare professionals towards endpoints and MCIDs are compared to those used by professional organisations for the development of a new T2DM guideline in primary care.

Chapter 3 of this thesis describes the considerations of primary healthcare professionals leading to the decision to prescribe new medicines, also focusing on the role of the pharmaceutical industry in this decision-making. **Chapter 3.1** assesses the reasons why primary care healthcare professionals decide positively or negatively about new medicines that are not recommended in guidelines, focusing on non-recommended insulins. **Chapter 3.2** describes an analysis of persuasion strategies used in marketing materials for new medicines from pharmaceutical companies.

The next part of this thesis (**chapter 4**) outlines the prescription patterns of new medicines in primary care. In **chapter 4.1**, a retrospective cohort study aims to identify practice variation and analyses the patient and practice characteristics associated with the prescription of new insulins. **Chapter 4.2** describes the prescription patterns of direct oral anticoagulants (DOACs) and incretin-based therapies in primary care over a 13-year period and studies the association between the prescription of both new medicine classes.

The general discussion, **chapter 5**, provides an overview of all findings in this thesis and discusses implications for the improvement of rational use of new medicines and recommendations for further research.

REFERENCES

1. European Medicines Agency (EMA). Annual report 2021. Available from: https://www.ema.europa.eu/en/about-us/annual-reports-work-programmes. Updated 2022. Accessed October 28, 2022.
2. Lichtenberg FR. The impact of new drug launches on longevity: Evidence from longitudinal, disease-level data from 52 countries, 1982-2001. Int J Health Care Finance Econ. 2005;5(1):47-73. doi: 10.1007/s10754-005-6601-7 [doi].
3. Wieseler B, McGauran N, Kaiser T. New drugs: Where did we go wrong and what can we do better? BMJ. 2019;366:l4340. doi: 10.1136/bmj.l4340 [doi].
4. Avorn J. Two centuries of assessing drug risks. N Engl J Med. 2012;367(3):193-197. doi: 10.1056/NEJMp1206652.
5. Rosen CJ. Revisiting the rosiglitazone story--lessons learned. N Engl J Med. 2010;363(9):803-806. doi: 10.1056/NEJMp1008233.
6. Krumholz HM, Ross JS, Presler AH, Egilman DS. What have we learnt from vioxx? BMJ. 2007;334(7585):120-123. doi: 334/7585/120 [pii].
7. Lubloy A. Factors affecting the uptake of new medicines: A systematic literature review. BMC Health Serv Res. 2014;14:469-469. doi: 10.1186/1472-6963-14-469 [doi].
8. Kozyrskyj A, Raymond C, Racher A. Characterizing early prescribers of newly marketed drugs in Canada: A population-based study. Eur J Clin Pharmacol. 2007;63(6):597-604. doi: 10.1007/s00228-007-0277-5 [doi].
9. Dieleman JL, Squires E, Bui AL, et al. Factors associated with increases in US health care spending, 1996-2013. JAMA. 2017;318(17):1668-1678. doi: 10.1001/jama.2017.15927 [doi].
10. Kroneman M, Boerma W, van den Berg M, Groenewegen P, de Jong J, van Ginneken E (2016). The Netherlands: Health system review. Health Systems in Transition. 2016;18(2):1-239.
11. Tamblyn R, McLeod P, Hanley JA, Girard N, Hurley J. Physician and practice characteristics associated with the early utilization of new prescription drugs. Med Care. 2003;41(8):895-908. doi: 10.1097/00005650-200308000-00004 [doi].
12. Garjón FJ, Azparren A, Vergara I, Azaola B, Loayssa JR. Adoption of new drugs by physicians: A survival analysis. BMC Health Serv Res. 2012;12:56-56. doi: 10.1186/1472-6963-12-56 [doi].
13. Florentinus SR. New drugs in general practice: prescribing patterns and external influences. [Utrecht]: Utrecht University, 2006. 172 p.
14. De Jong JD. Explaining medical practice variation: social organization and institutional mechanisms. [Utrecht]: Nivel, 2008. 240 p.
15. Ciani O, Jommi C. The role of health technology assessment bodies in shaping drug development. Drug Des Devel Ther. 2014;8:2273-2281. doi: 10.2147/DDDT.S49935.
16. Henshall C, Sansom L, Eichler HG, et al. Understanding the role and evidence expectations of health technology assessment and coverage/payer bodies: What are they looking for, and how and why does this differ from what regulators require? Ther Innov Regul Sci. 2014;48(3):341-346. doi: 10.1177/2168479013512488.
17. van Dijk L, de Jong JD, Westert GP, de Bakker DH. Variation in formulary adherence in general practice over time (2003-2007). Fam Pract. 2011;28(6):624-631. doi: 10.1093/fampra/cmr043 [doi].
18. Lugtenberg M, Burgers JS, Besters CF, Han D, Westert GP. Perceived barriers to guideline adherence: A survey among general practitioners. BMC Fam Pract. 2011;12:98-98. doi: 10.1186/1471-2296-12-98 [doi].

19. Panteli D, Legido-Quigley H, Reichebner C, et al. Clinical Practice Guidelines as a quality strategy. In: Busse R, Klazinga N, Panteli D, et al., editors. Improving healthcare quality in Europe: Characteristics, effectiveness and implementation of different strategies [Internet]. Copenhagen (Denmark): European Observatory on Health Systems and Policies; 2019. (Health Policy Series, No. 53.) 9. Available from: https://www.ncbi.nlm.nih.gov/books/NBK549283/.
20. McLeod C, Norman R, Litton E, Saville BR, Webb S, Snelling TL. Choosing primary endpoints for clinical trials of health care interventions. Contemp Clin Trials Commun. 2019;16:100486. doi: 10.1016/j.conctc.2019.100486.
21. Lipska KJ, Krumholz HM. Is hemoglobin A1c the right outcome for studies of diabetes? JAMA. 2017;317(10):1017-1018. doi: 10.1001/jama.2017.0029 [doi].
22. Reaney M, Elash CA, Litcher-Kelly L. Patient reported outcomes (PROs) used in recent phase 3 trials for type 2 diabetes: A review of concepts assessed by these PROs and factors to consider when choosing a PRO for future trials. Diabetes Res Clin Pract. 2016;116:54-67. doi: S0168-8227(16)30073-0 [pii].
23. Wieczorek A, Rys P, Skrzekowska-Baran I, Malecki M. The role of surrogate endpoints in the evaluation of efficacy and safety of therapeutic interventions in diabetes mellitus. Rev Diabet Stud. 2008;5(3):128-135. doi: 10.1900/RDS.2008.5.128 [doi].
24. Mol PG, Arnardottir AH, Straus SM, et al. Understanding drug preferences, different perspectives. Br J Clin Pharmacol. 2015;79(6):978-987. doi: 10.1111/bcp.12566 [doi].
25. Mercieca-Bebber R, King MT, Calvert MJ, Stockler MR, Friedlander M. The importance of patient-reported outcomes in clinical trials and strategies for future optimization. Patient Relat Outcome Meas. 2018;9:353-367. doi: 10.2147/PROM.S156279.
26. Knottnerus JA, Knottnerus BJ. Decision-making given surrogate outcomes. J Clin Epidemiol. 2022;145:174-178. doi: S0895-4356(22)00009-9 [pii].
27. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. framing the question and deciding on important outcomes. J Clin Epidemiol. 2011;64(4):395-400. doi: 10.1016/j.jclinepi.2010.09.012 [doi].
28. Sterne JA, Smith GD. Sifting the evidence-what's wrong with significance tests? Phys Ther. 2001;81(8):1464-1469. doi: 10.1093/ptj/81.8.1464 [doi].
29. Man-Son-Hing M, Laupacis A, O'Rourke K, et al. Determination of the clinical importance of study results. J Gen Intern Med. 2002;17(6):469-476. doi: jgi11111 [pii].
30. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials. 1989;10(4):407-415. doi: 0197-2456(89)90005-6 [pii].
31. Donohue JF. Minimal clinically important differences in COPD lung function. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2005.
32. Hedayat AS, Wang J, Xu T. Minimum clinically important difference in medical studies. Biometrics. 2015;71(1):33-41. doi: 10.1111/biom.12251 [doi].
33. Jayadevappa R, Cook R, Chhatre S. Minimal important difference to infer changes in health-related quality of life-a systematic review. J Clin Epidemiol. 2017;89:188-198. doi: 10.1016/j.jclinepi.2017.06.009.
34. Mol-Alma H. Discovering the Dynamics of the Minimal Clinically Important Difference of Health Status Instruments in Patients with Chronic Obstructive Pulmonary Disease. [Groningen]: University of Groningen, 2020. 269 p. doi: 10.33612/diss.136223443.
35. CHMP (2012). Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD). EMA/CHMP/700491/2012. 10.1183/09031936.00099306.

36. Zorginstituut Nederland (2015). Umeclidinium (incruse) bij onderhoudsbehandeling bij een chronische obstructieve longziekte (COPD). Available from: https://www.zorginstituutnederland.nl/publicaties/adviezen/2015/03/13/umeclidinium-incruse-bij-onderhoudsbehandeling-bij-een-chronische-obstructieve-longziekte-copd. 13 March 2015. Accessed Jan 6, 2023.
37. Nederland Huisartsen Genootschap (NHG). NHG-Standaard COPD. [M26]. Utrecht: NHG; 2022.
38. Cowie MR, Bozkurt B, Butler J, et al. How can we optimise health technology assessment and reimbursement decisions to accelerate access to new cardiovascular medicines? Int J Cardiol. 2022;365:61-68. doi: S0167-5273(22)01089-0 [pii].
39. Ofori-Asenso R, Hallgreen CE, De Bruin ML. Improving interactions between health technology assessment bodies and regulatory agencies: A systematic review and cross-sectional survey on processes, progress, outcomes, and challenges. Front Med (Lausanne). 2020;7:582634. doi: 10.3389/fmed.2020.582634.
40. HTx. HTx Project | Next Generation Health Technology Assessment [Internet]. 2020 [cited 2023 Jan 6]. Available from: https://www.htx-h2020.eu/.
41. Gauthier B, Singh SR, Virani A, Staples H, Colbourne A. Perspectives and experiences of health care professionals and patients regarding treatments for type 2 diabetes. Can Pharm J (Ott). 2014;147(1):45-54. doi: 10.1177/1715163513506547 [doi].
42. Sox HC. Resolving the tension between population health and individual health care. JAMA. 2013;310(18):1933-1934. doi: 10.1001/jama.2013.281998 [doi].
43. Kaldjian LC. Patient care and population health: Goals, roles and costs. J Public Health Res. 2014;3(2):311. doi: 10.4081/jphr.2014.311 [doi].
44. Prosser H, Almond S, Walley T. Influences on GPs' decision to prescribe new drugs-the importance of who says what. Fam Pract. 2003;20(1):61-68. doi: 10.1093/fampra/20.1.61.
45. Medlinskiene K, Tomlinson J, Marques I, Richardson S, Stirling K, Petty D. Barriers and facilitators to the uptake of new medicines into clinical practice: A systematic review. BMC Health Serv Res. 2021;21(1):1198-4. doi: 10.1186/s12913-021-07196-4.
46. Prosser H, Walley T. New drug uptake: Qualitative comparison of high and low prescribing GPs' attitudes and approach. Fam Pract. 2003;20(5):583-591. doi: 10.1093/fampra/cmg516.
47. Hailu AD, Workneh BD, Kahissay MH. Influence of pharmaceutical marketing mix strategies on physicians' prescribing behaviors in public and private hospitals, dessie, ethiopia: A mixed study design. BMC Public Health. 2021;21(1):65-2. doi: 10.1186/s12889-020-10063-2 [doi].
48. Leonardo Alves T, Lexchin J, Mintzes B. Medicines information and the regulation of the promotion of pharmaceuticals. Sci Eng Ethics. 2019;25(4):1167-1192. doi: 10.1007/s11948-018-0041-5 [doi].
49. Spurling GK, Mansfield PR, Montgomery BD, et al. Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: A systematic review. PLoS Med. 2010;7(10):e1000352. doi: 10.1371/journal.pmed.1000352.
50. Jones MI, Greenfield SM, Bradley CP. Prescribing new drugs: Qualitative study of influences on consultants and general practitioners. BMJ. 2001;323(7309):378-381. doi: 10.1136/bmj.323.7309.378 [doi].
51. Ahmed RR, Vveinhardt J, Streimikiene D, Awais M. Mediating and marketing factors influence the prescription behavior of physicians: An empirical investigation. Amfiteatru Economic Journal, ISSN 2247-9104, The Bucharest University of Economic Studies, Bucharest. 2016;18(41):153-167.
52. Sharma S, Akhoon N, Moe HW, Nair DR, Shashidhar V. A study of perceptions and exposure of drug promotional literature among clinicians in a teaching hospital. Perspect Clin Res. 2021;12(3):140-145. doi: 10.4103/picr.PICR_36_19 [doi].

53. Larkin I, Ang D, Steinhart J, et al. Association between academic medical center pharmaceutical detailing policies and physician prescribing. JAMA. 2017;317(17):1785-1795. doi: 10.1001/jama.2017.4039 [doi].
54. Jeuck JE. Direct-mail advertising to doctors. The Journal of Business of the University of Chicago. 1940;13(1):17-38. http://www.jstor.org/stable/2350143.
55. Sah S. Conflicts of interest and your physician: Psychological processes that cause unexpected changes in behavior. J Law Med Ethics. 2012;40(3):482-487. doi: 10.1111/j.1748-720X.2012.00680.x [doi].
56. Sah S, Fugh-Berman A. Physicians under the influence: Social psychology and industry marketing strategies. J Law Med Ethics. 2013;41(3):665-672. doi: 10.1111/jlme.12076 [doi].
57. Eisend M. The third-person effect in advertising: A meta-analysis. Journal of Advertising. 2017;46(3):377-394. https://doi.org/10.1080/00913367.2017.1292481. doi: 10.1080/00913367.2017.1292481.
58. Gettings J, O'Neill B, Chokshi DA, et al. Differences in the volume of pharmaceutical advertisements between print general medical journals. PLoS One. 2014;9(1):e84790. doi: 10.1371/journal.pone.0084790 [doi].
59. Wilkes MS, Doblin BH, Shapiro MF. Pharmaceutical advertisements in leading medical journals: Experts' assessments. Ann Intern Med. 1992;116(11):912-919. doi: 10.7326/0003-4819-116-11-912 [doi].
60. Cardarelli R, Licciardone JC, Taylor LG. A cross-sectional evidence-based review of pharmaceutical promotional marketing brochures and their underlying studies: Is what they tell us important and true? BMC Fam Pract. 2006;7:13-13. doi: 1471-2296-7-13 [pii].
61. Othman N, Vitry A, Roughead EE. Quality of pharmaceutical advertisements in medical journals: A systematic review. PLoS One. 2009;4(7):e6350. doi: 10.1371/journal.pone.0006350 [doi].
62. Rogers EM. (2003). Diffusion of innovations (5th edition). The Free Press. New York.
63. Inman W, Pearce G. Prescriber profile and post-marketing surveillance. Lancet. 1993;342(8872):658-661. doi: 0140-6736(93)91763-C [pii].
64. Ohlsson H, Vervloet M, van Dijk L. Practice variation in a longitudinal perspective: A multilevel analysis of the prescription of simvastatin in general practices between 2003 and 2009. Eur J Clin Pharmacol. 2011;67(12):1205-1211. doi: 10.1007/s00228-011-1082-8.

2

Assessment of new medicines

2.1

Healthcare professionals' preferred efficacy endpoints and minimal clinically important differences in the assessment of new medicines for chronic obstructive pulmonary disease

Marloes Dankers
Marjorie H.J.M.G. Nelissen-Vrancken
Sara M.K. Surminski
Anke C. Lambooij
Tjard R. Schermer
Liset van Dijk

Front Pharmacol. 2020;10:1519.

ABSTRACT

Background

Registration authorities evaluate effects of new medicines for chronic obstructive pulmonary disease (COPD) on airway obstruction, dyspnea, health status and exacerbations. To establish clinical relevance, minimal clinically important differences (MCIDs) are used. The aim of this study was to investigate which efficacy endpoints and MCIDs healthcare professionals consider clinically relevant for new COPD medicines.

Materials and Methods

7,731 Healthcare professionals received an electronic questionnaire. Participants were asked for: 1) preferred efficacy endpoints for new COPD medicines and 2) cut-off values defining clinical relevance for forced expiratory volume in 1 sec (FEV_1), Transition Dyspnea Index (TDI) and St. George's Respiratory Questionnaire (SGRQ). Those cut-off values were compared to the MCIDs used by registration authorities, namely 100 ml for FEV_1, 1 unit for TDI and 4 units for SGRQ.

Results

227 Healthcare professionals responded to the questionnaire. Most preferred efficacy endpoints were exacerbations (51.0%), airway obstruction (46.9%) and health status (44.9%). Mean cut-off values for TDI and SGRQ were significantly higher than the corresponding MCIDs, mean differences 1.5 (95%CI = 1.3 – 1.8, $p > 0.001$) and 7.0 (95%CI = 5.1 – 8.8, $p < 0.001$), respectively. The mean cut-off value for FEV_1 was comparable to the MCID (mean difference 2.2, 95%CI = -19.9 – 24.3, $p = 0.84$).

Conclusions

Healthcare professionals largely agree with efficacy endpoints used for the evaluation of new COPD medicines. However, they seem to prefer higher cut-off values for clinical relevance for TDI and SGRQ than the registration authorities. Effects of new medicines on TDI and SGRQ that are considered clinically relevant by registration authorities do, therefore, not necessarily reflect healthcare professionals' perspectives on clinical relevance.

INTRODUCTION

New medicines are evaluated by registration authorities in order to assess their benefit-risk balance. The assessment of clinical relevance of new medicines by the registration authorities depends heavily on clinical trials. A common approach in clinical trials to investigate clinical effects is the use of patient-reported outcomes (PROs) [1]. PROs represent the patient perspective, quantifying the extent to which a disease impacts their health and functioning [2]. To establish the clinical relevance of a specific improvement on an endpoint, minimal clinically important differences (MCIDs) are used. An MCID is the smallest difference which patients perceive as beneficial and which would mandate a change in patient treatment [3]. Establishing whether an improvement on a clinical endpoint exceeds the MCID is a way to evaluate the clinical relevance of a (new) pharmacological treatment [4-6].

In the last decade, multiple new medicines for the treatment of chronic obstructive pulmonary disease (COPD) obtained market access [7-10]. Assessment of new COPD medicines includes the evaluation of effects on several efficacy endpoints, including airway obstruction, dyspnea, health status, and exacerbations. Frequently used parameters are forced expiratory volume in 1 sec (FEV_1), Transition Dyspnea Index (TDI) and St. George's Respiratory Questionnaire (SGRQ) for airway obstruction, dyspnea and health status, respectively [7-11]. Although FEV_1 is an objective endpoint and highly reproducible [12], it has a relatively poor correlation with symptoms [2,13]. PROs like dyspnea and health status might better reflect the impact of the disease on COPD patient's daily life. Improvements of 100 ml, one units and four units are validated MCIDs for FEV_1, TDI, and SGRQ, respectively [3,4,12,14]. Although these values are widely adopted, some debate about the acceptability of these MCIDs exists, especially for FEV_1 [3]. Values up to 140 ml are suggested as MCID for FEV_1 [12]. There is no clear MCID for the evaluation of exacerbations [15].

Since FEV_1, TDI, and SGRQ and their corresponding MCIDs are used by registration authorities for the evaluation of clinical efficacy of new medicines for the treatment of COPD, they are of crucial importance for the market access of these new medicines. Physicians and other healthcare professionals who prescribe (or advise about) those medicines have to rely on the assessment of new medicines by registration authorities. It is therefore of particular interest to know their opinions about the endpoints and MCIDs used in the assessment of clinical relevance of new medicines. Although expert-opinions can be included in the establishment of an MCID (in addition to the use of statistical and anchor-based approaches) [4,16], it is to our knowledge unknown how healthcare professionals assess the clinical importance of endpoints and their MCIDs

used for new COPD medicines. The aims of this study are therefore: 1) to investigate which efficacy endpoints healthcare professionals consider clinically relevant in the assessment of new medicines for COPD, and 2) to investigate which MCIDs healthcare professionals consider relevant for the frequently used endpoints FEV_1, TDI, and SGRQ.

MATERIALS AND METHODS

Background

Airway obstruction (measured by FEV_1), dyspnea (measured by TDI), and health status (measured by SGRQ) are important efficacy endpoints in the assessment of new medicines for COPD [11]. FEV_1 is the volume of air that is forcibly exhaled in the 1st second. The trough (pre-bronchodilator) FEV_1 is most commonly used in clinical trials evaluating the efficacy of COPD medicines [2]. A commonly used MCID for trough FEV_1 is 100 ml [3,4,12,14]. TDI is a validated evaluative instrument that measures changes in the severity of dyspnea by grading functional impairment, magnitude of task and magnitude of effort. Each parameter is graded from -3 to +3, adding up to a total score ranging from -9 to +9 [12]. The MCID is 1 unit [3,4,12,14]. SGRQ has been developed to measure health status in patients with respiratory disease. It is a self-administered questionnaire that measures health status in the subdomains symptoms, activity and impacts, with a total score ranging from 0 to 100 [2,12]. A difference of four units is considered clinically relevant [3,4,12,14].

Design

This investigation was part of a more extensive online survey about the opinion of Dutch healthcare professionals regarding the clinical relevance of new medicines for the treatment of type 2 diabetes mellitus (T2DM) and COPD. No ethical approval was needed. According to the Dutch legislation, neither obtaining informed consent nor approval by a medical ethics committee is obligatory for carrying out research among healthcare professionals that does not include patient data.

Participants

Participants for the online survey were obtained from the Customer relationship management (CRM) of the Dutch Institute for Rational Use of Medicine (IRUM). This CRM has multiple purposes, but is predominantly used for sending newsletters and information about the IRUMs activities. The CRM contained 7,731 email addresses of Dutch healthcare professionals (predominantly physicians, pharmacists, practice nurses, respiratory nurses, and diabetes nurses).

Data Collection

The invitation to fill out the questionnaire was sent by email (with a link to the questionnaire) on 15 November 2016. The online survey was closed two weeks later. All healthcare professionals received one reminder after 1 week. Participants did not receive a financial compensation, although every 10th participant was offered a free online accredited medicine course.

Questionnaire and Measurements

The full questionnaire consisted of 39 questions, among them 19 questions about new medicines for COPD. Responders were first asked for their profession. Next, they were asked whether they were involved in the management of patients with T2DM or COPD in their daily clinical practice. Only healthcare professionals working with COPD patients were asked to fill out the COPD section of the questionnaire.

The content of the COPD section of the questionnaire was based on the requirements for clinical trials for new COPD medicines, as described in the Guideline on clinical investigation of medicinal products in the treatment of COPD [11] and the MCIDs mentioned in the public assessment reports of new medicines for COPD [7-10].

The COPD section of the questionnaire consisted of three parts. The first part investigated the healthcare professionals preferred efficacy endpoints for the assessment of clinical relevance of new COPD medicines. Healthcare professionals were first informed about the need of efficacy endpoints in clinical trials and then asked which efficacy endpoints they considered clinically relevant for the assessment of new COPD medicines. All questions were open-ended in order to enhance the chance of getting reliable and sincere answers.

The second part investigated cut-off values for clinical relevance for FEV_1, TDI, and SGRQ. Healthcare professionals were informed about these endpoints and asked for a cut-off value for clinical relevance compared to placebo. All questions were open-ended. The MCIDs for FEV_1, TDI, and SGRQ were not mentioned before, in order to stimulate healthcare professionals to base their answer on their own clinical experience without being influenced by the validated MCIDs. Since TDI and SGRQ are not routinely used in daily clinical practice in the Netherlands, the questionnaire gave a brief description of these endpoints, including the range of those scales. This enabled responders to estimate a clinically relevant difference, regardless of their familiarity with those parameters. The third part about safety endpoints was not included in this analysis.

The online survey was programmed in NetQuestionnaire and pre-tested by three general practitioners, two pharmacists and three practice nurses for reasons of understandability and content. Since they experienced more difficulties with the COPD section compared to the T2DM section, the T2DM section was positioned before the COPD section to enhance the overall response rate.

Data Analysis

Responders were categorized by profession (physician, pharmacist, practice nurse, and other). The group "other" was excluded from further analysis. Responders who were both a physician and pharmacist were analysed as physicians. All different types of nurses (for example, practice nurses, respiratory nurses, and nurse practitioners) were analysed together as practice nurses.

After collection of the endpoints mentioned by the responders, six different categories of endpoints based on Global strategy for prevention, diagnosis and management of COPD 2019 report [17] were defined. Those categories were 1) exacerbations (including hospital admissions, infections, use of antibiotics and oral steroids), 2) airway obstruction (including parameters used to define airway obstruction like FEV_1), 3) health status (including quality of life, disease burden, Clinical COPD Questionnaire (CCQ) wellbeing and daily functioning), 4) respiratory symptoms (including dyspnea, cough, Medical Research Council (MRC) dyspnea scale, use of short-acting bronchodilators), 5) exercise intolerance (including condition, physical activity), 6) mortality, and 7) other (including morbidity, oxygen dependency or saturation, and adverse events). Subsequently, all answers were categorized by two researchers (based on consensus) and frequencies were calculated. Some healthcare professionals mentioned the Global Initiative for Chronic Obstructive Lung Disease (GOLD) status as preferred endpoint. Since GOLD includes airway obstruction, exacerbations and health status [17], each answer that mentioned GOLD was counted into these three categories. The categorization was verified by one independent researcher.

All cut-off values in open text fields were recoded into numeric variables. Impossible values for TDI and SGRQ (i.e., values exceeding the parameter range) were excluded. Based on expert opinions, FEV_1 values > 0 and < 1 ml and FEV_1 values > 1,499 ml were considered implausible and therefore also excluded, as were values in other units than asked (e.g., percentages instead of milliliters). Ranges (e.g., 50 – 75) were converted to averages (e.g., 67.5). Cut-off values for FEV_1, TDI and SGRQ were compared to the corresponding MCIDs by a one-sample T-test. Results were considered significant when $p < 0.05$.

All results were analysed with IBM SPSS Statistics 24.

RESULTS

A total of 556 responders (6.6%) started the questionnaire. Only healthcare professionals working with COPD patients in daily practice were included in this analysis. The final population consisted of 227 healthcare professionals (88 physicians, 107 pharmacists, and 27 practice nurses), resulting in a response rate of 2.9% (Figure 1). The group of 88 physicians contained two physicians who were also pharmacists and one dispensing general practitioner. Those were analysed solely as physicians. Among the group of 27 practice nurses were 21 practice nurses, one respiratory nurse, one physician assistant, one nurse practitioner, one trainee nurse practitioner, one geriatric nurse, and one practice nurse who was also a respiratory nurse and diabetes nurse. Those were analysed together as practice nurses.

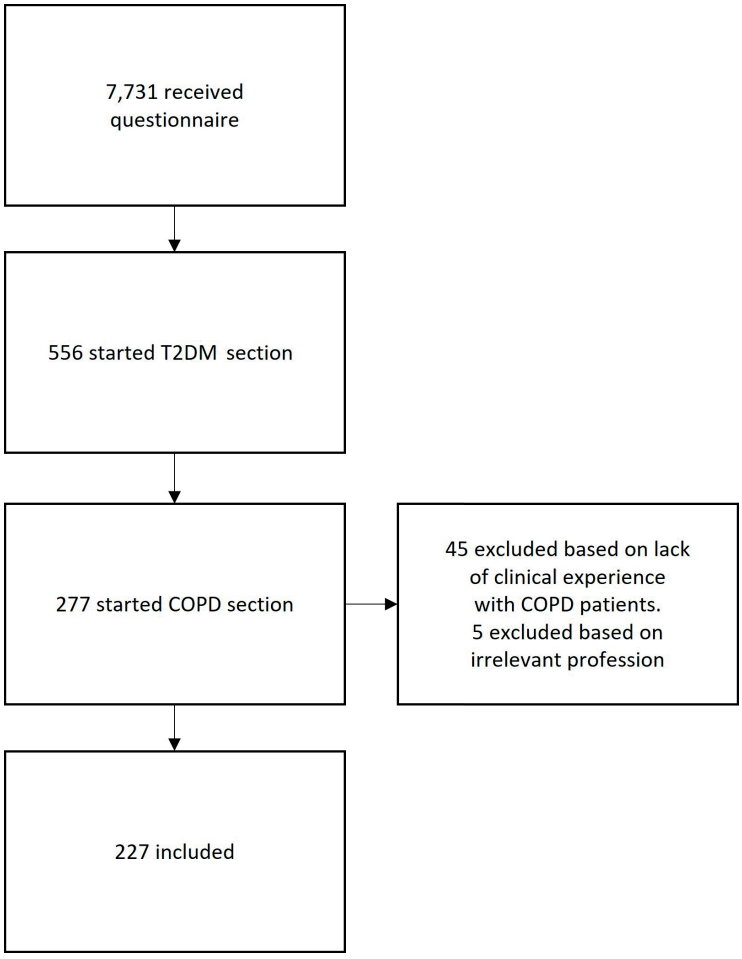

Figure 1. Response. COPD = chronic obstructive pulmonary disease, T2DM = type 2 diabetes mellitus.

Endpoints

196 healthcare professionals mentioned their efficacy endpoints of preference. The most frequently mentioned endpoints were exacerbations (51.0%), airway obstruction (46.9%), and health status (44.9%) (Table 1).

Table 1: Preferred efficacy endpoints in the evaluation of new COPD medicines.

Endpoints	Frequency
Exacerbations	51.0%
Airway obstruction[a]	46.9%
Health status	44.9%
Respiratory symptoms	30.6%
Mortality	23.0%
Exercise intolerance	9.2%
Other	11.2%

[a] *Two responders (1%) mentioned inspiratory capacity as most preferred endpoint. Since this is closely related to airway obstruction, those answers were counted into this category.*

MCIDs

Healthcare professionals were asked for a cut-off value that defined clinical relevance for FEV_1, TDI, and SGRQ. For both TDI and SGRQ, cut-off values according to healthcare professionals (2.5 and 11.0 units, respectively) were significantly higher than the MCIDs used by the European Medicines Agency (EMA) (one unit and four units, respectively) (Table 2). Mean differences for TDI and SGRQ compared to MCIDs were 1.5 (95% CI = 1.3 – 1.8, $p < 0.001$) and 7.0 (95% CI = 5.1 – 8.8, $p < 0.001$). Pharmacists mentioned the highest cut-off values for both TDI (2.8 units; followed by 2.4 units by physicians and 2.2 units by practice nurses) and SGRQ (12.2 units, followed by 11.5 units by practice nurses and 9.5 units by physicians).

The mean cut-off value for FEV_1 (102.2 ml) according to healthcare professionals was comparable to the MCID (100 ml), mean difference 2.2 ml (95% CI = -19.9 – 24.3, $p = 0.84$). Mean cut-off values according to pharmacists, physicians and practice nurses were 100.8 ml, 115.3 ml, and 72.1 ml, respectively. None of these cut-off values were significantly different from the MCID.

Table 2: Cut-off values for FEV_1, TDI, and SGRQ according to healthcare professionals, compared to the corresponding MCID.

		n	Mean (SD)	Mean difference compared to MCID (95%CI)	p
FEV_1 (ml) MCID = 100 ml	*All*	105	102.2 (114.1)	2.2 (-19.9 – 24.3)	0.84
	Physicians	44	115.3 (108.8)	15.3 (-17.8 – 48.3)	0.36
	Pharmacists	44	100.8 (133.6)	0.75 (-39.9 – 41.4)	0.97
	Practice nurses	17	72.1 (57.8)	-27.9 (-57.6 – 1.9)	0.064
TDI (unit) MCID = 1 unit	*All*	109	2.5 (1.4)	1.5 (1.3 – 1.8)	< 0.001*
	Physicians	44	2.4 (1.3)	1.4 (1.0 – 1.7)	< 0.001*
	Pharmacists	53	2.8 (1.5)	1.8 (1.4 – 2.2)	< 0.001*
	Practice nurses	12	2.2 (1.6)	1.2 (0.16 – 2.2)	= 0.027*
SGRQ (unit) MCID = 4 units	*All*	119	11.0 (10.1)	7.0 (5.1 – 8.8)	< 0.001*
	Physicians	50	9.5 (6.4)	5.5 (3.7 – 7.3)	< 0.001*
	Pharmacists	56	12.2 (11.9)	8.2 (5.0 – 11.3)	< 0.001*
	Practice nurses	13	11.5 (13.4)	7.5 (-0.56 – 15.6)	0.065

95%CI = 95% Confidence Interval, FEV_1 = forced expiratory volume in 1 sec, MCID = minimal clinically important difference, SD = standard deviation, SGRQ = St. George's Respiratory Questionnaire, TDI = Transition Dyspnea Index.
** Statistically significant different compared to MCID, based on one-sample T-test. Results were considered significant when $p < 0.05$.*

DISCUSSION

This study investigated which endpoints and MCIDs healthcare professionals considered clinically relevant for the evaluation of the efficacy of new medicines for COPD. Dutch healthcare professionals seem slightly more critical than registration authorities in the assessment of the clinical relevance of those new medicines. Although the preferred endpoints roughly correspond with the ones used in clinical trials, healthcare professionals prefer higher cut-off values for clinical relevance for TDI and SGRQ than the MCIDs used by registration authorities. This stricter view of clinical relevance is not seen for airway obstruction, since the average cut-off value for FEV_1 was comparable to the MCID. In general, physicians and practice nurses were less critical than pharmacists. This may display a difference in the clinical experience of healthcare professionals. Practice nurses and physicians more often see patients and measure endpoints like airway obstruction, dyspnea and health status than pharmacists. That might enhance their ability of estimating the expected medicine-induced improvement.

To our knowledge, this is the first study that specifically investigated the opinions of healthcare professionals about the endpoints and MCIDs used for the assessment of clinical efficacy of new COPD medicines. Expert opinions on the MCID for FEV_1 have,

however, been published before. The cut-off values for FEV_1 according to a small group of opinion leaders on this topic were generally higher than the MCID of 100 ml and thus also higher than the cut-off value for FEV_1 found in our investigation [3].

The differences between the cut-off values found in this investigation and established MCIDs might reflect the challenges with MCIDs as stated in other publications [3,14,18]. Factors such as heterogeneity in population and disease, trial duration, Hawthorne effects, withdrawal rates, and baseline disease severity may affect the size of benefit relative to the MCID [14,18]. It is therefore suggested that MCIDs should be used as an indicative value rather than as an absolute cut-off point [14]. The EMA, however, uses MCIDs to define the clinical relevance of new medicines. The cut-off values found in our study would have consequences for the evaluation of the clinical relevance of new COPD medicines. Multiple new (single-agent) inhalation medicines (aclidinium, glycopyrronium, indacaterol, and umeclidinium) for the treatment of COPD have been approved in Europe in the last decade. According to the EMA assessment of those medicines, roughly 50% of all improvements on FEV_1, TDI, and SGRQ exceeded the MCID and were thus considered clinically relevant [7-10]. When using the mean cut-off values found in the current study, instead of the MCIDs, none of the improvements on TDI and SGRQ would still have been clinically relevant. A new medicine that is considered "clinically relevant" by registration authorities does, therefore, not necessarily reflect healthcare professionals' views on clinical relevance. Since healthcare professionals have a stricter view of cut-off values for clinical relevance, defining clinical relevance by use of MCIDs might lead to overestimation of the expected treatment benefit.

Our results indicate that healthcare professionals consider exacerbations as the most important endpoint. Evaluation of the clinical importance of a reduction in exacerbations was not included in this investigation. Although evaluation of exacerbations is also part of the assessment procedure of new COPD medicines, there is no specific MCID used [7-10]. Defining an MCID for COPD exacerbations is problematic, because the impact of exacerbations is influenced dramatically by the used definition of (the severity of) an exacerbation and the influence of baseline status [15]. The use of exacerbation-free time instead of frequency (or severity) of exacerbations might better reflect the burden of exacerbations in COPD patients [19]. Future work should reveal the clinical relevance of a reduction in incidence or severity of exacerbations, or the increase of exacerbation-free time.

This study only included the assessment of the efficacy of new medicines for COPD. This is only a part of the assessment of new medicines, since safety and ease of use are also of clinical importance [7-10]. Our investigation did also not include patient

preferences on endpoints and MCIDs. A comprehensive literature review of patient preferences for the management of COPD revealed that the most important issues to patients with severe disease were symptom control, impact of disease on daily life, and positive relationship with the primary caregiver [20]. Another study reported the most reported ideal treatment factors based on interviews with 72 patients with asthma or COPD. These patients mentioned improved sleep, speed of action, and length of relief as most important aspects of treatment [21]. Patients perspectives on MCIDs are to our knowledge still unknown.

This investigation was meant as a first study to explore the opinion of different healthcare professionals (physicians, pharmacists, and practice nurses) on clinical relevance of endpoints and cut-off values. Since this study is based on the opinion of healthcare professionals working with COPD patients in daily practice, it provides a clear view of how clinical relevance of new medicines is considered in the daily practice of physicians, pharmacists and practice nurses. The main strength of this investigation is the exploratory and open character which was stimulated by the questionnaire with open-ended answers. There are, nonetheless, some limitations of this study. First, the results cannot be generalized to all Dutch healthcare professionals. Since the IRUM's CRM was used, only healthcare professionals who were somehow interested in pharmaceutical care were included in this study. Second, approximately half of the responders were pharmacists. In general, they will have less clinical experience than physicians and practice nurses. The overrepresentation of pharmacists could have influenced the mean cut-off values. However, the analysis of the cut-off values per profession showed that the results of the different professions were generally in line with each other. Third, the response rate was poor, with only 6.6 percent response to the general questionnaire and 2.9 percent to the COPD section. The number of responders that completed the questions about cut-off values was even lower. There are some possible explanations for this. Since the healthcare professionals were enrolled in a CRM instead of a research panel, they did not routinely participate in investigations and were not used to be approached for research via this panel. Another contributing factor to the low response was the fact that this research was part of a more extensive investigation towards the opinion of healthcare professionals about new medicines. A substantial number of healthcare professionals dropped out before the COPD section. However, unless the poor response rate, there was still a considerable number of healthcare professionals available for analysis. Fourth, the questions about cut-off values for TDI and SGRQ might have been fairly difficult to answer, since these instruments are not routinely used in Dutch clinical practice. This seems to be reflected by the wide range of cut-off values for clinical relevance. To maximize the probability of getting reliable results, the questionnaire referred to the range of scores for TDI and SGRQ. This enabled

healthcare professionals unfamiliar with these scales to estimate a clinically relevant difference. However, this does not completely rule out the possibility of inaccuracy in the mentioned cut-off values for TDI and SGRQ.

Despite these limitations, this study suggests that healthcare professionals are more critical than registration authorities in defining the clinical relevance of the efficacy of new medicines for the treatment of COPD. Larger and more representative ad hoc trials are needed to focus the topic and confirm these results. In the meantime, the established MCIDs should be used with caution, since new medicines that exceed the MCID do not necessarily meet the expectations of clinical relevance according to healthcare professionals. Defining clinical relevance by using MCIDs might, therefore, lead to overestimation of the expected treatment benefit of new COPD medicines by healthcare professionals.

REFERENCES

1. Hedayat A. S., Wang J., Xu T. (2015). Minimum clinically important difference in medical studies. Biometrics 71 (1), 33–41. 10.1111/biom.12251
2. Jones P., Miravitlles M., van der Molen T., Kulich K. (2012). Beyond FEV1in COPD: a review of patient-reported outcomes and their measurement. Int. J. Chron. Obstruct. Pulmon. Dis. 7, 697–709. 10.2147/COPD.S32675
3. Donohue J. F. (2005). Minimal clinically important differences in COPD lung function. COPD 2 (1), 111–124. 10.1081/COPD-200053377
4. Make B. (2007). How can we assess outcomes of clinical trials: The MCID Approach. COPD: J. Chronic. Obstruct. Pulmon. Dis. COPD. 4 (3), 191–194. 10.1080/15412550701471231
5. Koynova D., Lühmann R., Fischer R. (2013). A framework for managing the minimal clinically important difference in clinical trials. Ther. Innov. Regul. Sci. 47 (4), 447–454. 10.1177/2168479013487541
6. Bartels R. H. M. A., Donk R. D., Verhagen W. I. M., Hosman A. J. F., Verbeek A. L. M. (2017). Reporting the results of meta-analyses: a plea for incorporating clinical relevance referring to an example. Spine J. 17 (11), 1625–1632. 10.1016/j.spinee.2017.05.019
7. CHMP (2009). Assessment report: Onbrez Breezhaler, INN: indacaterol, Procedure No. EMEA/H/C/001114. (December). Available from: http://www.emea.europa.eu.
8. CHMP (2012). Assessment report: Eklira Genuair, INN: aclidinium bromide. Procedure No. EMEA/H/C/002211. (May). Available from: http://www.emea.europa.eu.
9. CHMP (2012). Assessment report: Seebri Brezhaler, INN: glycopyrronium bromide. Procedure No. EMEA/H/C/002430. (August). Available from: http://www.emea.europa.eu.
10. CHMP (2014). Assessment report: Incruse, INN: umeclidinium bromide. Procedure No. EMEA/H/C/002809/0000. (February). Available from: http://www.emea.europa.eu.
11. CHMP (2012). Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD). EMA/CHMP/700491/2012. 10.1183/09031936.00099306
12. Cazzola M., MacNee W., Martinez F. J., Rabe K. F., Franciosi L. G., Barnes P. J., et al. (2008). Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur. Respir. J. 31 (2), 416–469. 10.1007/164_2016_70
13. Singh D. (2017). Evaluation of new drugs for asthma and COPD: Endpoints, biomarkers and clinical trial design. Handb. Exp. Pharmacol. 237, 243–264. 10.3109/15412555.2012.733463
14. Jones P. W., Beeh K. M., Chapman K. R., Decramer M., Mahler D. A., Wedzicha J. A. (2014). Minimal clinically important differences in pharmacological trials. Am. J. Respir. Crit. Care Med. 189 (3), 250–255. 10.1097/00002281-200203000-00006
15. Chapman K. R., Bergeron C., Bhutani M., Bourbeau J., Grossman R. F., Hernandez P., et al. (2013). Do we know the minimal clinically important difference (MCID) for COPD exacerbations. COPD 10 (2), 243–249. 10.3109/15412555.2012.733463
16. Beaton D. E., Boers M., Wells G. A. (2002). Many faces of the minimal clinically important difference (MCID): a literature review and directions for future research. Curr. Opin. Rheumatol. 14 (2), 109–114. 10.1081/COPD-200050649
17. Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2019). GOLD 2019 Global Strategy for the Diagnosis, Management and Prevention of COPD. 10.1038/s41533-018-0079-5
18. Kiley J. P., Ram J. S., Croxton T. L., Weinmann G. G. (2005). Challenges associated with estimating minimal clinically important differences in COPD - The NHLBI perspective. COPD 2 (1), 43–46. 10.2147/COPD.S82179

19. Boer L. M., Bischoff E. W., Borgijink X., Vercoulen J. H., Akkermans R. P., Kerstjens H. A. M., et al. (2018). Exacerbation-free time' to assess the impact of exacerbations in patients with chronic obstructive pulmonary disease (COPD): a prospective observational study. NPJ Prim. Care Respir. Med. 28 (1), 12. 10.1007/s12325-017-0557-0
20. Bereza B. G., Troelsgaard Nielsen A., Valgardsson S., Hemels M. E., Einarson T. R. (2015). Patient preferences in severe COPD and asthma: a comprehensive literature review. Int. J. Chron. Obstruct. Pulmon. Dis. 10, 739–744. 10.2147/COPD.S82179
21. Svedsater H., Roberts J., Patel C., Macey J., Hilton E., Bradshaw L. (2017). Life impact and treatment preferences of individuals with asthma and chronic obstructive pulmonary disease: results from qualitative interviews and focus groups. Adv. Ther. 34 (6), 1466–1481. 10.1007/s12325-017-0557-0

2.2

Alignment between outcomes and minimal clinically important differences in the Dutch type 2 diabetes mellitus guideline and healthcare professionals' preferences

Marloes Dankers
Marjorie H.J.M.G. Nelissen-Vrancken
Bertien H. Hart
Anke C. Lambooij
Liset van Dijk
Aukje K. Mantel-Teeuwisse

Pharmacol Res Perspect. 2021;9(3):e00750.

ABSTRACT

To evaluate the clinical benefit of new medicines for type 2 diabetes mellitus (T2DM), the Dutch guideline committee T2DM in primary care established the importance of outcomes and minimal clinically important differences (MCIDs). The present study used an online questionnaire to investigate healthcare professionals' opinions about the importance of outcomes and preferences for MCIDs. A total of 211 physicians, pharmacists, practice nurses, diabetes nurses, nurse practitioners and physician assistants evaluated the importance of mortality, macro- and microvascular morbidity, HbA1c, body weight, quality of life, (overall) hospital admissions and severe and other hypoglycemia on a 9-point scale. All outcomes were considered critical (mean scores 7-9), except for body weight and other hypoglycemia (mean scores 4-6). Only HbA1c and hospital admissions were valued differently by the guideline committee (not critical). Other relevant outcomes according to the respondents were adverse events, ease of use and costs. Median MCIDs were 4 mmol/mol for HbA1c (guideline: 5 mmol/mol) and 3 kg for body weight (guideline: 5 kg weight gain and 2,5 kg weight loss). Healthcare professionals preferred relative risk reductions of 20% for mortality (guideline: 10%) and macrovascular morbidity (guideline: 25%) and 50% for other hypoglycaemia (guideline: 25%). The MCID of 25% for microvascular morbidity, hospital admissions and severe hypoglycaemia corresponded to the guideline-MCID. Healthcare professionals' preferences were thus comparable to the views of the guideline committee. However, healthcare professionals had a stricter view on the importance of HbA1c and hospital admissions and the MCIDs for mortality and other hypoglycemia.

INTRODUCTION

The last two decades, new pharmacological treatments have become available for the treatment of type 2 diabetes mellitus (T2DM), including dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose-cotransporter 2 (SGLT2) inhibitors. Most of these drugs have found their ways into national and international clinical guidelines [1,2].

To evaluate new pharmacological treatments, guideline committees have to specify the criteria the medicines have to meet. Therefore, the importance of outcomes and cut-off values for a clinical benefit on these outcomes have to be established. The importance of outcomes can be scored according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. GRADE recommends the use of a 9-point scale. A score of 1 – 3 indicates limited importance, 4 – 6 important, but not critical, and 7 – 9 critical importance [3]. Subsequently, cut-off values for a clinical benefit can be defined [4]. Those cut-off points, also known as minimal clinically important differences (MCIDs) or minimal important differences (MIDs), are used to evaluate the clinical relevance of a difference between two treatments [5].

For the evaluation of pharmacological treatments for T2DM, a considerable number of outcomes can be relevant, varying from direct outcomes for clinical efficacy (e.g. mortality) to surrogate outcomes (e.g. HbA1c), safety outcomes (e.g. hypoglycemia) and patient reported outcomes (PROs) like quality of life [6-10]. Validated MCIDs are not available for T2DM medicines. The decisions about importance of outcomes and MCIDs in treatment guidelines are therefore based on expert opinions and guideline committee consensus [4,11,12].

The abovementioned approach for the definition of importance of outcomes and corresponding MCIDs was also followed in het process of updating the Dutch clinical guideline for the treatment of T2DM in primary care in 2018 [4]. The outcomes mortality, macrovascular and microvascular morbidity, HbA1c, body weight, quality of life, (overall) hospital admissions, severe hypoglycemia, other hypoglycemia (not specified, mild or modest) and other adverse events were evaluated by the guideline committee for their relative importance. Subsequently, the guideline committee established the MCIDs for those outcomes [4]. The MCIDs were based on previously defined MCIDs in other national and international guidelines [2,11,12], non-specific thresholds for relative risks and standardized mean differences (SMD) provided by GRADE [13] and expert opinion in the guideline committee [4]. An overview of outcomes, their relative importance and MCIDs used during the Dutch T2DM guideline development can be found in Table 1.

Table 1: Overview of importance and MCIDs of outcomes used in the update of the T2DM guideline [2].

Outcomes	Importance[a]	Cut-off point for clinical relevance	MCID based on
All-cause mortality	Critical	RRR 10% (RR < 0,9 or RR > 1,1)	Expert opinion guideline committee
Macrovascular morbidity	Critical	RRR 25% (RR < 0,75 of RR > 1,25)	GRADE [13]
Microvascular morbidity	Critical	RRR 25% (RR < 0,75 or RR > 1,25)	GRADE [13]
Quality of life	Critical	Every statistically significant difference or SMD = 0,5	GRADE [13]
Severe hypoglycemia	Critical	RRR 25% (RR < 0,75 of RR > 1,25)	GRADE [13]
Other adverse events	Critical or important[b]	Every statistically significant difference or SMD = 0,5	GRADE [13]
Hospital admissions	Important	RRR 25% (RR < 0,75 of RR > 1,25)	GRADE [13]
Change in HbA1c	Important	0,5% or 5 mmol/mol	NICE guideline Type 2 diabetes in adults: management [11]
Change in body weight	Important	5% in case of both treatments cause weight gain 2,5% in case of one treatment causes weight loss and the other causes weight gain (or had a neutral effect on weight)	Dutch guideline T2DM in secondary care [12]
Other hypoglycemia (not specified or mild or modest)	Important	RRR 25% (RR < 0,75 of RR > 1,25)	GRADE [13]

MCID = minimal clinically important difference, RR = relative risk, RRR = relative risk reduction, SMD = standardized mean difference, T2DM = type 2 diabetes mellitus.

[a] Minor differences existed in relative importance between different healthcare questions. The importance shown is based on the importance for most healthcare questions.

[b] Depending on the severity of the adverse event.

The treatment recommendations in the final guideline heavily depend on the classification of importance of outcomes and MCIDs. Since the final guideline is leading for the treatment choices healthcare professionals in primary care make, it is of particular interest to know the degree of alignment between the guideline committee and the end users of the guideline. There is limited or no evidence concerning the views of healthcare professionals about the importance of outcomes and MCIDs used in guideline development or in the evaluation of blood glucose lowering drugs. Therefore, the aim of this study was to investigate healthcare professionals' opinions about the importance of outcomes and preferences for MCIDs used in the evaluation of new medicines for the T2DM guideline.

MATERIALS AND METHODS

Design

An online questionnaire was developed to investigate healthcare professionals' opinions about outcomes and MCIDs used in the evaluation of new T2DM medicines. According to the Dutch legislation, neither obtaining informed consent nor approval by a medical ethics committee is obligatory for conducting research among healthcare professionals that does not include patient data. Therefore, no ethical approval was needed.

Participants

Participants for the online questionnaire were approached using the mailing list for newsletters of the Dutch Institute for Rational Use of Medicine (IRUM). The mailing list contained 12,115 email addresses of stakeholders in pharmaceutical care, such as healthcare professionals and policy makers. Since there was no information about the profession of the subscribers, the questionnaire was sent to all subscribers. The respondents were asked for their profession in the questionnaire. Therefore, the selection of relevant professions could be made afterwards.

Data collection

The invitation to fill out the questionnaire was sent by email with a link to the online questionnaire on 17 February 2020. All subscribers received one reminder after 10 days (27 February 2020). The online questionnaire was closed on 13 March 2020. Participants did not receive a financial compensation, although every 10th participant was offered a free online accredited course about the treatment of T2DM, which is part of the IRUM continuous medical education program.

Questionnaire and measurements

The questionnaire is available in Appendix 1. The content of the questionnaire was based on the outcomes and cut-off points for clinical relevance used during the development of the T2DM guideline [4]. The questionnaire was developed by the researchers and fine-tuned during several sessions. Thereafter, the questionnaire was pre-tested by six healthcare professionals (a general practitioner, a public pharmacist, a hospital pharmacist, a practice nurse and two diabetes nurses). Based on their suggestions, an open-ended question that asked for other relevant outcomes was added. As expected, the test panel experienced the most difficulties with the questions about MCIDs, especially about relative risks. To simplify these questions, some minor linguistic changes were made. Also, an option 'I do not know/no opinion' was added to all questions about MCIDs.

The final questionnaire was programmed in Enalyzer. The questionnaire consisted of 24 questions. Respondents were first asked whether they were actively involved in the management of T2DM patients in their daily clinical practice. Only healthcare professionals working with T2DM patients were asked to complete the questionnaire. They were asked to score the importance of the outcomes used for the evaluation of new T2DM medicines on a 9-point scale, assuming they were a member of a guideline committee. Respondents could also (optionally) mention other relevant outcomes. The questionnaire then explained the situation where a new treatment was compared to a control treatment. Respondents were asked which difference they would define as MCID. Because of the expected difficulty of estimating relative risks, the questionnaire stated a fictional situation where an absolute number of patients in the control group of 1.000 patients experienced the outcome. Respondents were asked which (absolute) number of outcomes in the treatment group would demonstrate a clinical relevant difference. A fictional example was given for clarification purposes. All questions were open-ended, but only reasonable values (based on expert opinion) were permitted. The last part of the questionnaire was used for validation purposes. The questionnaire mentioned the used MCIDs for clinical relevance for HbA1c and mortality in the Dutch guideline, and asked the respondents whether they agreed with these values. These responses were triangulated with the corresponding open ended answers.

Data analysis

Respondents were categorized by profession. Other professions than physicians, pharmacists, practice nurses, diabetes nurses, nurse practitioners and physician assistants (physician associates) were not included in this analysis, because they were not considered as end–users of the guideline who have either prescription authority (physicians, diabetes nurses, nurse practitioners and physician assistants) or a direct influence on prescription behaviour (practice nurses and pharmacists). No distinction was made between healthcare professionals in primary and secondary care.

Mean scores for importance of the different outcomes (on a 9-point scale) were calculated. Differences in the scores for importance between outcomes were compared by paired samples T-test, and differences between professions with One-way ANOVA. Results were considered statistically significant when $p < 0.05$. The other outcomes mentioned in the open-ended questions were categorized by two researchers (based on consensus). One independent researcher verified the categorization.

For the analysis of cut-off points, one highly unlikely value for body weight decrease (a difference of 90 kg) was excluded from further analysis. Respondents who found every difference relevant were assumed to support the lowest difference possible (1).

The distribution of the cut-off points was plotted for all variables and medians were calculated. All results were analysed with IBM SPSS Statistics 24.

RESULTS

Characteristics of healthcare professionals

A total of 394 respondents started the questionnaire, of whom 329 were healthcare professionals working with T2DM patients. Other professions than physicians, pharmacists, diabetes nurses, practice nurses, nurse practitioners and physician assistants were excluded (n = 83, predominantly healthcare assistants and nurses other than practice nurses). Another 35 respondents dropped-out before the questions about relevance of outcomes. Therefore, the final population consisted of 211 healthcare professionals, including 44 physicians (predominantly general practitioners), 55 pharmacists (predominantly community pharmacists), 69 practice nurses, 27 diabetes nurses, 14 nurse practitioners and two physician assistants. Data of nurse practitioners and physician assistants were combined in the analysis, due to the low number of respondents and the similarity in profession.

Table 2: Characteristics of respondents.

	Physicians (n = 44)	**Pharmacists (n = 55)**	**Practice nurses (n = 69)**	**Diabetes nurses (n = 27)**	**Nurse practitioners/ physician assistants (n = 16)**
Female sex	20 (46%)	38 (69%)	68 (99%)	25 (93%)	11 (69%)
Age (years)					
20 – 39	8 (18%)	22 (40%)	7 (10%)	0 (0%)	2 (13%)
40 – 59	27 (61%)	26 (47%)	41 (59%)	21 (78%)	10 (63%)
≥ 60	9 (21%)	7 (13%)	21 (30%)	6 (22%)	4 (25%)
Working experience (years)					
< 5	6 (14%)	9 (16%)	5 (7%)	0 (0%)	7 (44%)
5 – 9	6 (14%)	7 (13%)	10 (15%)	1 (4%)	4 (25%)
10 – 14	4 (9%)	6 (11%)	26 (38%)	5 (19%)	2 (13%)
15 – 19	4 (9%)	4 (7%)	21 (30%)	14 (52%)	1 (6%)
≥ 20	24 (55%)	29 (53%)	7 (10%)	7 (26%)	2 (13%)
Number of patients contacts per week					
< 5	21 (48%)	9 (16%)	2 (3%)	3 (11%)	11 (69%)
5 – 10	17 (39%)	9 (16%)	17 (25%)	4 (15%)	4 (25%)
11 – 20	5 (11%)	11 (20%)	32 (46%)	11 (41%)	1 (6%)
≥ 20	1 (2%)	26 (47%)	18 (26%)	9 (33%)	0 (0%)

The distribution of sex, age, years of working experience and number of patient contacts per week is shown in Table 2. The location of the practices was well distributed among the Netherlands. The majority of the physicians and pharmacists was well-experienced (≥ 20 years of working experience).

Relevance of outcomes

Healthcare professionals valued severe hypoglycemia as the most important outcome measure (mean score 8.30), followed by mortality (8.14) and quality of life (8.13) (Table 3). All outcomes were considered less important than severe hypoglycemia, except for mortality (p = 0.074). However, small differences did not affect the importance according to the GRADE scaling: other hypoglycemia and body weight were seen as important outcomes (score between 4 and 6), all other outcomes were of critical importance (score between 7 and 9).

Table 3: Mean (SD) importance of outcomes measures, scored on a 9-point scale.

Outcome measure	Mean score importance (SD)	Importance according to GRADE scaling
Severe hypoglycemia	8.30 (0.818)	Critical
Mortality	8.14 (1.032)	Critical
Quality of life	8.13 (0.991)*	Critical
Macrovascular morbidity	8.00 (0.933)**	Critical
Microvascular morbidity	7.95 (0.911)**	Critical
Hospital admissions	7.65 (1.104)**	Critical
HbA1c	7.04 (1.388)**	Critical
Other hypoglycemia[a]	6.64 (1.625)**	Important
Body weight	6.46 (1.360)**	Important

SD = standard deviation.
[a] Mild, modest or not-specified.
** P = 0.01.*
*** P < 0.001 (all compared to severe hypoglycemia).*

There were some differences in the assessment of importance of outcomes between professions (Figure 1). Diabetes nurses gave the highest scores for many outcomes, meaning that they valued outcomes more important than other professions. Physicians and pharmacists most often gave the lowest scores. Statistically significant differences (p < 0.05) between professions were found for all outcomes, except for mortality (p = 0.716) and quality of life (p = 0.138).

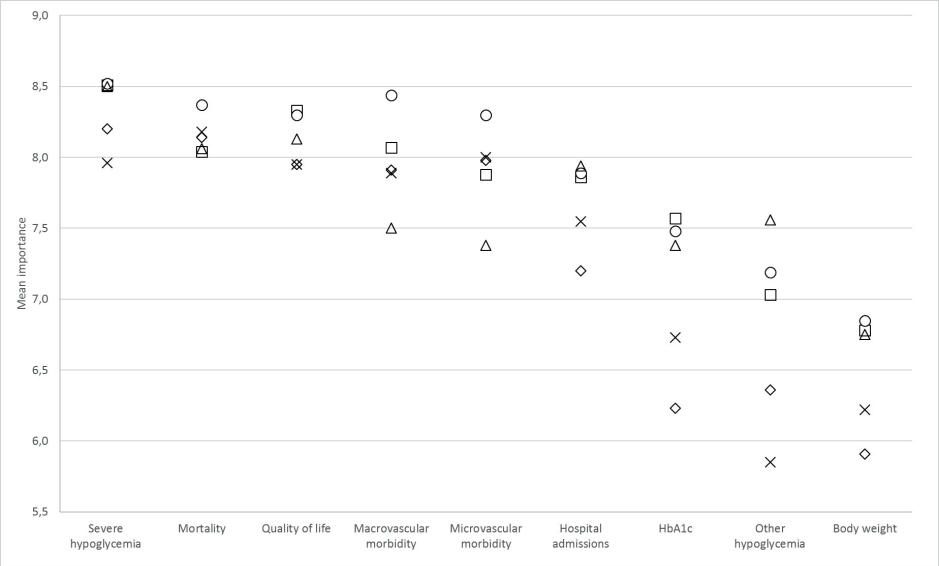

Figure 1: Mean importance of outcomes according to different professions. ◇ Physicians; X Pharmacists; □ Practice nurses; ○ Diabetes nurses; △ Nurse practitioners/physician assistants.

Of the 211 respondents, 114 healthcare professionals (54%) mentioned additional parameters they considered relevant in the assessment of blood glucose lowering drugs. Table 4 shows the outcome measures mentioned by at least two respondents. Adverse events (44.7%), ease of use (41.2%) and costs (10.5%) were most often mentioned.

Table 4: Other relevant outcomes mentioned by healthcare professionals.

Outcome measure	Number of respondents (%)
Adverse events[a]	51 (44.7)
Ease of use	47 (41.2)
Costs	12 (10.5)
Renal effects[b]	8 (7.0)
Effects on insulin use	4 (3.5)
Drug interactions	3 (2.6)
Glucose parameters other than HbA1c	2 (1.8)

[a] *Adverse events include some specific adverse events, like gastro-intestinal adverse events (n = 2), psychological adverse events (n = 2), lactate acidosis (n = 1) and fall risk (n = 1).*

[b] *Renal effects include renal adverse events as well as use by patients with renal impairment.*

MCIDs

MCIDs were investigated for HbA1c, body weight (increase as well as decrease), mortality, macrovascular and microvascular morbidity, hospital admissions, severe and other hypoglycemia. A considerable number of respondents found every difference clinically relevant or had no opinion (Table 5).

Table 5: Response on MCID-questions.

	N	Every difference relevant (%)	No opinion (%)
HbA1c	192	19%	21%
Body weight increase	191	29%	15%
Body weight decrease	185	25%	11%
Mortality	156	27%	19%
Macrovascular morbidity	156	22%	22%
Microvascular morbidity	156	21%	24%
Hospital admissions	156	24%	20%
Severe hypoglycemia	156	28%	16%
Other hypoglycemia	156	13%	27%

Respondents who had no opinion were excluded from further analysis. The results of the remaining healthcare professionals can be found in Figure 2. Median MCIDs according to healthcare professionals were 4 mmol/mol for HbA1c, 3 kg for weight increase as well as decrease, 20% for both mortality and macrovascular morbidity, 25% for microvascular morbidity, hospital admissions and severe hypoglycaemia and 50% for other hypoglycaemia.

For validity reasons, respondents were asked whether they agreed with the MCID used in the clinical guideline for HbA1c (5 mmol/mol) and mortality (RRR = 10%). Figure 3 shows the correspondence of this answer (x-axis) with the earlier preferred MCID, mentioned as open answer (y-axis). Although the answers roughly correspond, the wide range of answers (especially for mortality) shows that there was a considerable number of respondents whose answers were not in line. For example, a substantial amount of the respondents preferred an MICD < 10% for mortality according to the close-ended question, but previously mentioned an MCID > 10% in the open-ended question. Most likely, this indicates interpreting difficulties with the estimation of MCIDs, especially for RRRs.

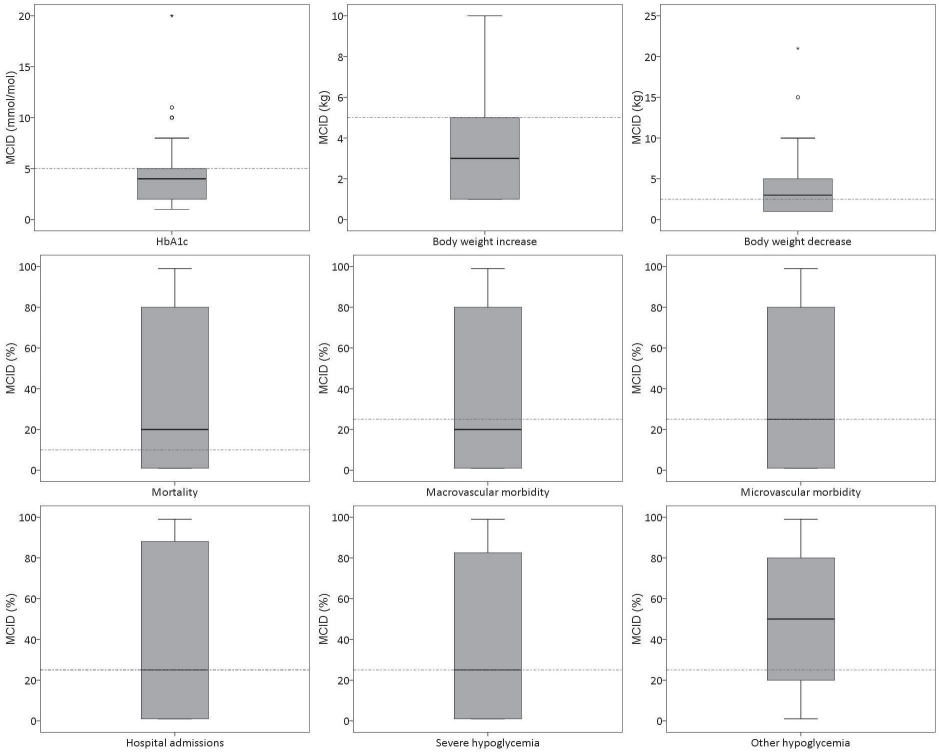

Figure 2 (A – I): Boxplots of MCIDs for outcomes. Dotted lines indicate the MCIDs used in guideline development.

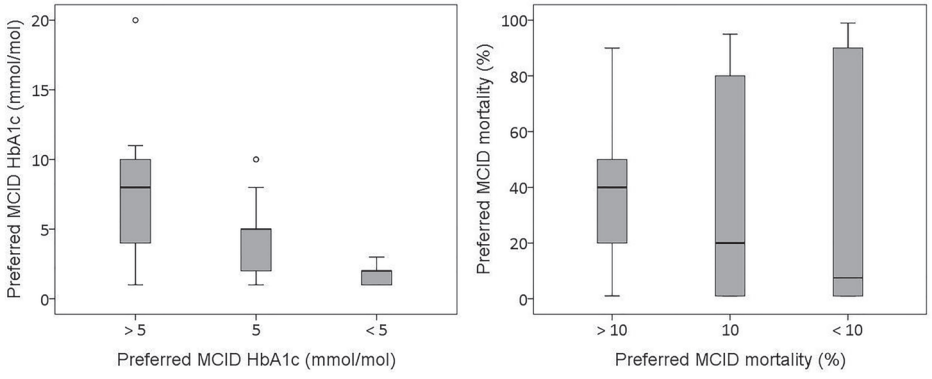

Figure 3 (A and B): Correspondence of close-ended (x-axis) and open-ended (y-axis) questions about preferred MCIDs for HbA1c and mortality.

DISCUSSION

In the evaluation of new T2DM medicines, healthcare professionals considered most outcomes used in the Dutch T2DM guideline in primary care as critically important. Exceptions were other hypoglycemia and change in body weight. Severe hypoglycemia was valued as the most important outcome, followed by mortality and quality of life. As additional parameters, adverse events, ease of use and costs were also seen as relevant. The preferred median MCIDs for HbA1c, body weight, macrovascular and microvascular morbidity, hospital admissions and severe hypoglycemia were comparable with the MCIDs used in the development of the Dutch T2DM guideline. For mortality and other hypoglycemia, healthcare professionals preferred higher median MCIDs [4]. However, this result should be interpreted with caution, because of the difficulties the respondents experienced with the estimation of MCIDs.

The views of healthcare professionals on importance of outcomes roughly correspond with the evaluation by the guideline committee. Compared to the guideline committee, only HbA1c and hospital admissions were valued differently (critical instead of important). The relevance of adverse events, ease of use and costs did also align. These outcomes were also considered during the process of the clinical guideline development, although at a later stage [4].

Remarkably, a safety outcome (severe hypoglycemia) was seen as most important, even more important than mortality and other efficacy parameters. Especially practice nurses, diabetes nurses and nurse practitioners/physician assistants valued the importance of severe hypoglycemia. Pharmacists gave the lowest scores for the importance of hypoglycemia (both severe and other). This difference might reflect the intensity of patient contacts among these professions. Healthcare professionals with many patient contacts will most likely have a more profound experience with hypoglycemia and thus are confronted with the impact of severe hypoglycemia on patients [14-16]. However, other explanations for the differences between professions cannot be excluded, since the distribution of sex, age and years of working experience were also markedly different between the professions.

The results of importance of outcomes are in line with a study by Mol et al. [17], that showed that physicians valued cardiovascular benefits of T2DM drugs as the most important aspect in making regulatory decisions. HbA1c, hypoglycemia and weight gain did also significantly affect physicians' choices [17]. A study by Gauthier et al. [16] however, showed that prescribers considered the overall efficacy in achieving glycemic control as the most important factor in choosing a blood glucose lowering drug if a patient

failed on metformin. Also, cost and insurance coverage, risk of hypoglycemia, weight gain, short- and long-term adverse events and quality of life were valued as important considerations. Clinical efficacy outcomes, like mortality and macro- and microvascular morbidity were barely mentioned [16]. The differences between the results of Gauthier et al. compared to our investigation and the study by Mol et al. [17] might be explained by the setting. Gauthier et al. investigated considerations in prescribing blood glucose lowering drugs to individual patients, while the investigation by Mol et al. and our study focused on decision-making at the population level in regulatory science and guideline development, respectively. In daily practice, decisions might be more influenced by short term outcomes on patient level, while clinical guidelines and regulatory agencies particularly focus on long term outcomes and population level [18,19]. Additionally, cultural differences and a shift towards valuing direct outcomes for clinical efficacy over surrogate outcomes during the last years could also have contributed [6,10]. Our study did not involve patients views on clinical relevance of T2DM drugs. However, their views have been investigated intensively elsewhere. Patients value glucose control, body weight, ease of use, hypoglycemia and other side effects important [14-16,20-22]. The views of patients—as well as the views of healthcare professionals—are mostly in line with those of regulators [17].

Our study also showed that healthcare professionals experience difficulties with estimating MCIDs, as was already concluded during the development of the questionnaire and the responses of the test panel. Despite the changes made for reasons of understandability, approximately 20 percent of the respondents had no opinion or did not answer the questions about MCIDs. Moreover the wide range of answers given, especially for RRRs, also indicate difficulties with the interpretation of these relative outcome measures [23,24]. However, the validation questions show that—despite the difficulties—there was reasonable alignment and the answers therefore give an indication about the estimation of MCIDs by healthcare professionals. The median MCIDs for HbA1c and body weight decrease were very close to the MCIDs used in guideline committees. The distinction made by the guideline committee between MCIDs for body weight decrease and increase was not seen in our results: the median MCID according to healthcare professionals was the same for both situations. The median MCIDs for other hypoglycemia was obviously higher (50%) than for mortality and macrovascular morbidity (20%) and microvascular morbidity, hospital admissions and severe hypoglycemia (25%). This also aligns with the establishment of relative importance of those outcomes, since other hypoglycemia was, among these outcome measures, also seen as the least important outcome. Due to these interpreting difficulties, no further analyses were performed on the MCIDs according to type of healthcare professional.

To the best of our knowledge, this is the first study that investigated the views of healthcare professionals about MCIDs used in the evaluation of T2DM medicines. However, we previously reported the correspondence of preferred outcomes and MCIDs for COPD medicines between healthcare professionals and regulatory agencies. Healthcare professionals preferred higher cut-off values for clinical relevance for COPD-related PROs than the MCIDs used by registration authorities [25]. In addition, the need for focus on clinical relevance in addition to statistical significance is often highlighted, in the conducting as well as reporting and interpretation of clinical trials [26,27]. The difficulties in the interpretation of risks and clinical relevance found in this study also highlights the need for education of healthcare professionals about the interpretation of clinical benefit of (new) medicines [23,24,28]. Moreover, the clinical relevance of new medicines can be over- or underestimated by healthcare professionals if the used outcomes and MCIDs in the evaluation of those medicines are not clearly communicated, especially since the views of healthcare professionals do not necessarily correspond with those of regulators and guideline committees.

This investigation was meant as a first study to explore the opinion of healthcare professionals on outcomes and MCIDs used in the evaluation of new medicines in the Dutch T2DM guideline in primary care. Since this study is based on the opinions of healthcare professionals working with T2DM patients, it provides a clear view of how clinical relevance of new medicines is considered in their daily practice. A main strength of this investigation is the exploratory and open character which was stimulated by the questionnaire with open-ended answers.

There are, nonetheless, some limitations of this study. First, the response rate seemed poor. This can be explained by the use of the mailing list for newsletters of the IRUM, which contains both email addresses of healthcare professionals and other stakeholders in pharmaceutical care. Since the profession of the subscribers was not known, it was not possible to target the invitation for the questionnaire. Although there was still a considerable number of 211 respondents, this approach might have limited the validity and generalizability of this study, also because only healthcare professionals that subscribed to the IRUMs newsletter and therefore will be interested in pharmaceutical care and IRUMs activities were included in this study. Second, no distinction could be made between healthcare professionals from primary and secondary care. Although most physicians and pharmacists were working in primary care, the work setting of the diabetes nurses and physician assistants/nurse practitioners was not known. Last, the questions about MCIDs, especially for RRRs were fairly difficult, as can be seen in the proportion of respondents that did not answer these questions and the wide range of answers. The examples given in the questionnaire for clarification purposes could

thereby have influenced the respondents. However, from the results of the validation questions it can be concluded that the majority of respondents interpreted the questions correctly, and the results for MCIDs can therefore be interpreted, albeit with caution.

This study must be seen as a first exploratory investigation towards the alignment of outcomes and MCIDs between the guideline committee T2DM and end users of the guideline. This study suggests that the views of healthcare professionals on the evaluation of importance of outcomes and MCIDs for the evaluation of new T2DM medicines are in line with the views in the guideline committee. However, HbA1c and hospital admissions were more important according to healthcare professionals and the MCIDs for mortality and other hypoglycemia were higher than the MCIDs used in the guideline. For those parameters, healthcare professionals were therefore more strict in defining clinical relevance than the guideline committee. Future research should confirm these results by the use of a larger representative group of healthcare professionals. In the meantime, clinical guideline committees should clearly communicate about how clinical relevance is established, so end users of the guideline can easily track the way new medicines were evaluated.

REFERENCES

1. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255-323.
2. Nederland Huisartsen Genootschap (NHG) . NHG-Standaard diabetes mellitus type, vol. 2. [M01]. Utrecht: NHG; 2018.
3. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol. 2011;64(4):395-400.
4. Nederland Huisartsen Genootschap (NHG) . Totstandkoming en methoden NHG-Standaard Diabetes mellitus type 2 (M01). Utrecht: NHG; 2018.
5. Hedayat AS, Wang J, Xu T. Minimum clinically important difference in medical studies. Biometrics. 2015;71(1):33-41.
6. Rodriguez-Gutierrez R, McCoy RG. Measuring what matters in diabetes. JAMA. 2019;321(19):1865-1866.
7. Reaney M, Elash CA, Litcher-Kelly L. Patient reported outcomes (PROs) used in recent phase 3 trials for type 2 diabetes: A review of concepts assessed by these PROs and factors to consider when choosing a PRO for future trials. Diabetes Res Clin Pract. 2016;116:54-67.
8. Wieczorek A, Rys P, Skrzekowska-Baran I, Malecki M. The role of surrogate endpoints in the evaluation of efficacy and safety of therapeutic interventions in diabetes mellitus. Rev Diabet Stud. 2008;5(3):128-135.
9. Zannad F, Stough WG, Pocock SJ, et al. Diabetes clinical trials: Helped or hindered by the current shift in regulatory requirements? Eur Heart J. 2012;33(9):1049-1057.
10. Lipska KJ, Krumholz HM. Is hemoglobin A1c the right outcome for studies of diabetes? JAMA. 2017;317(10):1017-1018.
11. National Institute for Health and Care Excellence (NICE) . Type 2 diabetes in adults: management Clinical Guideline. [NG28]. London: NICE; 2015.
12. Nederlandse Internisten Vereniging (NIV) . Diabetes mellitus type 2 in de tweede lijn. Utrecht: NIV; 2018.
13. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. rating the quality of evidence–imprecision. J Clin Epidemiol. 2011;64(12):1283-1293.
14. Bøgelund M, Vilsbøll T, Faber J, Henriksen JE, Gjesing RP, Lammert M. Patient preferences for diabetes management among people with type 2 diabetes in denmark - a discrete choice experiment. Curr Med Res Opin. 2011;27(11):2175-2183.
15. Hauber AB, Mohamed AF, Johnson FR, Falvey H. Treatment preferences and medication adherence of people with type 2 diabetes using oral glucose-lowering agents. Diabet Med. 2009;26(4):416-424.
16. Gauthier B, Singh SR, Virani A, Staples H, Colbourne A. Perspectives and experiences of health care professionals and patients regarding treatments for type 2 diabetes. Can Pharm J (Ott). 2014;147(1):45-54.
17. Mol PG, Arnardottir AH, Straus SM, et al. Understanding drug preferences, different perspectives. Br J Clin Pharmacol. 2015;79(6):978-987.
18. Kaldjian LC. Patient care and population health: Goals, roles and costs. J Public Health Res. 2014;3(2):311.
19. Sox HC. Resolving the tension between population health and individual health care. JAMA. 2013;310(18):1933-1934.

20. Hayes RP, Bowman L, Monahan PO, Marrero DG, McHorney CA. Understanding diabetes medications from the perspective of patients with type 2 diabetes: Prerequisite to medication concordance. Diabetes Educ. 2006;32(3):404-414.
21. Mohamed AF, Zhang J, Johnson FR, et al. Avoidance of weight gain is important for oral type 2 diabetes treatments in sweden and germany: Patient preferences. Diabetes Metab. 2013;39(5):397-403.
22. Gelhorn HL, Stringer SM, Brooks A, et al. Preferences for medication attributes among patients with type 2 diabetes mellitus in the UK. Diabetes Obes Metab. 2013;15(9):802-809.
23. Brooks AP, Kibble SE, Alderson SA. The understanding of terms in evidence-based medicine: A pilot study. Eur Diabet Nurs. 2009;6(3):95-99.
24. Akobeng AK. Understanding measures of treatment effect in clinical trials. Arch Dis Child. 2005;90(1):54-56.
25. Dankers M, Nelissen-Vrancken MHJMG, Surminski SMK, Lambooij AC, Schermer TR, van Dijk L. Healthcare professionals' preferred efficacy endpoints and minimal clinically important differences in the assessment of new medicines for chronic obstructive pulmonary disease. Front Pharmacol. 2020;10:1519.
26. Sterne JA, Smith GD. Sifting the evidence-what's wrong with significance tests? Phys Ther. 2001;81(8):1464-1469.
27. Man-Son-Hing M, Laupacis A, O'Rourke K, et al. Determination of the clinical importance of study results. J Gen Intern Med. 2002;17(6):469-476.
28. Sedgwick P, Hall A. Teaching medical students and doctors how to communicate risk. BMJ. 2003;327(7417):694-695.

SUPPLEMENT

Questionnaire

Introduction

The *Instituut Verantwoord Medicijngebruik* (Institute for Rational Use of Medicine) studies the added value of new medicines in primary care. This questionnaire focuses on the criteria that guideline committees use to evaluate the clinical relevance (added value) of new medicines for type 2 diabetes mellitus (T2DM).

Answering the questionnaire takes approximately 10 minutes. Every 10th participant receives a free accredited online course on the treatment of T2DM. If you are interested in this course, please enter your e-mail address at the end of the questionnaire. We will only use your e-mail address to send the login code for the online course. All data will be processed anonymously.

Starting questions

We would first like to ask you some general questions about yourself and your working experience.

1. Are you involved in the daily treatment of patients with T2DM?
- o Yes
- o No (end of questionnaire)

2. What is your gender?
- o Woman
- o Man
- o Gender-neutral

3. What is your age?
- o Younger than 20 years
- o 20 to 39 years
- o 40 to 59 years
- o 60 years or older

4. What is your current profession?
- o Physician (forward to 5)
- o Pharmacist (forward to 6)
- o Practice nurse (forward to 7)
- o Diabetes nurse (forward to 7)
- o Nurse practitioner (forward to 7)
- o Physician Assistant (forward to 7)
- o Other, namely {open field} (forward to 7)

5. What is your specialization?
- o General practitioner with special interest in T2DM
- o General practitioner (including general practitioner trainee and dispensing general practitioner)
- o Internist
- o Other, namely {open field}

(forward to 7).

6. What is your specialization?
- o Community pharmacist (including community pharmacist specialist trainee)
- o Hospital pharmacist (including hospital pharmacist trainee)
- o Pharmacist in outpatient pharmacy in hospital
- o Other, namely {open field}

7. How many years of working experience in your current profession do you have?
- o Less than 5 years
- o 5 to 9 years
- o 10 to 14 years
- o 15 to 19 years
- o 20 years or more

8. What are the first 2 digits of the zip code for your working area? (We only use this answer to look at regional distribution).
{Open question: only answers between 10 and 99 allowed).

9. On average, how many T2DM patient contacts (for this condition) do you have per week?
o Less than 5
o 5 to 10
o 11 to 20
o More than 20

Outcome measures

The last years, new T2DM medicines have become available (DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors). In order to develop a clinical guideline, the guideline committee first determines medicine relevant effects. We call this the outcome measures. For example, a new medicine for T2DM can be evaluated on the outcome measure 'mortality', but also on 'HbA1c' or 'hypoglycaemia'. The following questions concern your opinion on the importance of these outcome measures. In other words: should improvement of this outcome measure be included in the evaluation of a medicine?

You are a member of the guideline committee. According to you, how important are the effects of a blood glucose-lowering medicine on the following outcome measures? Please give your answer on a scale from 1 to 9, 1 meaning limited importance, 9 meaning critical importance.

- Mortality
- Macrovascular morbidity
- Microvascular morbidity
- HbA1c
- Body weight
- Quality of life
- Hospital admissions
- Severe hypoglycaemia
- Mild, moderate, or unspecified hypoglycaemia

{Answers on a scale of 1 - limited importance to 9 - critical}.

10. Are there other outcome measures you consider relevant when evaluating new medicine for T2DM? Which outcome measure(s)?
{Open question, not obligatory}.

Clinically relevant improvements

A guideline committee must also determine which difference in effect size between the new medicine and a control medicine is large enough to have added value for the patient. We call this difference or improvement clinically relevant. In the following questions you can indicate when you consider a difference to be clinically relevant.

11. HbA1c.

We compare a new medicine for T2DM with a control agent. The new medicine causes a larger HbA1c decrease in patients. What difference in HbA1c decrease between the control agent and the new agent do you consider clinically relevant?

For example, in the control group, the HbA1c decreases by 8 mmol/mol. In the group with the new medicine, the HbA1c decreases by 10 mmol/mol. Your answer is then 2 mmol/mol.

- Give your answer in mmol/mol (in whole numbers).
- Do you think every difference is clinically relevant? Then your answer should be "1".
- If you don't know or don't have an opinion, your answer should be '0'.

{Open question, only answers between 0 and 25 allowed}.

12. Body weight gain.

Both the new medicine and the control agents increase body weight. What difference in body weight gain between the control agent and the new agent do you consider clinically relevant?

For example, in the control group the body weight increases by 5 kg. In the group with the new agent, the body weight increases by 2 kg. Your answer is then 3 kg.

- Assume an average body weight of 100 kg.
- Assume that both the control agent and the new agent increase the body weight.
- Give your answer in kg (whole numbers).
- Do you think every difference is clinically relevant? Then your answer should be "1".
- If you don't know or don't have an opinion, your answer should be '0'.

{Open question, only answers between 0 and 99 allowed}.

13. Body weight decrease.

The new medicine reduces the body weight compared to the control agent. What difference in body weight reduction between the control and new agent do you consider clinically relevant?

For example, in the control group the body weight increases by 2 kg. In the group with the new medicine, the body weight decreases by 1 kg. Your answer is then 3 kg.

- Assume an average body weight of 100 kg.
- Assume the control agent increases or does not affect the body weight and the new agent decreases the body weight.
- Give your answer in kg (whole numbers).
- Do you think every difference is clinically relevant? Then your answer should be "1".
- If you don't know or don't have an opinion, your answer should be '0'.

{Open question, only answers between 0 and 99 allowed}.

Other outcomes

We compare a new T2DM medicine with a control agent.

1,000 patients use the control agent, of which 100 patients experience the outcome of interest.
1,000 other patients use the new medicine.

For how many outcomes in the group with the new medicine do you consider the difference to be clinically relevant?

For example, 100 out of 1,000 patients in the control group die. You think the difference in mortality is clinically relevant if only 20 out of 1,000 patients with the new medicine die. Your answer is then 20.

- Give your answer in number of outcomes (whole numbers).
- Do you think every difference is clinically relevant? Then your answer should be "99".
- If you don't know or don't have an opinion, your answer should be '0'.

14. Mortality {Open question, only answers between 0 and 99 allowed}.
15. Macrovascular morbidity {Open question, only answers between 0 and 99 allowed}.
16. Microvascular morbidity {Open question, only answers between 0 and 99 allowed}.
17. Hospital admissions {Open question, only answers between 0 and 99 allowed}.
18. Severe hypoglycaemia {Open question, only answers between 0 and 99 allowed}.

19. Mild, moderate or unspecified hypoglycaemia {Open question, only answers between 0 and 99 allowed}.

Cut-off values in guidelines

Guideline committees have established cut-off values for clinical relevance for some outcome measures. The following questions regard your opinion on these cut-off values for HbA1c and mortality.

20. For HbA1c, the Dutch guideline T2DM in primary care (2018) considers a difference of 5 mmol/mol clinically relevant. What do you think of this value?

- o Too low (I only consider a difference clinically relevant if it is greater than 5 mmol/mol)
- o Good
- o Too high (I consider differences less than 5 mmol/mol already clinically relevant)

21. For mortality, the Dutch guideline T2DM in primary care (2018) considers a relative risk reduction of 10% clinically relevant. What do you think of this value?

- o Too low (I only consider a difference clinically relevant if it is greater than 10%)
- o Good
- o Too high (I consider differences less than 10% already clinically relevant)

Final questions

You have reached the end of the questionnaire. Every 10th participant in the questionnaire receives a free accredited online course on the treatment of T2DM. If you are interested in this free course, please enter your e-mail address below.

22. Do you have any comments or questions regarding this questionnaire? {open question, not obligatory}.

23. What is your email address? {open question, not obligatory}.

Thank you for your cooperation! Click on ‘end survey’ to send your answers.

3

Factors influencing decision-making

3.1

Non-adherence to guideline recommendations for insulins: a qualitative study amongst primary care practitioners

Marloes Dankers
Marieke J.E. van den Berk-Bulsink,
Marinka van Dalfsen-Slingerland
Marjorie H.J.M.G. Nelissen-Vrancken
Aukje K. Mantel-Teeuwisse
Liset van Dijk

BMC Prim Care. 2022;23(1):150.

ABSTRACT

Background

Guideline adherence is generally high in Dutch general practices. However, the prescription of insulins to type 2 diabetes mellitus patients is often not in line with the guideline, which recommends NPH insulin as first choice and discourages newer insulins. This qualitative study aimed to identify the reasons why primary care healthcare professionals prescribe insulins that are not recommended in guidelines.

Methods

Digital focus groups with primary care practitioners were organised. A topic list was developed, based on reasons for preferred insulins obtained from literature and a priori expert discussions. The discussions were video and audio-recorded, transcribed verbatim and coded with a combination of inductive and deductive codes. Codes were categorized into an existing knowledge, attitudes and behaviour model for guideline non-adherence.

Results

Four focus groups with eleven general practitioners, twelve practice nurses, six pharmacists, four diabetes nurses and two nurse practitioners were organised. The prescription of non-recommended insulins was largely driven by argumentation in the domain of attitudes. Lack of agreement with the guideline was the most prominent category. Most of those perspectives did not reflect disagreement with the guideline recommendations in general, but were about advantages of non-recommended insulins, which led, according to the healthcare professionals, to better applicability of those insulins to specific patients. The belief that guideline-recommended insulins were less effective, positive experience with other insulins and marketing from pharmaceutical companies were also identified as attitude-related barriers to prescribe guideline-recommended insulins. One additional category in the domain of attitudes was identified, namely the lack of uniformity in policy between healthcare professionals in the same practice. Only a small number of external barriers were identified, focusing on patient characteristics that prevented the use of recommended insulins, the availability of contradictory guidelines and other, mostly secondary care, healthcare providers initiating non-recommended insulins. No knowledge-related barriers were identified.

Conclusions

The prescription of non-recommended insulins in primary care is mostly driven by lack of agreement with the guideline recommendations and different interpretation of evidence. These insights can be used for the development of interventions to stimulate primary care practitioners to prescribe guideline-recommended insulins.

BACKGROUND

Substantial evidence exists that adherence to clinical practice guidelines positively affects the quality of primary care. Guideline adherence has been associated with more patient satisfaction with their treatment [1] and improved patient outcomes [2]. In addition, guideline adherence can improve the process and structure of care [3] and reduce costs [4].

A country with a long history of developing and implementing clinical guidelines in primary care is the Netherlands [2]. National guidelines covering the majority of conditions and diseases in general practice are developed by the Dutch College of General Practitioners (NHG) [5]. Virtually all (97%) Dutch general practitioners have a positive attitude towards those guidelines [6]. Moreover, 89% of Dutch general practitioners believe that guideline adherence contributes to better quality of care. Adherence to these guidelines among general practitioners is therefore generally high, around 75% [6,7], but varies among types of diseases and recommendations, with some areas of poor adherence [7,8].

One area with poor guideline adherence is the prescription of insulins for type 2 diabetes mellitus (T2DM) patients. In Dutch general practice, where the majority of insulins for T2DM are prescribed [9], less than 20% of T2DM patients needing insulin treatment starts with the guideline-recommended NPH insulin. Instead, insulin glargine 100 U/ml and insulin detemir – which are mentioned as less favourable, alternative options – are often initiated. In addition, approximately 25% of all insulin users uses one of the newer agents insulin glargine 300 U/ml or insulin degludec, which gained market access in 2013 and 2015, respectively [10]. Those two newer insulins are not recommended, because of the lack of evidence-based advantages in terms of efficacy or safety, and higher costs [11]. The Dutch guideline is in line with most international guidelines for the treatment of T2DM that also favour NPH insulin for insulin-naïve patients and do not recommend the use of insulin glargine 300 U/ml and insulin degludec [12,13]. In spite of this, the declining popularity of NPH insulin and rapid adoption of newer insulins is a worldwide trend [10,14-20], resulting in substantial increases in total insulin expenditures [20-24]. Although previous observational research showed that the prescription of newer insulins was related to several patient and practice characteristics, most reasons for this guideline non-adherence could not be elucidated [10]. According to Cabana et al., potential barriers to guideline adherence can be organised in a knowledge, attitudes, behaviour framework, which states that before a guideline can affect patient outcomes, it first affects healthcare professionals' knowledge, then attitudes and finally behaviour. In this model, the behaviour of the healthcare professional is determined by knowledge

(is the healthcare professional familiar with the guideline), attitude (is he or she willing to perform the recommendation) and external barriers (do factors which are beyond their control hamper the execution of the recommendation) [25]. It is yet unknown to what extent these barriers to physician adherence to guidelines also apply for the prescription of guideline-recommended insulins.

To ensure quality of primary care and prevent increasing expenditure on insulins for T2DM patients, insight in the reasons for guideline non-adherence concerning the prescription of insulins is of crucial importance. The aim of this qualitative study is therefore to identify the reasons why primary care healthcare professionals prefer non-recommended insulins, focusing on the prescription of other insulins than NPH insulin for insulin-naïve patients and the prescription of newer insulins to both insulin-naïve and prevalent insulin users.

METHODS

Focus group discussions were performed with primary care healthcare professionals to study their preferences and accompanying argumentation for insulin treatment in T2DM patients. Focus groups were preferred over individual interviews since they allow participants to interact with each other. Focus groups have therefore been associated with a wider range of views and ideas than can be collected by using individual interviews [26,27].

Setting

This study was carried out among Dutch general practitioners, practice nurses, diabetes nurses, nurse practitioners and pharmacists. In the Dutch healthcare system, most T2DM patients are treated in primary care [9]. The majority of general practices deploy nurses (i.e. practice nurses, diabetes nurses or nurse practitioners) to take care of T2DM patients [28,29]. While diabetes nurses and nurse practitioners have a formal prescriptive authority, practice nurses do not [30]. Practice nurses have, however, a prominent role in the management of T2DM patients, including advising general practitioners about the preferred treatment [31]. Pharmacists have no prescriptive authority, but do have an important advisory role in the pharmaceutical treatment in the Netherlands. They were also involved because of their insight in the actual prescription patterns, both from general practitioners and secondary care providers.

Two out of four focus group meetings were held during PharmacoTherapy Audit Meetings (PTAMs). Since this study was carried out during the second wave of COVID-19, recruiting general practitioners outside regular activities would have been extremely difficult. We

therefore planned to organise the focus group discussions during regular meetings with general practitioners, so no additional time-investment was necessary. PTAMs are regular meetings between general practitioners and pharmacists (and sometimes nurses) in the same region. PTAMS are organised to exchange information and views about pharmacotherapy with the aim of improving the prescribing and dispensing of medicines [32]. Almost all Dutch general practitioners and pharmacists participate in a PTAM in their region.

Since nurses are not always invited at PTAMs, two additional focus group meetings with practice and diabetes nurses were organised. Since the daily work of these professionals was less bothered by the COVID-19 pandemic, and to obtain a more heterogeneous representation than from PTAMs, these focus groups were specifically organised for the purpose of this research. To attract a broad range of nurses, individual participants were recruited through open enrolment.

Subjects

Both PTAMs and individual practice and diabetes nurses were recruited by an open call for participation through the newsletter and social media of the Dutch Institute for the Rational Use of Medicine (IRUM). A snowballing technique was used with the participants (PTAM or nurse) being asked to invite other PTAMs or nurses.

The two open enrolment groups with practice and diabetes nurses were organised with at least five participants and a maximum of eight. The number of participants in the PTAMs depended on local situations. All participants gave written informed consent before the start of the focus group discussions. According to Dutch legislation, approval by a medical ethics committee was not necessary, since no patients were involved in this study and the participants of the focus group discussions were not exposed to interventions [33].

Data collection

We prepared a topic list based on the model of Cabana et al. [25] and argumentation for preferred insulins obtained from literature and a priori expert discussions. The topic list was fine-tuned during several sessions within the research team. Covered topics were the preferred initial insulins, the prescription of newer insulins and corresponding argumentation in the domains of knowledge, attitudes and external barriers.

The focus group discussions were organised in October and November 2020. Due to the COVID-19 pandemic, we used a virtual focus group methodology using Zoom Video Communications. The discussions lasted 45 – 75 min and were facilitated by MD as moderator. MvdB and (in three of four groups) MvD were observers.

Data analysis

The discussions were video and audio-recorded and transcribed verbatim using automatic generated transcripts performed by AmberScript, which were manually verified and corrected. The transcripts were coded and analysed in Atlas.ti 9.1.5.0. Coding was performed with a combination of deductive and inductive codes. Deductive codes were derived from the argumentation for preferred insulins obtained from literature and a priori expert discussions and inductive codes from the focus groups itself. The coding focused on identifying reasons for prescribing of the preferred insulins. Those identified perspectives were subsequently classified into the categories of argumentation provided by the model of Cabana et al. (Fig. 1) [25]. This model distinguishes three domains of behaviour change: knowledge, attitudes and external barriers, which are further subdivided into categories. Barriers to guideline adherence related to knowledge can be classified into lack of familiarity with the guideline and lack of awareness. The domain of attitudes consists of lack of agreement (with specific guidelines or guidelines in general), lack of outcome expectancy, lack of self-efficacy and lack of motivation/inertia of previous practice. Both domains, together with external barriers related to patient, guideline and environmental factors define behaviour.

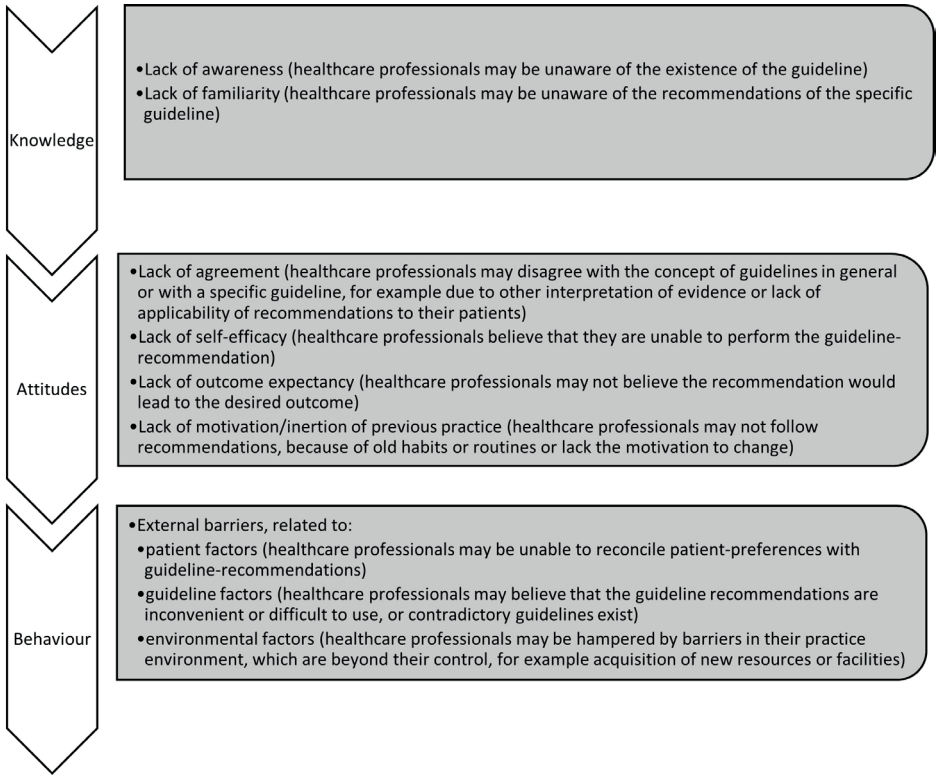

Figure 1: Domains and categories of guideline non-adherence, according to Cabana et al. [25].

Two out of four transcripts were independently coded by a second researcher (MvdB), using the codebook from the first coder (MD). Any disagreements were solved by discussion between both coders and a third researcher (LvD). The classification of codes into the model of Cabana et al. was discussed within the research team.

RESULTS

We conducted four focus group discussions. In the two PTAMs, eleven general practitioners, six pharmacists, two nurse practitioners and one practice nurse participated. The two open enrolment groups consisted of eleven practice nurses and four diabetes nurses. The exact number of different professionals per focus group meeting can be found in Table 1.

Table 1: Number of participating healthcare professionals in the different focus group discussions.

	PTAM 1	PTAM 2	Open enrolment 1	Open enrolment 2	Total
General practitioner	5	6			11
Pharmacist	3	3			6
Nurse practitioner		2			2
Practice nurse		1	6	5	12
Diabetes nurse			2	2	4
Total	8	12	8	7	35

PTAM = PharmacoTherapy Audit Meeting.

In most practices, the nurses had the most prominent role in initiating insulins, although the general practitioner held the final responsibility. In daily practice, most nurses operated largely independent of the general practitioner, initiating treatments by themselves, including the practice nurses without formal prescriptive authority. Since pharmacists do not initiate insulins themselves, the preferred choices of insulins below refer to general practitioners and nurses only. The perspectives of pharmacists are however included in the analysis of reasons for guideline adherence and non-adherence.

Choice of insulin

Healthcare professionals were familiar with the five different intermediate or long-acting insulins (NPH insulin, insulin detemir, insulin glargine 100 U/ml, insulin glargine 300 U/ml and insulin degludec) and appreciated their availability to customize the therapy for individual patients. However, almost all healthcare professionals had one preferred insulin they most often initiated and had most experience with.

> But it is often a-a-a prescribing preference, you start with something, gain experience with it and then run with it. *General practitioner, #1*

> But I am glad that there are opportunities to switch. And it is also a little customization that you're providing.
> *Practice nurse, #3*

A substantial number of participating healthcare professionals was guideline-adherent, i.e. preferred NPH insulin as first choice in most situations and did not regularly prescribe newer insulins. Positive experience and following the guideline were the most common reasons for the initiation of guideline-recommended insulins. Also, the lower costs and adequate efficacy were mentioned. In a minority of situations, guideline-adherence was prompted by the general practitioner who required the nurse to prescribe guideline-recommended insulins despite her[1] own preference for other insulins.

Reasons for guideline non-adherence

During the focus group discussions, two different situations of guideline non-adherence were discussed: the prescription of other insulins than NPH insulin (i.e. insulin glargine 100 U/ml, insulin glargine 300 U/ml, insulin detemir or insulin degludec) to insulin-naïve patients and the prescription of newer insulins (insulin glargine 300 U/ml and insulin degludec), regardless of the former use of other insulins. Some overlap in both situations exists, since the initiation of newer insulins to insulin-naïve patients automatically applies to both situations.

Almost half of the participants preferred the initiation of other insulins than NPH insulin to insulin-naïve patients. Insulin glargine 100 U/ml was the most popular alternative. Although most healthcare professionals did not regularly prescribe newer insulins, almost all had some experience with newer insulins. In most of the cases, newer insulins were prescribed to patients who were already using insulin, but had to switch to another insulin. In addition, a few healthcare professionals preferred the newer insulin degludec as first-choice for all their insulin-naïve patients. Others sometimes initiated newer insulins to insulin-naïve patients because of a specific situation requiring a deviation from their normally preferred insulin.

> I think to myself, wait a minute, I've done this before [the initiation of new insulins]. I prescribed someone their first Tresiba [insulin degludec], but what was the reason for this? Because the FlexTouch in particular is quite a pleasant device. And it involved someone with a hand disability […]. And then with that the FlexTouch turned out to be an ideal device. So basically I prescribed Tresiba out of practical considerations.
> *Diabetes nurse, #2*

In Table 2, all argumentation for the prescription of non-recommended insulins are classified according to the model of Cabana et al. and assigned to both situations of guideline-non-adherence, i.e. initiation of other insulins than NPH insulin to insulin-naïve patients and initiation of newer insulins, regardless of the former use of

1 Due to privacy reasons, all healthcare professionals are referred to as 'her', irrespective of sex.

other insulins. The majority of argumentation applied to both situations. Most of the mentioned reasons were in the domain of attitudes, and especially related to a lack of agreement with guideline recommendations. No barriers in the domains of knowledge were identified. We did discover one new perspective in the domain of attitudes, namely lack of uniformity in policy, which refers to healthcare professionals in the same practice with opposing preferences.

Table 2: Argumentation for non-recommended insulins, classified according to Cabana et al. [25].

	Specific argumentation	Initiation of other insulins than NPH insulin to insulin-naïve patients	Initiation of newer insulins
Knowledge			
Lack of familiarity			
Lack of awareness (of guideline)			
Attitudes			
Lack of agreement	Flexibility in time	X	X
	Hypoglycemia	X	X
	Release profile	X	X
	Future-proof	X	X
	Uniformity device	X	X
	Body weight	X	
	Flexibility injection site	X	
	Injection volume		X
Lack of outcome expectancy	Efficacy	X	X
Lack of self-efficacy			
Lack of motivation/ inertion of previous practice	Image/marketing	X	X
	Experience	X	X
Lack of uniformity in policy[a]	Opposing views in the same practice	X	X
External barriers			
Patient factors	Inability to resuspend	X	
	Ease of use		X
Guideline factors	Contradictory guidelines		X
Environmental factors	Continuation of prescriptions from other prescribers		X

[a] *Newly identified category, not described in the model of Cabana et al.*

Knowledge

According to Cabana et al., barriers in the domain of knowledge refer to the lack of familiarity with or awareness of the guideline [25]. No such barriers were identified during the focus group discussions.

Attitude

Perspectives concerning attitude were most frequent, with lack of agreement as the most prominent category.

Lack of agreement

Most perspectives concerning lack of agreement did not reflect disagreement with the guideline recommendations in general, but were about minor advantages which led to better applicability of non-recommended insulins to specific patients in the participants' view. Healthcare professionals preferred those insulins because of the flexibility, both in injection sites (only mentioned for insulins other than NPH insulin) and time. The flexibility in time was especially mentioned as an advantage for people who make long-distance flights, go on holiday, prefer to sleep in (for example during the weekend) or depend on caregivers for the administration of insulin. During the focus group discussions, this argumentation was put into perspective by some healthcare professionals, stating that the advantage of flexibility only applied to a minority of patients and should not justify the massive use of non-recommended insulins.

> Anyway, not everyone wants to sleep in on a Saturday or Sunday and not everyone likes travelling. So you know, I think that's also a reason to choose a cheaper variant, simply because many people in the Netherlands have and will develop diabetes and will require insulin at some point.
> *Practice nurse, #3*

Another perspective concerned the uniformity of devices. For patients combining an intermediate or long-acting insulin with a short-acting insulin, healthcare professionals preferred uniformity in injection devices to enhance the ease of use. In those situations, the type of injection device was more leading than the type of insulin. Healthcare professionals also sometimes chose for a non-recommended insulin taking the future into account. They argued it was better to start with an insulin that would be sufficient for the next years, especially for younger patients. Others opposed this reasoning and stated it was better to start with a cheaper insulin and switch only if necessary, taking into account the higher costs of non-recommended insulins.

> Yes, and that's why I think it's somewhat remarkable that practice nurse X just said "I prefer to start with this [insulin degludec], because then I might be able to continue it for a long time". Meanwhile I'm thinking, you don't know what will be sufficient for the patient. So if you are going to do that [prescribe newer insulins] in advance, you are already going to bet on a very expensive one, while a cheaper one may be sufficient.
> *Practice nurse, #2*

Other reasons for preferring non-recommended insulins were related to the release profile which gives a longer time-in-range for patients, making them feel better. Finally, the lower injection volume of insulin glargine 300 U/ml compared to insulin glargine 100 U/ml was mentioned as a reason for the prescription of this newer insulin.

Some healthcare professionals disagreed with the evidence the guideline referred to. According to the guideline, the differences between insulins in effects on hypoglycemia and body weight are marginal and therefore there is no reason to prescribe more expensive insulins [11]. Lower risk of hypoglycemia and less gain of body weight were however used as justification to prescribe other insulins. This argumentation was challenged by others, claiming that the fear of hypoglycemia, both by healthcare professionals and patients, was probably more relevant than the actual risk of hypoglycemia.

> But I doubt if it [choosing glargine 100 U/ml instead of NPH insulin because of the risk of hypoglycemia] is because of the fear rather than the actual risk of nocturnal hypoglycemia.
> *General practitioner, #1*

Lack of outcome expectancy

One perspective concerning the lack of outcome expectancy was identified. Some healthcare professionals preferred non-recommended insulins for poorly controlled T2DM patients, because they believed guideline-recommended insulins had a lower glucose-lowering potential than other insulins. For example, one general practitioner stated she usually prescribed NPH insulin, but chose another insulin if glucose levels were extremely high. She expected other insulins to have a more profound effect on glucose levels.

Lack of motivation/inertion of previous practice

Some healthcare professionals chose non-recommended insulins because they had positive experiences (apart from glucose control, which is categorized as 'outcome expectancy') after prescribing them. They also pointed out the positive image of 'innovative' insulins. Other healthcare professionals argued that image is mostly constructed by marketing of pharmaceutical industries and mentioned the difficulties of distinguishing real advantages of newer insulins from marketing activities.

> But I believe Insulatard [NPH insulin] has a somewhat pompous image. So sometimes you have a relatively young patient and you think, should I choose another one [insulin]? But I think that's more the result of marketing than the actual effect of the medicine.
> *Diabetes nurse, #2*

Lack of uniformity in policy

One additional category in the domain of attitudes was discussed, referring to a lack of uniformity in policy regarding the prescription of insulins. In some practices, the general practitioner and nurse did not have the same insulin preference, but were not aware of this difference. For example, one general practitioner thought she followed the guideline, prescribing NPH insulin to her patients. But when her actual prescription pattern was analysed, she discovered that most prescriptions were for other insulins. This was due to the preference of the practice nurse, whose prescriptions for non-recommended insulins were authorised by the general practitioner. On the other hand, some nurses stated they wanted to prescribe newer insulins to their patients, but were not allowed to do so, because the general practitioner stimulated them to adhere to the guideline.

> Ahh, I prefer NPH insulin. But I checked my actual prescriptions, and then I saw something else. Ahh… the practice nurse, she'd choose Lantus [insulin glargine 100 U/ml] every time.
> *General practitioner, #1*

External barriers

Patient factors

In some situations, patients' abilities restricted the use of guideline-recommended insulins. For example, patients using NPH insulin need to resuspend the insulin before administration. According to the healthcare professionals, not all patients are capable to do this, thus requiring another insulin. In the same domain, the ease of use of the device was mentioned as reason for the prescription of newer insulins. For example, dysfunctional hand function could require a switch to a non-recommended insulin with a better device applicability.

Guideline factors

One guideline-related factor was identified, concerning the prescription of insulin glargine 300 U/ml, namely the presence of contradictory guidelines. A guideline specifically aimed at diabetes nurses gave other recommendations about switching to insulin glargine 300 U/ml (at 40 or 80 units) than the guideline aimed at general practitioners, which led to confusion.

Environmental factors

As environmental factor, the continuation of prescriptions from former prescribers was pointed out. In most cases, this referred to secondary care providers initiating the use of newer insulins. Most healthcare professionals were familiar with internists and/or diabetes nurses from hospitals who initiated newer insulins to their patients, thereby stimulating primary care practitioners to iterate prescriptions for newer insulins. Also,

the continuation of insulin prescriptions from other general practitioners for newly registered patients was mentioned.

DISCUSSION

Although Dutch general practitioners are generally guideline-adherent, the prescription of insulins is often not in line with current treatment recommendations. The present study showed that this non-adherence is largely driven by the lack of agreement with the guideline recommendations, as well as other attitudes of prescribers. A few barriers related to environmental factors, namely patients' abilities, contradictory guidelines and continuation of prescriptions from other healthcare professionals, were discussed in relation to guideline non-adherence. No factors concerning the knowledge of guideline recommendations were identified.

Our study described two situations of guideline non-adherence: the prescription of other insulins than NPH insulin to insulin-naïve patients and the prescription of newer insulins to all patients. Due to the similarity in argumentation, both situations were analysed and described simultaneously. There are however some differences, especially in the moments when guideline non-adherence occurs. The Dutch guideline T2DM advises NPH insulin as the preferred insulin for all new patients, but provides some room to switch prevalent users of NPH insulin to insulin glargine 100 U/ml or insulin detemir. In contrast, newer insulins (insulin glargine 300 U/ml and insulin degludec) are discouraged for all patients, including prevalent users of insulin [11]. Participants in our study prescribed newer insulins most often to prevalent users, who – according to the healthcare professionals – needed to switch their insulin. Although less frequent, newer insulins were also prescribed to insulin-naïve patients.

The prescription of non-recommended insulins was mostly related to perspectives in the domain of attitudes, which is in accordance with previous studies towards guideline non-adherence in different therapeutical areas in the Netherlands [6,34]. Most argumentation identified in our study indicated different perspectives on the efficacy (glucose-lowering potential), safety (hypoglycemia, body weight) and applicability (flexibility in injection time and site, applicability of device) of the insulins to patients. This indicates that guideline-non adherence to insulin recommendations is mostly intentional and a deliberate decision of healthcare professionals, which is in line with the results of other studies towards guideline non-adherence [6,34,35]. However, the validity of argumentation in the domains of attitudes can be argued – which also occurred during the focus group discussions –, albeit on different levels. First, some perspectives identified

in this study can be challenged with the current evidence. For example, the guideline committee that developed the Dutch primary care guideline on T2DM concluded after thorough review of the literature that no clinically relevant differences in hypoglycemia risk exists between intermediate- and long-acting insulins [11]. Nevertheless, the lower risk of hypoglycemia was frequently used as justification by participants in our study to prescribe non-recommended insulins. Reasons like these led often to discussions between the participants in the focus groups, indicating that contrasting interpretation of evidence is indeed an important factor that explains the differences between prescribers in the prescription of insulins. Second, some argumentation (for example flexibility in injection site) do not refer to discussions about evidence, but to the question whether these 'customization' perspectives justify the use of more expensive insulins by large groups of patients. In general, guidelines are developed based on population advantages, taking into account the long term outcomes on population level. In daily practice, decisions might be more influenced by other considerations, like short term outcomes on patient level, and less on cost-efficacy on population level [36-38]. Both views can be contradictory if a non-recommended treatment would account for minor advantages for patients at higher costs. Finally, marketing and image of newer insulins were mentioned as important factors in the attitudes towards insulins. Most healthcare professionals were aware of this mechanism, realising that the positive and innovative image of newer insulins was probably mostly constructed by marketing and therefore no valid reason for the prescription of newer insulins. Still, the innovative image did account for the prescription of non-recommended insulins.

We did identify one new category of attitude-related barriers, namely the lack of uniformity in policy. This barrier reflected opposing views in the same practice, with healthcare professionals not being aware of each other preferences. This barrier could lead both to guideline-adherence, in the case one healthcare professional was stimulating the other to prescribe guideline-recommended insulins, and (unintentional) non-adherence, in the case healthcare professionals were not aware of each other's preference for non-recommended insulins. This newly identified barrier in addition to the model of Cabana et al. most probably reflects the increasing complexity and number of different healthcare professionals in primary care since the development of the model of Cabana in 1999 [28,31] and points out the importance of good communication and coordination of policy between healthcare professionals.

The lack of knowledge-related barriers for guideline adherence found in our study was not surprising, because of the long history of using clinical guidelines and the prominent role of current guidelines in the post-graduate education of healthcare professionals in primary care in the Netherlands [34]. In addition, T2DM is a frequent condition in

primary care [39] and healthcare professionals are well educated about this disease. It can however not be excluded that knowledge-related barriers were overlooked, because healthcare professionals being more familiar with the guideline and treatment of T2DM were more likely to sign up for the focus group discussions. Some external barriers to follow the guideline were identified. The first external barrier reflected barriers at patient level, referring to physical limitations that prevented the use of specific insulins or devices. Second, one guideline-factor was identified, namely the availability of different recommendations about the number of units that require switching from insulin glargine 100 U/ml to insulin glargine 300 U/ml. Third, as environmental barrier, the continuation of prescriptions from other prescribers were mentioned. Although these perspectives were mentioned less often than the barriers in the domain of attitude, these external barriers and explicitly the role of the secondary care should not be marginalized. New medicines initiated by secondary care providers are often subsequently iterated in general practice. Due to this mechanism, primary care providers will become familiar with new medicines, which can lead to adoption of these medicines by the primary care provider herself [40].

The main strength of our study is the use of focus groups with different professionals. Since we included all healthcare professionals, irrespective of their preferred insulins, this resulted in a balanced overview on the preferences and perspectives of the prescription of insulins. In addition, the use of the existing framework to classify barriers to guideline adherence allowed for a thorough evaluation of argumentation. There are also some limitations. The qualitative study design is by definition a possible source of bias, as the interpretation of argumentation and the classification into domains and categories can be subjective. By using two coders and the verification of the coding and classification by a third researcher, we minimised this risk. In addition, since four focus group discussions were budgeted, we did not formally went on with organising until data saturation was reached. However, because few new perspectives were identified during the last focus group and the views of a large number of 35 healthcare professionals were included, we presume data saturation and a complete overview on the topic. Furthermore, selection bias might have occurred in this study, since healthcare professionals interested in the dynamics between guideline-recommendations and actual prescription behaviour were probably more likely to sign up for the focus group discussions. In addition, the use of PTAMs as focus groups might also have limited the range of perspectives found in our study. PTAMs are organised to coordinate and align prescription behaviour. Likely, beliefs and perspectives of healthcare professionals participating in the same PTAM are more uniform than from a random population of healthcare professionals. To obtain a broader view, we additionally organised two focus group discussions for nurses with open enrolment.

The results of our study can be used to develop interventions directed at healthcare professionals in primary care to stimulate rational prescribing of insulins. The prominence of barriers in the domain of attitudes suggests that interventions to stimulate better prescription behaviour should be directed to the views and perspectives of healthcare professionals on insulins, rather than on external barriers and knowledge of the guideline. Most perspectives did not reflect disagreement with the guideline recommendations in general, but were about minor advantages which led to better applicability of other insulins to specific patients in the participants' view. The finding that healthcare professionals in the focus group discussions regularly challenged each other's argumentation for non-recommended insulins indicates that there is indeed opportunity for improvement and points out the importance of good and regular communication. Therefore, thorough explanation of treatment recommendations in guidelines, including the description of clinically relevant differences and cost-efficacy is warranted and could stimulate qualitative and cost-effective prescription of insulins.

CONCLUSIONS

This study shed light on the reasons why Dutch primary care practitioners often prefer non-recommended insulins. Lack of agreement with the guideline recommendations and different interpretation of evidence are the most prominent reasons for the prescription of non-recommended insulins. These insights can be used when developing interventions directed at healthcare professionals to stimulate the qualitative and cost-efficient prescription of insulins in primary care.

REFERENCES

1. Gross R, Tabenkin H, Porath A, et al. The relationship between primary care physicians' adherence to guidelines for the treatment of diabetes and patient satisfaction: Findings from a pilot study. Fam Pract. 2003;20(5):563–9. https://doi.org/10.1093/fampra/cmg512.
2. Barth JH, Misra S, Aakre KM, et al. Why are clinical practice guidelines not followed? Clin Chem Lab Med. 2016;54(7):1133–9. https://doi.org/10.1515/cclm-2015-0871.
3. Lugtenberg M, Burgers JS, Westert GP. Effects of evidence-based clinical practice guidelines on quality of care: A systematic review. Qual Saf Health Care. 2009;18(5):385–92. https://doi.org/10.1136/qshc.2008.028043[doi].
4. Brown PD. Adherence to guidelines for community-acquired pneumonia: Does it decrease cost of care? Pharmacoeconomics. 2004;22(7):413–20 (doi: 2271[pii]).
5. Nederland Huisartsen Genootschap (NHG). Utrecht: NHG. www.nhg.org. Assessed 19 Nov 2021
6. Lugtenberg M, Burgers JS, Besters CF, Han D, Westert GP. Perceived barriers to guideline adherence: A survey among general practitioners. BMC Fam Pract. 2011;12:98–98. https://doi.org/10.1186/1471-2296-12-98[doi].
7. van Dijk L, de Jong JD, Westert GP, de Bakker DH. Variation in formulary adherence in general practice over time (2003–2007). Fam Pract. 2011;28(6):624–31. https://doi.org/10.1093/fampra/cmr043[doi].
8. Lubloy A. Factors affecting the uptake of new medicines: A systematic literature review. BMC Health Serv Res. 2014;14:469–469. https://doi.org/10.1186/1472-6963-14-469.
9. van Avendonk MJ, Gorter KJ, van den Donk M, Rutten GE. Insulin therapy in type 2 diabetes is no longer a secondary care activity in the netherlands. Prim Care Diabetes. 2009;3(1):23–8. https://doi.org/10.1016/j.pcd.2008.10.007[doi].
10. Dankers M, Hek K, Nelissen-Vrancken M, Houweling B, Mantel Teeuwisse A, van Dijk L. Newer long-acting insulin prescriptions to type 2 diabetes patients: Prevalence and practice variation. Br J Gen Pract. 2022;72(719):e430–6. https://doi.org/10.3399/BJGP.2021.0581.
11. Nederland Huisartsen Genootschap (NHG). NHG-Standaard diabetes mellitus type 2. Utrecht: NHG; 2018. [M01].
12. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: management Clinical Guideline. London: NICE; 2015. [NG28].
13. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the american diabetes association (ADA) and the european association for the study of diabetes (EASD). Diabetes Care. 2018;41(12):2669–701. https://doi.org/10.2337/dci18-0033.
14. Zhang H, Barner JC, Moczygemba LR, Rascati KL. Assessment of basal insulin adherence using 2 methodologies among texas medicaid enrollees with type 2 diabetes. J Manag Care Spec Pharm. 2020;26(11):1434–44. https://doi.org/10.18553/jmcp.2020.26.11.1434.
15. Ikeda S, Crawford B, Sato M. Utilization patterns of insulin therapy and healthcare services among japanese insulin initiators during their first year: A descriptive analysis of administrative hospital data. BMC Health Serv Res. 2016;16:6–2. https://doi.org/10.1186/s12913-016-1264-2.
16. Rathmann W, Haastert B, Riebel P, et al. Prescription of insulin glargine in primary care practices in germany. Exp Clin Endocrinol Diabetes. 2007;115(4):252–6. https://doi.org/10.1055/s-2007-972562.

17. Lipska KJ, Ross JS, Van Houten HK, Beran D, Yudkin JS, Shah ND. Use and out-of-pocket costs of insulin for type 2 diabetes mellitus from 2000 through 2010. JAMA. 2014;311(22):2331–3. https://doi.org/10.1001/jama.2014.6316.
18. Xu Y, Gomes T, Mamdani MM, Juurlink DN, Cadarette SM, Tadrous M. Analysis of trends in insulin utilization and spending across canada from 2010 to 2015. Can J Diabetes. 2019;43(3):179-185.e1 (doi: S1499-2671(18)30200-4 [pii]).
19. Heymann AD, Kritz V, Hemo B, Kertes J, Becker M. A changed pattern of insulin use following the introduction of basal analog insulin treatment in primary care. Prim Care Diabetes. 2013;7(1):57–61. https://doi.org/10.1016/j.pcd.2012.12.005.
20. Sarkar S, Heyward J, Alexander GC, Kalyani RR. Trends in insulin types and devices used by adults with type 2 diabetes in the united states, 2016 to 2020. JAMA Netw Open. 2021;4(10):e2128782. https://doi.org/10.1001/jamanetworkopen.2021.28782.
21. Schumock GT, Stubbings J, Hoffman JM, et al. National trends in prescription drug expenditures and projections for 2019. Am J Health Syst Pharm. 2019;76(15):1105–21. https://doi.org/10.1093/ajhp/zxz109.
22. Bang C, Mortensen MB, Lauridsen KG, Bruun JM. Trends in antidiabetic drug utilization and expenditure in denmark: A 22-year nationwide study. Diabetes Obes Metab. 2020;22(2):167–72. https://doi.org/10.1111/dom.13877.
23. Brismar K, Benroubi M, Nicolay C, Schmitt H, Giaconia J, Reaney M. Evaluation of insulin initiation on resource utilization and direct costs of treatment over 12 months in patients with type 2 diabetes in europe: Results from INSTIGATE and TREAT observational studies. J Med Econ. 2013;16(8):1022–35. https://doi.org/10.3111/13696998.2013.812040.
24. Malkani S. Are newer insulins always the better option? Curr Opin Endocrinol Diabetes Obes. 2019;26(2):77–83. https://doi.org/10.1097/MED.0000000000000469.
25. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA. 1999;282(15):1458–65 (doi: jrv90041 [pii]).
26. Guest G, Namey E, Taylor J, Eley N, McKenna K. Comparing focus groups and individual interviews: Findings from a randomized study. Int J Soc Res Methodol. 2017;20(6):693–708. https://doi.org/10.1080/13645579.2017.1281601.
27. Kitzinger J. Qualitative research. introducing focus groups. BMJ. 1995;311(7000):299–302. https://doi.org/10.1136/bmj.311.7000.299.
28. Maier CB, Aiken LH. Task shifting from physicians to nurses in primary care in 39 countries: A cross-country comparative study. Eur J Public Health. 2016;26(6):927–34. https://doi.org/10.1093/eurpub/ckw098.
29. Halter M, Drennan V, Chattopadhyay K, et al. The contribution of physician assistants in primary care: A systematic review. BMC Health Serv Res. 2013;13:223–223. https://doi.org/10.1186/1472-6963-13-223.
30. Maier CB. Nurse prescribing of medicines in 13 european countries. Hum Resour Health. 2019;17(1):95–6. https://doi.org/10.1186/s12960-019-0429-6.
31. Houweling ST, Kleefstra N, van Hateren KJ, Groenier KH, Meyboom-de Jong B, Bilo HJ. Can diabetes management be safely transferred to practice nurses in a primary care setting? A randomised controlled trial. J Clin Nurs. 2011;20(9–10):1264–72. https://doi.org/10.1111/j.1365-2702.2010.03562.x.
32. Ter Brugge BPH, Bartelink MEL, Damoiseaux RAMJ, de Groot E. The use of evidence during group meetings of dutch general practitioners. Educ Prim Care. 2017;28(6):307–12. https://doi.org/10.1080/14739879.2017.1344934.

33. Nederlandse staat. Wet medisch-wetenschappelijk onderzoek met mensen. Available from: https://wetten.overheid.nl/BWBR0009408/2021-07-01. Assessed 3 Dec 2021.
34. Lugtenberg M, Zegers-van Schaick JM, Westert GP, Burgers JS. Why don't physicians adhere to guideline recommendations in practice? an analysis of barriers among dutch general practitioners. Implement Sci. 2009;4:54–54. https://doi.org/10.1186/1748-5908-4-54.
35. Arts DL, Voncken AG, Medlock S, Abu-Hanna A, van Weert HC. Reasons for intentional guideline non-adherence: A systematic review. Int J Med Inform. 2016;89:55–62. https://doi.org/10.1016/j.ijmedinf.2016.02.009.
36. Kaldjian LC. Patient care and population health: Goals, roles and costs. J Public Health Res. 2014;3(2):311. https://doi.org/10.4081/jphr.2014.311.
37. Mason A. New medicines in primary care: A review of influences on general practitioner prescribing. J Clin Pharm Ther. 2008;33(1):1–10. https://doi.org/10.1111/j.1365-2710.2008.00875.x.
38. Sox HC. Resolving the tension between population health and individual health care. JAMA. 2013;310(18):1933–4. https://doi.org/10.1001/jama.2013.281998.
39. van Schoonhoven AV, Gout-Zwart JJ, de Vries MJS, et al. Costs of clinical events in type 2 diabetes mellitus patients in the netherlands: A systematic review. PLoS ONE. 2019;14(9): e0221856. https://doi.org/10.1371/journal.pone.0221856.
40. Garjón FJ, Azparren A, Vergara I, Azaola B, Loayssa JR. Adoption of new drugs by physicians: A survival analysis. BMC Health Serv Res. 2012;12:56–56. https://doi.org/10.1186/1472-6963-12-56.

3.2

Marketing of medicines in primary care: an analysis of direct marketing mailings and advertisements

Marloes Dankers
Peeter W.J. Verlegh
Karla Weber
Marjorie H.J.M.G. Nelissen-Vrancken
Liset van Dijk
Aukje K. Mantel-Teeuwisse

PLoS One. 2023;18(8):e0290603

ABSTRACT

Introduction

Marketing materials from pharmaceutical companies attempt to create a positive image of marketed, often new, medicines. To gain more insight in strategies pharmaceutical companies use to influence primary care practitioners' attitudes towards marketed medicines, we investigated the use of persuasion strategies in direct marketing mailings and advertisements from pharmaceutical companies sent to general practitioners.

Methods

General practitioners in the Netherlands were recruited to collect all direct marketing mailings, meaning all leaflets, letters and other information sent by pharmaceutical industries to the practice during one month (June 2022). Direct marketing mailings and advertisements in collected medical journals concerning medicines or diseases (together called marketing materials) were analysed according to presence of one of the seven common persuasion strategies, i.e. reciprocity, consistency/commitment, social proof, liking, authority, scarcity and unity, as well as marketed medicine and year of introduction.

Results

Twenty general practices collected 68 unique marketing materials concerning 37 different medicines. Direct factor Xa inhibitors (n = 12), glucagon-like peptide-1 analogues (n = 5) and sodium-glucose co-transporter 2 inhibitors (n = 4) were the most frequently marketed medicines. The median year of introduction of all marketed medicines was 2012. All seven persuasion strategies were identified, with liking (64.7% of all materials) and authority (29.4%) as most prominent strategies, followed by social proof (17.6%), unity (14.7%), scarcity (13.2%), reciprocity (11.8%) and consistency/commitment (2.9%). In addition to those strategies, we identified emotional pressure (30.9%) as one commonly used new strategy.

Conclusion

Marketing materials sent to general practices use a wide range of persuasion strategies in an attempt to influence prescription behaviour. Primary care practitioners should be aware of these mechanisms through which pharmaceutical companies try to influence their attitudes towards new medicines.

INTRODUCTION

New medicines have been associated with increased longevity and can have benefits in terms of morbidity and health related quality of life [1,2]. However, not all new medicines have an added therapeutic value [2]. In addition, the benefit-risk ratio of new medicines has not been fully elucidated yet and new medicines are often more expensive than alternative treatments [3,4]. There is therefore an urgent need for the rational use of new medicines, both in terms of quality of care and healthcare costs, especially in the light of aging populations and rising healthcare costs [5].

In the Netherlands, primary care functions as gatekeeper of the healthcare system and plays an important role in the prescription of medicines [6]. The uptake of new medicines in primary care is often not equally distributed among physicians [7], and previous attempts to construct a universal profile of early adopters of new medicines failed [8,9]. The attitude of primary care practitioners towards new medicines is likely to play a major role in the decision to prescribe new medicines and might explain the large differences between healthcare professionals in the adoption of new medicines [10]. This attitude can be affected by a variety of factors, including marketing activities from pharmaceutical companies [11-13]. Marketing activities have been known for decades to stimulate the prescription of new medicines [14-19].

Marketing of new medicines in primary care reflects a broad set of activities, including both direct contact (e.g. medical representatives visiting the practice and educations organised by a company) and indirect contact (e.g. sponsored courses and ghost-writing) [14,19,20]. In the Netherlands, the marketing of medicines is strictly regulated and excessive inducement and financial relations between pharmaceutical companies and healthcare professionals are prohibited [21]. Marketing of medicines therefore often happens in more subtle ways and includes the use of direct marketing mailings. Direct marketing mail is described as any marketing material that is delivered physically to a prospect's mailbox, and thus covers all kinds of paper-based marketing materials, including newsletters, flyers and brochures [22]. Another paper-based marketing activity is the use of advertisements in (medical) journals [23]. The contents of these direct marketing mailings and advertisements, further referred to as 'marketing materials', are bound to a code of conduct. This code is supervised by the Dutch Foundation for the Code for Pharmaceutical Advertising. It outlines the requirements that marketing materials must adhere to, such as providing mandatory information (e.g., about indications and adverse events) and specifies the manner in which this information is presented [21].

Although the contents of marketing materials are regulated by the Dutch code, the manner in which materials aim to influence someone's attitude towards medicines are more difficult to regulate. Influencing someone's attitude can be achieved in different ways. To explore the influence strategies used in marketing materials, we used the generally accepted framework by Cialdini [24]. This framework describes seven strategies for persuasion, that could be used to convince the recipient of the advantages of a product [24,25]. Although different taxonomies to classify persuasion strategies exist, the framework of Cialdini is widely accepted and numerous studies have shown the effectiveness of those persuasion strategies in influencing attitudes and behaviour in different areas, including pharmaceutical marketing [26-28]. This framework therefore provides a useful basis to investigate persuasion strategies in marketing materials. Table 1 provides an overview and short description of these strategies. Whether all strategies occur in direct marketing mailings and advertisements from pharmaceutical companies and whether this occurs to a similar extent is unknown.

Table 1: Description of persuasion strategies by Cialdini and examples of how they can occur in pharmaceutical marketing [24,26].

Principle	Description	Example
Reciprocity	Feeling indebted to those who have helped you.	A gift from a pharmaceutical company makes healthcare professionals feeling indebted, which may lead them to change their practice in favour of the gift-giving company.
Consistency/ commitment	The urge to behave consistently and to commit to earlier decisions or opinions.	Agreeing to a small request (for example, a medical representative who asks a healthcare professional whether they agree that there should be more attention to disease X, or to try a new medicine on a small number of patients) increases the likelihood that the healthcare professional will start prescribing the medicine again in larger quantities.
Social proof	The practice of deciding what to do by looking at what others are doing.	The use of opinions of colleagues in marketing activities to sway healthcare professionals to adopt a particular therapy (e.g., 80% of your colleagues prescribe X).
Liking	The principle of being more likely to comply with requests made by people that are liked.	Industry representatives acting friendly towards healthcare professionals and appear to ask nothing in return, or the use of endearing pictures of patients to raise sympathy.
Authority	The use of individuals or institutions who are authoritative, credible and knowledgeable.	The use of key opinion leaders to convince healthcare professionals of the benefits of new medicines.
Scarcity	The concept that opportunities are more valuable when they are limited.	The marketing of a new medicine as 'one of a kind', or available to only a select number of practices.
Unity	The concept of shared identity which opens up to persuasion attempts.	A focus on cooperation and shared goals between industry and professionals will make professionals more willing to do something for the company they feel connected to.

To gain more insight in the strategies pharmaceutical companies use to influence primary care practitioners' views towards new medicines, the aim of this study was to investigate the presence and use of different persuasion strategies in marketing materials from pharmaceutical companies sent to general practitioners.

MATERIALS AND METHODS

Participant recruitment

General practitioners were recruited to collect all direct marketing mailings sent to the practice during one month. Based on a previous – non-published – pilot study, a number of 20 general practices was presumed to be enough to obtain a representative overview of direct marketing mailings. General practitioners were recruited in March and April 2022 by a call in the newsletter and social media channels of the Dutch Institute for the Rational Use of Medicine (IRUM) and members of the research team. In addition, a call was published in the Dutch Journal of Medicine ('Nederlands Tijdschrift voor Geneeskunde') [29]. Finally, symposia and conferences aimed at healthcare professionals where IRUM was represented were used to invite general practitioners.

General practitioners willing to participate were further informed about the purpose of the study and the data - including practice characteristics - that were to be collected. Practices willing to participate gave consent to participate by e-mail or telephone up to May 1, 2022. A digital confirmation of participation (by e-mail) was obtained for all practices. To investigate the representativeness of practices, publicly available information on the practice characteristics location, number of general practitioners per practice, practice type (solo, duo or group), dispensing status and urbanisation of the location of the practice were identified by internet search.

According to Dutch legislation, approval by a medical ethics committee was not necessary, since no patients were involved in this study and the participating healthcare professionals were not exposed to interventions [30].

Data collection

General practitioners were asked to collect all physical marketing mailings from pharmaceutical companies sent by mail from June 1 to 30, 2022. Detailed instructions were sent in the first week of May 2022. The instructions were repeated on May 31, including a final reminder to start the collection. Instructions included the collection of all direct marketing mailings, including leaflets, letters and other information sent by mail to the practice by pharmaceutical industries. Medical journals including advertisements

were not to be collected, although practices were invited to collect sponsored inserts. In case of doubt, the practice was invited to collect the mailing, enabling the researches to make a selection afterwards, if necessary. A reminder to end the collection was sent by e-mail on June 30, 2022. The materials were subsequently either picked up by a member of the research team or sent to the IRUM. Practices that did not start the collection or lost their collected materials were excluded from further analysis.

Data analysis

An overview was made of all materials received per practice by the principal investigator (MD). Multiple brochures for the same medicine in one envelop were considered as one material. Medical journals and sponsored inserts or adjusted covers were counted as separate materials. Thereafter, the selection of relevant direct marketing mailings and advertisements was made. The selection was based on two criteria regarding the sender of the mail (pharmaceutical company) and the subject (medicine or disease, to include disease awareness). All other materials were excluded.

Although medical journals were not meant to be collected and included in this analysis, we decided post hoc to include medicine advertisements in collected journals as well. This was done because of the large number of collected medical journals, despite the instruction not to do so. Moreover, advertisements in medical journals fulfilled both inclusion criteria (sender and subject) and were therefore suitable for analysis.

After inclusion and before further analysis, the marketing materials were anonymized. All unique direct marketing mailings and advertisements were classified according to the name of the marketed medicine, the medicine class (based on the Anatomical Therapeutic Chemical Classification system (ATC) 5th level) and the year of marketing approval. The year of marketing approval was based on the marketed indication. If multiple indications were marketed, the year of approval for the first indication was mentioned. The median year of approval of the medicines in all marketing materials (meaning that medicines that were marketed multiple times were also included multiple times) was calculated to gain insight in the novelty of marketed medicines. Subsequently, for every marketing material the persuasion strategies according to Cialdini's classification were captured. Prior to this analysis, a research guideline with a description of each persuasion strategy including examples from former collected marketing materials was developed and finetuned during several discussion sessions with the research team. This guideline was developed with deductive and inductive research, meaning that we analysed the pilot materials on the presence of both the strategies according to Cialdini's classification (deductive analysis) and other strategies (inductive analysis). During this development, one additional persuasion strategy,

namely emotional pressure, was identified. This additional strategy made use of the sense of responsibility or even sense of guilt of healthcare professionals, resulting in emotional pressure to do the right thing (i.e., prescribing the company's medicine). This was achieved by emphasizing the responsibility of the healthcare professional to take care of patients, often by mentioning the action the healthcare professional had to perform ("you can help her", "your patients need you to"). The strategy had some overlap with commitment, liking and unity. However, the sole focus on sense of responsibility and sense of guilt was considered as a distinct strategy to persuade the healthcare professional to prescribe the marketed medicine. After careful considerations and thorough discussions with the research team, this strategy was therefore added to the research guideline. The analysis of the collected materials was performed independently by two researchers who were primarily involved in the development of the guiding document, one with a background in pharmacy (MD) and one in marketing (PV). In addition, two other independent research assistants, one with a background in pharmacy (KW) and one in marketing (RJ), performed the analysis after being trained in using the guiding document. Cohen's kappa was calculated to measure inter-rater reliability between the two primary investigators and the investigators with the same background. Consensus was to be reached by the two primary investigators, with the opinion of a third independent researcher if needed in case of disagreement.

All results were analysed with IBM SPSS Statistics 28.0.1.1 (15).

RESULTS

Baseline characteristics

Twenty-two practices signed up for the collection. Twenty out of 22 practices started and finished the collection and were thus included in the analysis and reported upon below. The characteristics of all included practices can be found in Table 2. Practices were well distributed across the Netherlands, 9 out of all 12 provinces were represented. The mean number of general practitioners per practice was 3.9 (range 1 - 11). Three participating practices were dispensing practices.

A total of 361 materials were collected (range 0 – 92 per practice) by the 20 included practices. One of the twenty practices only recently opened and did not receive any materials. Two other practices spontaneously reported incomplete collection, due to changing staff or inadequate communication between professionals. After removal of all duplicates, 149 unique materials (range 0 – 43 per practice) remained. Seventeen items were medical journals, which contained 38 unique medicine advertisements. 132 were

Table 2: Characteristics of participating practices.

	Number of practices (%)
Practice type	
Solo	1 (5.0)
Duo	6 (30.0)
Group	13 (65.0)
Number of general practitioners per practice	
1	1 (5.0)
2 to 4	12 (60.0)
≥ 5	7 (35.0)
Dispensing status	
Yes	3 (15.0)
No	17 (85.0)
Urbanisation level of location of practice[a]	
Very strong	4 (20.0)
Strong	5 (25.0)
Moderate	0 (0)
Little	9 (45.0)
Not	2 (10.0)

[a] *Level of urbanisation is defined as very strong (≥ 2500 addresses/km^2), strong (1500 - 2500 addresses/km^2), moderate (1000 – 1500 addresses/km^2), little (500 - 1000 addresses/km^2) or not (< 500 addresses/km^2) [31].*

other marketing materials, of which 30 fulfilled the inclusion criteria (range 0 – 14 per practice). A total number of 68 marketing materials were included for analysis (Figure 1).

Characteristics of marketing materials

Six different types of marketing materials were identified. Advertisements in medical journals (n = 38) were most prominent, followed by marketing brochures (n = 13), sponsored inserts or covers of medical journals (n = 6) and invitations for education organised by pharmaceutical companies (n = 5). In addition, five information letters from companies about registration or reimbursement of medicines and one invitation to a company's stand with information on a specific disease on an upcoming medical symposium were identified. The identified materials concerned a total of 37 different marketed medicines (S1 Table). Eleven marketing materials did not mention a specific medicine. Direct factor Xa inhibitors (n = 12) were the most frequently marketed

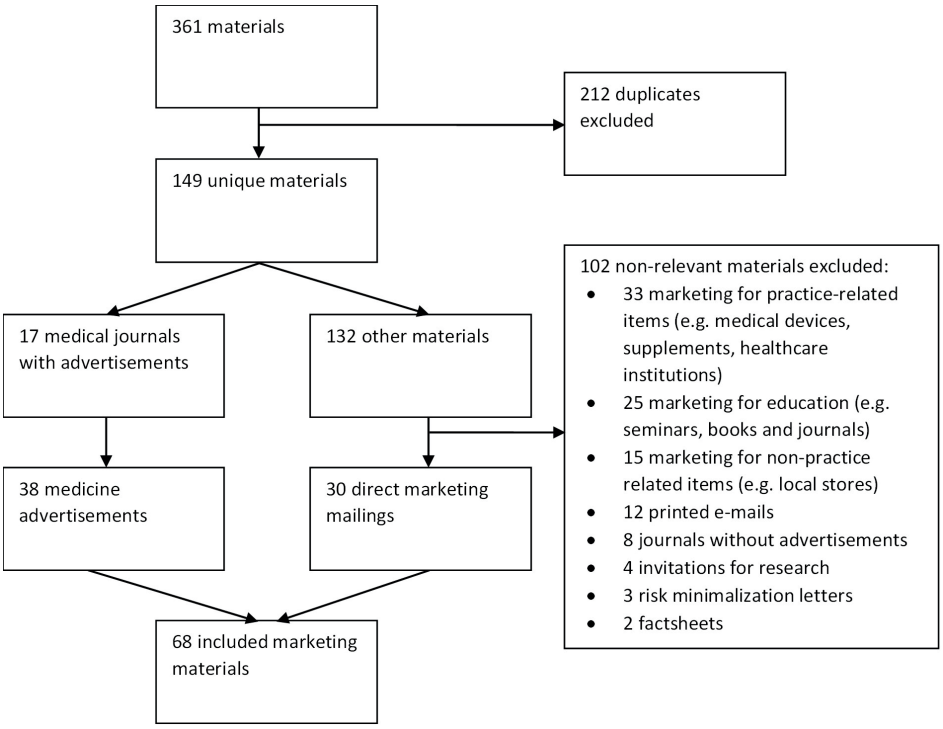

Figure 1: Selection of marketing materials.

medicines, followed by glucagon-like peptide-1 (GLP-1) receptor agonists (n = 5) and sodium-glucose co-transporter 2 (SGLT2) inhibitors (n = 4). The median year of introduction of all medicines was 2012 (range 1966 – 2022).

Persuasion strategies

For the allocation of persuasion strategies, the Cohen's kappa coefficient between the two primary investigators was 0.65, indicating, according to Cohen, substantial agreement [32]. The agreement between two researchers with the same background was slightly higher (0.71 for both pharmaceutical experts and 0.80 for both marketing experts). Ultimately, agreement between the two primary researchers was reached in all cases without the need for a call from a third researcher. The frequency of identified persuasion strategies, based on consensus between the two primary investigators, can be seen in Table 3. A total of 126 persuasion strategies were found in 68 materials. No large differences existed between direct marketing mailings and advertisements. All different seven categories defined by Cialdini were identified, with liking (64.7% of all marketing materials) and authority (29.4%) as the most represented persuasion strategies. We identified emotional pressure as an additional category, which was present in 30.9% of all materials.

Table 3: Frequency of persuasion strategies found in collected marketing materials.

Persuasion strategy	Overall (n = 68) n (%[a])	Direct marketing mailings (n = 30) n (%[a])	Advertisements (n = 38) n (%[a])
Reciprocity	8 (11.8%)	7 (23.3%)	1 (2.6%)
Consistency/commitment	2 (2.9%)	2 (6.7%)	0 (0%)
Social proof	12 (17.6%)	7 (23.2%)	5 (13.2%)
Liking	44 (64.7%)	19 (63.3%)	25 (65.8%)
Authority	20 (29.4%)	9 (30.0%)	11 (28.9%)
Scarcity	9 (13.2%)	3 (10.0%)	6 (15.8%)
Unity	10 (14.7%)	6 (20.0%)	4 (10.5%)
Emotional pressure[b]	21 (30.9%)	9 (30.0%)	12 (31.6%)

[a] *Percentages do not add up to 100% because multiple strategies can be used in one marketing material.*
[b] *Newly identified category, not described by Cialdini.*

Reciprocity

Reciprocity refers to the obligation to help those who have helped you and is often expressed by providing someone with something that could be considered as a gift. In the marketing materials, examples of reciprocity were found eight times. For example, some invitations for sponsored educations advertised free meals and accreditation points. Other examples were offering free samples, books and placebo-inhalers. Most identified gifts were relatively small. The gifts were both aimed at the practice as a whole (for example training inhalers) or at individual general practitioners (for example accreditation points).

> Invitation for a sponsored education with free meals and accreditation points.
> *#Marketing material 37, invitation for education.*

Consistency/commitment

Consistency refers to behaving consistently and to commit to earlier decisions or opinions. In marketing materials, this can be achieved by the use of (semi-)rhetorical questions. A positive answer on these often obligate questions automatically implies that the marketed medicine is the best option. This mechanism was identified two times in the collected materials.

> "Do you and your patients prefer ease of use and ease of prescription?"
> *#Marketing material 24, brochure.*

Social proof

Social proof is the use of opinions of colleagues to promote a product. In marketing materials, this can be achieved by using opinions or actions of other healthcare

professionals. A referral to a healthcare professional who is positioned as an expert in the field, was considered as authority and not social proof.

In the collected materials, we found several marketing materials stating 'the most prescribed medicine for disease X'. Remarkably, in a specific therapeutic class, the statement of being the most prescribed medicine was found for two different medicines, referring to different investigations. Social proof was also used more subtly by the use of specific pictures referring to other physicians' actions, for example by using white coats or stethoscopes.

"Most prescribed [medicine class X] in the Netherlands."
#Marketing material 4, brochure.

Liking

Liking is the creation of a positive feeling about a company or product. Liking was the most identified persuasion strategy and used in almost two-thirds of all marketing materials. Liking was most often achieved by the use of sympathetic pictures, for example of friendly-looking patients, beautiful landscapes and animals. Liking was achieved by portraying patients as sad people who could be helped on one hand and as self-confident people who had already been helped by the product on the other hand.

A portrait of a happy-looking boy playing the guitar accompanied with the phrase "Be who you want to be"
#Marketing material 59, advertisement.

Authority

Authority refers to the use of individuals or institutions who are authoritative, credible and knowledgeable. In addition, authority can also be created by focusing on the authority of the product itself, by emphasizing the status of the medicine. Authority was identified twenty times and attained by mentioning the authority of the pharmaceutical company as well as the use of authority of others to emphasize the medicines' benefit. Authority of the company was for example emphasized by mentioning the years of experience in a specific field. Materials also referred to the authority of others, for example by referring to guidelines, official institutions like registration authorities and professional organisations, and individual medical experts. Authority was also achieved by focusing on the seniority of the product.

"[Medicine X] has been a reliable [medicine group X] for almost 50 years and has been used by 3 million Dutch women."
#Marketing material 8, sponsored cover.

Scarcity

Scarcity refers to limited options that are considered more valuable. In marketing materials, this can be achieved by focusing on the unique status of a product. The collected marketing materials made use of this scarcity by referring to a medicine as 'the only one'. Often, the phrase 'the first and only' was used. Emphasized characteristics referred among others to indications, dosage forms and mechanisms of action.

"[Medicine X] is the first and so far only selective [medicine group X] registered for the aforementioned indication."
#Marketing material 19, information letter.

Unity

Unity is the principle of shared identity, which can be explained as shared identity between the producer and healthcare professionals. In marketing materials, this was expressed by positioning the company next to the professional, to emphasize that they were on the same side and had the same goals. This was often done by using the word 'together', but also by phrases like 'we can help you' and statements implying that the company was helping the healthcare professional by providing them with therapeutic options for their patients.

"Together we tackle overweight."
#Marketing material 38, invitation for education.

Emotional pressure

In addition to the persuasion strategies defined by Cialdini, one more strategy was identified in the materials, which was the second most common, after liking. This strategy made use of the sense of responsibility or even sense of guilt of healthcare professionals. This strategy was often achieved by addressing healthcare professionals to do what was best for their patients (i.e. prescribing the company's medicine).

"Provide your patients with [disease X] and ['old' medicine X] with better chances with ['new' medicine Y]."
#Marketing material 79, advertisement in magazine.
An image of a granddaughter hugging her grandfather, accompanied with the phrase: "838 additional hugs from grandfather, due to the protection you provide your [disease X] patients with."
#Marketing material 15, sponsored cover.
"For which T2DM patient do you want to do more?"
#Marketing material 13, brochure.

DISCUSSION

Marketing materials sent by pharmaceutical companies to general practitioners used a wide range of persuasion strategies, of which liking and authority were the most common.

All other persuasion strategies defined by Cialdini [24], i.e. reciprocity, consistency/ commitment, social proof, scarcity and unity, were also used, often in combinations. In addition to these strategies, one additional category, coined 'emotional pressure', was identified. The presence of eight different persuasion strategies in 68 marketing materials indicates that pharmaceutical companies use a wide range of strategies to influence the attitudes of healthcare professionals towards prescribing their (new) medicines.

The identified persuasion strategies were achieved by use of text and images and often a combination of these. Persuasion strategies in marketing materials were identified on different levels. Although most materials were aimed at creating a positive image of a specific medicine, marketing materials also focused on disease awareness or positively portraying the company itself. The identified persuasion strategies have been associated with different motives of persuaders. Reciprocity, liking and unity have been primarily associated with cultivation of a relationship. Social proof and authority are often used to reduce uncertainty, and consistency and scarcity are regularly involved if call to action is the primary goal [24]. The presence of all these different persuasion strategies in the marketing materials implies that all goals are being pursued. However, with liking and authority as the most prominent Cialdini strategies [24], it can be argued that building a relationship and reducing uncertainty are the most prominent goals of the investigated materials.

In addition to the persuasion strategies described by Cialdini [24], we identified one additional strategy, which was described as emotional pressure. This strategy makes use of the sense of responsibility of healthcare professionals, implying that the prescription of the marketed medicine is the best care they can provide for their patients. The importance of emotion in persuasion has been recognized before [33,34]. In consumer research, a similar tactic of using emotions to elicit feelings of accountability and responsibility has been studied in the promotion of socially responsible products and behaviours [35]. This newly identified strategy in addition to the model of Cialdini most probably reflects the unique situation of medicine marketing, where the choice for a specific product is made by a professional, rather than by a consumer. Since the Cialdini principles are not exclusively developed for medicine marketing, this might explain why this principle based on professional attitude was identified in the collected marketing materials, but not described in Cialdini's framework.

The presence of persuasion strategies in marketing activities of pharmaceutical companies has been described before [26]. However, to the best of our knowledge, this is the first study to investigate the use of the persuasion described by Cialdini in marketing

materials from pharmaceutical companies. In previous research, direct marketing brochures and advertisements have been shown to have little or no educational value [36-38]. In addition, studies have also shown that marketing materials contain inaccurate or even misleading statements [23,36-39]. Although marketing activities have been shown to directly influence prescription behaviour [14-18,20,40,41], healthcare professionals still underestimate their vulnerability to marketing, thinking they themselves are not affected by marketing activities [14,18,24]. In the advertising literature, this is known as the third person effect, the illusion that advertising influences other people but not me [42]. The strategies used however have been proven to influence behaviour, even if the recipient is not aware of this. The crux of these persuasion strategies is that they produce a distinct kind of automatic, mindless compliance [24]. The ultimate effect of the identified persuasion strategies, also in relation to other marketing activities such as visits by medical representatives and sponsored educations, was not investigated in this study and calls for further research. However, because of the proven efficacy of these persuasion strategies [24,25], and the proven impact of other marketing activities by pharmaceutical companies on prescription behaviour [14-18,20,40,43], there is no reason to believe that the marketing materials would not influence healthcare professionals. The lack of educational value and the wide presence of persuasion strategies makes it even more clear that direct marketing mails and advertisements should be viewed as promotional information and emphasizes the urge to create awareness of the mechanisms marketing materials use to influence decision-making.

Our study focused solely on marketing materials sent to general practices. The decision to include advertisements in addition to direct marketing mailings was made post hoc. Since the identified persuasion strategies in direct marketing mailings and advertisements did not really differ, the decision to include both seems justified. Marketing brochures and advertisements from other sources – for example symposia, sales representatives or medical journals not collected by the general practices – were not included. In addition, other marketing activities such as digital marketing and indirect marketing were not assessed in this study. Different marketing activities from pharmaceutical companies are known to reinforce each other and have a synergistic effect on prescription behaviour [14,41]. It is therefore important to realise that the persuasion strategies identified in this study are only a small part of all attempts to influence prescription behaviour. Although marketing materials are only a small part of all marketing activities, it has been present for decades. Already in 1939, the amount and effect of direct marketing mailings towards healthcare professionals were investigated. At that time, the average number of advertising mail per healthcare professional was approximately four pieces per day [18]. In our study, the number of unique marketing materials per general practice in four weeks' time ranged from 0 to

43. It is not known whether the wide range of received materials reflects a real difference in the extent of that pharmaceutical companies target general practices, or a difference between practices in the adherence to collection instructions. A number of practices spontaneously reported incomplete or inadequate collection, indicating that no firm conclusions about the number of marketing materials could be made. The number of collected marketing materials in our study indicate that marketing materials should still be seen as a relevant element of all marketing activities.

A wide range of introduction years of the marketed medicines was identified in this study. The novelty of the marketed medicines was less than anticipated, with 2012 as median introduction year and 1966 as first introduction year. The wide range of introduction years is probably related to the relatively slow uptake of new medicines in Dutch general practices [44,45], explaining why pharmaceutical companies continue marketing activities years after the launch of their product. It also points out the importance of alertness to marketing activities, even if medicines are not considered to be new anymore.

The main strength of this study is the large number of included marketing materials – obtained from brochures and medical journals collected by general practices – and the focus on persuasion strategies in text and image, resulting in a clear overview of how medicines are marketed in direct marketing mails and advertisements by pharmaceutical companies. There are however also some limitations. First, it is not known whether the included marketing materials were representative for all marketing materials, since we included only marketing materials sent to a limited number of practices during one month and it is not known whether all practices followed the exact instructions. In addition, the decision to include advertisements as well was made post hoc, indicating that the included advertisements did not reflect the total number of advertisements in this month. However, although the marketed medicines are likely to be time-dependent, the identification of all different persuasion strategies makes it unlikely that the conclusions about the use of persuasion strategies would significantly alter when including other marketing materials. Second, the allocation of persuasion strategies to marketing materials can be subjective. However, the interrater analysis showed a substantial agreement between the different assessors and the use of two researchers with marketing expertise and pharmaceutical expertise minimised this risk.

This study provides a clear overview of marketing materials sent to general practices in June 2022 and sheds light on the used persuasion strategies. Primary care practitioners should be aware of these mechanisms used by companies, to ensure that they are as little as possible influenced by this kind of marketing. Furthermore, practitioners should

be educated in recognizing and countering these kind of persuasion strategies in order to prevent unwanted influence [46]. Training in resistance strategies [47] may provide a valid starting point.

REFERENCES

1. Lichtenberg FR. The impact of new drug launches on longevity: Evidence from longitudinal, disease-level data from 52 countries, 1982-2001. Int J Health Care Finance Econ. 2005;5(1):47-73. doi: 10.1007/s10754-005-6601-7 [doi].
2. Wieseler B, McGauran N, Kaiser T. New drugs: Where did we go wrong and what can we do better? BMJ. 2019;366:l4340. doi: 10.1136/bmj.l4340 [doi].
3. Lubloy A. Factors affecting the uptake of new medicines: A systematic literature review. BMC Health Serv Res. 2014;14:469-469. doi: 10.1186/1472-6963-14-469 [doi].
4. Kozyrskyj A, Raymond C, Racher A. Characterizing early prescribers of newly marketed drugs in Canada: A population-based study. Eur J Clin Pharmacol. 2007;63(6):597-604. doi: 10.1007/s00228-007-0277-5 [doi].
5. Dieleman JL, Squires E, Bui AL, et al. Factors associated with increases in US health care spending, 1996-2013. JAMA. 2017;318(17):1668-1678. doi: 10.1001/jama.2017.15927 [doi].
6. Kroneman M, Boerma W, van den Berg M, Groenewegen P, de Jong J, van Ginneken E (2016). The Netherlands: Health system review. Health Systems in Transition. 2016;18(2):1-239.
7. Tamblyn R, McLeod P, Hanley JA, Girard N, Hurley J. Physician and practice characteristics associated with the early utilization of new prescription drugs. Med Care. 2003;41(8):895-908. doi: 10.1097/00005650-200308000-00004 [doi].
8. Dybdahl T, Andersen M, Søndergaard J, Kragstrup J, Kristiansen IS. Does the early adopter of drugs exist? A population-based study of general practitioners' prescribing of new drugs. Eur J Clin Pharmacol. 2004;60(9):667-672. doi: 10.1007/s00228-004-0797-1.
9. Dankers M, Hek K, Mantel-Teeuwisse AK, Van Dijk L, Nelissen-Vrancken HJMG. Adoption of new medicines in primary care: A comparison between the uptake of new oral anticoagulants and diabetes medicines. Submitted 2022.
10. Dankers M, Hek K, Nelissen-Vrancken M, Houweling ST, Mantel-Teeuwisse A, van Dijk L. Newer long-acting insulin prescriptions for patients with type 2 diabetes: Prevalence and practice variation in a retrospective cohort study. Br J Gen Pract. 2022;72(719):e430-e436. doi: 10.3399/BJGP.2021.0581 [doi].
11. Dankers M, van den Berk-Bulsink, M. J. E., van Dalfsen-Slingerland M, Nelissen-Vrancken, H. J. M. G., Mantel-Teeuwisse AK, van Dijk L. Non-adherence to guideline recommendations for insulins: A qualitative study amongst primary care practitioners. BMC Prim Care. 2022;23(1):150-5. doi: 10.1186/s12875-022-01760-5 [doi].
12. Jones MI, Greenfield SM, Bradley CP. Prescribing new drugs: Qualitative study of influences on consultants and general practitioners. BMJ. 2001;323(7309):378-381. doi: 10.1136/bmj.323.7309.378 [doi].
13. Prosser H, Almond S, Walley T. Influences on GPs' decision to prescribe new drugs-the importance of who says what. Fam Pract. 2003;20(1):61-68. doi: 10.1093/fampra/20.1.61.
14. Hailu AD, Workneh BD, Kahissay MH. Influence of pharmaceutical marketing mix strategies on physicians' prescribing behaviors in public and private hospitals, dessie, ethiopia: A mixed study design. BMC Public Health. 2021;21(1):65-2. doi: 10.1186/s12889-020-10063-2 [doi].
15. Sharma S, Akhoon N, Moe HW, Nair DR, Shashidhar V. A study of perceptions and exposure of drug promotional literature among clinicians in a teaching hospital. Perspect Clin Res. 2021;12(3):140-145. doi: 10.4103/picr.PICR_36_19 [doi].

16. Vancelik S, Beyhun NE, Acemoglu H, Calikoglu O. Impact of pharmaceutical promotion on prescribing decisions of general practitioners in eastern turkey. BMC Public Health. 2007;7:122-122. doi: 1471-2458-7-122 [pii].
17. Wood SF, Podrasky J, McMonagle MA, et al. Influence of pharmaceutical marketing on medicare prescriptions in the district of columbia. PLoS One. 2017;12(10):e0186060. doi: 10.1371/journal.pone.0186060 [doi].
18. Jeuck JE. Direct-mail advertising to doctors. The Journal of Business of the University of Chicago. 1940;13(1):17-38. http://www.jstor.org/stable/2350143.
19. Leonardo Alves T, Lexchin J, Mintzes B. Medicines information and the regulation of the promotion of pharmaceuticals. Sci Eng Ethics. 2019;25(4):1167-1192. doi: 10.1007/s11948-018-0041-5 [doi].
20. Ahmed RR, Vveinhardt J, Streimikiene D, Awais M. Mediating and marketing factors influence the prescription behavior of physicians: An empirical investigation. Amfiteatru Economic Journal, ISSN 2247-9104, The Bucharest University of Economic Studies, Bucharest. 2016;18(41):153-167.
21. Stichting Code Geneesmiddelen Reclame (CGR). Zelfregulering in geneesmiddelenreclame. https://www.cgr.nl/home. Accessed Jan 27, 2023.
22. Elrod JK, Fortenberry JL,Jr. Direct marketing in health and medicine: Using direct mail, email marketing, and related communicative methods to engage patients. BMC Health Serv Res. 2020;20(Suppl 1):822. doi: 10.1186/s12913-020-05603-w [doi].
23. Othman N, Vitry A, Roughead EE. Quality of pharmaceutical advertisements in medical journals: A systematic review. PLoS One. 2009;4(7):e6350. doi: 10.1371/journal.pone.0006350 [doi].
24. Cialdini RB. Influence, new and expanded the psychology of persuasion. New York: Harper Business; 2021.
25. Cialdini RB, Goldstein NJ. Social influence: Compliance and conformity. Annu Rev Psychol. 2004;55(1):591-621. doi: 10.1146/annurev.psych.55.090902.142015.
26. Sah S, Fugh-Berman A. Physicians under the influence: Social psychology and industry marketing strategies. J Law Med Ethics. 2013;41(3):665-672. doi: 10.1111/jlme.12076 [doi].
27. Zalake M, Siqueira AGd, Vaddiparti K, Lok B. The effects of virtual human's verbal persuasion strategies on user intention and behavior. International Journal of Human-Computer Studies. 2021;156:102708. doi: 10.1016/j.ijhcs.2021.102708.
28. Orji R, Mandryk RL, Vassileva J. (2015). Gender, Age, and Responsiveness to Cialdini's Persuasion Strategies. In: MacTavish, T., Basapur, S. (eds) Persuasive Technology. PERSUASIVE 2015. Lecture Notes in Computer Science(), vol 9072. Springer, Cham. https://doi.org/10.1007/978-3-319-20306-5_14
29. Dankers M. Hoe worden nieuwe geneesmiddelen gepromoot? Analyse van marketingmaterialen in de huisartsenpraktijk. Ned Tijdschr Geneeskd. 2022;166(D6754).
30. Nederlandse staat. Wet medisch-wetenschappelijk onderzoek met mensen. [Internet]. Available from: https://wetten.overheid.nl/BWBR0009408/2021-07-01. [Assessed 13 March 2023].
31. Centraal Bureau voor de Statistiek (CBS). Stedelijkheid (van een gebied). Den Haag: CBS 2023. https://www.cbs.nl/nl-nl/onze-diensten/methoden/begrippen/stedelijkheid--van-een-gebied--. Accessed March 10, 2023.
32. McHugh ML. Interrater reliability: The kappa statistic. Biochem Med (Zagreb). 2012;22(3):276-282.
33. Miceli M, Rosis Fd, Poggi I. Emotional and non-emotional persuasion. Appl Artif Intell. 2006;20(10):849-879. doi: 10.1080/08839510600938193.
34. Petty RE, Briñol P. Emotion and persuasion: Cognitive and meta-cognitive processes impact attitudes. Cogn Emot. 2015;29(1):1-26. doi: 10.1080/02699931.2014.967183.

35. Peloza J, White K, Shang J. Good and guilt-free: The role of self-accountability in influencing preferences for products with ethical attributes. J Market. 2013;77(1):104-119. doi: 10.1509/jm.11.0454.
36. Gettings J, O'Neill B, Chokshi DA, et al. Differences in the volume of pharmaceutical advertisements between print general medical journals. PLoS One. 2014;9(1):e84790. doi: 10.1371/journal.pone.0084790 [doi].
37. Wilkes MS, Doblin BH, Shapiro MF. Pharmaceutical advertisements in leading medical journals: Experts' assessments. Ann Intern Med. 1992;116(11):912-919. doi: 10.7326/0003-4819-116-11-912 [doi].
38. PLoS Medicine Editors. PLoS medicine and the pharmaceutical industry. PLoS Med. 2006;3(7):e329. doi: e329.
39. Cardarelli R, Licciardone JC, Taylor LG. A cross-sectional evidence-based review of pharmaceutical promotional marketing brochures and their underlying studies: Is what they tell us important and true? BMC Fam Pract. 2006;7:13-13. doi: 1471-2296-7-13 [pii].
40. Larkin I, Ang D, Steinhart J, et al. Association between academic medical center pharmaceutical detailing policies and physician prescribing. JAMA. 2017;317(17):1785-1795. doi: 10.1001/jama.2017.4039 [doi].
41. Spurling GK, Mansfield PR, Montgomery BD, et al. Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: A systematic review. PLoS Med. 2010;7(10):e1000352. doi: 10.1371/journal.pmed.1000352.
42. Eisend M. The third-person effect in advertising: A meta-analysis. Journal of Advertising. 2017;46(3):377-394. doi: 10.1080/00913367.2017.1292481.
43. Spurling G, Mansfield P. General practitioners and pharmaceutical sales representatives: Quality improvement research. Qual Saf Health Care. 2007;16(4):266-270. doi: 16/4/266 [pii].
44. de Jong LA, Koops M, Gout-Zwart JJ, et al. Trends in direct oral anticoagulant (DOAC) use: Health benefits and patient preference. Neth J Med. 2018;76(10):426-430.
45. Overbeek JA, Heintjes EM, Prieto-Alhambra D, et al. Type 2 diabetes mellitus treatment patterns across Europe: A population-based multi-database study. Clin Ther. 2017;39(4):759-770. doi: S0149-2918(17)30129-7 [pii].
46. Mansfield PR, Lexchin J, Wen LS, et al. Educating health professionals about drug and device promotion: Advocates' recommendations. PLoS Med. 2006;3(11):e451. doi: 10.1371/journal.pmed.0030451.
47. Knowles ES & Linn JA (eds.). (2004). Resistance and persuasion (1st ed.). Psychology Press. https://doi.org/10.4324/9781410609816.

SUPPLEMENT

S1 Table: Characteristics of marketed medicines.

Medicine	Medicine group	Number of materials	Year of marketing approval[a]
Allergen extracts[b]	Allergen extracts	1	2003
Allergen extracts[b]	Allergen extracts	1	2006
Apixaban	Direct factor Xa inhibitors	2	2011
Bempedoic acid	Other lipid modifying agents	1	2020
Benralizumab	Other systemic drugs for obstructive airway diseases	1	2018
Bimekizumab	Interleukin inhibitors	1	2021
C1-inhibitor, plasma derived	Drugs used in hereditary angioedema	1	2011
Clobetasol	Corticosteroids, very potent (group IV)	1	2004
Dapagliflozin	SGLT2 inhibitors	2	2012
Denosumab	Other drugs affecting bone structure and mineralization	1	2010
Dexamethasone (ocular)	Corticosteroids, plain	1	2010
Dexamfetamine	Centrally acting sympathomimetics	1	2021
Dulaglutide	GLP-1 receptor agonists	1	2014
Edoxaban	Direct factor Xa inhibitors	1	2015
Empagliflozin	SGLT2 inhibitors	2	2014
Emtricitabine, tenofovir alafenamide and bictegravir	Antivirals for treatment of HIV infections, combinations	1	2018
Filgotinib	Selective immunosuppressants	1	2020
Finerenone	Aldosterone antagonists	3	2022
Formoterol and beclometasone	Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics	1	2007
Formoterol, glycopyrronium bromide and beclometasone	Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids	1	2017
Formoterol, glycopyrronium bromide and budesonide	Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids	1	2020
Hydrocortisone	Glucocorticoids	1	2011
Liraglutide	GLP-1 receptor agonists	3	2015
Lisdexamfetamine	Centrally acting sympathomimetics	1	2019

S1 Table: Characteristics of marketed medicines. (continued)

Medicine	Medicine group	Number of materials	Year of marketing approval[a]
Medroxyprogesterone	Progestogens	2	2011
Methenamine	Other antibacterials	1	1966
Naloxegol	Peripheral opioid receptor antagonists	1	2014
Norelgestromin and ethinylestradiol	Progestogens and estrogens, fixed combinations	1	2002
Norethisterone	Estren derivatives	1	1990
Ofatumumab	Selective immunosuppressants	1	2021
Plastic IUD with progestogen[c]	Intrauterine contraceptives	1	2021
Plastic IUD with progestogen[c]	Intrauterine contraceptives	1	1996
Rivaroxaban	Direct factor Xa inhibitors	9	2008
Semaglutide	GLP-1 receptor agonists	1	2020
Testosterone[d]	3-oxoandrosten (4) derivatives	1	2016
Testosterone[d]	3-oxoandrosten (4) derivatives	1	2005
Testosterone[d]	3-oxoandrosten (4) derivatives	1	2002
Tildrakizumab	Interleukin inhibitors	1	2018
Tiotropium bromide	Anticholinergics	1	2001
Upadacitinib	Selective immunosuppressants	1	2019
Vilanterol, umeclidinium bromide and fluticasone furoate	Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids	1	2017

GLP-1 = glucagon-like peptide-1, IUD = intrauterine device, SGLT2 = sodium-glucose co-transporter 2.

[a] *The year of registration refers to the year of registration for the marketed indication. If multiple indications were marketed, the first year was mentioned.*

[b] *The marketing materials for allergen extracts were for different patented products and have therefore different years of introduction.*

[c] *The marketing materials for levonorgestrel were for different dosage forms and have therefore different years of introduction.*

[d] *The marketing materials for testosterone were for different dosages and dosage forms and have therefore different years of introduction.*

4

Prescription patterns

4.1

Newer long-acting insulin prescriptions for patients with type 2 diabetes: prevalence and practice variation in a retrospective cohort study

Marloes Dankers
Karin Hek
Marjorie H.J.M.G. Nelissen-Vrancken
Sebastiaan T. Houweling
Aukje K. Mantel-Teeuwisse
Liset van Dijk

Br J Gen Pract. 2022;72(719):e430-e436.

ABSTRACT

Background

Little is known about prescription patterns of expensive non-recommended newer long-acting insulins (glargine 300 U/mL and degludec) for patients with type 2 diabetes mellitus (T2DM).

Aim

To identify practice variation in, and practice- and patient-related characteristics associated with, the prescription of newer long-acting insulins to patients with T2DM in primary care.

Design and setting

A retrospective cohort study in Dutch general practices (Nivel Primary Care Database).

Method

A first prescription for intermediate or long-acting insulins in 2018 was identified in patients aged ≥ 40 years using other T2DM drugs. Per practice, the median percentage and interquartile range (IQR) of patients with newer insulin prescriptions were calculated. Multilevel logistic regression models were constructed to calculate intraclass correlation coefficients (ICCs) and quantify the association of patient and practice characteristics with prescriptions for newer insulins (odds ratios [ORs] and 95% confidence intervals [CIs]).

Results

In total, 7757 patients with prescriptions for intermediate or long-acting insulins from 282 general practices were identified. A median percentage of 21.2% (IQR 12.5 – 36.4%) of all patients prescribed intermediate or long-acting insulins per practice received a prescription for newer insulins. After multilevel modelling, the ICC decreased from 20% to 19%. Female sex (OR 0.77, 95% CI = 0.69 to 0.87), age ≥ 86 years compared with 40 – 55 years (OR 0.22, 95% CI = 0.15 to 0.34), prescriptions for metformin (OR 0.66, 95% CI = 0.53 to 0.82), sulfonylurea (OR 0.58, 95% CI = 0.51 to 0.66), or other newer T2DM drugs (OR 3.10, 95% CI = 2.63 to 3.66), and dispensing practices (OR 1.78, 95% CI = 1.03 to 3.10) were associated with the prescription of newer insulins.

Conclusion

The inter-practice variation in the prescription of newer insulins is large and could only be partially explained by patient- and practice-related differences. This indicates substantial opportunities for improvement.

INTRODUCTION

New medicines are often expensive and have a risk–benefit ratio that has not been fully elucidated yet [1,2]. Therefore, clinical guidelines usually do not recommend their use, especially if less expensive and evidence-based alternatives are available [3]. This is also reflected in the most current type 2 diabetes mellitus (T2DM) guidelines, which do not recommend the use of insulin glargine 300 U/mL and insulin degludec [4-6]. These two most recently introduced long-acting insulins, further referred to as 'newer insulins', gained market access in 2013 and 2015, respectively.

In the Netherlands, the majority of insulins for T2DM are prescribed in primary care [7]. The guideline of the Dutch College of General Practitioners *NHG-Standaard Diabetes mellitus type 2* advises against the use of the newer insulins, for reasons of non-evidence-based advantages compared with other intermediate and long-acting insulins [5]. In addition, insulin degludec has an unknown long-term safety and is more expensive than other insulins. In the Netherlands, insulin glargine 300 U/mL is also slightly more expensive than other insulins, and safety concerns about high-strength concentration and risk of dose error exist.

The Dutch guideline considers NPH-insulin as the first choice with insulin glargine 100 U/mL and insulin detemir as potential alternatives in specific situations [5]. Although adherence to guidelines is generally high among Dutch general practitioners (GPs) [8,9], the popularity of insulin glargine 300 U/ml and insulin degludec in Dutch practice is rapidly increasing [10]. However, little is known about patterns of newer insulin use in patients with T2DM and especially information on practice variation and practice- and patient-related characteristics associated with the prescription of newer long-acting insulins is lacking. In previous research, a number of patient and practice characteristics have been positively associated with the prescription of new medicines, including male sex, younger age, and practice location [11,12]. Whether these factors also apply to the prescription of newer insulins is unknown.

To stimulate better quality of care and prevent increasing expenditure on insulins for patients with T2DM, insight into the prescription patterns of non-recommended newer insulins is warranted. This study therefore aimed to identify practice variation in, and practice and patient characteristics associated with, the prescription of newer insulins to patients with T2DM in primary care, 3 – 5 years after their introduction.

METHOD

Study setting and participants

Data from the Nivel Primary Care Database (Nivel-PCD) were used. Nivel-PCD collects data from routine electronic health records from a dynamic sample of approximately 500 general practices in the Netherlands (roughly 10% of the Dutch population).

Data include information on patient characteristics, consultations, morbidity, prescriptions, lab test results, and the patient's main diabetes practitioner (primary or secondary care provider). The age and sex distribution of listed patients is representative of the general Dutch population [13].

All patients with one or more prescriptions for intermediate-acting insulins (Anatomical Therapeutic Chemical Classification system [ATC code] A10AC) or long-acting insulins (A10AE) in 2018 were included. To distinguish between T1DM and T2DM, only patients using insulins, aged ≥ 40, and using one or more other blood glucose-lowering drugs were included [14].

Insulin-naive patients were defined as having no prescription for any insulin (A10A) in 2017. Prescriptions for insulin glargine 100 U/ml and insulin glargine 300 U/ml were distinguished based on unique product codes. Prescriptions for insulin glargine with unknown product codes were excluded from further analysis (n = 47).

Determinants

Patient characteristics

Age, sex, the number of chronic diseases, duration of T2DM (based on date of first diagnosis), and prescriptions for blood glucose lowering drugs other than insulin at any time in 2018 were included as patient characteristics.

Age was divided into four categories (40 – 55 years; 56 – 70 years; 71 – 85 years; and ≥ 86 years). T2DM duration was divided into six categories (0 – 5 years; 6 – 10 years; 11 – 15 years; 16 – 20 years; ≥ 21 years; and unknown). As a result of inaccurate recording of the year of diagnosis for a subset of patients (for example, the year of diagnosis was '01-01-1900'), duration was considered unknown if age at diagnosis was < 40 years.

In order to evaluate comorbidities, a selection of 29 chronic diseases was made, using constructed disease episodes of recorded morbidity data from the electronic health records [15,16]. The number of chronic diseases was divided into three categories (0 – 1, 2 – 4, and ≥ 5) [17].

Practice characteristics

Practice type (that is, solo, duo, and group) was analysed. Missing values (n = 19) were considered as a distinct category 'unknown'. In addition, dispensing practices were distinguished from non-dispensing practices, with practices with unknown status (n = 12) being considered as non-dispensing. This was done because the vast majority of practices in the Netherlands are non-dispensing and so it is unlikely that a dispensing status would not be recorded accurately.

The socioeconomic status (SES) of the location of the practice (developed by the Netherlands Institute for Social Research) [18], the percentage of patients aged ≥ 70 years, and practice size were divided in tertiles [17]. The degree of urbanisation of practice locations was divided into five categories.

Analysis

The number of patients with a prescription for an intermediate or long-acting insulin in 2018 was established for the entire cohort and for insulin-naive patients. The percentage of patients with a prescription for a newer insulin (insulin glargine 300 U/ml or insulin degludec) compared with all patients with an intermediate or long-acting insulin per practice was also analysed and the median percentage per practice and interquartile range (IQR) was calculated.

Multivariate logistic regression analyses were performed on the entire cohort to assess the association of patient and practice characteristics with prescriptions for newer long-acting insulins (Stata SE version 16.1). To examine inter-practice variation, multilevel models with patients (level 1) clustered within general practices (level 2) were constructed, using a random-effects model.

An empty model (model 1) with only the dependent variable (patients receiving a prescription for a newer insulin) was constructed to establish the a priori chance of a patient receiving a prescription for a newer insulin. In model 2, all patient characteristics were added. Model 3 contained all patient characteristics (level 1) and practice characteristics (level 2).

All variables were included simultaneously, so all independent variables in the multilevel analysis were mutually adjusted for, thereby minimising the risk of confounding by these factors. The likelihood-ratio test was performed to establish the 'fit' of both models. Odds ratios (ORs), 95% confidence intervals (95% CIs), and P-values were calculated to indicate the association between prescriptions for newer insulins and the dependent variables. Intraclass correlation coefficients (ICC) were calculated to indicate the relative

contribution of variation at the practice level (level 2) to the total variation. Missing values were considered as an unknown category in the multivariate analysis.

As the patient's main diabetes practitioner was unknown for a subset of patients and prescriptions from secondary care providers could have contributed to the results, an additional multilevel analysis with only those patients with the GP as the main responsible treating physician for T2DM was also performed.

RESULTS

Baseline characteristics

A total of 7757 patients from 282 general practices received a prescription for an intermediate or long-acting insulin (Tables 1 and 2). There were 1159 patients (14.9%) who were insulin-naive. Insulin-naive patients were younger and had a shorter duration of T2DM than the overall population. The patient's main diabetes practitioner was known for 4529/7757 (58.4%) of all patients, 4032/7757 (52.0%) for the GP, and 497/7757 (6.4%) for the specialist.

Patients with newer insulins and practice variation

In total, 25.6% (1983/7757) of all patients received a prescription for one of the newer insulins (14.0% degludec and 11.5% glargine 300 U/mL) (Table 3). The proportion of patients with a prescription for newer insulins was comparable between insulin-naive and non-naive patients.

The median percentage of patients with prescriptions per practice for newer insulins compared with all intermediate and long-acting insulins was 21.2% (IQR 12.5 – 36.4%) (Figure 1), showing considerable practice variation. Differences in prescribing patterns for these two newer insulins can be found in Supplementary Figures S1 and S2 for glargine 300 U/mL and degludec, respectively.

Determinants of patients with prescriptions for newer insulins

The a priori odds for a prescription of a newer insulin was 29% (OR empty model, Table 4). The corresponding ICC was 0.20 (95% CI = 0.17 to 0.25), meaning that 20% of the observed variability could be attributed to differences between practices. There was only a minor decrease in the ICC after including both patient and practice characteristics (from 0.20 to 0.19), suggesting that most of the practice variation could not be explained by the factors included in the model (data not shown).

Table 1: Baseline characteristics of patients.

Characteristic	All patients (n = 7757)	Insulin-naive patients (n = 1159)
Sex, n (%)		
Male	4268 (55.0)	647 (55.8)
Female	3489 (45.0)	512 (44.2)
Age, years, mean (SD)	67.4 (11.0)	65.8 (12.0)
Age, in categories, *n* (%)		
40 – 55 years	1221 (15.7)	258 (22.3)
56 – 70 years	3324 (42.9)	464 (40.0)
71 – 85 years	2859 (36.9)	376 (32.4)
≥ 86 years	353 (4.6)	61 (5.3)
Number of chronic diseases, mean (SD)	3.7 (1.8)	3.5 (1.8)
Chronic diseases, in categories		
0 – 1 diseases	665 (8.6)	127 (11.0)
2 – 4 diseases	4882 (62.9)	746 (64.4)
≥ 5 diseases	2210 (28.5)	286 (24.7)
Duration of T2DM, years, mean (SD)	13.1 (6.1)	9.9 (5.9)
Duration of T2DM, in categories		
0 – 5 years	708 (9.1)	256 (22.1)
6 – 10 years	1624 (20.9)	309 (26.7)
11 – 15 years	2217 (28.6)	308 (26.6)
16 – 20 years	1465 (18.9)	129 (11.1)
≥ 21 years	790 (10.2)	41 (3.5)
Unknown	953 (12.3)	116 (10.0)
Number of blood glucose lowering drugs, mean (SD)	1.5 (0.62)	1.9 (0.73)
Drug		
Metformin	7098 (91.5)	1033 (89.1)
Sulfonylurea	3502 (45.1)	863 (74.5)
Dipeptidyl peptidase-4 inhibitors	286 (3.7)	167 (14.4)
Glucagon-like peptide-1 receptor agonists	399 (5.1)	74 (6.4)
Sodium-glucose co-transporter 2 inhibitors	306 (3.9)	63 (5.4)
Acarbose	15 (0.2)	2 (0.2)
Meglitinides	13 (0.2)	1 (0.1)
Thiazolidinediones	31 (0.4)	8 (0.7)

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

Table 2: Baseline characteristics of practices.

Characteristic	All patients		Insulin-naive patients	
	Practices (n = 282)	Patients (n = 7757)	Practices (n = 262)	Patients (n = 1159)
Type of practice, n (%)				
Single-handed practice	67 (23.8)	1534 (19.8)	61 (23.3)	209 (18.0)
Duo practices	95 (33.7)	1939 (25.0)	86 (32.8)	278 (24.0)
Group practices	101 (35.8)	3852 (49.7)	97 (37.0)	598 (51.6)
Unknown	19 (6.7)	432 (5.6)	18 (6.9)	74 (6.4)
Dispensing practice[a], n (%)	8 (2.8)	185 (2.4)	7 (2.7)	24 (2.1)
Practice size, mean number of patients (SD)	—	3902.5 (2402.0)	—	3964.7 (2419.7)
Practice size groups[b], n (%)				
Small	94 (33.3)	1592 (20.5)	78 (29.8)	206 (17.8)
Medium	94 (33.3)	1948 (25.1)	90 (34.4)	307 (26.5)
Large	94 (33.3)	4217 (54.4)	94 (35.9)	646 (55.7)
Degree of urbanisation (location of practice), n (%)				
Very strong	71 (25.2)	2184 (28.2)	69 (26.3)	389 (33.6)
Strong	69 (24.5)	1864 (24.0)	62 (23.7)	267 (23.0)
Moderate	64 (22.7)	1799 (23.2)	60 (22.9)	244 (21.1)
Little	44 (15.6)	1143 (14.7)	41 (15.6)	172 (14.8)
Not	34 (12.1)	767 (9.9)	30 (11.5)	87 (7.5)
SES (location of practice), n (%)				
Low	94 (33.3)	2944 (38.0)	92 (35.1)	420 (36.2)
Moderate	94 (33.3)	2618 (33.8)	85 (32.4)	387 (33.4)
High	94 (33.3)	2195 (28.3)	85 (32.4)	352 (30.4)
% aged ≥ 70 years[c]				
Low	94 (33.3)	2382 (30.7)	87 (33.2)	376 (32.4)
Moderate	94 (33.3)	2483 (32.0)	85 (32.4)	387 (33.4)
High	94 (33.3)	2892 (37.3)	90 (34.4)	396 (34.2)

SD = standard deviation, SES = socioeconomic status.

[a] Status was unknown for 12 practices.

[b] Small: 1337 – 2599 patients; medium 2601 – 3782 patients; large 3828 – 16923 patients.

[c] Low: < 12.6%; medium = 12.7 – 16.2%; high > 16.2%.

Table 3: Number of patients with a prescription for intermediate and long-acting insulins.

Type of insulin	All patients, n (%) (n = 7757)	Insulin-naive patients, n (%) (n = 1159)
Newer insulins	1983 (25.6)	282 (24.3)
Glargine 300 U/ml	895 (11.5)	120 (10.4)
Degludec	1088 (14.0)	162 (14.0)
Other insulins	5774 (74.4)	877 (75.7)
NPH-insulin	1330 (17.1)	303 (26.1)
Glargine 100 U/ml	3516 (45.3)	501 (43.2)
Detemir	928 (12.0)	73 (6.3)

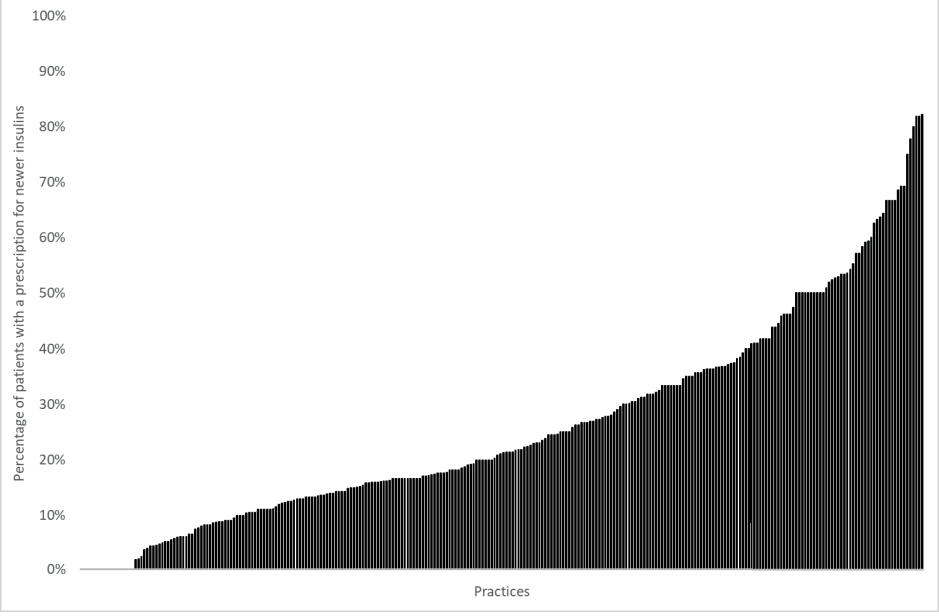

Figure 1: Percentage of patients with a prescription for a newer insulin relative to all prescriptions for intermediate or long-acting insulins. The x-axis shows the practices, the y-axis represents the percentage of patients with prescriptions for newer insulins. Each bar represents one practice. Median = 21.2%, interquartile range (IQR) = 12.5 - 36.4%.

Some factors were associated with prescriptions for newer insulins. At the patient level, female sex (OR 0.77, 95% CI = 0.69 to 0.87), prescriptions for metformin (OR 0.66, 95% CI = 0.53 to 0.82) or sulfonylurea (OR 0.58, 95% CI = 0.51 to 0.66), and older age (OR 0.22, 95% CI = 0.15 to 0.34, for patients aged ≥ 86 years compared with patients aged 40 – 55 years) were inversely associated with prescriptions for newer insulins (Table 4).

Table 4: Results of multivariate analysis.

	Empty model		Model 1		Model 2	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Overall outcome	0.29**	0.26 to 0.33	—	—	—	—
Female sex	—	—	0.77**	0.69 to 0.87	0.77**	0.69 to 0.87
Age, years						
40 – 55 years	Reference	—	—	—	—	—
56 – 70 years	—	—	0.70**	0.58 to 0.85	0.70**	0.58 to 0.85
71 – 85 years	—	—	0.38**	0.31 to 0.47	0.38**	0.30 to 0.47
≥ 86 years	—	—	0.23**	0.15 to 0.34	0.22**	0.15 to 0.34
Chronic disease						
0 – 1 chronic diseases	Reference	—	—	—	—	—
2 – 4 chronic diseases	—	—	1.15	0.93 to 1.43	1.15	0.93 to 1.43
≥ 5 chronic diseases	—	—	1.27*	1.00 to 1.62	1.27	1.00 to 1.62
Years since T2DM diagnosis						
0 – 5 years T2DM	Reference	—	—	—	—	—
6 – 10 years T2DM	—	—	1.10	0.88 to 1.38	1.11	0.89 to 1.39
11 – 15 years T2DM	—	—	0.98	0.78 to 1.23	0.99	0.79 to 1.24
16 – 20 years T2DM	—	—	0.94	0.73 to 1.20	0.94	0.74 to 1.21
≥ 21 years T2DM	—	—	1.24	0.93 to 1.64	1.24	0.93 to 1.64
Unknown[c]	—	—	—	—	—	—
Prescription for metformin	—	—	0.66**	0.53 to 0.82	0.66**	0.53 to 0.82
Prescription for sulfonylurea	—	—	0.58**	0.51 to 0.66	0.58**	0.51 to 0.66
Prescription for DPP-4 inhibitors, GLP-1 receptor agonists, or SGLT2 inhibitors	—	—	3.12**	2.65 to 3.68	3.10**	2.63 to 3.66
Type of practice						
Single-handed practice	Reference	—	—	—	—	—
Duo practices	—	—	—	—	0.87	0.60 to 1.25
Group practices	—	—	—	—	0.91	0.61 to 1.37
Unknown[a]	—	—	—	—	—	—
Dispensing practice	—	—	—	—	1.78**	1.03 to 3.10
Practice size						
Small practice size	Reference	—	—	—	—	—
Medium practice size	—	—	—	—	1.49**	1.07 to 2.08
Large practice size	—	—	—	—	0.80	0.55 to 1.17

Table 4: Results of multivariate analysis. (continued)

	Empty model		Model 1		Model 2	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Urbanisation						
Very strong urbanisation	Reference	—	—	—	—	—
Strong urbanisation	—	—	—	—	1.26	0.86 to 1.84
Moderate urbanisation	—	—	—	—	1.01	0.69 to 1.46
Little urbanisation	—	—	—	—	0.87	0.56 to 1.33
No urbanisation	—	—	—	—	0.99	0.61 to 1.61
SES						
Low SES	Reference	—	—	—	—	—
Moderate SES	—	—	—	—	0.90	0.65 to 1.24
High SES	—	—	—	—	0.85	0.62 to 1.17
Patients ≥ 70 years						
Low number of patients ≥ 70 years	Reference	—	—	—	—	—
Moderate number of patients ≥ 70 years	—	—	—	—	1.26	0.91 to 1.74
High number of patients ≥ 70 years	—	—	—	—	1.49**	1.08 to 2.05

95%CI = 95% Confidence Interval, DPP-4 = dipeptidyl peptidase-4, GLP-1 = glucagon-like peptide-1, OR = odds ratio, SES = socioeconomic status, SGLT2 = sodium-glucose co-transporter 2, T2DM = type 2 diabetes mellitus.

[a] Data not shown.

** P = 0.05.*

*** P < 0.001.*

Prescriptions for newer blood glucose lowering drugs other than insulins (dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium-glucose co-transporter 2 (SGLT2) inhibitors) were the strongest predictor for a prescription for newer insulins: OR 3.10 (95% CI = 2.63 to 3.66). No significant association between prescriptions for newer insulins and the number of chronic diseases nor duration of T2DM was found (Table 4).

GPs in practices that dispense medication themselves prescribed newer insulins more often (OR 1.78, 95% CI = 1.03 to 3.10) (Table 4). Other practice characteristics were not consistently related to the prescriptions for newer insulins.

The multivariate analysis for patients with the GP as main practitioner consisted of 4032 patients in 213 practices. No relevant differences were observed compared with the main analyses (Supplementary Table S1).

DISCUSSION

Summary

In Dutch primary care, approximately a quarter of patients with T2DM with intermediate or long-acting insulins were prescribed the newer long-acting insulins insulin degludec or insulin glargine 300 U/ml, in spite of the current guideline advising other intermediate or long-acting insulins [5]. Practice variation was extensive and largely remained after correction for patient and practice characteristics. Except for dispensing practices, no practice characteristics were unambiguously related to the prescription of newer insulins.

Male patients, younger patients, and patients with prescriptions for other newer blood glucose lowering agents (which do not have a prominent place in the Dutch guideline for T2DM) were more likely to receive a prescription for newer insulins. Patients with prescriptions for metformin or sulfonylurea were less likely to receive a prescription for newer insulins.

It therefore seems that guideline adherence in an earlier stage of T2DM treatment (that is, the prescription of metformin, sulfonylurea but not the other newer agents) is associated with guideline adherence in the later stages of T2DM management.

The major part of practice variation could not be explained. Therefore, other determinants are likely to have a significant influence on the prescription of newer insulins in primary care.

Strengths and limitations

The main strength of this study is the use of a large and representative database from which medication prescriptions as well as patient and practice characteristics could be retrieved, thus avoiding selection bias, which might be inherent to population surveys [13]. The large number of patients (n = 7757) and general practices (n = 282) contributed to stable and robust multilevel models.

There are, however, some limitations. As only a selection of patient and practice characteristics were included in this study, it is not known to which extent other factors (for example, the patient's health status) contributed to the practice variation, and may confound the present results. Furthermore, it was not possible to distinguish insulin prescriptions by GPs from prescriptions by specialists. Although the main practitioner was identified for almost 60% of the included patients, it was not known whether this physician had indeed initiated insulin therapy. Nevertheless, as the analysis that

was restricted to patients with the GP as main practitioner yielded similar results, a prominent role for differences between prescribers is unlikely. Finally, as diagnosis was not always recorded accurately, it was not possible to distinguish T2DM from T1DM based on recorded episodes, and the date of diagnosis was not always recorded accurately. However, as the analysis selected by age (≥ 40 years) and by prescriptions for other blood glucose lowering drugs than insulin, the possibility of including patients with T1DM was minimal.

Comparison with existing literature

Most studies on insulin use focused on between-class variation (that is, comparison with the use of rapid-acting insulins and premixed insulins) rather than the in-between class variation [19–25].

A recent analysis from the UK showed that prescription rates for long-acting insulins increased between 2003 and 2018, whereas prescription rates of NPH-insulin decreased. In the UK, of all patients who started degludec between 2013 – 2018, 38% started in 2018, indicating ongoing growth in uptake after its introduction in 2013 [26].

An analysis by Zhang et al. of 5034 American patients with T2DM initiating insulins between 2014 and 2017 indicated that 6.5% used one of the newer insulins [27]. Although there are substantial differences between the healthcare systems in the US and the Netherlands, the findings in the current study (which is more recent) of 26.0% might reflect increasing uptake over time. According to Zhang et al., users of newer insulins more often used more medications at baseline and were more likely to have experience with GLP-1 receptor agonists [27].

Brunetti et al. found that users of insulin degludec were more likely to have used other blood glucose lowering drugs before the initiation of insulin [26]. The positive association with prescriptions for other newer blood glucose lowering agents was confirmed in the present study. Of note, in the current study prescriptions for metformin and sulfonylurea were found to be inversely related. Although in this study any association with the number of other medicines was not investigated, the lack of association with chronic diseases is not supportive for a strong association.

In the Netherlands, guideline adherence is generally high [8,9] and it is therefore remarkable that a quarter of patients with intermediate or long-acting insulins were prescribed non-recommended newer insulins. The rapid uptake shows similarities with earlier investigations towards the uptake of the first generation of insulin analogues. After their market introduction, insulin glargine 100 U/ml and insulin detemir were rapidly

adopted, resulting in increasing dispensing rates and healthcare costs [23,25,28–30]. Significant regional variations in the use of the — at that moment — newer insulins were found [23,28].

Patient-level factors, such as age and comorbidities, were thought to have a significant impact on the prescription rates [28], a suggestion that is only partially confirmed in the current investigation. The first-generation insulin analogues were more often adopted in internal medicine practices than in general practices. Owing to similarities in rapid uptake of the first and second generations of insulin analogues, the lessons learned from the uptake of first-generation insulin analogues will most likely also apply to the current situation.

The factors associated with the use of new medicines may vary between therapeutic areas [1]. In line with the current findings, a recent analysis of the use of new medicines, irrespective of therapeutic area, in Switzerland found that male sex and younger age enhanced the probability of using new medicines, whereas the number of comorbidities had little impact [12]. In contrast with the current findings, the practice location and proportion of older people in general practice have also been associated with the use of new medicines [11]. Other factors, such as strong scientific commitment, high exposure to marketing, and extensive communication with colleagues, were also strongly associated with the use of (all) new medicines [1]. As the current study could not investigate those determinants, it is not clear whether these factors also contribute to the prescriptions for newer insulins. As the majority of practice variation could not be explained by the determinants investigated in the current study, it is likely that external influences also affected the prescription of newer insulins.

Implications for research and practice

The inter-practice variation in the prescription of newer insulins is large and could only be partially explained by patient- and practice-related differences. Therefore, more research into the reasons for non-adherence to guidelines is warranted, keeping in mind that physician beliefs and attitudes towards newer medicines may play a prominent role. This could lead to both relevant insights for guideline makers as well as directions for physician-centred interventions to stimulate qualitative and cost-effective prescribing behaviour.

In conclusion, in Dutch general practice, a substantial number of patients with T2DM received prescriptions for newer insulins, which are not recommended by the current guideline. After correcting for patient and practice characteristics, practice variation remained substantial. Other factors, such as physician beliefs and attitudes, are

therefore likely to influence the prescription of newer insulins and there is a need for further research to examine this.

REFERENCES

1. Lubloy A (2014) Factors affecting the uptake of new medicines: a systematic literature review. BMC Health Serv Res 14, 469.
2. Kozyrskyj A, Raymond C, Racher A (2007) Characterizing early prescribers of newly marketed drugs in Canada: a population-based study. Eur J Clin Pharmacol 63, 6, 597–604.
3. Dent TH, Hawke S (1997) Too soon to market. BMJ 315, 7118, 1248–1249.
4. National Institute for Health and Care Excellence (2015) Type 2 diabetes in adults: management NG28 (NICE, London) https://www.nice.org.uk/guidance/ng28 (accessed 1 Apr 2022).
5. Netherlands General Practitioners Association (NHG) (2018) NHG-Standaard diabetes mellitus type 2 [M01], https://richtlijnen.nhg.org/standaarden/diabetes-mellitus-type-2 (accessed 1 Apr 2022) (In Dutch).
6. Davies MJ, D'Alessio DA, Fradkin J, et al. (2018) Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 41, 12, 2669–2701.
7. van Avendonk MJ, Gorter KJ, van den Donk M, Rutten GE (2009) Insulin therapy in type 2 diabetes is no longer a secondary care activity in the Netherlands. Prim Care Diabetes 3, 1, 23–28.
8. Lugtenberg M, Burgers JS, Besters CF, et al. (2011) Perceived barriers to guideline adherence: a survey among general practitioners. BMC Fam Pract 12, 98.
9. van Dijk L, de Jong JD, Westert GP, de Bakker DH (2011) Variation in formulary adherence in general practice over time (2003–2007). Fam Pract 28, 6, 624–631.
10. Healthcare Institute Netherlands GIP databank, [In Dutch]. https;//www.gipdatabank.nl (accessed 1 Apr 2022).
11. Tamblyn R, McLeod P, Hanley JA, et al. (2003) Physician and practice characteristics associated with the early utilization of new prescription drugs. Med Care 41, 8, 895–908.
12. Decollogny A, Piaget-Rossel R, Taffe P, Eggli Y (2018) Determinants of new drugs prescription in the Swiss healthcare market. BMC Health Serv Res 18, 1, 9.
13. Nivel Nivel Primary Care Database, https://www.nivel.nl/en/nivel-zorgregistraties-eerste-lijn/nivel-primary-care-database (accessed 28 April 2022).
14. Lo-Ciganic W, Zgibor JC, Ruppert K, et al. (2011) Identifying type 1 and type 2 diabetic cases using administrative data: a tree-structured model. J Diabetes Sci Technol 5, 3, 486–493.
15. Sinnige J, Korevaar JC, Westert GP, et al. (2015) Multimorbidity patterns in a primary care population aged 55 years and over. Fam Pract 32, 5, 505–513.
16. Nielen MMJ, Spronk I, Davids R, et al. (2019) Estimating morbidity rates based on routine electronic health records in primary care: observational study. JMIR Med Inform 7, 3, e11929.
17. Sinnige J, Braspenning JC, Schellevis FG, et al. (2016) Inter-practice variation in polypharmacy prevalence amongst older patients in primary care. Pharmacoepidemiol Drug Saf 25, 9, 1033–1041.
18. Knol F, Boelhouwer J, Veldheer V (2012) Statusontwikkeling van wijken in Nederland 1998–2010 (Social and Cultural Planning Office, The Hague) [Status development of neighbourhoods in the Netherlands 1998–2010].
19. Ogbera AO, Kuku SF (2012) Insulin use, prescription patterns, regimens and costs — a narrative from a developing country. Diabetol Metab Syndr 4, 1, 50.
20. Olamoyegun MA, Akinlade AT, Ala OA (2018) Audit of insulin prescription patterns and associated burden among diabetics in a tertiary health institution in Nigeria. Afr Health Sci 18, 4, 852–864.

21. Shrestha H, Tamrakar R, Shrestha A, Amatya S (2018) Insulin prescription pattern among type 2 DM patients visiting outpatient department at a tertiary hospital in Kathmandu, Nepal. J Diabetes Endocrinol Assoc Nepal 1, 1, 3–7.
22. Landon BE, Zaslavsky AM, Souza J, Ayanian JZ (2018) Trends in diabetes treatment and monitoring among Medicare beneficiaries. J Gen Intern Med 33, 4, 471–480.
23. Rathmann W, Haastert B, Riebel P, et al. (2007) Prescription of insulin glargine in primary care practices in Germany. Exp Clin Endocrinol Diabetes 115, 4, 252–256.
24. Ikeda S, Crawford B, Sato M (2016) Utilization patterns of insulin therapy and healthcare services among Japanese insulin initiators during their first year: a descriptive analysis of administrative hospital data. BMC Health Serv Res 16, 6.
25. Lipska KJ, Ross JS, Van Houten HK, et al. (2014) Use and out-of-pocket costs of insulin for type 2 diabetes mellitus from 2000 through 2010. JAMA 311, 22, 2331–2333.
26. Brunetti VC, Yu OHY, Platt RW, Filion KB (2021) Initiation of four basal insulins and subsequent treatment modification in people treated for type 2 diabetes in the United Kingdom: changes over the period 2003–2018. Diabet Med 38, 8, e14603.
27. Zhang H, Barner JC, Moczygemba LR, Rascati KL (2020) Assessment of basal insulin adherence using 2 methodologies among Texas Medicaid enrollees with type 2 diabetes. J Manag Care Spec Pharm 26, 11, 1434–1444.
28. Xu Y, Gomes T, Mamdani MM, et al. (2019) Analysis of trends in insulin utilization and spending across Canada from 2010 to 2015. Can J Diabetes 43, 3, 179–185.e1.
29. Heymann AD, Kritz V, Hemo B, et al. (2013) A changed pattern of insulin use following the introduction of basal analog insulin treatment in primary care. Prim Care Diabetes 7, 1, 57–61.
30. Kent DJ, McMahill-Walraven CN, Panozzo CA, et al. (2019) Descriptive analysis of long- and intermediate-acting insulin and key safety outcomes in adults with type 2 diabetes mellitus. J Manag Care Spec Pharm 25, 11, 1162–1171.
31. Diening JAA (1982) Dutch Civil Law. Reason Liabil 7, 39–60.

SUPPLEMENT

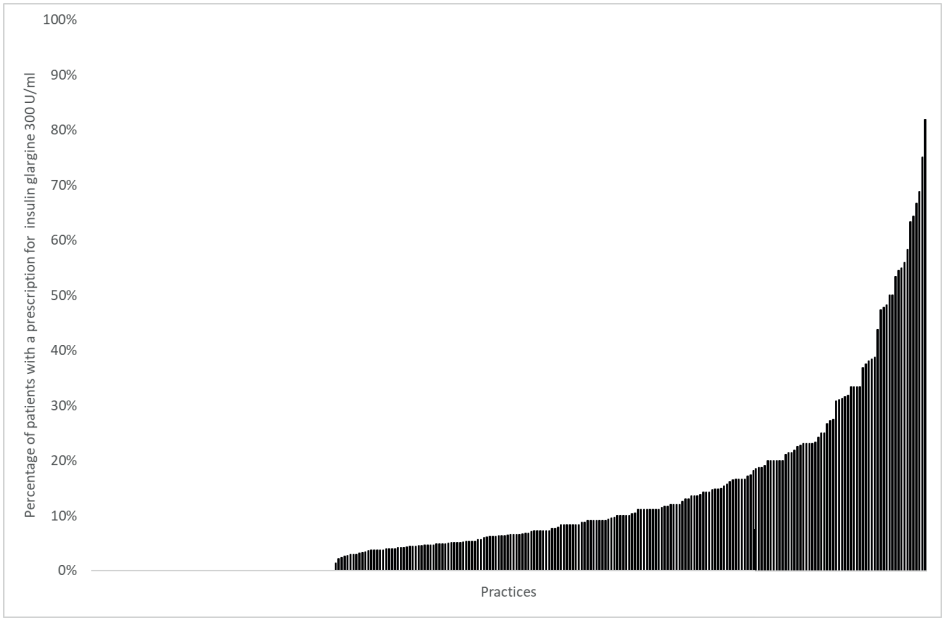

Figure S1: Percentage of patients with a prescription for insulin glargine 300 U/ml relative to all prescriptions for intermediate or long-acting insulins. The x-axis shows the practices, while the y-axis represents the percentage of patients with a prescription for insulin glargine 300 U/ml. Each bar represents one practice.

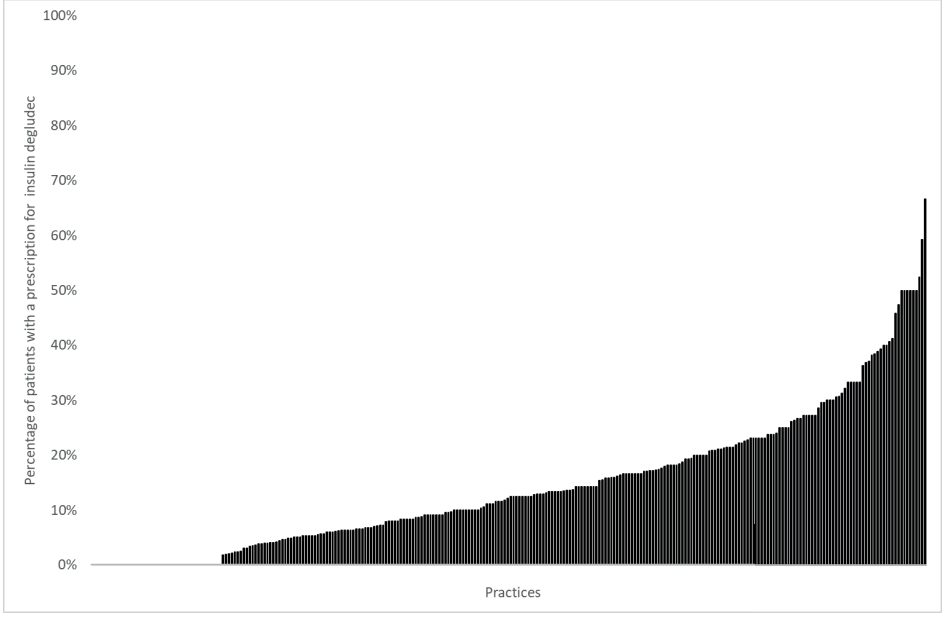

Figure S2: Percentage of patients with a prescription for insulin degludec relative to all prescriptions for intermediate or long-acting insulins. The x-axis shows the practices, while the y-axis represents the percentage of patients with a prescription for insulin degludec. Each bar represents one practice.

Table S1: Results of multivariate analysis for only patients with general practitioner as main practitioner.

	Empty model		Model 1		Model 2	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Overall outcome	0.13*	0.10 - 0.17	—	—	—	—
Female sex	—	—	0.69*	0.57 – 0.84	0.69*	0.57 – 0.84
Age, years						
40 – 55 years	Reference	—	—	—	—	—
56 – 70 years	—	—	0.49*	0.36 – 0.68	0.49*	0.36 – 0.68
71 – 85 years	—	—	0.30*	0.21 – 0.44	0.31*	0.21 – 0.44
≥ 86 years	—	—	0.25*	0.14 – 0.44	0.25*	0.14 – 0.44
Chronic disease						
0 – 1 chronic diseases	Reference	—	—	—	—	—
2 – 4 chronic diseases	—	—	1.14	0.80 – 1.63	1.14	0.80 – 1.62
≥ 5 chronic diseases	—	—	1.16	0.78 – 1.72	1.16	0.78 – 1.72
Years since T2DM diagnosis						
0 – 5 years T2DM	Reference	—	—	—	—	—
6 – 10 years T2DM	—	—	0.97	0.67 – 1.39	0.98	0.68 – 1.42
11 – 15 years T2DM	—	—	0.92	0.64 – 1.34	0.93	0.64 – 1.35
16 – 20 years T2DM	—	—	0.93	0.63 – 1.37	0.93	0.63 – 1.38
≥ 21 years T2DM	—	—	1.08	0.68 – 1.72	1.09	0.69 – 1.73
Unknown[b]	—	—	—	—	—	—
Prescription for metformin	—	—	0.66*	0.46 – 0.95	0.66*	0.46 – 0.95
Prescription for sulfonylurea	—	—	0.76*	0.62 – 0.93	0.76*	0.62 – 0.93
Prescription for DPP-4 inhibitors, GLP-1 receptor agonists, or SGLT2 inhibitors	—	—	2.28*	1.65 – 3.14	2.23*	1.61 – 3.07
Type of practice						
Single-handed practice	Reference	—	—	—	—	—
Duo practices	—	—	—	—	0.60	0.30 – 1.19
Group practices	—	—	—	—	0.55	0.26 – 1.18
Unknown[a]	—	—	—	—	—	—
Dispensing practice	—	—	—	—	2.42*	1.01 – 5.80
Practice size						
Small practice size	Reference	—	—	—	—	—
Medium practice size	—	—	—	—	2.14*	1.13 – 4.05
Large practice size	—	—	—	—	0.93	0.44 – 1.96

Table S1: Results of multivariate analysis for only patients with general practitioner as main practitioner. (continued)

	Empty model		Model 1		Model 2	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Urbanisation						
Very strong urbanisation	Reference	—	—	—	—	—
Strong urbanisation	—	—	—	—	1.69	0.83 – 3.44
Moderate urbanisation	—	—	—	—	1.24	0.63 – 2.46
Little urbanisation	—	—	—	—	0.90	0.39 – 2.08
No urbanisation	—	—	—	—	1.60	0.63 – 4.05
SES						
Low SES	Reference	—	—	—	—	—
Moderate SES	—	—	—	—	0.89	0.47 – 1.67
High SES	—	—	—	—	1.27	0.70 – 2.29
Patients ≥ 70 years						
Low number of patients ≥ 70 years	Reference	—	—	—	—	—
Moderate number of patients ≥ 70 years	—	—	—	—		
High number of patients ≥ 70 years	—	—	—	—		
Variance			2.30 (1.68 – 3.14)		1.87 (1.36 – 2.58)	
ICC			0.41 (0.34 – 0.49)		0.36 (0.29 – 0.44)	
LR-test			p < 0.001		p = 0.0219	

95%CI = 95% Confidence Interval, DPP-4 = dipeptidyl peptidase-4, GLP-1 = glucagon-like peptide-1, ICC = intraclass correlation coefficient, LR-test = likelihood-ratio test, OR = odds ratio, SES = socioeconomic status, SGLT2 = sodium-glucose co-transporter 2, T2DM = type 2 diabetes mellitus.

[a] Data not shown.

** P < 0.001.*

4.2

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

Marloes Dankers
Karin Hek
Aukje K. Mantel-Teeuwisse
Liset van Dijk
Marjorie H.J.M.G. Nelissen-Vrancken

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.

			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	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.

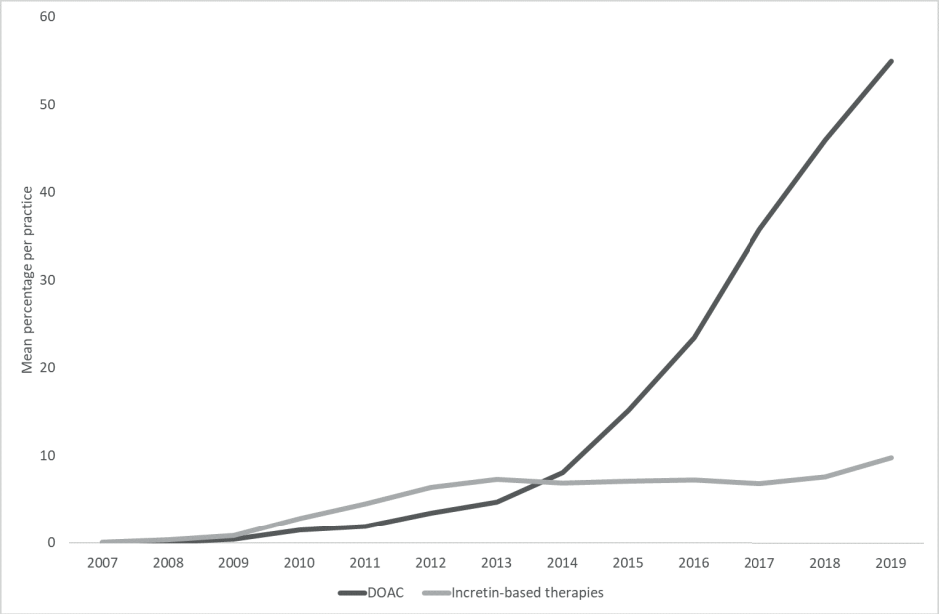

Figure 1: Mean percentage of patients per practice with prescriptions for DOACs and incretin-based therapies compared to all patients with anticoagulants and T2DM medication, respectively.

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.

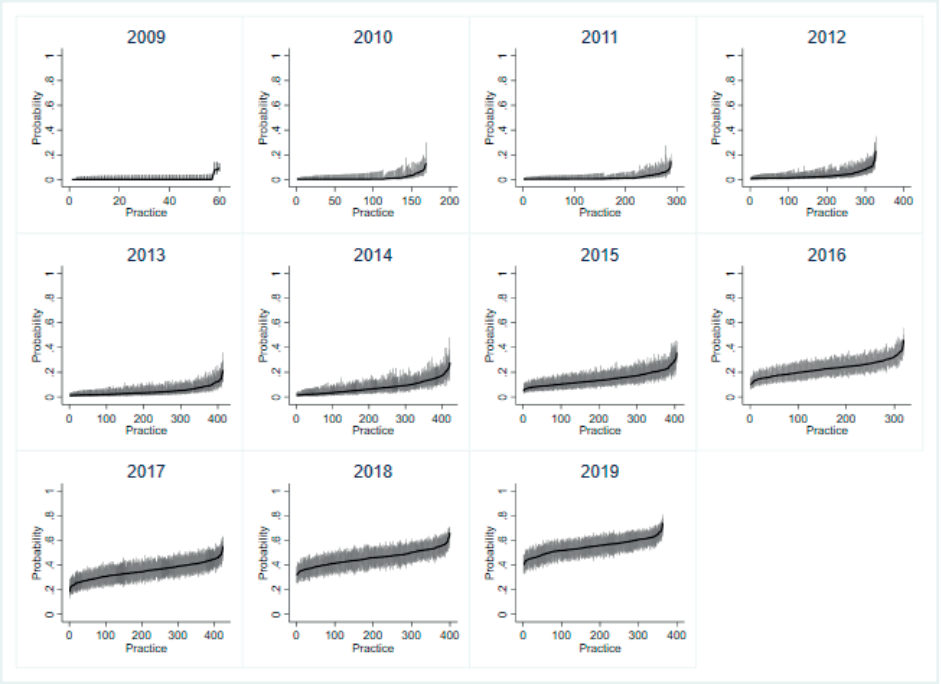

Figure 2: Variation in the prescription of DOACs from 2009 – 2019 (2008 not available due to too few values). The figure shows the variation within a practice (indicated by the length of each bar individually) as well as the variation between practices (indicated by the range of y-values per practice).

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.

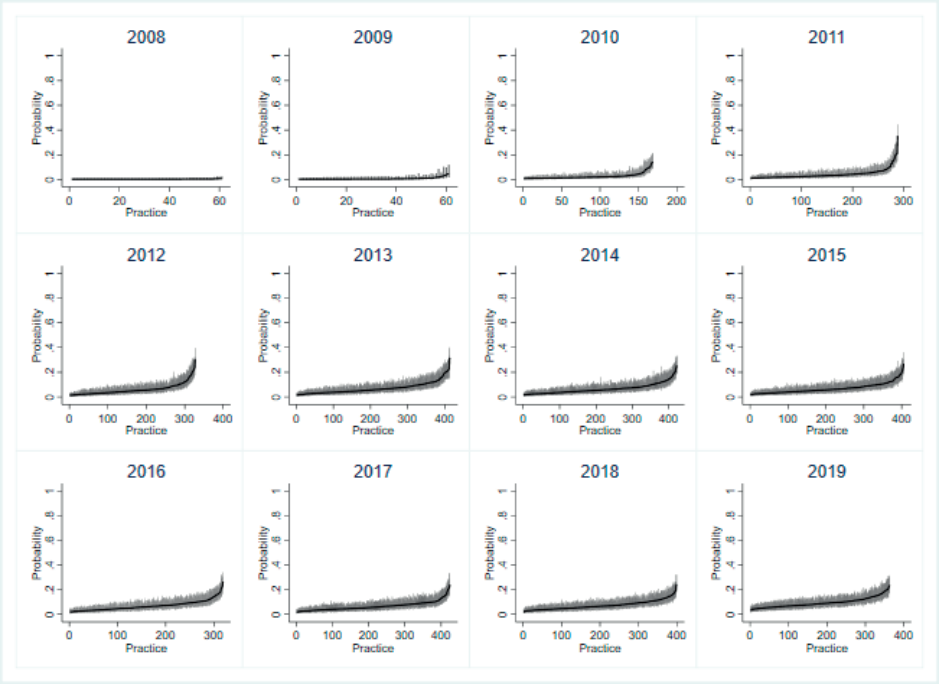

Figure 3: Variation in the prescription of incretin-based therapies from 2008 – 2019 (2007 not available due to too few values). The figure shows the variation within a practice (indicated by the length of each bar individually) as well as the variation between practices (indicated by the range of y-values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

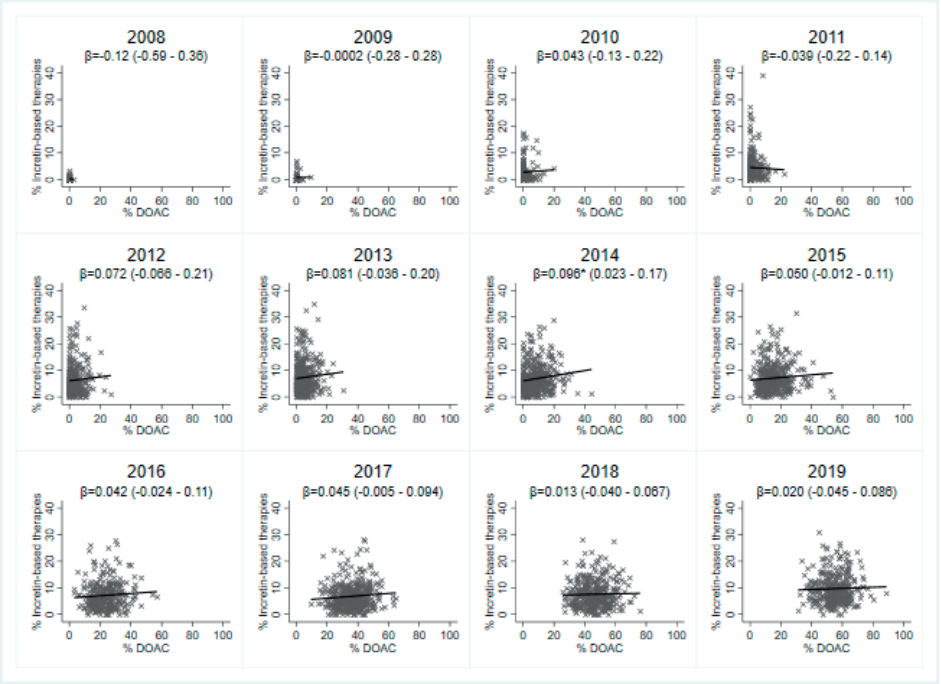

Figure 4: Correlation between prescription of DOACs and incretin-based therapies. The x-axis shows the percentage of patients with prescriptions for DOACs (among all anticoagulant users), the y-axis the percentage of patients with prescriptions for incretin-based therapies (among the total number of 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.

REFERENCES

1. Lichtenberg FR. The impact of new drug launches on longevity: Evidence from longitudinal, disease-level data from 52 countries, 1982-2001. Int J Health Care Finance Econ. 2005;5(1):47-73. doi: 10.1007/s10754-005-6601-7 [doi].
2. Lubloy A. Factors affecting the uptake of new medicines: A systematic literature review. BMC Health Serv Res. 2014;14:469-469. doi: 10.1186/1472-6963-14-469 [doi].
3. Kozyrskyj A, Raymond C, Racher A. Characterizing early prescribers of newly marketed drugs in Canada: A population-based study. Eur J Clin Pharmacol. 2007;63(6):597-604. doi: 10.1007/s00228-007-0277-5 [doi].
4. Decollogny A, Piaget-Rossel R, Taffe P, Eggli Y. Determinants of new drugs prescription in the swiss healthcare market. BMC Health Serv Res. 2018;18(1):9-1. doi: 10.1186/s12913-017-2775-1 [doi].
5. Tamblyn R, McLeod P, Hanley JA, Girard N, Hurley J. Physician and practice characteristics associated with the early utilization of new prescription drugs. Med Care. 2003;41(8):895-908. doi: 10.1097/00005650-200308000-00004 [doi].
6. Inman W, Pearce G. Prescriber profile and post-marketing surveillance. Lancet. 1993;342(8872):658-661. doi: 0140-6736(93)91763-C [pii].
7. Dankers M, Hek K, Nelissen-Vrancken M, Houweling ST, Mantel-Teeuwisse A, van Dijk L. Newer long-acting insulin prescriptions for patients with type 2 diabetes: Prevalence and practice variation in a retrospective cohort study. Br J Gen Pract. 2022;72(719):e430-e436. doi: 10.3399/BJGP.2021.0581 [doi].
8. Garjón FJ, Azparren A, Vergara I, Azaola B, Loayssa JR. Adoption of new drugs by physicians: A survival analysis. BMC Health Serv Res. 2012;12:56-56. doi: 10.1186/1472-6963-12-56 [doi].
9. Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie, (KNMP). G-standaard handelsproducten. kennisbank.knmp.nl. Accessed, April 15, 2022.
10. Lugtenberg M, Burgers JS, Besters CF, Han D, Westert GP. Perceived barriers to guideline adherence: A survey among general practitioners. BMC Fam Pract. 2011;12:98-98. doi: 10.1186/1471-2296-12-98 [doi].
11. van Dijk L, de Jong JD, Westert GP, de Bakker DH. Variation in formulary adherence in general practice over time (2003-2007). Fam Pract. 2011;28(6):624-631. doi: 10.1093/fampra/cmr043 [doi].
12. de Jong LA, Koops M, Gout-Zwart JJ, et al. Trends in direct oral anticoagulant (DOAC) use: Health benefits and patient preference. Neth J Med. 2018;76(10):426-430.
13. Nederlands Huisartsen Genootschap (NHG). NHG-Standaard diabetes mellitus type 2 M01. www.nhg.org. Updated 2018. Accessed, April 15, 2022.
14. Rottenkolber M, Schmiedl S, Ibánez L, et al. Prescribers' compliance with summary of product characteristics of dabigatran, rivaroxaban and apixaban-A european comparative drug utilization study. Basic Clin Pharmacol Toxicol. 2021;128(3):440-454. doi: 10.1111/bcpt.13517 [doi].
15. Overbeek JA, Heintjes EM, Prieto-Alhambra D, et al. Type 2 diabetes mellitus treatment patterns across europe: A population-based multi-database study. Clin Ther. 2017;39(4):759-770. doi: S0149-2918(17)30129-7 [pii].
16. Peeters MT, Vroman F, Schreuder TA, van Oostenbrugge RJ, Staals J. Decrease in incidence of oral anticoagulant-related intracerebral hemorrhage over the past decade in the Netherlands. Eur Stroke J. 2022;7(1):20-27. doi: 10.1177/23969873211062011 [doi].

17. van den Heuvel, J. M., Hövels AM, Büller HR, Mantel-Teeuwisse AK, de Boer A, Maitland-van der Zee, A. H. NOACs replace VKA as preferred oral anticoagulant among new patients: A drug utilization study in 560 pharmacies in the netherlands. Thromb J. 2018;16:7-y. eCollection 2018. doi: 10.1186/s12959-017-0156-y [doi].
18. Harskamp RE, Himmelreich JCL, Wong GWM, Teichert M. Prescription patterns of direct oral anticoagulants and concomitant use of interacting medications in the netherlands. Neth Heart J. 2021;29(9):451-459. doi: 10.1007/s12471-021-01612-4 [doi].
19. Rafaniello C, Arcoraci V, Ferrajolo C, et al. Trends in the prescription of antidiabetic medications from 2009 to 2012 in a general practice of southern italy: A population-based study. Diabetes Res Clin Pract. 2015;108(1):157-163. doi: S0168-8227(15)00006-6 [pii].
20. Flory JH, Li J, Dawwas GK, Leonard CE. Compared to commercially insured patients, medicare advantage patients adopt newer diabetes drugs more slowly and adhere to them less. Endocrinol Diabetes Metab. 2021;4(3):e00245. doi: 10.1002/edm2.245 [doi].
21. Mardetko N, Nabergoj Makovec U, Locatelli I, Janez A, Kos M. Uptake of new antidiabetic medicines in 11 european countries. BMC Endocr Disord. 2021;21(1):127-3. doi: 10.1186/s12902-021-00798-3.
22. Jones MI, Greenfield SM, Bradley CP. Prescribing new drugs: Qualitative study of influences on consultants and general practitioners. BMJ. 2001;323(7309):378-381. doi: 10.1136/bmj.323.7309.378 [doi].
23. Prosser H, Almond S, Walley T. Influences on GPs' decision to prescribe new drugs-the importance of who says what. Fam Pract. 2003;20(1):61-68. doi: 10.1093/fampra/20.1.61.
24. Dybdahl T, Andersen M, Søndergaard J, Kragstrup J, Kristiansen IS. Does the early adopter of drugs exist? A population-based study of general practitioners' prescribing of new drugs. Eur J Clin Pharmacol. 2004;60(9):667-672. doi: 10.1007/s00228-004-0797-1.
25. Lava SAG, Simonetti GD, Ferrarini A, Ramelli GP, Bianchetti MG. Regional differences in symptomatic fever management among paediatricians in switzerland: The results of a cross-sectional web-based survey. Br J Clin Pharmacol. 2013;75(1):236-243. doi: 10.1111/j.1365-2125.2012.04311.x.
26. van den Donk M, Opstelten W, Dutch College of General Practioners, (NHG). Important changes in the dutch college of general practitioners (NHG) practice guideline 'atrial fibrillation': Revised practice guideline issued. Ned Tijdschr Geneeskd. 2013;157(38):A6697.
27. Diening JAA. Dutch Civil Law. Reason. Liabil. 1982, 7, 39–60.

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.*

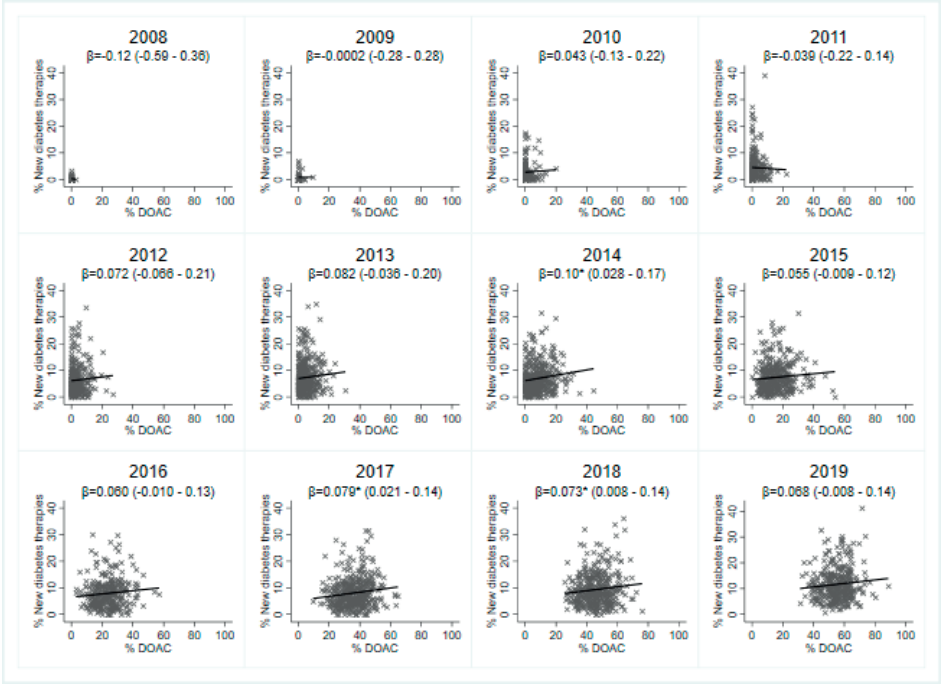

Figure S1: Correlation between prescription of DOACs and new diabetes therapies (DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors). The x-axis shows the percentage of patients with prescriptions for DOACs (among all anticoagulant users), the y-axis the percentage of patients with prescriptions 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.*

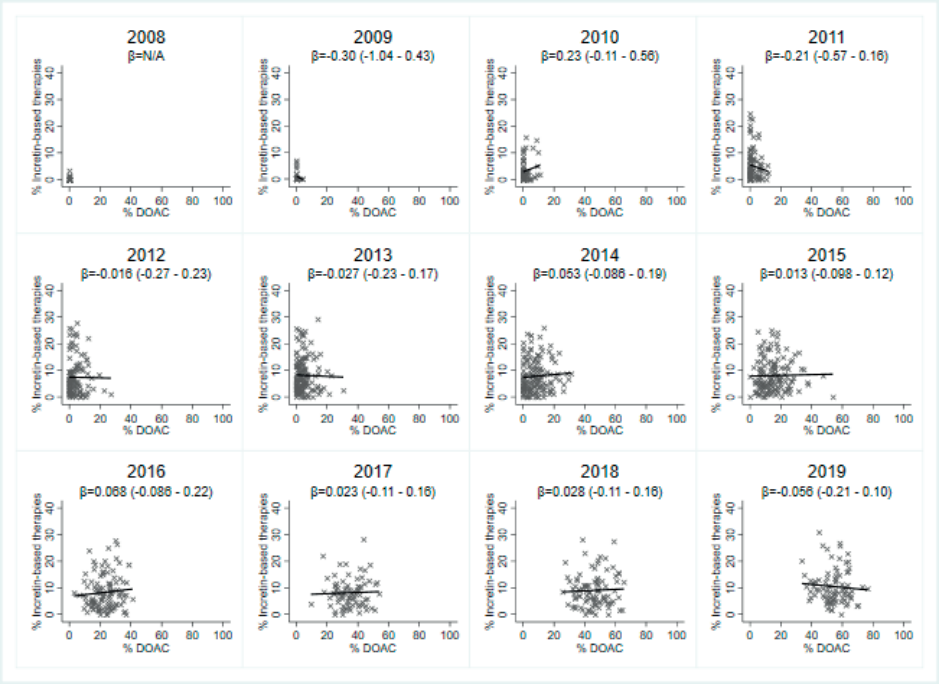

Figure S2: Correlation between prescription of DOACs and incretin-based therapies for solo practices only. The x-axis shows the percentage of patients with prescriptions for DOACs (among all anticoagulant users), the y-axis the percentage of patients with prescriptions for incretin-based therapies (among 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.*


5

General discussion

New medicines can have advantages in terms of morbidity, longevity and quality of life [1,2]. However, the use of new medicines can also involve negative aspects, including safety risks and increasing healthcare costs [3,4]. Rational use of new medicines in primary care is therefore important to maintain quality of care and prevent increasing healthcare costs. The overall aim of this thesis was to gain insight into the perspectives and practices of healthcare professionals in primary care towards new medicines, focusing on the assessment criteria of new medicines, factors that are associated with the decision of individual healthcare professionals to prescribe new medicines and the actual prescription patterns of new medicines in primary care.

MAIN FINDINGS FROM THIS THESIS

Assessment criteria

Chapter 2 of this thesis focused on healthcare professionals' preferences for outcomes and minimal clinically important differences (MCIDs) used in the evaluation of new medicines in relation to the standards used by registration authorities and professional organisations. With questionnaires, the preferred endpoints and MCIDs for chronic obstructive pulmonary disease (COPD) and type 2 diabetes mellitus (T2DM) by a sample of Dutch healthcare professionals, including general practitioners, pharmacists and practice nurses, were investigated. As for COPD (**2.1**), the preferred endpoints by healthcare professionals corresponded to the clinical endpoints which the European Medicines Agency (EMA) uses for the evaluation of new medicines. However, healthcare professionals preferred higher MCIDs for dyspnea and health status than currently used by the EMA, meaning that healthcare professionals were more strict in defining clinical relevance on these endpoints than the registration authority. This stricter view on what is considered a clinically relevant difference was also seen for assessment criteria for new T2DM medicines (**2.2**). Compared to the professional organisation that developed the Dutch T2DM guideline, healthcare professionals had a stricter view on the importance of the outcomes HbA1c and hospital admissions and the MCIDs for mortality and other hypoglycemia. An additional finding of this study was that healthcare professionals experienced difficulties estimating the desired relative risk measures. A substantial part of the respondents had no opinion or did not answer the questions about MCIDs and the wide range of answers given indicated interpretation difficulties of especially relative outcome measures.

Factors impacting decision-making

Chapter 3 of this thesis focused on internal and external factors that are associated with the decision of individual healthcare professionals to prescribe new medicines. In focus

group discussions with primary care practitioners, the reasons for the prescription of new, non-recommended insulins were investigated (**3.1**). Non-adherence to prescription guidelines was largely driven by argumentation in the domain of attitudes, with lack of agreement with the guideline recommendations and different interpretation of evidence as most prominent perspectives. External factors, including patients' abilities to use the insulin as instructed, contradictory guidelines, continuation of prescriptions from other healthcare professionals and marketing by pharmaceutical companies were also impacting the decision to prescribe new insulins. The impact of the pharmaceutical industry was further investigated in **3.2**, focusing on the persuasion strategies present in 69 unique direct marketing materials from pharmaceutical companies, collected by general practices in the Netherlands. All seven persuasion strategies defined by Cialdini [5] and one newly identified strategy, namely emotional pressure, were present in the materials, with liking, emotional pressure and authority as the most prominent strategies. The presence of eight different persuasion strategies indicates that pharmaceutical companies use a wide range of strategies to influence the attitudes of healthcare professionals towards prescribing their (new) medicines and that healthcare professionals should become more aware of these attempts to influence their prescription behaviour.

Prescription of new medicines

Chapter 4 of this thesis focused on prescription patterns of new medicines in Dutch general practices. In retrospective cohort studies with data from Nivel Primary Care Database, the prescription of new insulins, 3 – 5 years after their introduction, and uptake of anticoagulants and incretin-based therapies during 2007 – 2019 were investigated. New insulins (**4.1**) accounted for a median of 21.2% (interquartile range (IQR) = 12.5 – 36.4%) of all insulin prescriptions. Dispensing practices, male patient sex, younger age of patients, and prescriptions for other new blood glucose lowering agents were positively associated with newer insulin prescriptions. On the contrary, patients with prescriptions for metformin or sulphonylurea were less likely to receive a prescription for newer insulins. Large variation between general practices existed, even after correction for differences at patient and practice level. As for direct-acting oral anticoagulants (DOACs) and incretin-based medicines (**4.2**), the uptake patterns were markedly different from each other. For DOACs, the uptake remained very low for a couple of years and then substantially increased. For incretin-based therapies, the uptake steadily increased during the first years of introduction and then stabilized. No correlation was found between the uptake of both new classes of medicines, meaning that early adoption of one type of new medicine could not predict the early adoption of other new medicines.

In this last chapter, the results will be placed in a broader perspective. Two main conclusions derived from this thesis will be further discussed, followed by recommendations based on these conclusions.

THE UPTAKE OF NEW MEDICINES IN PRIMARY CARE IS UNPREDICTABLE

This thesis shows that the uptake of new medicines in primary care is unpredictable and no clear profile of the early adopter of new medicines exists, as we found great differences between the adoption of three different groups of new medicines (**4.1, 4.2**). Also, a large variation between practices exists in the prescription of new medicines in primary care, which cannot be explained by variation in practice and patient characteristics (**4.1**). Finally, early adoption of one group of new medicines could not predict the early adoption of another group of new medicines, although we did find a correlation between new medicines intended for the same condition (**4.1, 4.2**).

Different adoption profiles

Among the three different medicine groups in this thesis, new insulins were rapidly adopted which resulted in more prescriptions than expected based on the guideline recommendations (**4.1**). The adoption of DOACs went slowly in the first years after their introduction, but then rapidly increased (**4.2**). And finally, the incretin-based therapies showed a rapid adoption in the first years, followed by a period of stabilization (**4.2**).

Despite their different adoption profiles, DOACs and incretin-based therapies have in common that their adoption in the Netherlands was generally slower than in other countries [6-9]. Differences in uptake between countries can be explained by, among others, changes in country-specific clinical guidelines, national medicines policies and reimbursement decisions [7]. The exact reason for the relative slow uptake of new medicines in the Netherlands is not known. Contributing factors are, among others, an already good-functioning healthcare system, including the Thrombosis Services, leading to a limited need of new therapies [10], a relative long period between registration and reimbursement [9], a well-functioning system of clinical guidelines of which most general practitioners are adherent to [9,11,12] and multiple initiatives aimed at the stimulation of rational use of new medicines [13,14].

Taken into account the generally slow adoption of new medicines in Dutch primary practice [9,15-17], the popularity of new insulins in Dutch primary care is even more remarkable. Three to five years after their introduction, new insulins accounted for more

than a quarter of all insulin prescriptions in primary care (**4.1**). The popularity of those new insulins shows resemblance with the introduction of the insulin analogues almost 20 years ago. Insulin glargine 100 U/ml and insulin detemir were also rapidly adopted, despite professional organisations recommending other insulins [18-23].

The differences in pace of adoption of newer insulins, DOACs and incretin-based medicines correlate with the relative degree of innovation and the place in therapy. New insulins can be considered less innovative than DOACs and incretin-based medicines. New insulins are examples of structural innovations, meaning that they have the same mode of action as already existing insulins. DOACs and incretin-based medicines are pharmacological innovations that focus on a new therapeutic target [24]. Structural innovations are, compared to pharmacological innovations, associated with fewer uncertainties in the benefit-risk balance, which can explain the rapid adoption of newer insulins compared to DOACs and incretin-based therapies. When comparing the uptake profiles of DOACs and incretin-based medicines, their differences might be explained by their different places in therapy. Incretin-based medicines can be *added* to blood-glucose lowering medicines the patient already uses, while DOACs have to *replace* the existent treatment. The addition of a new medicine might be less troublesome to healthcare professionals than the replacement of a familiar medicine with a new one.

Whether the relative degree of innovation is indeed an explanation for the differences in adoption profiles of the studied and other medicines remains to be elucidated. Differences between the relative degree of innovation and the number of adopters in the first months have been described before. However, it can also be argued that medicines with new acting mechanisms are more likely to be rapidly adopted than me-too medicines, because of their greater potential for therapeutic advantages [25]. More studies towards the possible relation between degree of innovation and uptake are warranted.

Practice variation and associated patient and practice characteristics

In addition to the adoption profiles, we also studied practice variation in the prescription of new medicines and the relation with patient and practice characteristics. We concluded that practice variation was large. No strong predictors at patient or practice level for the early adoption of new medicines in primary care were identified (**4.1**, **4.2**).

Variation between practices is common and not problematic in itself, since patients and practices may differ, which calls for different treatments [26]. However, if the prescription of new medicines was solely based on medical reasons, a more balanced distribution between practices would be expected than we found and which was also

found in previous research. For example, in studies among British general practitioners, 42% of prescriptions for new medicines were initiated by 10% of the physicians [27]. The variation in the prescription of new medicines found in our studies was also large, especially in the first years after introduction. Even after adjustment for differences between patient and practice characteristics, we found a substantial part of the variation at the practice level (**4.1**, **4.2**). We identified some patient and practice characteristics (including dispensing state as practice characteristic and sex, age and former use of medicines as patient characteristics) which were associated with the prescription of new medicines. However, the associations were weak and could not explain the large practice variation in the prescription of new medicines (**4.1**). The lack of strong predictors for the early adoption of new medicines in primary care is confirmed in other studies. A systematic review from 2021 found a broad range of factors affecting the uptake of new medicines, which could be grouped into patient, prescriber, medicine, organisational, and external environment factors [28]. Although many factors have been identified, correlations with the early prescription of new medicines are often weak and differ among studies [24,29,30]. Early prescription of new medicines could not be predicted by a vast set of patient and practice characteristics [29]. The idea of the existence of a general profile of 'the early adopter' is therefore questionable [31,32]. Our studies confirm that early adoption of new medicines is not solely dependent on a vast set of patient and practice characteristics and indicate that other factors are important in the understanding of early adoption profiles of new medicines.

Correlation between uptake of new medicines

In addition to the above-mentioned lack of predictive characteristics for the early adoption of new medicines, we did conclude that early adoption of one group of new medicine could not predict the early adoption of another group of new medicines (**4.2**), although a correlation did exist between the early adoption of new medicines meant for the same condition (**4.1**).

In 2004, Dybdahl et al. demonstrated for four new medicine groups (angiotensin II receptor blockers, triptans, selective cyclo-oxygenase-2 antagonists and esomeprazole) that early adoption of one group of new medicines was poorly associated with adoption of other new medicines [31]. This finding was confirmed in our study, in which we failed to relate the prescription of DOACs to the prescription of incretin-based medicines (**4.2**). Interestingly, we did find an association between the adoption of new medicines meant for the same disease (i.e., dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporter 2 (SGLT2) inhibitors on one hand and new insulins on another hand) **(4.1**). These differences might be explained by the concept of domain-specific innovation. This concept describes

the tendency of someone to acquire information and new products within a specific product domain [33]. Domain-specific innovation might explain why early prescription of DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors is associated with early prescription of new insulins, but not DOACs. However, whether domain-specific innovation is indeed the explanation for the patterns found in our studies remains to be elucidated. Former studies showed that prescription of new medicines by general practitioners could not be related to previous prescribing of medicines in the same therapeutic class [32] or self-reported therapeutic interests [34]. In other words, affinity with a therapeutic area is no predictor for the early prescription of new medicines in that therapeutic area, which argues against the concept of domain-specific innovation. It can however not be excluded that an association exists between affinity with *innovations* in a therapeutic area and early prescription of new medicines. This gap in understanding calls for further research.

SCIENTIFIC EVIDENCE PLAYS A LIMITED ROLE IN THE DECISION TO PRESCRIBE NEW MEDICINES

The lack of uniformity and explanatory patient and practice characteristics in the uptake of new medicines in primary care raises the question which considerations of healthcare professionals lead to the prescription of new medicines. This thesis shows that the prescription of new medicines is often driven by non-scientific argumentation. First, we concluded that healthcare professionals found it difficult to interpret and estimate realistic benefits and risks of new medicines (**2.1**, **2.2**). Second, we identified individual attitudes of healthcare professionals towards new medicines as the most important factor in the decision to prescribe new medicines. These attitudes were related to argumentation that often lacked scientific rationale, as was also concluded by healthcare professionals themselves (**3.1**). Third, healthcare professionals are constantly exposed to marketing activities from pharmaceutical companies. Those activities are known to stimulate the prescription of new medicine, rather than to stimulate the *rational* prescription of new medicine (**3.2**).

Interpreting benefit-risk balance

A realistic estimation of the desired benefits and risks should be the scientific basis for the decision to prescribe new medicines by healthcare professionals. However, chapter **2.1** and **2.2** show that a balanced estimation of benefits and risks by healthcare professionals is hampered. If a solid scientific basis exists, alignment between preferences for evaluation criteria among healthcare professionals, and between healthcare professionals and official institutions would be expected. However, healthcare

professionals had in general stricter preferences for evaluation criteria and thresholds for clinical relevance of new COPD and T2DM medicines than official organisations (**2.1**, **2.2**). Moreover, large differences also existed *between* healthcare professionals (**2.1**, **2.2**). Finally, healthcare professionals experienced great difficulties in understanding and estimating risk measures, especially relative risk reductions for T2DM medicines (**2.2**). Taken together, those findings illustrate the difficulties healthcare professionals experience in estimating and interpreting realistic effects of new medicines. These difficulties hamper a balanced evaluation of benefits and risks and may lead to unrealistic expectations and even irrational prescription of new medicines.

Different views from healthcare professionals and official organisations on the clinical relevance of new medicines have been described before [35,36]. As already stated in the general introduction, different evaluation domains to assess new medicines exist at various moments. While official institutions rely on scientific evidence to assess quality, the benefit-risk-balance, cost-effectiveness and additional therapeutic value at population level, an individual healthcare professional has to evaluate what is the best option for an individual patient. Individual considerations can differ from considerations at population level. It has been shown before that decisions in daily practice might be more influenced by short term outcomes at the patient level, while clinical guidelines and regulatory agencies particularly focus on long term outcomes and population level [37,38]. Considering what is best for a patient is of course good clinical practice, as long as it is based on realistic expectations. However, our studies, together with previous research also show that healthcare professionals find it hard to estimate and interpret realistic benefits and harms of medicines [39,40].

Whether the interpretation differences in realistic outcomes and improvements on these outcomes found in our studies led to over- or underestimation of benefits and risks of new medicines was not investigated. Theoretically, both situations are possible, as indicated in the example below.

According to chapter 2.1: healthcare professionals prefer an MCID of 11 points for SGRQ. The MCID used by registration authorities is 4 units. A new COPD medicine improves the SGRQ with 5 units. The EMA therefore concludes that this medicine gives a clinically relevant improvement of health related quality of life.
***Healthcare professional 1** is really interested in new COPD medicines and studies the original clinical study and evaluation by the EMA. She notices that the improvement on SGRQ is 5 units, which she thinks is not clinically relevant. The healthcare professional concludes the new COPD medicine gives no clinically relevant improvement according to her own standards and decides not to prescribe the new COPD medicine to her patients.*
***Healthcare professional 2** reads a short article about the new COPD medicine, stating 'clinically relevant improvement of health related quality of life according to the EMA'. The healthcare professional concludes the new COPD medicine gives a clinically relevant improvement according to an official institution and decides to prescribe the new medicine to her patients. She is unaware that the medicine does not meet her own expectations of clinical relevance, which is set at 11 points.*

Although not investigated in our studies, situation two seems most plausible. General practitioners have been shown to acquire information about new medicines in an opportunistic way, rather than based on active searches of new medicine information [41]. Moreover, the expected consequence, namely the overestimation of benefits is also confirmed in a systematic review towards expectations of clinicians towards treatments, screening and tests. Based on 48 studies, of which 20 focused on treatments, the authors concluded that clinicians rarely had accurate expectations of benefits or harms of medicinal interventions. Both over- and underestimation was present, although benefits were mostly overestimated and harms underestimated. This therapeutic illusion or unjustified enthusiasm could lead to inappropriate use of interventions [42]. The different views of healthcare professionals and registration authorities towards benefits and risks of new medicines have also been described in a study performed by the EMA. They concluded that better communication about benefits and risks of medicines is necessary, given the divergent views and perspectives [43].

Importance of attitude

The attitudes of healthcare professionals play an important role in the decision to prescribe new insulins. Those attitudes markedly differed between professionals and were made up of different argumentation, which often lacked scientific rationale (**3.1**). Previous studies towards reasons for guideline non-adherence have confirmed the importance of individual attitudes of healthcare professionals [11,44]. Specifically for the prescription of new medicines, individual beliefs of healthcare professionals have been related to early prescription, rather than objective evaluation of the literature [30]. In addition, the decision to prescribe new medicines is prone to the mode of exposure to pharmacological information and social influences [41]. The prescription of new, non-guideline recommended new medicines seems therefore mostly dependent on individual choices of healthcare professionals, rather than on robust scientific evidence.

Interestingly, the argumentation used by healthcare professionals to justify the use of new medicines was not only challenged by current scientific evidence, but also by other healthcare professionals. Moreover, some healthcare professionals also tended to challenge their own argumentation (**3.1**). While this might raise even more questions about the sustainability of argumentation, it also indicates that prescription of new medicines can become more aligned and rational by stimulating independent interprofessional communication and discussion. The importance of interprofessional communication has also been shown before. Pharmacotherapy audit meetings (PTAMs), in which general practitioners and community pharmacists exchange information and views about pharmacotherapy with the aim of improving the prescribing and dispensing of medicines, have been shown to be associated with rational use of medicine. Previous

studies have demonstrated that healthcare professionals participating in high-quality PTAMs are less likely to prescribe new medicines [45]. Moreover, participating in PTAMs contributes to the overall quality and cost-effectiveness of prescribing, especially if the quality level of PTAM is high [46-48]. PTAMs are therefore considered as an important setting to stimulate the rational use of (new) medicines [49]. In order to reduce the practice variation caused by non-scientific argumentation, interprofessional communication might play an important role.

Pharmaceutical industry

The rationality in the prescription of new medicines is further complicated by the presence and activities of companies with commercial interests in the use of new medicines. In our study, we found that healthcare professionals mentioned marketing activities of pharmaceutical companies as reason for the prescription of new medicines (**3.1**). In addition, we found that marketing materials from pharmaceutical companies made use of multiple persuasion strategies to create a positive attitude towards new medicines (**3.2**).

The pharmaceutical industry has been known for decades to try to persuade healthcare professionals to prescribe their new medicines. In this thesis, only marketing materials were studied. But even in this small part of all marketing activities, multiple persuasion strategies were identified. Adding those results to former demonstrated lack of educational value in marketing materials [50-52], it becomes clear that these materials have little to do with scientific rationale in the decision to prescribe new medicines. Numerous studies have shown that any form of interference by the pharmaceutical industry can lead to more prescriptions for new medicines. Investigated interventions include among others promotional literature [53,54], commercial medicine information from sales representatives [55], gifts from pharmaceutical companies [56] and pharmaceutical sales representatives [57] or a combination of activities [52,58]. Moreover, marketing activities have also been associated with nonrational prescription behaviour [59] and restriction of marketing activities is associated with reductions in prescription of new medicines [60]. Healthcare professionals themselves also acknowledged the influence of marketing activities from pharmaceutical companies on their behaviour (**3.1**). However, studies also proof that most healthcare professionals still underestimate their vulnerability to marketing, thinking they themselves are not affected by marketing activities [5,54,58]. It can therefore be concluded that marketing activities from pharmaceutical companies contribute to non-scientific argumentation to prescribe new medicines. Restriction of marketing activities and awareness of persuasion strategies can contribute to more rational prescription of new medicines.

IMPLICATIONS FOR INITIATIVES AIMED AT THE RATIONAL USE OF MEDICINES

The unpredictability of uptake of new medicines and limited role of scientific evidence in the decision to prescribe new medicines urge for initiatives to continuously stimulate the rational use of new medicines. The stimulation of rational use of new medicines should start with the education of aspirant healthcare professionals. Education about how to evaluate benefits and risks of new medicines, and how pharmaceutical companies try to influence decision-making should be part of educational programmes of all healthcare professionals. In addition to the education of aspirant healthcare professionals, initiatives directed at practicing healthcare professionals are also warranted. In the Netherlands, the programme 'MedicijnBalans' of the Dutch Institute for the Rational Use of Medicine (IRUM) is set up by the Ministry of Health, Wellbeing and Sports to stimulate the rational use of new medicines by healthcare professionals. MedicijnBalans provides unbiased information about new medicines and stimulates the discussion about the added value of new medicines before their uptake in guidelines. Several lessons, aimed at MedicijnBalans and equivalent interventions to stimulate the rational use of new medicines, can be derived from this thesis:

1. **Gain insight into the considerations, context and perspectives for every medicine group individually, before developing interventions**.

This thesis clearly shows that no general profile of early adoption of new medicine exists and that considerations and contexts regarding new medicines differ between different therapeutical classes. In order to develop interventions to stimulate the rational use of a certain class of new medicines, insight in the attitudes and external factors influencing prescription behaviour is essential. Those findings cannot just be extrapolated from one medicine group to another.

2. **Communicate clearly about the expected benefits and risks of new medicines**.

This thesis shows that expectations of new medicines by healthcare professionals do not necessarily align with those by official organisations. The interpretation of – most notably – relative risk measures and terms like 'clinical relevance' differs and can lead to overestimation or underestimation of the benefits and risks of new medicines. Transparency and clear communication about the expected benefits and risks, avoiding the use of relative risk measures and multi-interpretable terminology are essential in the unbiased information about new medicines. The need of clear communication does apply to all organisations who communicate about (new) medicines, including

registration authorities, Health Technology Assessment (HTA) bodies, education institutes and professional organisations.

3. **Stimulate communication among healthcare professionals**.

This thesis showed that healthcare professionals were willing to discuss viewpoints and the differences in argumentation. In order to stimulate the rational use of new medicines, interprofessional communication, for example in PTAMs, might help to minimize practice variation and prevent unrealistic expectations of new medicines.

4. **Pay attention to the persuasion strategies of the pharmaceutical industry**.

This thesis shows that multiple persuasion strategies are present in only a small subset of marketing activities from pharmaceutical companies. Initiatives aimed at the rational use of new medicine should be aware of these mechanisms, both to prevent themselves from being influenced and to educate healthcare professionals about these mechanisms. Initiatives to stimulate the rational use of new medicines could also make use of the same mechanisms, to persuade healthcare professionals to the rational use of medicine.

IMPLICATIONS FOR FURTHER RESEARCH

In addition to the conclusions and recommendations drawn from this thesis, the findings have also resulted in directions for further research. To obtain more insight in the perspectives and practices of primary care healthcare professionals related to new medicines, more research is warranted.

The first finding calling for further investigation is whether the general principle of domain-specific innovation applies to the prescription of new medicines. Our finding that the prescription of new diabetes medicines was associated with the prescription of new insulins but not DOACs implicates that the general concept of domain-specific innovation also applies to the prescription of new medicines. This hypothesis warrants further investigation. Further research could focus on associations between the prescriptions of other new medicines in the same therapeutic areas, but also on the relation between non-pharmacological innovations (for example new medical devices) and prescription of new medicines in the same therapeutic area.

A second direction for further research includes the stricter views on endpoints and MCIDs for the evaluation of new medicines by healthcare professionals. Whether this also results in stricter definition of clinical relevance of new medicines cannot be concluded from this thesis, since different medicine groups, years and samples of healthcare professionals are investigated among the studies. It is therefore not known whether these stricter views of evaluation criteria also result in stricter views of the clinical relevance of the new medicines. Future research has to determine how healthcare professionals evaluate the clinical benefit of new medicines, how their assessment relates to that of official institutions and whether an association exists between the definition of evaluation criteria for clinical relevance and ultimate evaluation of clinical relevance of new medicines.

Third, the persuasion strategies used by pharmaceutical industries calls for further studies. To date, it is not known to which extent these strategies affect healthcare professionals. From former studies, it is known that these persuasion strategies activate automatic decision-making processes. To which degree these strategies also affect attitudes and behaviour of healthcare professionals remains to be elucidated. Further research could focus on the impact of these different persuasion strategies on attitudes towards new medicines and prescription behaviour of healthcare professionals.

Overall, this thesis makes clear that initiatives aimed at the rational use of medicines are warranted and offers some lessons for these initiatives. Further research should investigate the impact of these initiatives and confirm whether these initiatives indeed stimulate the rational use of new medicines.

CONCLUSION

Healthcare professionals are, compared to official institutions, in general more strict in defining clinical relevance of new medicines. The attitude of healthcare professionals towards new medicines is an important factor in the decision to prescribe new medicines, and the prescription of new medicines markedly differs between general practices. The unpredictability in the uptake of new medicines and limited role of scientific evidence in decisions to prescribe new medicines indicate room for improvement. Therefore, initiatives to continuously stimulate the rational use of new medicines in primary care are warranted, to ensure that new medicines are prescribed to patients who need them and withheld from patients who do not.

REFERENCES

1. Lichtenberg FR. The impact of new drug launches on longevity: Evidence from longitudinal, disease-level data from 52 countries, 1982-2001. Int J Health Care Finance Econ. 2005;5(1):47-73. doi: 10.1007/s10754-005-6601-7 [doi].
2. Wieseler B, McGauran N, Kaiser T. New drugs: Where did we go wrong and what can we do better? BMJ. 2019;366:l4340. doi: 10.1136/bmj.l4340 [doi].
3. Lubloy A. Factors affecting the uptake of new medicines: A systematic literature review. BMC Health Serv Res. 2014;14:469-469. doi: 10.1186/1472-6963-14-469 [doi].
4. Kozyrskyj A, Raymond C, Racher A. Characterizing early prescribers of newly marketed drugs in Canada: A population-based study. Eur J Clin Pharmacol. 2007;63(6):597-604. doi: 10.1007/s00228-007-0277-5 [doi].
5. Cialdini RB. Influence, new and expanded the psychology of persuasion. New York: Harper Business; 2021.
6. Overbeek JA, Heintjes EM, Prieto-Alhambra D, et al. Type 2 diabetes mellitus treatment patterns across europe: A population-based multi-database study. Clin Ther. 2017;39(4):759-770. doi: S0149-2918(17)30129-7 [pii].
7. Mardetko N, Nabergoj Makovec U, Locatelli I, Janez A, Kos M. Uptake of new antidiabetic medicines in 11 european countries. BMC Endocr Disord. 2021;21(1):127-3. doi: 10.1186/s12902-021-00798-3.
8. de Jong LA, Koops M, Gout-Zwart JJ, et al. Trends in direct oral anticoagulant (DOAC) use: Health benefits and patient preference. Neth J Med. 2018;76(10):426-430.
9. Croonen H. Nieuwe geneesmiddelen: Nederland hekkensluiter in Europa. Medisch Contact. 2 Jul 2014. Available from: https://www.medischcontact.nl/nieuws/laatste-nieuws/artikel/nieuwe-geneesmiddelen-nederland-hekkensluiter-in-europa.
10. van den Heuvel, J. M., Hövels AM, Büller HR, Mantel-Teeuwisse AK, de Boer A, Maitland-van der Zee, A. H. NOACs replace VKA as preferred oral anticoagulant among new patients: A drug utilization study in 560 pharmacies in the netherlands. Thromb J. 2018;16:7-y. eCollection 2018. doi: 10.1186/s12959-017-0156-y [doi].
11. Lugtenberg M, Burgers JS, Besters CF, Han D, Westert GP. Perceived barriers to guideline adherence: A survey among general practitioners. BMC Fam Pract. 2011;12:98-98. doi: 10.1186/1471-2296-12-98 [doi].
12. van Dijk L, de Jong JD, Westert GP, de Bakker DH. Variation in formulary adherence in general practice over time (2003-2007). Fam Pract. 2011;28(6):624-631. doi: 10.1093/fampra/cmr043 [doi].
13. Instituut Verantwoord Medicijngebruik (IVM). Nieuwe geneesmiddelen - MedicijnBalans. Available from: www.medicijngebruik.nl/nieuwe-geneesmiddelen. Updated 2022. Accessed April 15, 2022.
14. Stichting Geneesmiddelenbulletin. Ge-bu. Available from: www.ge-bu.nl. Updated 2023. Accessed March 31, 2023.
15. De Metz J, Lambooij A. Het gebruik van cholesterolverlagers in zeven Europese landen. Instituut Verantwoord Medicijngebruik. 2022.
16. de Metz J, Lambooij A, Dankers M. Het gebruik van diabetesmiddelen in negen landen in de periode 2017 tot en met 2021. Instituut Verantwoord Medicijngebruik. 2023.

17. De Metz J, Lambooij A, Van Dalfsen M. Het voorschrijven van vitamine K-antagonisten en bloedglucoseverlagende middelen: Een indirecte meting van het effect van MedicijnBalans. Instituut Verantwoord Medicijngebruik. 2021.
18. Visser ST, Vegter S, Boersma C, De Grooth R, Postma MJ. Drug-use patterns of initially prescribed insulin detemir and insulin glargine in the netherlands; a comparative analysis using pharmacy data from iadb.nl. (Value in Health 13(7):A285).
19. Rathmann W, Haastert B, Riebel P, et al. Prescription of insulin glargine in primary care practices in germany. Exp Clin Endocrinol Diabetes. 2007;115(4):252-256. doi: 10.1055/s-2007-972562 [doi].
20. Lipska KJ, Ross JS, Van Houten HK, Beran D, Yudkin JS, Shah ND. Use and out-of-pocket costs of insulin for type 2 diabetes mellitus from 2000 through 2010. JAMA. 2014;311(22):2331-2333. doi: 10.1001/jama.2014.6316 [doi].
21. Xu Y, Gomes T, Mamdani MM, Juurlink DN, Cadarette SM, Tadrous M. Analysis of trends in insulin utilization and spending across canada from 2010 to 2015. Can J Diabetes. 2019;43(3):179-185.e1. doi: S1499-2671(18)30200-4 [pii].
22. Heymann AD, Kritz V, Hemo B, Kertes J, Becker M. A changed pattern of insulin use following the introduction of basal analog insulin treatment in primary care. Prim Care Diabetes. 2013;7(1):57-61. doi: 10.1016/j.pcd.2012.12.005 [doi].
23. Kent DJ, McMahill-Walraven CN, Panozzo CA, et al. Descriptive analysis of long- and intermediate-acting insulin and key safety outcomes in adults with type 2 diabetes mellitus. J Manag Care Spec Pharm. 2019;25(11):1162-1171. doi: 10.18553/jmcp.2019.19042 [doi].
24. Decollogny A, Piaget-Rossel R, Taffe P, Eggli Y. Determinants of new drugs prescription in the swiss healthcare market. BMC Health Serv Res. 2018;18(1):9-1. doi: 10.1186/s12913-017-2775-1 [doi].
25. Garjón FJ, Azparren A, Vergara I, Azaola B, Loayssa JR. Adoption of new drugs by physicians: A survival analysis. BMC Health Serv Res. 2012;12:56-56. doi: 10.1186/1472-6963-12-56 [doi].
26. De Jong JD. Explaining medical practice variation: social organization and institutional mechanisms. [Utrecht]: Nivel, 2008. 240 p.
27. Inman W, Pearce G. Prescriber profile and post-marketing surveillance. Lancet. 1993;342(8872):658-661. doi: 0140-6736(93)91763-C [pii].
28. Medlinskiene K, Tomlinson J, Marques I, Richardson S, Stirling K, Petty D. Barriers and facilitators to the uptake of new medicines into clinical practice: A systematic review. BMC Health Serv Res. 2021;21(1):1198-4. doi: 10.1186/s12913-021-07196-4.
29. Tamblyn R, McLeod P, Hanley JA, Girard N, Hurley J. Physician and practice characteristics associated with the early utilization of new prescription drugs. Med Care. 2003;41(8):895-908. doi: 10.1097/00005650-200308000-00004 [doi].
30. Prosser H, Walley T. New drug uptake: Qualitative comparison of high and low prescribing GPs' attitudes and approach. Fam Pract. 2003;20(5):583-591. doi: 10.1093/fampra/cmg516.
31. Dybdahl T, Andersen M, Søndergaard J, Kragstrup J, Kristiansen IS. Does the early adopter of drugs exist? A population-based study of general practitioners' prescribing of new drugs. Eur J Clin Pharmacol. 2004;60(9):667-672. doi: 10.1007/s00228-004-0797-1.
32. Dybdahl T, Andersen M, Kragstrup J, Kristiansen IS, Søndergaard J. General practitioners' adoption of new drugs and previous prescribing of drugs belonging to the same therapeutic class: A pharmacoepidemiological study. Br J Clin Pharmacol. 2005;60(5):526-533. doi: BCP2463 [pii].

33. Araujo CF, Ladeira WJ, Santini FdO, Sampaio CH. Domain-specific innovativeness: A meta-analysis in business and consumer. RAI Revista de Administração e Inovação. 2016;13(2):99-106. https://www.sciencedirect.com/science/article/pii/S1809203916300134. doi: 10.1016/j.rai.2016.03.003.
34. Dybdahl T, Søndergaard J, Kragstrup J, Kristiansen IS, Andersen M. Primary care physicians' adoption of new drugs is not associated with their clinical interests: A pharmacoepidemiologic study. Scand J Prim Health Care. 2011;29(2):117-121. doi: 10.3109/02813432.2011.570024.
35. Mol PG, Arnardottir AH, Straus SM, et al. Understanding drug preferences, different perspectives. Br J Clin Pharmacol. 2015;79(6):978-987. doi: 10.1111/bcp.12566 [doi].
36. Gauthier B, Singh SR, Virani A, Staples H, Colbourne A. Perspectives and experiences of health care professionals and patients regarding treatments for type 2 diabetes. Can Pharm J (Ott). 2014;147(1):45-54. doi: 10.1177/1715163513506547 [doi].
37. Kaldjian LC. Patient care and population health: Goals, roles and costs. J Public Health Res. 2014;3(2):311. doi: 10.4081/jphr.2014.311 [doi].
38. Sox HC. Resolving the tension between population health and individual health care. JAMA. 2013;310(18):1933-1934. doi: 10.1001/jama.2013.281998 [doi].
39. Brooks AP, Kibble SE, Alderson SA. The understanding of terms in evidence-based medicine: A pilot study. European Diabetes Nursing. 2009;6(3):95-99. https://doi.org/10.1002/edn.143. doi: 10.1002/edn.143.
40. Akobeng AK. Understanding measures of treatment effect in clinical trials. Arch Dis Child. 2005;90(1):54-56. doi: 90/1/54 [pii].
41. Prosser H, Almond S, Walley T. Influences on GPs' decision to prescribe new drugs-the importance of who says what. Fam Pract. 2003;20(1):61-68. doi: 10.1093/fampra/20.1.61.
42. Hoffmann TC, Del Mar C. Clinicians' expectations of the benefits and harms of treatments, screening, and tests: A systematic review. JAMA Intern Med. 2017;177(3):407-419. doi: 10.1001/jamainternmed.2016.8254.
43. European Medicines Agency (EMA). Information on benefit-risk of medicines: Patients', consumers' and healthcare professionals' expectations. Updated 2009. Accessed March 31, 2023.
44. Lugtenberg M, Zegers-van Schaick JM, Westert GP, Burgers JS. Why don't physicians adhere to guideline recommendations in practice? an analysis of barriers among dutch general practitioners. Implement Sci. 2009;4:54-54. doi: 10.1186/1748-5908-4-54 [doi].
45. Florentinus SR, van Hulten R, Kloth MEM, et al. The effect of pharmacotherapy audit meetings on early new drug prescribing by general practitioners. Ann Pharmacother. 2007;41(2):319-324. doi: 10.1345/aph.1H250.
46. Teichert M, van der Aalst A, de Wit H, Stroo M, De Smet, PAGM. How useful are prescribing indicators based on the DU90% method to distinguish the quality of prescribing between pharmacotherapy audit meetings with different levels of functioning? Eur J Clin Pharmacol. 2007;63(12):1171-1177. doi: 10.1007/s00228-007-0362-9.
47. Vervloet M, Meulepas MA, Cals JWL, Eimers M, van der Hoek, Lucas S, van Dijk L. Reducing antibiotic prescriptions for respiratory tract infections in family practice: Results of a cluster randomized controlled trial evaluating a multifaceted peer-group-based intervention. NPJ Prim Care Respir Med. 2016;26:15083. doi: 10.1038/npjpcrm.2015.83.
48. Muijrers PEM, Grol, Richard P T M, Sijbrandij J, Janknegt R, Knottnerus JA. Differences in prescribing between GPs: Impact of the cooperation with pharmacists and impact of visits from pharmaceutical industry representatives. Fam Pract. 2005;22(6):624-630. doi: 10.1093/fampra/cmi074.

49. Macé F, Peyron C, De Vriese C, Nelissen-Vrancken M, Ruggli M, Brülhart M. General Practitioners-Community Pharmacists Peer Groups: Potentialities and limits through their implementation in several countries. Submitted.
50. Gettings J, O'Neill B, Chokshi DA, et al. Differences in the volume of pharmaceutical advertisements between print general medical journals. PLoS One. 2014;9(1):e84790. doi: 10.1371/journal.pone.0084790 [doi].
51. Wilkes MS, Doblin BH, Shapiro MF. Pharmaceutical advertisements in leading medical journals: Experts' assessments. Ann Intern Med. 1992;116(11):912-919. doi: 10.7326/0003-4819-116-11-912 [doi].
52. PLoS Medicine Editors. PLoS medicine and the pharmaceutical industry. PLoS Med. 2006;3(7):e329. doi: e329.
53. Sharma S, Akhoon N, Moe HW, Nair DR, Shashidhar V. A study of perceptions and exposure of drug promotional literature among clinicians in a teaching hospital. Perspect Clin Res. 2021;12(3):140-145. doi: 10.4103/picr.PICR_36_19 [doi].
54. Jeuck JE. Direct-mail advertising to doctors. The Journal of Business of the University of Chicago. 1940;13(1):17-38. http://www.jstor.org/stable/2350143.
55. Vancelik S, Beyhun NE, Acemoglu H, Calikoglu O. Impact of pharmaceutical promotion on prescribing decisions of general practitioners in eastern turkey. BMC Public Health. 2007;7:122-122. doi: 1471-2458-7-122 [pii].
56. Wood SF, Podrasky J, McMonagle MA, et al. Influence of pharmaceutical marketing on medicare prescriptions in the district of columbia. PLoS One. 2017;12(10):e0186060. doi: 10.1371/journal.pone.0186060 [doi].
57. Spurling G, Mansfield P. General practitioners and pharmaceutical sales representatives: Quality improvement research. Qual Saf Health Care. 2007;16(4):266-270. doi: 16/4/266 [pii].
58. Hailu AD, Workneh BD, Kahissay MH. Influence of pharmaceutical marketing mix strategies on physicians' prescribing behaviors in public and private hospitals, dessie, ethiopia: A mixed study design. BMC Public Health. 2021;21(1):65-2. doi: 10.1186/s12889-020-10063-2 [doi].
59. Wazana A. Physicians and the pharmaceutical industry: Is a gift ever just a gift? JAMA. 2000;283(3):373-380. doi: 10.1001/jama.283.3.373.
60. Larkin I, Ang D, Steinhart J, et al. Association between academic medical center pharmaceutical detailing policies and physician prescribing. JAMA. 2017;317(17):1785-1795. doi: 10.1001/jama.2017.4039 [doi].

6

Summary

New medicines can improve treatment outcomes and can be beneficial for patients. However, because of the often unknown long term safety of new medicines, their use can also be harmful. Therefore, both excessive enthusiasm and latency about new medicines can have impact on patients' health and life. Adding the often high costs of new treatments, it becomes clear that rational use of new medicines is particularly important, both in terms of quality of care and healthcare costs. Insight in the prescription of new medicines and the considerations of healthcare professionals to prescribe new medicines is therefore particularly relevant. The primary research objective of this thesis was thus to study the perspectives and practices of primary care healthcare professionals towards new medicines.

The introduction (**chapter 1**) describes the processes prior to the prescription of new medicines. New medicines have to undergo many evaluations in order to be authorised, reimbursed, recommended and prescribed. Before the actual assessment starts, assessment criteria have to be established. Consensus on importance of clinical outcomes and meaningful improvements on these outcomes, defined by Minimal Clinically Important Differences (MCIDs), are therefore the first step. Once available for prescription, healthcare professionals make the final decision to prescribe the new medicine or not. This process is known to be influenced by many factors. The early prescription of new medicines is often not equally distributed among physicians, meaning that both early adopters and laggards exist. This indicates room for improvement in the rational use of new medicines and offers directions for further research.

In **chapter 2**, the preferences for evaluation criteria of new medicines by individual healthcare professionals were studied and compared to those of registration authorities and professional organisations. Both studies in this chapter indicate that healthcare professionals largely agree with outcomes and MCIDs used in the evaluation of new medicines for chronic obstructive pulmonary disease (COPD) and type 2 diabetes mellitus (T2DM) respectively, although they have stricter views on some criteria. This means that new medicines that are considered clinically relevant by registration authorities do not necessarily reflect healthcare professionals' perspectives on clinical relevance. This can lead to overestimation or underestimation of benefits and harms of new medicines. **Chapter 2.1** focuses on COPD. With an online survey among 227 healthcare professionals, the preferences for efficacy endpoints and cut-off values for improvement on these outcomes were studied. Exacerbations (51.0%), airway obstruction (46.9%) and health status (44.9%) were the most preferred efficacy endpoints. Preferred cut-off values for clinical relevance for the Transition Dyspnea Index (TDI) and St. George's Respiratory Questionnaire (SGRQ) were significantly higher than the MCIDs used by the European Medicines Agency (EMA), mean differences 1.5 (95% confidence interval

(CI) = 1.3 – 1.8, p < 0.001) and 7.0 (95%CI = 5.1 – 8.8, p < 0.001), respectively. The mean cut-off value for forced expiratory volume in 1 sec (FEV_1), was comparable to the MCID (mean difference 2.2, 95%CI = -19.9 – 24.3, p = 0.84). The results show that healthcare professionals largely agreed with efficacy endpoints used for the evaluation of new COPD medicines, but preferred higher cut-off values for clinical relevance for dyspnea and health-related quality of life than the registration authorities. **Chapter 2.2** addresses new medicines for T2DM and compares the preferences of healthcare professionals to those of the Dutch guideline committee. With a similar study design, the preferences of healthcare professionals towards endpoints and MCIDs for T2DM medicines were investigated. According to 211 healthcare professionals, severe hypoglycemia, mortality, quality of life, macrovascular morbidity, microvascular morbidity, hospital admissions and HbA1c are of critical importance in the assessment of new T2DM medicines. Other hypoglycemia and body weight were considered important. This was comparable to the views of the guideline committee. Only HbA1c and hospital admissions were valued differently by the committee (important but not critical). Healthcare professionals preferred a median MCID of 4 mmol/mol for HbA1c (guideline: 5 mmol/mol) and 3 kg for body weight (guideline: 5 kg weight gain and 2,5 kg weight loss). Preferred MCIDs for mortality and macrovascular morbidity were, mentioned as relative risk reductions (RRRs), 20% (guideline: 10% and 25%, respectively) and 50% for other hypoglycaemia (guideline: 25%). The MCID of 25% for microvascular morbidity, hospital admissions and severe hypoglycaemia corresponded to the guideline-MCID. An additional finding of this study was the difficulty healthcare professionals experienced with estimating and interpreting realistic benefits and risks of new medicines, indicated by the wide range of answers given (especially for RRRs) and the large proportion of respondents that did not answer the questions about MCIDs. From this study, it was concluded that healthcare professionals' preferences were comparable to the views of the guideline committee. However, healthcare professionals had a stricter view on the importance of HbA1c and hospital admissions and the MCIDs for mortality and other hypoglycemia.

In **chapter 3**, factors that influence the decision of individual healthcare professionals to prescribe new medicines were investigated, also focusing on the strategies pharmaceutical companies use to influence this decision-making. In this chapter, it is concluded that the attitudes of healthcare professionals are important in the decision to prescribe new medicines. Also, the pharmaceutical industry uses many strategies in order to influence this attitude and persuade healthcare professionals to prescribe new medicines. **Chapter 3.1** focuses on the argumentation of healthcare professionals to prescribe new and non-recommended insulins to T2DM patients. Four focus group discussions were organised with general practitioners (n = 11), practice nurses (n = 12), pharmacists (n = 6), diabetes nurses (n = 4) and nurse practitioners (n = 2). The argumentation for the

prescription of non-recommended insulins was categorized into an existing behaviour model for guideline non-adherence, distinguishing argumentation in the domains knowledge, attitude and behaviour. The prescription of non-recommended insulins was largely driven by argumentation in the domain of attitudes. Lack of agreement with the guideline was the most prominent category of arguments within this domain. The belief that guideline-recommended insulins were less effective, positive experience with other insulins, marketing from pharmaceutical companies and the lack of uniformity in policy between healthcare professionals in the same practice were also identified as attitude-related barriers to prescribe guideline-recommended insulins. A small number of external barriers were identified, focusing on patient characteristics that prevented the use of recommended insulins, the existence of contradictory guidelines and other, mostly secondary care, healthcare providers initiating non-recommended insulins. **Chapter 3.2** studies persuasion strategies pharmaceutical companies use to influence the prescription of new medicines by healthcare professionals. A total of 68 marketing materials, collected by 20 general practices, were analysed according to the presence of seven common persuasion strategies, i.e. reciprocity, consistency/commitment, social proof, liking, authority, scarcity and unity. All seven strategies were found. Liking (64.7% of all materials) and authority (29.4%) were the most prominent strategies, followed by social proof (17.6%), unity (14.7%), scarcity (13.2%), reciprocity (11.8%) and consistency/commitment (2.9%). One new strategy, emotional pressure, was identified which was present in 30.9% of the materials. The wide range of used persuasion strategies indicates that pharmaceutical companies try to influence the decision-making process in many ways.

Chapter 4 describes the practice variation in the prescription of new medicines in primary care and the association of prescription of new medicines with specific patient characteristics, practice characteristics and prescription of other new medicines. In this chapter, it is concluded that large practice variation in the prescription of new medicines exists, especially in the first years after introduction, which cannot be explained by different patient or practice characteristics. In addition, no correlation exists between the early prescription of new medicines meant for different diseases. **Chapter 4.1** targets the prescription of new insulins to T2DM patients. A cohort of 7,757 patients with prescriptions for intermediate or long-acting insulins from 282 general practices was constructed using the Nivel Primary Care Database. A median percentage of 21.2% (interquartile range (IQR) = 12.5 – 36.4%) of all patients prescribed intermediate or long-acting insulins per practice received a prescription for newer insulins. The Intraclass Correlation Coefficient (ICC) was 0.20, meaning that twenty percent of the observed variability could be attributed to differences between practices. The ICC marginally decreased to 0.19 after multilevel modelling with patient and practice characteristics.

Female sex (odds ratio (OR) = 0.77, 95% confidence interval (CI) = 0.69 to 0.87), age ≥ 86 years compared with 40 – 55 years (OR = 0.22, 95% CI = 0.15 to 0.34), prescriptions for metformin (OR = 0.66, 95% CI = 0.53 to 0.82), sulfonylurea (OR = 0.58, 95% CI = 0.51 to 0.66), or other newer T2DM drugs (OR = 3.10, 95% CI = 2.63 to 3.66), and dispensing practices (OR = 1.78, 95% CI = 1.03 to 3.10) were associated with the prescription of newer insulins. It is concluded that the inter-practice variation in the prescription of newer insulins is large and can only be partially explained by patient- and practice-related differences. In **chapter 4.2**, another retrospective cohort study with prescription data from the Nivel Primary Care Database is described. This study investigated the uptake, practice variation and correlation in the prescription of direct-acting oral anticoagulants (DOACs) and incretin-based therapies. The study period ranged from introduction of these medicines, around 2007, until recommendation in guidelines, around 2019. Per year, 46 to 424 practices and 179,933 to 1,654,376 patients were included. The mean percentage of patients per practice using DOACs, compared to the use of DOACs and vitamin K antagonists (VKAs), or incretin-based therapies, compared to the use of all diabetes medication except insulin, increased to 54.9% and 9.7%, respectively in 2019. 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. In this study, it is concluded that different adoption profiles per new medicine group exist and that early adoption of new medicines is not likely to be a personal trait.

In the general discussion (**chapter 5)**, the results of the individual studies are placed in a broader perspective. Two main conclusions derived from the studies are discussed. At first, we conclude that the uptake of new medicines in primary care is unpredictable. This conclusion is based on three findings. First, we found great differences in the adoption of new insulins, DOACs and incretin-based medicines, indicating that the uptake is different for every new medicine. Second, we found large variation between primary care practices in the prescription of new medicines, which cannot be explained by variation in practice and patient characteristics. Third, the early uptake of one group of new medicines did not predict the early uptake of other new medicines. Together, these findings indicate that adoption profiles of new medicines differ per medicine group, and early adoption cannot be easily predicted by patient characteristics, practice characteristics or early prescription of other new medicines.

The second main conclusion of this thesis is that scientific evidence only plays a limited role in the deliberations leading to the prescription of new medicines. This conclusion is again based on three findings. First, a balanced evaluation of benefits and risks by healthcare professionals is hampered because of difficulties they experience

in interpreting and estimating realistic benefits and risks of new medicines. Second, individual attitudes of healthcare professionals, often related to argumentation that lacked scientific rationale, were most important in the decision to prescribe new medicines. Third, marketing materials from pharmaceutical companies aimed to influence prescription behaviour by use of multiple persuasion strategies. These findings illustrate that the decision to prescribe new medicines is not purely based on scientific rationale, but that many other factors influence this decision-making.

Both conclusions urge for initiatives to continuously stimulate the rational use of new medicines, like the programme MedicijnBalans of the Dutch Institute for the Rational Use of Medicine, to ensure that new medicines are prescribed to patients who need them and withheld from patients who do not.

7

Appendices

7.1

Nederlandstalige samenvatting

Ieder jaar komen er nieuwe geneesmiddelen beschikbaar. Nieuwe geneesmiddelen kunnen voordelen hebben, maar ook nadelen. Een voordeel is dat nieuwe geneesmiddelen beter kunnen werken dan bestaande geneesmiddelen. Een nadeel is dat de veiligheid op lange termijn onbekend is. Ook zijn nieuwe geneesmiddelen vaak duurder dan geneesmiddelen die al op de markt zijn. Het is daarom belangrijk dat artsen nieuwe geneesmiddelen alleen voorschrijven als het echt nodig is. In dit proefschrift onderzoeken we nieuwe geneesmiddelen in de eerstelijnszorg. Dit is de zorg waar een patiënt direct naar toe kan gaan, zonder verwijzing. Voorbeelden van de eerstelijnszorg zijn de huisartsenpraktijk en apotheek. Dit proefschrift beschrijft de keuzes en visies van zorgverleners in de eerstelijnszorg ten aanzien van nieuwe geneesmiddelen.

HOE KOMT EEN NIEUW GENEESMIDDEL BIJ DE PATIËNT?

Hoofdstuk 1 is de inleiding op dit proefschrift. Een arts kan een nieuw geneesmiddel niet zomaar voorschrijven. Meerdere instanties moeten het geneesmiddel eerst beoordelen. Zo is er een instantie die bepaalt of een geneesmiddel op de markt mag komen, een instantie die adviseert over de vergoeding en een instantie die bepaalt of het geneesmiddel in de behandelrichtlijnen voor artsen komt. Bij al deze beoordelingen is de belangrijkste vraag of het positieve effect van een nieuw middel (de werking) opweegt tegen de mogelijke nadelen (de bijwerkingen).

Voor een goede beoordeling is het belangrijk om de spelregels voor de beoordeling af te spreken. Die spelregels bestaan allereerst uit het vaststellen van de *eindpunten* waarop de verantwoordelijke instanties geneesmiddelen gaan beoordelen. Een eindpunt is datgene wat onderzoekers meten om het effect van het geneesmiddel vast te stellen. Eindpunten zijn bijvoorbeeld het verminderd optreden van een ziekte of een symptoom, of een laboratoriumuitslag. Vaak zijn meerdere eindpunten mogelijk. Niet elk eindpunt is even relevant. Daarom moeten verantwoordelijke instanties per ziekte afspreken welke eindpunten zij gebruiken om nieuwe geneesmiddelen te beoordelen. Naast het bepalen van de eindpunten moeten er ook afspraken zijn over wanneer een effect ‘goed genoeg’ is. In het geneesmiddelonderzoek gebruiken we hiervoor de term *klinisch relevant*. Instanties stellen afkapwaarden vast om de klinische relevantie te bepalen. Deze afkapwaarden noemen we MCID’s (Minimal Clinically Important Differences). Met de MCID bepalen instanties of een bepaalde verbetering op een eindpunt klinisch relevant is.

Na alle beoordelingen moet de zorgverlener besluiten het nieuwe geneesmiddel wel of niet voor te schrijven. Uit eerdere onderzoeken weten we dat zorgverleners heel

verschillende keuzes maken. Sommige zorgverleners schrijven nieuwe geneesmiddelen heel snel voor. Andere zorgverleners zijn juist afwachtend. In dit proefschrift hebben we daarom onderzocht hoe zorgverleners omgaan met nieuwe geneesmiddelen.

In dit proefschrift hebben we drie onderwerpen onderzocht:

1. Welke voorkeuren hebben zorgverleners voor eindpunten en MCID's in de beoordeling van nieuwe geneesmiddelen? En hoe verhouden deze voorkeuren zich tot die van officiële beoordelingsinstanties?
2. Welke factoren maken dat een zorgverlener besluit een nieuw geneesmiddel voor te schrijven? En hoe probeert de farmaceutische industrie dit besluit te beïnvloeden?
3. Hoe vaak schrijven zorgverleners nieuwe geneesmiddelen voor? En hangt het voorschrijven van nieuwe geneesmiddelen samen met bepaalde eigenschappen van patiënten, huisartsenpraktijken en het voorschrijven van andere nieuwe geneesmiddelen?

VOORKEUREN

Hoofdstuk 2 van dit proefschrift beschrijft twee onderzoeken. Hierin vergelijken we de voorkeuren van zorgverleners voor eindpunten en MCID's met de voorkeuren van officiële instanties. Uit beide onderzoeken blijkt dat zorgverleners wat strenger zijn dan de officiële instanties. Een geneesmiddel dat volgens een instantie klinisch relevant is, is dus niet per definitie ook klinisch relevant in de ogen van een zorgverlener.

In **hoofdstuk 2.1** hebben we de voorkeuren voor eindpunten en MCID's onderzocht voor de longziekte COPD. We hebben daarvoor een vragenlijst gemaakt. Hiermee hebben we zorgverleners gevraagd welke eindpunten en MCID's ze relevant vinden voor de beoordeling van nieuwe geneesmiddelen voor COPD. De eindpunten hebben we vergeleken met de voorkeuren van de instantie die beoordeelt of een geneesmiddel op de markt mag komen (de registratieautoriteit). De vragenlijst is ingevuld door 227 zorgverleners. Zij vonden longaanvallen, vernauwing van luchtwegen en kwaliteit van leven de belangrijkste eindpunten. Dit kwam goed overeen met de eindpunten die de registratieautoriteit gebruikt. In de voorkeuren voor MCID's waren wel wat verschillen. Zorgverleners wilden een MCID van 2,5 punt voor de schaal waarop benauwdheid wordt gemeten. De registratie-autoriteit gebruikt een MCID van 1 punt. Om een klinisch relevante verbetering van kwaliteit van leven vast te stellen, wilden de zorgverleners een MCID van 11 punten. De registratieautoriteit gebruikt 4 punten. De voorkeur voor de MCID voor de vernauwing van luchtwegen was vergelijkbaar. Zorgverleners hadden de voorkeur voor een MCID van 102 ml, instanties voor 100 ml.

In **hoofdstuk 2.2** hebben we een vergelijkbaar onderzoek gedaan, maar dan naar nieuwe geneesmiddelen bij diabetes mellitus type 2. De voorkeuren van zorgverleners hebben we vergeleken met de voorkeuren van de instantie die de richtlijnen voor artsen opstelt. Aan dit onderzoek deden 211 zorgverleners mee. We hebben met een vragenlijst gevraagd hoe belangrijk zij verschillende eindpunten vonden. De belangrijkste eindpunten waren volgens de zorgverleners: ernstige hypoglykemieën (te lage bloedsuikers), sterfte, kwaliteit van leven, schade aan de grote bloedvaten (bijvoorbeeld van het hart, de hersenen en de benen), schade aan de kleine bloedvaten (bijvoorbeeld van de nieren, ogen en vingers), ziekenhuisopnames en HbA1c (een maat om de hoeveelheid suiker in het bloed te bepalen). Zorgverleners vonden overige hypoglykemieën en lichaamsgewicht ook belangrijk, maar minder cruciaal dan de eerstgenoemde eindpunten. Dit kwam redelijk overeen met de voorkeuren van de richtlijninstantie. Zij vonden alleen ziekenhuisopname en HbA1c minder cruciaal. De voorkeuren van zorgverleners voor MCID's waren als volgt:

- HbA1c: 4 mmol/mol (richtlijn: 5 mmol/mol).
- Lichaamsgewicht: 3 kg (richtlijn: 5 of 2,5 kg, afhankelijk van of mensen aankwamen door het geneesmiddel, of juist afvielen).
- Sterfte: 20% (richtlijn: 10%).
- Schade aan de grote bloedvaten: 20% (richtlijn: 25%).
- Schade aan de kleine bloedvaten: 25% (richtlijn: 25%).
- Ziekenhuisopnames: 25% (richtlijn: 25%).
- Ernstige hypoglykemieën: 25% (richtlijn: 25%).
- Overige (niet-ernstige) hypoglykemieën: 50% (richtlijn: 25%).

Ook hier waren er dus enkele verschillen tussen de zorgverleners en de richtlijnmakers. Meestal waren de zorgverleners strenger dan de richtlijninstantie. We zagen in dit onderzoek ook dat zorgverleners het lastig vinden een reële inschatting te maken van de effecten van nieuwe geneesmiddelen.

FACTOREN

Hoofdstuk 3 van dit proefschrift beschrijft twee onderzoeken naar factoren die de keuze beïnvloeden om nieuwe geneesmiddelen voor te schrijven. Uit deze onderzoeken blijkt dat de houding van zorgverleners ten opzichte van nieuwe geneesmiddelen belangrijk is. De farmaceutische industrie probeert met allerlei beïnvloedingsstrategieën die houding te beïnvloeden.

In **hoofdstuk 3.1** beschrijven we een onderzoek naar de argumenten van zorgverleners om nieuwe geneesmiddelen voor te schrijven. Het onderzoek gaat over nieuwe insulines bij patiënten met diabetes mellitus type 2. De richtlijn voor huisartsen raadt de nieuwe insulines af. Toch schrijven zorgverleners de nieuwe insulines regelmatig voor. We hebben groepsdiscussies met huisartsen, praktijkondersteuners, diabetesverpleegkundigen en apothekers georganiseerd. Hierin hebben we de redenen besproken om deze nieuwe insulines voor te schrijven. De belangrijkste redenen hadden te maken met hoe zorgverleners aankijken tegen de insulines. Ze waren het bijvoorbeeld niet eens met de overwegingen in de richtlijn. Zorgverleners waren ervan overtuigd dat de aanbevolen insulines in de richtlijn minder goed werkten. Ook hadden ze goede ervaringen met de nieuwe insulines. Marketing vanuit de farmaceutische industrie speelde ook een rol bij het voorschrijven van nieuwe insulines. Er waren ook externe factoren waardoor zorgverleners nieuwe insulines voorschreven. Deze factoren kon de zorgverlener niet zelf beïnvloeden. Dit ging bijvoorbeeld om patiënten die hun handen niet goed meer konden gebruiken en daarom een specifiek injectiesysteem nodig hadden. Tegenstrijdige richtlijnen waren een andere externe factor die leidde tot het voorschrijven van nieuwe insulines. Tot slot herhaalden zorgverleners soms voorschriften voor nieuwe insulines van andere zorgverleners.

In **hoofdstuk 3.2** gaan we verder in op de marketing. Twintig huisartsenpraktijken hebben tijdens één maand alle (papieren) post van de farmaceutische industrie bewaard. Dit leverde 68 verschillende papieren marketingmaterialen op. Deze marketingmaterialen hebben we onderzocht op de aanwezigheid van zeven bekende beïnvloedingsprincipes. De meest gebruikte was *sympathie/gunnen*. Dit kwam voor in 65% van alle materialen. Hierbij probeert de farmaceutische industrie sympathie op te roepen voor hun geneesmiddel of bedrijf. Dit doen ze bijvoorbeeld door plaatjes te gebruiken van vriendelijke of zielige patiënten. *Autoriteit* (het gebruiken van geloofwaardige instanties of personen om een geneesmiddel aan te prijzen) kwam bij 29% voor en *sociaal bewijs* (benadrukken dat andere zorgverleners ook positief zijn over het geneesmiddel) bij 18%. In 15% van de materialen vonden we het principe *eenheid*. Hierbij benadrukt de farmaceutische industrie dat zij en de arts samen het beste willen voor de patiënt. *Schaarste*, het benadrukken van de unieke status van een geneesmiddel, kwam voor in 13% van de marketingmaterialen. In 12% van de materialen vonden we het principe *wederkerigheid*. Dit betekent dat de zorgverlener een (klein) cadeau krijgt, zoals een gratis maaltijd bij een scholing of een mooi boek, wat ertoe moet leiden dat hij of zij het nieuwe geneesmiddel gaat voorschrijven. Het laatste principe was *consistentie/commitment*. Deze vonden we in 3% van de materialen. Dit principe maakt gebruik van retorische vragen die de zorgverlener moeten laten besluiten om het nieuwe geneesmiddel voor te schrijven. Tot slot vonden we één nieuw

beïnvloedingsprincipe. *Emotionele druk* kwam voor in 31% van de materialen. Hierbij werd de arts aangesproken om het beste te doen voor zijn of haar patiënt.

VOORSCHRIJVEN

Hoofdstuk 4 van dit proefschrift beschrijft twee onderzoeken naar het voorschrijven van nieuwe geneesmiddelen door huisartsen. Uit deze onderzoeken blijkt dat er grote verschillen zijn tussen huisartsenpraktijken. Huisartsen in sommige praktijken schrijven veel nieuwe geneesmiddelen voor en anderen juist weinig. Die verschillen zijn niet goed te verklaren doordat de praktijken verschillende type patiënten hebben.

In **hoofdstuk 4.1** beschrijven we een onderzoek naar het voorschrijven van nieuwe insulines. Hiervoor gebruikten we de Nivel Zorgregistraties eerste lijn. Dit is een grote database met gegevens over huisartsenpraktijken en hun patiënten, zoals voorschriften en aandoeningen. Voor dit onderzoek gebruikten we de gegevens van ruim 7.700 patiënten uit 282 verschillende huisartsenpraktijken. Meer dan een kwart van alle patiënten met een insuline gebruikte een nieuw insuline. De verschillen tussen praktijken waren groot. Sommige huisartsenpraktijken schreven nooit nieuwe insulines voor. Bij andere praktijken kreeg meer dan 80% van alle patiënten met een insuline een nieuw insuline. Apotheekhoudende huisartsen schreven de nieuwe insulines vaker voor dan niet-apotheekhoudende huisartsen. Mannen en jongere patiënten hadden meer kans om een nieuw insuline te krijgen. De kans op een nieuw insuline was ook afhankelijk van andere geneesmiddelen voor diabetes die de patiënt al gebruikte. Patiënten die al voorkeursgeneesmiddelen uit de richtlijn gebruikten, kregen minder vaak een nieuw insuline. Patiënten die andere nieuwe geneesmiddelen gebruikten voor diabetes, kregen juist vaker een nieuw insuline. Tot slot hebben we bepaald of de kans op een nieuw insuline vooral bepaald werd door verschillen tussen patiënten of door verschillen tussen praktijken. In de ideale situatie zouden vergelijkbare patiënten dezelfde behandeling krijgen, onafhankelijk van de huisartsenpraktijk waar ze behandeld worden. Het bleek echter dat praktijken een belangrijke rol speelden: zij bepaalden 20% van alle verschillen. In vergelijking met andere geneesmiddelen en eerdere onderzoeken is dat veel.

In **hoofdstuk 4.2** beschrijven we een onderzoek waarin we het voorschrijven van twee groepen nieuwe geneesmiddelen vergelijken. We onderzochten nieuwe antistollingsmiddelen en nieuwe geneesmiddelen (anders dan insuline) bij diabetes mellitus type 2. Hiervoor gebruikten we opnieuw de Nivel Zorgregistraties eerste lijn. We hebben het totale aantal voorschriften van deze nieuwe geneesmiddelen bepaald tussen

2007 (het moment dat ze op de markt kwamen) en 2019. Het voorschrijven van beide groepen verliep heel anders. Huisartsen schreven de nieuwe antistollingsmiddelen in de eerste jaren bijna niet voor. Vanaf 2014 nam het voorschrijven heel snel toe. In 2019 gebruikten meer patiënten een nieuw antistollingsmiddel dan een oud middel. Het voorschrijven van de nieuwe diabetesgeneesmiddelen nam juist in de eerste jaren gestaag toe. Vanaf 2013 bleef het voorschrijven lang stabiel. In 2019 gebruikte bijna 10% van alle diabetespatiënten een nieuw diabetesgeneesmiddel. De verschillen tussen huisartsenpraktijken waren groot. Dit gold voor zowel de antistollingsmiddelen als de geneesmiddelen bij diabetes. In de eerste jaren werd bij de antistollingsmiddelen 75% van alle verschillen bepaald door verschillen tussen de huisartsenpraktijken. Bij de geneesmiddelen tegen diabetes was dit 33%. In 2019 waren de verschillen veel kleiner geworden: minder dan 1% van alle verschillen kwam nog door verschillen tussen de huisartsenpraktijken. Er was geen verband tussen het voorschrijven van de nieuwe middelen. De praktijken met veel nieuwe antistollingsmiddelen waren andere praktijken dan met veel nieuwe diabetesgeneesmiddelen.

BESCHOUWING

In **hoofdstuk 5** beschrijven we de conclusies van alle hoofdstukken. Op grond van de onderzoeken trekken we twee belangrijke conclusies.

De eerste conclusie is: het voorschrijven van nieuwe geneesmiddelen in de eerstelijnszorg is onvoorspelbaar. Uit onze onderzoeken blijkt dat de voorschrijfpatronen verschillen per geneesmiddel. Nieuwe insulines, nieuwe diabetesmiddelen (anders dan insuline) en nieuwe antistollingsmiddelen hadden allemaal andere voorschrijfpatronen. Ook kunnen we het voorschrijven van nieuwe geneesmiddelen niet goed verklaren door verschillen tussen patiënten en huisartsenpraktijken. Tot slot is er geen samenhang in het voorschrijven van verschillende nieuwe geneesmiddelengroepen.

De tweede conclusie is: wetenschappelijk bewijs speelt maar een beperkte rol in het besluit van zorgverleners om nieuwe geneesmiddelen voor te schrijven. De wetenschappelijke basis voor nieuwe geneesmiddelen bestaat uit een grondige inschatting en interpretatie van de effecten en risico's. Uit onze onderzoeken blijkt dat zorgverleners die inschatting en interpretatie moeilijk vinden. Ook spelen veel andere factoren dan wetenschappelijk bewijs een rol in de keuze om nieuwe geneesmiddelen voor te schrijven. Tot slot beïnvloedt de farmaceutische industrie keuzes met allerlei strategieën.

Uit deze twee conclusies volgt dat het belangrijk is zorgverleners te blijven stimuleren om nieuwe geneesmiddelen alleen voor te schrijven als het echt nodig is. We doen daarom aanbevelingen voor initiatieven gericht op verantwoord gebruik van nieuwe geneesmiddelen. Deze initiatieven moeten eraan bijdragen dat zorgverleners nieuwe geneesmiddelen alleen voorschrijven aan patiënten die ze nodig hebben.

7.2

Dankwoord

De afgelopen jaren heb ik met heel veel plezier aan dit proefschrift gewerkt. Zowel het resultaat als het plezier waren er niet geweest zonder de hulp van velen. Als eerste natuurlijk mijn promotieteam: **Liset van Dijk**, **Aukje Mantel-Teeuwisse** en **Marjorie Nelissen**. Jullie meedenken, altijd snelle reacties op mijn – meestal op vrijdagmiddag verstuurde – voorstellen en stukken, laagdrempeligheid en betrokkenheid hebben gemaakt dat dit boekje er ligt. **Liset**, toen ik eind 2018 bij jou binnenstapte om voorzichtig te peilen of (promotie)onderzoek een optie was, zag jij direct mogelijkheden en kansen. Dat enthousiasme heeft me laten beginnen aan dit traject en heeft al die tijd de energie erin gehouden. Jouw kennis, contacten, pragmatisme en het overal zien van mogelijkheden zijn de start en katalysator geweest van al het onderzoek. **Aukje**, jouw kennis van de geneesmiddelenregulering was een grote hulp. Jij wist in al mijn concept-stukken altijd precies de vinger te leggen op wat er 'niet liep'. En meer dan dat: met jouw voorstellen en suggesties kwam ik waar ik vastliep altijd weer verder. Tot slot **Marjorie**: ik heb geen moment hoeven nadenken over welke IVM'er ik als copromotor wilde. Jouw altijd scherpe blik, bereidheid om mee te denken en collegialiteit zijn een inspiratie. Ik ben door collega's wel eens 'Marjorie 2' genoemd, en dat beschouw ik als een groot compliment.

Dank ook aan alle zorgverleners die hebben meegewerkt aan de focusgroepen, inzameling van marketingmaterialen en het testen en invullen van enquêtes. Het is alleen dankzij jullie - vaak vrijwillige - inzet dat de onderzoeken resultaten opgeleverd hebben.

Dan iedereen die een bijdrage heeft geleverd aan de verschillende artikelen. Namens IVM allereerst **Marieke** en **Marinka**: één van de vele gewaardeerde M&M-teams van het IVM. Jullie harde werk aan het insulineproject heeft hoofdstuk 3.1 en 4.1 mogelijk gemaakt. Dankzij jullie liep zelfs de organisatie van focusgroepen met zorgverleners in coronatijd soepel. **Anke**, er was een tijd dat je – als ik je op vrijdag belde – al wist hoe laat het was en opnam als SPSS helpdesk. Jouw bereidheid om mee te denken over indicatoren, syntaxen, onderzoeksvragen (en wat eigenlijk niet?) was en is een grote hulp. Dank dat je altijd beschikbaar bent om mee te denken. Dank ook aan de stagiaires die hebben meegewerkt aan de onderzoeken, in het bijzonder **Sara** en **Karla. Sara**, jouw onderzoek betekende het begin van mijn promotie en ik vind het ontzettend leuk dat we nog steeds regelmatig contact hebben. **Karla**, jij was de drijvende kracht achter het laatste onderzoek en hebt een grote bijdrage geleverd aan het verzamelen en interpreteren van de marketingmaterialen. Zelfs stakende huisartsen en boeren die de snelweg blokkeerden, konden jou er niet van weerhouden om het hele land door te rijden om de materialen te verzamelen. Dank voor jullie inzet en ik gun iedereen collega's zoals jullie. **Fatima** en **Naomi**, jullie transcriptiewerk maakte onderzoek 3.1

mogelijk. En **Lisanne**, jouw uitzoekwerk was een grote hulp bij onderzoek 3.2. Daarvoor ook mijn dank.

Collega's van het Nivel: met een onderzoeksdag op vrijdag in lockdown-tijd heb ik jullie weinig in het echt gezien en gesproken, maar digitaal des te meer. **Karin**: jouw voorbereidende werk voor de onderzoeken met de Nivel Zorgregistraties was onmisbaar, net als je hulp bij de analyses, controle van de syntaxen, interpretatie van de uitkomsten en het schrijven van de artikelen. En **Claire**, zonder jou hadden er heel rare dingen in de artikelen gestaan over multilevel-analyses. Dank voor al je geduldige uitleg als ik weer eens vastliep. **Tjard**, jouw kennis over COPD-onderzoek was een grote hulp bij mijn eerste pogingen om data te analyseren en een wetenschappelijk artikel te schrijven.

Ook wil ik graag de overige coauteurs bedanken. **Bertien** en **Bas**, jullie specialistische kennis van diabetes hebben de artikelen op een hoger niveau gebracht en ze bovenal beter laten aansluiten bij de dagelijkse praktijk van de huisarts. **Peeter**, jij bood bij mijn laatste onderzoek spontaan je hulp aan toen het onderzoek zich steeds meer op het gebied van marketing in plaats van farmacie ging begeven. Jouw kennis en hulp was onmisbaar: je hebt me in korte tijd veel geleerd over marketing en me enthousiast gemaakt voor een nieuw vakgebied. In het kader van de wederkerigheid hoop ik je nog een keer te trakteren op koffie bij Hygge.

En dan zijn er nog zoveel namen te noemen van de collega's bij het IVM die direct of indirect tot hulp geweest zijn. Een speciaal woord van dank aan **Ruud**: zonder jouw vertrouwen was er van dit hele promotietraject niets terechtgekomen en was ik er überhaupt nooit aan begonnen. Dank dat je me dat vertrouwen altijd weer schenkt. **Monique**, al sinds ik bij IVM werk ben jij vaak mijn luisterend oor, en niet zelden hoor je aan de manier waarop ik m'n telefoon opneem al hoe het ervoor staat. De laatste jaren is onze samenwerking steeds intensiever geworden, en daar ben ik blij mee. **Ellen**, mijn 'onderzoeks-thuiswerk-vrijdag' betekende het einde van onze bijpraatmomentjes op vrijdagochtend in jouw kantoor. Maar gedurende het hele traject ben je regelmatig betrokken geweest als ik weer eens voor de uitdaging stond om mijn teksten te vertalen in beeld. Dank voor je creativiteit en je bereidheid om op de vreemdste momenten mee te denken (ik herinner me druk appverkeer op een late vrijdagavond vanwege een benodigd grafisch abstract). **Marianne**, de voorkant is van jouw hand en is de beste binnenkomer van mijn boekje geworden die ik me had kunnen wensen. Lieve IVM'ers: het boekje zou te dik worden als ik jullie allemaal bij naam zou noemen, maar dat neemt niet weg dat jullie een belangrijke rol speelden en spelen. Jullie accepteerden mijn radiostiltes op vrijdag en toonden niet-aflatende interesse in de voortgang van mijn onderzoek. Bij jullie voel ik me al ruim 11 jaar thuis.

Paranimfen **ome Gert** en **Arjanna**. Met jullie heb ik mijn familie en vrienden letterlijk achter me staan en dat kan ik me niet beter wensen. **Ome Gert en tante Adri**, met elkaar beklimmen we toppen en worstelen we ons door dalen. Dank dat jullie al die jaren en in alle omstandigheden mee oplopen. **Arjanna**: met ruim 30 jaar vriendschap blijft er altijd ruimte voor meer gesprekken en meer thee. Dankjewel voor je trouwe vriendschap. Ik hoop dat er, geheel volgens de verwachtingen van Saar, Krijn en Jet, nog veel momenten met paardenthee en barbecues volgen bij jou en Niels.

Lieve farmacievriendinnen **Hanneke**, **Iris**, **Marieke, Marije** en **Petra**. Met jullie kan ik inhoudelijk sparren over mijn onderzoeken, promotie-ervaringen uitwisselen en het hebben over wat er zoal verder bij het leven hoort. **Astrid**, ooit was er sprake van gedeelde smart over onderzoek(stages). Met dat onderzoek is het bij mij uiteindelijk goed gekomen, maar belangrijker vind ik dat onze vriendschap voortduurt en we allebei onze weg hebben gevonden. **Anne** en **Tjibbe**, jullie interesse in mijn onderzoek en optimisme in het leven is een grote inspiratie. **Johanne**, over de vraag of kwalitatief onderzoek leuker is dan kwantitatief en of er wel of geen tabellen in thuishoren, zullen we het wel nooit eens worden. Maar gesprekken met jou, wandelend door Zuilen of tegenwoordig meestal op afstand, doen me altijd goed. **Mensen van Kerk op Zuilen** en in het bijzonder de **kring**, jullie verwondering over mijn plezier in onderzoek doen, maakten gesprekken erover eigenlijk alleen maar leuker. En dank voor alle keren dat we het leven inclusief de moeilijkheden daarvan kunnen delen. In het bijzonder **Annemarthe** en **René**, een deel van dit proefschrift is nog bij jullie op de bank ontstaan. Ik hoop dat er nog vele kring- en spelletjesavonden volgen en ik blijf met liefde achtergelaten spullen terugbrengen naar jullie.

Klaas, **Cora, Sanne** en **Sven**, ook jullie hadden altijd interesse in mijn onderzoek. De delen van mijn proefschrift geschreven aan de campingtafel in Buren, gevolgd door avonden met spelletjes, boeken en gesprekken, behoren tot de beste herinneringen. Zelfs slapeloze nachten door muizen, harde muziek, onweer en wind doen niets af aan de fijne gezamenlijke momenten.

Lieve familie: jullie zijn de basis van alles. **Mama**, **Matty**, **Willem** en **Rike**, veel onderzoeksvrijdagen eindigden met de gezellig-chaotische maaltijden met altijd minstens drie onaffe gesprekken op de Rivierdijk. Ik ben dankbaar dat we, ondanks en met het gemis van papa, een hecht gezin blijven vormen. Papa's onderzoeksgenen zijn ontegenzeggelijk belangrijk geweest om dit proefschrift te kunnen schrijven. Maar zonder jullie steun en aanwezigheid had ik nooit de stappen durven zetten die me hebben gebracht tot waar ik nu ben. Lieve jongste familieleden **Mette** en **Jildou**: Er was weinig fijner dan op vrijdagmiddag aan onderzoeken te schrijven, wetende dat jullie aan

de andere kant van de muur lagen te slapen. **Mette**, jij hielp met het verwerken van het commentaar op hoofdstuk 3.1 en **Jildou**, de significantie-sterretjes in hoofdstuk 4.1 zijn van jouw hand. Ik hoop dat jullie net zo blij worden van wat je ooit gaat doen als ik dat van onderzoek word.

Toen ik naging op welke plekken ik aan dit proefschrift heb gewerkt, lijkt dat mijn hele leven wel te bevatten. Van IVM, Nivel en mijn eigen huis, tot aan mijn oude slaapkamer in mijn ouderlijk huis (naast slapende nichtjes), mijn oude middelbare school (tegenover mijn zus), de camping (voor de tenttrailer van familie) en op de bank bij vrienden. Dank aan ieder die daar deel van uitmaakt en het leven met mij deelt.

7.3

List of publications

THIS THESIS

Publications

Dankers M, Verlegh PWJ, Weber K, Nelissen-Vrancken HJMG, Van Dijk L, Mantel-Teeuwisse AK. Marketing of medicines in primary care: an analysis of direct marketing mailings and advertisements. PLoS One. 2023;18(8):e0290603

Dankers M, van den Berk-Bulsink MJE, van Dalfsen-Slingerland M, Nelissen-Vrancken HJMG, Mantel-Teeuwisse AK, van Dijk L. Non-adherence to guideline recommendations for insulins: a qualitative study amongst primary care practitioners. BMC Prim Care. 2022;23(1):150.

Dankers M, Hek K, Nelissen-Vrancken M, Houweling ST, Mantel-Teeuwisse A, van Dijk L. Newer long-acting insulin prescriptions for patients with type 2 diabetes: prevalence and practice variation in a retrospective cohort study. Br J Gen Pract. 2022;72(719):e430-e436.

Dankers M, Nelissen-Vrancken HJMG, Hart BH, Lambooij AC, van Dijk L, Mantel-Teeuwisse AK. Alignment between outcomes and minimal clinically important differences in the Dutch type 2 diabetes mellitus guideline and healthcare professionals' preferences. Pharmacol Res Perspect. 2021;9(3):e00750.

Dankers M, Nelissen-Vrancken HJMG, Surminski SMK, Lambooij AC, Schermer TR, van Dijk L. Healthcare Professionals' Preferred Efficacy Endpoints and Minimal Clinically Important Differences in the Assessment of New Medicines for Chronic Obstructive Pulmonary Disease. Front Pharmacol. 2020;10:1519.

Submitted

Dankers M, Hek K, Mantel-Teeuwisse AK, Van Dijk L, Nelissen-Vrancken HJMG. Adoption of new medicines in primary care: A comparison between the uptake of new oral anticoagulants and diabetes medicines. *Submitted 2022*.

OTHER SCIENTIFIC PUBLICATIONS

Janknegt R, **Dankers M**. Long-acting insulin analogues. Drug selection by means of the System of Objectified Judgement Analysis (SOJA). Generics and Biosimilars Initiative Journal (GaBI Journal). 2022;11(1):25-34.

Dankers M, Nelissen-Vrancken HJMG, Berger MY, Bonten MJM, van Gerven JMA, Kunst PWA, Muller M, Olde Rikkert MGM, Rosendaal FR. Recente en toekomstige behandelingen bij COVID-19. Ned Tijdschr Geneeskd. 2022;166:D6675.

Veereschild HM, Noorthoorn EO, Nijman HLI, Mulder CL, **Dankers M**, Van der Veen JA, Loonen AJM, Hutschemaekers GJM. Diagnose, indicate, and treat severe mental illness (DITSMI) as appropriate care: A three-year follow-up study in long-term residential psychiatric patients on the effects of re-diagnosis on medication prescription, patient functioning, and hospital bed utilization. Eur Psychiatry. 2020;63(1):e47.

Dankers M, Hart B, Van Dalfsen M. Update medicamenteuze behandeling diabetes mellitus type 2. Huisarts Wet 2020;63:DOI:10.1007/s12445-020-0548-2.

PROFESSIONAL PUBLICATIONS (SELECTION)

Tarrahi FZ, **Dankers M**. Plaats voor geneesmiddelen bij obesitas? Dé Verpleegkundig Specialist. 2023;18(1).

Polat H, **Dankers M**. IVM: claim fabrikant over finerenon is onduidelijk. Pharm Weekbl. 2023;158(7).

Dankers M, Polat H. SGLT2-remmers en GLP1-agonisten bij diabetes mellitus type 2. Dé Verpleegkundig Specialist. 2022;17(3).

Dankers M. Hoe worden nieuwe geneesmiddelen gepromoot? Ned Tijdschr Geneeskd. 2022;166:D6754.

Polat H, **Dankers M**. Prominentere plek nieuwe geneesmiddelen hartfalen. Pharm Weekbl. 2022;157(40/41).

Dankers M, van Dalfsen-Slingerland M. Vrijwel geen plaats voor DPP-4-remmer in vernieuwd deel diabetesrichtlijn. Pharm Weekbl. 2022;157(29/30).

Van Dalfsen M, **Dankers M**. Obesitas: een groeiend probleem. PiL. 2022;12(2).

Dankers M. Polat H. SGLT2-remmers. Tijdschrift voor Praktijkondersteuners en Praktijkverpleegkundigen. 2022(4).

Dankers M. Eerste orale GLP1-agonist geïntroduceerd. Ned Tijdschr Geneeskd. 2020;164:C4643.

Dankers M, van Dalfsen-Slingerland M. Diabetes type 2: minder CV-risico bij gebruik van dulaglutide. Pharm Weekbl. 2021;156(46).

Van den Berk-Bulsink MJE, van Dalfsen-Slingerland M, **Dankers M.** Omzetten naar biosimilar insuline vraagt extra aandacht en tijd. Pharm Weekbl. 2021;156(9).

Kok L, Geels P, **Dankers M**. Iets minder amputaties, meer kans op bloedingen. Pharm Weekbl. 2021;156(5).

Dankers M, Nelissen-Vrancken HJMG, Lambooij AC. Medicamenteuze behandeling COVID-19. PiL. 2021;11(3).

Dankers M, van Dalfsen M, van El W. Nieuwe ontwikkelingen in de behandeling van diabetes mellitus type 2. Dé Verpleegkundig Specialist. 2020;15(4).

Kok L, van den Berk-Bulsink MJE, **Dankers M**. Medicamenteuze behandeling bij migraine. Dé Verpleegkundig Specialist. 2020;15(1).

Van den Berk M, Appelman S, van Dalfsen M, **Dankers M**. Groot verschil in werkingsduur lijkt niet aannemelijk. Pharm Weekbl. 2020;155(44).

Kok L, van den Berk-Bulsink MJE, **Dankers M**. Medicamenteuze behandeling van migraine. PiL. 2020;10(1).

Dankers M, Hart B, Van Dalfsen M. Behandeling DM2. Tijdschrift voor Praktijk-ondersteuners en Praktijkverpleegkundigen. 2020(4).

Lambooij A, Kok L, **Dankers, M**. Cholesterolverlaging voorbij de statines. Dé Verpleegkundig Specialist. 2019;14(1).

Dankers M. Vaginitis bij SGLT2-remmers. Ned Tijdschr Geneeskd. 2019;163:C4297.

Van Haaften M, van Dalfsen M, **Dankers M**. Insuline degludec geeft minder ernstige hypo's dan glargine. Pharm Weekbl. 2019;154(47).

Dankers M, Stroo M, Lambooij A. Canagliflozine: minder nierfalen en cardiovasculaire sterfte. Pharm Weekbl. 2019;154(31/32).

Eikelboom D, Lambooij A, **Dankers M**. Goed onderzoek nodig naar meerwaarde extrafijne deeltjes. Pharm Weekbl. 2019;154(9).

7.4

About the author

Marloes Dankers was born on June 13th, 1988 in Hardinxveld-Giessendam. She completed her secondary school (VWO) at De Lage Waard in Papendrecht. In 2006, she started to study Pharmacy at Utrecht University. She obtained her bachelor's degree in Pharmacy in 2009 and her master's degree in 2012. During her time at secondary school and university, Marloes worked as assistant-lab technician at Eurofins Medinet B.V. in Breda, where she developed her interest for medicines and research.

After her master's degree, she started working as pharmacist/adviser at the Institute for Rational Use of Medicine (IRUM) and as teacher in the bachelor programme Pharmacy at Utrecht University. Since 2014, she has worked fulltime at the IRUM. In 2019, thanks to the collaboration between IRUM and Nivel, Netherlands Institute for Health Services Research, she started to combine her position at the IRUM with the PhD research at University of Groningen. Her PhD research was supervised by prof. Liset van Dijk (Nivel/ University of Groningen), prof. Aukje Mantel-Teeuwisse (Utrecht University) and dr. Marjorie Nelissen-Vrancken (IRUM).

Marloes is also a reviewer of the Dutch medical journal 'PiL', member of the pharmacotherapy panel of the Dutch Journal of Medicine, member of the guideline committee 'Diabetes mellitus type 2' of the Dutch College of General Practitioners and member of the advisory board of the pharmacists 'Medicine and society' of the Royal Dutch Pharmacists Association. Marloes has been working on 'MedicijnBalans', the IRUM-programme aimed at the rational use of new medicine in primary care, since 2012. Since 2014, she is project leader of this programme.

New medicines can improve treatment outcomes and can be beneficial for patients. However, because of the often unknown long term safety of new medicines, their use can also be harmful. Therefore, both excessive enthusiasm and latency about new medicines can have impact on patients' health and life.

Adding the often high costs of new treatments, it becomes clear that rational use of new medicines is particularly important, both in terms of quality of care and healthcare costs.

Insight in the prescription of new medicines and the considerations of healthcare professionals to prescribe new medicines is therefore particularly relevant. This thesis describes the perspectives and practices of primary care healthcare professionals towards new medicines.

Marloes Dankers