Flinterman, L.E., Kuiper, J.G., Korevaar, J.C., Dijk, L. van, Hek, K., Houben, E., Herings, R., Franken, A.A.M., Graaf, J.P. de, Horikx, A., Janssens, M., Meijer, R., Wijbenga, A., Puijenbroek, E. van, Wolffenbuttel, B.H.R., Links, T.P., Bisschop, P.H., Fliers, E. Impact of a forced dose-equivalent levothyroxine brand switch on plasma TSH; a cohort study, Thyroid: 2020, 30(6), p. 821-828

Postprint version	:	2.0
Journal website	:	https://www.liebertpub.com/doi/abs/10.1089/thy.2019.0414
Pubmed link	:	https://www.ncbi.nlm.nih.gov/pubmed/32188356
DOI	:	10.1089/thy.2019.0414

This is a Nivel certified Post Print, more info at nivel.nl

Impact of a forced dose-equivalent levothyroxine brand switch on plasma TSH; a cohort study:

Linda E. Flinterman[*1] Josephina G. Kuiper[*2], Joke C, Korevaar[*1], Liset van Dijk[1,3], Karin Hek[1], Eline Houben[2], Ron Herings[2], Anton AM Franken[4], Johan P de Graaf[5], Annemieke Horikx[6], Marijke Janssens[7], Rietje Meijer[7], Anneke Wijbenga[7], Eugène van Puijenbroek[3,8], Bruce HR Wolffenbuttel[9], Thera P Links[9], Peter H Bisschop[**10], Eric Fliers[**10]**

1 Nivel, Netherlands institute for health services research, Utrecht, the Netherlands
2 PHARMO Institute for Drug Outcomes Research, Utrecht, the Netherlands
3 Dept. of PharmacoTherapy, -Epidemiology & -Economics (PTEE), Groningen Research Institute of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Groningen, Groningen, The Netherlands
4 Medicines Evaluation Board, Utrecht, the Netherlands
5 Dutch Pituitary Foundation, Nijkerk, the Netherlands
6 Royal Dutch Pharmacists Association, The Hague, the Netherlands
7 Dutch Thyroid Patient Organization (SON), Amersfoort, the Netherlands
8 Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, the Netherlands
9 University of Groningen, University Medical Center Groningen, Department of Endocrinology, Groningen, the Netherlands
10 Amsterdam UMC, University of Amsterdam, Department of Endocrinology and Metabolism, Amsterdam, the Netherlands

Linda E Flinterman, L.Flinterman@nivel.nl

Josephina G Kuiper, josine.kuiper@pharmo.nl

Joke C Korevaar. J.korevaar@nivel.nl

Liset van Dijk, L.vandijk@nivel.nl

Karin Hek, K.Hek@nivel.nl

Eline Houben, eline.houben@pharmo.nl

Ron Herings, ron.herings@pharmo.nl

Flinterman, L.E., Kuiper, J.G., Korevaar, J.C., Dijk, L. van, Hek, K., Houben, E., Herings, R., Franken, A.A.M., Graaf, J.P. de, Horikx, A., Janssens, M., Meijer, R., Wijbenga, A., Puijenbroek, E. van, Wolffenbuttel, B.H.R., Links, T.P., Bisschop, P.H., Fliers, E. Impact of a forced dose-equivalent levothyroxine brand switch on plasma TSH; a cohort study, Thyroid: 2020, 30(6), p. 821-828

Anton A. M. Franken, a.a.m.franken@isala.nl

Johan P de Graaf, j.degraaf@hypofyse.nl

Annemieke Horikx, a.horikx@knmp.nl

Marijke Janssens, marijke.janssens@casema.nl

Rietje Meijer, directeur@schildklier.nl

Anneke Wijbenga, voorzitter@schildklier.nl

Eugène van Puijenbroek e.vanpuijenbroek@lareb.nl

Bruce HR Wolffenbuttel bwo@umcg.nl;

Thera P Links t.p.links@umcg.nl;

Peter H. L. T. Bisschop p.h.bisschop@amsterdamumc.nl

Eric Fliers e.fliers@amsterdamumc.nl

*Equal contribution as first author

**Equal contribution as senior author

Running title: Impact of a forced levothyroxine switch on TSH

Abstract

Background: Patients with primary hypothyroidism are treated with levothyroxine in order to normalize their serum TSH. Finding the optimal dosage is a long-lasting process and a small change can have major impact. Currently, limited data are available on the impact of dose equivalent substitution between brands.
This study aimed to determine the effect of the shortage of the levothyroxine brand Thyrax® in the Netherlands and the resulting dose-equivalent switch to another brand on plasma TSH concentrations in a large cohort of patients.
Methods: Observational cohort study. Two registries representative for the Dutch population containing prescription and laboratory test data: the Nivel Primary Care Database and the PHARMO database network. Patients using at least 25 µg Thyrax® daily for one year or longer were included. Two cohorts were formed: a switch cohort consisting of patients who switched from Thyrax® to an alternative brand, and a Thyrax® cohort including patients who continued to use Thyrax®. Patients in the switch cohort did switch from Thyrax® to a different brand of levothyroxine in 2016 and had two consecutive TSH measurements on the same dose of levothyroxine, one before and one six weeks after the switch. Patients in the Thyrax® cohort had two consecutive TSH measurements on the same dose of Thyrax® that were six weeks apart.
Results: In the Thyrax® cohort, 19% of euthyroid patients using ≤100 µg had a TSH outside the reference range at the subsequent measurement as compared to 24% in the switch cohort ($p<0.0001$). For patients using >100 µg Thyrax® these figures were 24% and 63%, respectively ($p<0.0001$). Furthermore, patients using >50 µg Thyrax® were 4-5 times more likely to become hyperthyroid after a dose-equivalent switch to a different brand compared to patients who stayed on Thyrax®.
Conclusion: In euthyroid patients continuing the levothyroxine product Thyrax® at the same dose, TSH was out of range in 19-24% at least 6 weeks later. A dose-equivalent

switch from Thyrax® to other levothyroxine brands induced biochemical signs of overdosing in an even larger proportion (24-63%) of patients. The results indicate that a dose-equivalent levothyroxine brand switch may necessitate a dose adjustment in a large number of patients.

Introduction

Primary hypothyroidism is a common condition with an estimated prevalence in the general population ranging between 0.3% and 3.7% in the United States (USA) and between 0.2% and 5.3% in Europe depending on the definition used (1). Consequently, a considerable proportion of the adult population receives lifelong treatment with thyroid hormone. Standard treatment of hypothyroidism consists of daily oral administration of synthetic levothyroxine (LT4). The dose is titrated to achieve physiological plasma concentrations of thyroid stimulating hormone (TSH).

Patients with hypothyroidism should receive optimal substitution therapy reflected in a normal TSH so as to minimize thyroid related complaints. The standard treatment modality for hypothyroidism is substitution with levothyroxine (for review see (2)). Stable substitution is only possible if the LT4 bioavailability from LT4 containing tablets is constant. In recent years there have been several examples of changes in the formulation and packaging of LT4 tablets or availability of LT4 tablets necessitating a brand switch, that resulted in a sharp increase in reported side-effects in a number of European countries (3). In December 2013, the manufacturer of the levothyroxine brand Thyrax® in the Netherlands (Aspen) changed the packaging from vials to blisters, which resulted in by more than 2000 reports of side-effects to Lareb, the Dutch National Pharmacovigilance Centre. However, the reason for these complaints remain speculative at this stage, but may relate to differences in degradation of the product in relation to the packaging (4). In 2017 the manufacturer of Euthyrox® in France changed the formulation of Euthyrox® resulting in a steep increase of reported side effects among 3 million Euthyrox® users in France (5). The new formulation of Euthyrox® was introduced to the market after pharmacokinetic bioequivalence testing (6). As such, the new product was rated AB (therapeutically equivalent). These health issues prompted the European Thyroid Association (ETA) together with Thyroid Federation International (TFI), the umbrella organization for thyroid patient organizations from many parts of the world, to issue a position statement on the interchangeability of levothyroxine products in EU countries. The position statement recommends that patients should be maintained on the same formulation/brand name of levothyroxine, that manufacturers should carefully prepare the introduction of a formulation change together with representatives of relevant stakeholders, and that the preparation of a formulation change should include a monitoring plan to become active immediately after introduction. Moreover, the definitions of levothyroxine potency and bioequivalence requirements should be reevaluated (3).

Currently, very limited data are available on the impact of dose equivalent substitution between preparations on the biochemical control as reflected by plasma fT4 and TSH concentrations (6, 7). In 2016 the manufacturer of Thyrax® moved one of its production facilities from the Netherlands to Germany. Due to start-up issues at the new facility Thyrax® was unavailable for many months, and consequently approximately 350,000 patients using Thyrax® (~75% of all levothyroxine users in the Netherlands), had to switch to another LT4 brand. This undesirable situation in terms of public health offered an unique opportunity to study the effects of a forced levothyroxine brand switch by using data from two independent databases. The aim of the present study was to determine the effect of a dose equivalent levothyroxine brand switch resulting from a shortage of the levothyroxine brand Thyrax® on plasma TSH concentrations in a large cohort of patients.

Flinterman, L.E., Kuiper, J.G., Korevaar, J.C., Dijk, L. van, Hek, K., Houben, E., Herings, R., Franken, A.A.M., Graaf, J.P. de, Horikx, A., Janssens, M., Meijer, R., Wijbenga, A., Puijenbroek, E. van, Wolffenbuttel, B.H.R., Links, T.P., Bisschop, P.H., Fliers, E. Impact of a forced dose-equivalent levothyroxine brand switch on plasma TSH; a cohort study, Thyroid: 2020, 30(6), p. 821-828

Materials and methods

Study design and data sources

For this study data from two registries were used, the Nivel Primary Care Database and the PHARMO Database Network (PHARMO). The Nivel Primary Care Database (Nivel-PCD) contains routine collected electronic medical records from 500 general practices in the Netherlands and contains data about visits to the general practitioner (GP), the medical history of patients, prescriptions and results from lab-tests. The PHARMO is a populationbased network of health care databases combining data from different health care settings on a patient level, including out-patient pharmacies and clinical laboratories. The registries each contain a representative sample of the Dutch population. There is no overlap between the two samples of the two registries, therefore it was possible to pool the data without including patients twice. Separate baseline characteristics for the two registries are shown in Table 1. Based on their similarity both registries were pooled. From this pooled dataset two cohorts of patients were formed. The first cohort consists of patients who used the levothyroxine brand Thyrax® in 2014 (PHARMO) or 2015 (Nivel-PCD) (the Thyrax® cohort). The second cohort consists of patients who used Thyrax® in 2016 and were forced to switch to a different brand of levothyroxine in 2016 due to the shortage of Thyrax® (the switch cohort).

Selection of patients

From both cohorts patients who were known to have used at least 25µg Thyrax® daily for one year or longer were selected. Patients from the switch cohort needed to switch to a different brand of levothyroxine in 2016 and to have two consecutive measurements of TSH of the same dose of levothyroxine, one before and one after the switch. The first measurement of TSH took place while still using Thyrax® and the second measurement while using the new levothyroxine brand for at least six weeks. The median time interval between these measurements was 37 weeks (PHARMO) and 14 weeks (Nivel-PCD). Patients from the Thyrax® cohort needed to have two consecutive TSH measurements on the same dose of Thyrax® that were at least six weeks apart. The median time interval between these measurements was 25 weeks (PHARMO) and 28 weeks (Nivel-PCD). In Nivel-PCD, the date of prescription of medication is known, and in PHARMO the date of dispensing is known. As such, assumptions about the duration of use could be made. In the Netherlands, prescription drugs are allowed to be dispensed for a maximum medication use of 3 months. For the present study we assumed that patients who had two prescriptions/dispenses of levothyroxine that were less than six months apart represented continued use of levothyroxine. If two prescriptions/dispenses were apart for more than six months we assumed that patients used the medication for three months, discontinued the use of levothyroxine and restarted at the second prescription. Flow charts for the Thyrax® and the switch cohort are shown in Fig 1.

Statistical analysis

Baseline characteristics including age, sex and average dose of Thyrax®, were assessed for both cohorts separately. In order to unmask potential dose-dependent effects, all analyses were done separately for patients who used ≤ 100 µg and >100 µg levothyroxine, assuming that the impact of a brand switch might be more pronounced for patients using a higher dose. Measures of TSH were divided in hyperthyroid, normal and hypothyroid according to the Dutch guidelines for general practitioners (https://www.nhg.org/standaarden/volledig/nhg-standaard-schildklieraandoeningen). TSH concentrations were considered normal between 0.4 and 4.0 mIU/L, reflecting hyperthyroidism when lower than 0.4 mIU/L and hypothyroidism when higher than 4.0 mIU/L. For both cohorts the proportion of patients belonging to each of the TSH groups was compared between the first and second TSH measurement using a chi square test. As the effect of a brand switch on plasma TSH

appeared to be different for patients who used ≤ 100 µg or >100 µg levothyroxine, the patients were divided into six subgroups based on the dose (26-50 µg, 51-75 µg, 76-100 µg, 101-150 µg, 151-200 µg, >200 µg) to see if there was dose-equivalence for the whole range of doses for those who did and did not switch from brands of levothyroxine. Per subgroup the percentage of patients who were hyperthyroid or hypothyroid at the second measurement was calculated.

Results

Patients

For both cohorts about 2% of all patients in the combined registries used Thyrax®. The switch cohort consisted of 18,010 eligible patients and the Thyrax® cohort consisted of 41,777 eligible patients (Fig 1a and b). Most patients were excluded because they used Thyrax for less than a year and/or at a dose less than 25 µg per day. Of the selected Thyrax® users in the Thyrax® cohort, 20% had at least two consecutive measurements of TSH on the same dose of Thyrax® that were at least 6 weeks apart. For the switch cohort, 9% of the selected Thyrax® patients fulfilled the criteria. This lower percentage is mainly caused by the more strict criteria for the switch cohort: switch of levothyroxine brand and two consecutive measurements around this switch. In the end, 6438 patients fulfilled the criteria and were selected for the Thyrax® cohort and 1204 patients for the switch cohort (Table 1). Although the percentage of included patients was different for the switch cohort, the characteristics of both cohorts were similar (Table 1). In both cohorts 85% of the patients were women, and the mean age was around 60 years. Only the dose of Thyrax® used differed slightly between the two cohorts.

Changes in TSH concentrations between two measurements

Plasma TSH at the second measurement for patients with a normal, elevated or decreased initial TSH are shown in Fig 2a, b and c, respectively. Of the patients with a normal TSH at the first measurement, who used a low dose of Thyrax® (≤100 µg) and who did not switch to a different brand, 19% had a TSH outside the reference range at the second measurement (Fig 2a). When patients with a normal TSH at the first measurement used ≤100 µg Thyrax® and switched to a different brand, 24% had a TSH outside the reference range after the switch (Fig 2a). This difference in percentage TSH outside the reference range at the second measurement between the Thyrax® cohort and the switch cohort was statistically significant (p-value <0.00001). There was no statistically significant difference in percentage TSH outside the reference range at the second measurement between the Thyrax® cohort and the switch cohort for patients with a first TSH measurement outside the reference range.

For patients who used >100 µg Thyrax® a similar, but much more pronounced pattern was observed. Of the patients with a normal TSH at the first measurement who did not switch to a different brand 24% had a TSH outside the reference range at the next measurement. Of the patients who did switch 63% had a TSH level outside the reference range at the next measurement (Fig 2a) (p-value <0.00001). The majority of these patients had plasma TSH concentrations below the reference range, indicative of overdosing.

The observation that patients in the switch cohort who used >100 µg Thyrax® were more likely to become hyperthyroid at the second measurement than patients on a lower Thyrax® dose suggested that different brands are not bio-equivalent. To study dose-dependency in more detail the percentage of patients with a normal TSH at the first measurement who became hyperthyroid or hypothyroid at the second measurement was calculated for six different dose groups of levothyroxine (Table 2). We found that patients with a normal TSH who switched from Thyrax® to the same dose of a different brand of levothyroxine (either Euthyrox®, Levothyroxinenatrium Teva®,

Nycomed®, or Thyrofix®) were 4 to 5 times more likely to develop hyperthyroidism compared to patients who did not switch between brands if they used more than 50 µg of levothyroxine, whereas there was no obvious difference for patients using 50 µg or less. Patients were less likely to develop hypothyroidism compared to patients who did not switch between brands. This strongly suggests that the different brands of levothyroxine are not bio-equivalent.

Discussion

The population prevalence of thyroid hormone medication use by adults in the Netherlands was recently reported to be 3.1%. In 2016 approximately 350,000 patients using the levothyroxine brand Thyrax® had to switch to another LT4 brand. By analyzing data from two independent Dutch registries containing data on medication use and lab measurements, we were able to determine the effect of dose equivalent substitution between different LT4 preparations on plasma TSH concentrations. Of the patients with a normal TSH using ≤100 µg Thyrax® daily, a small but statistically significant increase in the proportion of patients with a TSH outside the reference range was identified at the next measurement in the switch cohort as compared with patients who continued use of Thyrax® (24% vs 19%). For patients using >100 µg, these figures were 63% and 24%, respectively ($p<0.0001$), indicating a substantial number of patients in need of a dose change after the brand switch. Furthermore, patients using >50 µg Thyrax® were 4-5 times more likely to become hyperthyroid after a dose-equivalent switch to a different levothyroxine brand compared to patients who stayed on Thyrax®. Thus, a dose-equivalent levothyroxine brand switch may induce biochemical signs of over- or underdosing in a large proportion of patients using >50 µg Thyrax® daily. This study also shows that when patients do not switch between brands and remain on the same dose, 20% will be out of range at a second measurement; however, it is unknown whether these patients experience clinical symptoms.

Although the interchangeability of different LT4 preparations has been hotly debated both in the scientific and in the public domain (3, 7), only very limited data are available on the impact of dose equivalent substitution between preparations on the biochemical control in patients with hypothyroidism (7). When the manufacturer of Thyrax® (Aspen) moved one of its production facilities from the Netherlands to Germany in 2016, Thyrax® became unavailable for many months in the Netherlands and approximately 350,000 patients using Thyrax® had to switch to another LT4 brand. This created a unique opportunity to provide the first population based study to address the consequences of a dose equivalent brand switch of levothyroxine on plasma TSH. That the motivation for the brand switch was not related to health issues, but rather to the availability of the medication, reduces the risk of selection bias and adds to the strength of the study. We used two different Dutch registries containing data on medication use and lab measurements. Both registries have shown to be representative for the Dutch population, but reflect a different parts of the population. Thus, the fact that baseline characteristics for the two registries were remarkably similar and TSH data could be pooled further strengthens the present study. Finally, the study is based on unbiased and objective data (brand, dose, TSH) instead of subjective data such as questionnaires and self-reported side effects.

A limitation of the present study is that changes in plasma TSH within the reference range following the switch are not addressed. However, TSH changes within the reference range following a small dose change are unlikely to result in changes in hypothyroid symptoms, well-being, or quality of life (10, 11).Furthermore, in the Nivel-PCD prescriptions from the GPs, no actual dispensing data are known, while the reverse is true for PHARMO. Therefore some patients might have a prescription which they did not collect at the pharmacy. However, this was the case both before and after the shortage of Thyrax®. Moreover, only patients using Thyrax® for more than one year were included, so they had obtained at least 4 prescriptions for Thyrax® and were regular users, making it likely that

the new prescription was also collected at the pharmacy. Furthermore, TSH measurements needed to be at least six weeks apart, so missing data included patients who had a shorter TSH interval, likely resulting from subjective complaints. This may have led to an underestimation of the percentage TSH outside the reference range at the second time point. A final weakness might be that some patients anticipating a shortage of Thyrax®, and as a consequence did not appear in our switch cohort. However, patients need a prescription provided by a health care provider to obtain Thyrax®, and we did not find any compression of frequency of prescriptions, making this less likely.

A relatively large number of studies have addressed the effect of a levothyroxine formulation change from tablets to a liquid formulation on plasma TSH. A recent systematic review and meta-analysis showed that a significant proportion of patients with suboptimal TSH on tablet LT4 showed improved TSH levels after switching to liquid formulation LT4 at unchanged dose. This indicates that a liquid form of levothyroxine may increase bioavailability compared to tablets, perhaps resulting from less sensitivity of the liquid formulation to factors reducing the absorption of LT4 tablets (8). Only few data are available on effects of generic versus brand-name LT4 tablets on TSH. A study in children with severe congenital hypothyroidism reported that generic and brand-name LT4 were not bioequivalent, but this was a rather small study in an academic medical center setting (9). To our knowledge, there are no population-based studies available on the effects of a brand or formulation change on serum TSH.

The present study focusses on two levothyroxine products to replace the brand-name drug Thyrax®, i.e., levothyroxine Teva and Euthyrox®. Thyrax® and Euthyrox® are both brand name stand-alone drugs and are not generics of each other. Levothyroxine Teva is a generic of L-thyroxin Henning®, which has been registered in Germany but not in the Netherlands. Thus, the products that were substituted cannot be considered AB rated. Therefore, the outcome of our study may not be surprising in the eyes of the regulator, but it certainly is in the eyes of most clinicians and their patients.

Over the past years, a number of European countries have seen major health issues, in particular increased prevalence of reported side effects, after a switch from one levothyroxine brand to another. Until now, it was not possible to ascertain whether these health issues were pharmacologically related to the brand change as data on the effect of the brand change on thyroid function tests were lacking. The present study reports an increased prevalence of biochemical hyperthyroidism after a dose-equivalent levothyroxine brand switch from Thyrax® to other brands of levothyroxine in the Netherlands in 2016, especially in patients using more than 100 µg of levothyroxine daily. This observation may explain the steep increase in the number of reported levothyroxine side effects in the Netherlands in 2016 (3). The results of the study suggest that there are differences in bioavailability between the different levothyroxine brands. Given the considerable prevalence of hypothyroidism, it is very likely that the brand change has led to significantly increased health care consumption and health care expenses. Thus, our study has implications for relevant stakeholders, including health care professionals, national endocrine societies, medicine evaluation boards, pharmacovigilance centres, pharmacists and GP associations, and thyroid patient organizations as it strongly supports a number of recommendations issued recently by the European Thyroid Association together with Thyroid Federation International (3). First, patients should be maintained on the same formulation/brand of levothyroxine, if possible. If a change is necessary, a blood test after six weeks should be performed to determine whether any adjustment to dosage is required. Second, manufacturers should carefully prepare the introduction of a formulation change together with representatives of relevant stakeholders in order to prevent insufficient communication and coordination. Third, the preparation of a formulation change should include a monitoring plan to become active immediately after introduction.

The extent of the burden of the forced brand switch following the Thyrax® shortage in the Netherlands in terms of mental stress for the patient, health care consumption and health care expenses is likely to be substantial. One of the key questions is how the observed increase in biochemical signs of hyperthyroidism after the switch for Thyrax® to other levothyroxine brands can be reconciled with the fact that the switch took place within the existing legal framework of regulations and monitoring. A similar question arose from observations in France, where Merck introduced a new formulation for the levothyroxine brand Levothyrox® based on the need for tighter specification (95% to 105%) over the whole shelf life. Similar to the Dutch situation, this change involved a large number of patients as 2.6 million patients were being treated in France with Merck's Levothyrox® in 2017 (data from the French Agence Nationale de Sécurité des Médicaments). In January 2018, 17,310 reports of adverse effects had been received by the French site for drug surveillance (BNPV, Base National de Pharmacovigilance) [(http://ansm.sante.fr/content/download/115249/.../Rapport_Levothyrox_CT-30-01- 2018.pdf). This large number of reported side effects was in contrast with a pharmacokinetic study showing that the new formulation meets potency specification and bioequivalence guidelines (6). These discrepancies should be the subject of future research. Furthermore, a joint and multidisciplinary effort is needed to limit the burden for patients with hypothyroidism, so as to prevent increased health care consumption and health care expenses when future brand or formulation changes are anticipated.

In summary, in euthyroid patients continuing the levothyroxine product Thyrax® at the same dose, TSH was out of range in 19-24% at least 6 weeks later. A dose-equivalent switch from Thyrax® to other levothyroxine brands induced biochemical signs of overdosing in an even larger proportion (24-63%) of patients. By inference, a substantial proportion of patients needed a dose adjustment after a levothyroxine brand switch. Future (forced) changes of brand or formulation should therefore be announced in time, accompanied by balanced patient information, be monitored closely, and include advice on dose adjustment if needed.

Acknowledgements and disclosures

Contributors

All authors participated in designing the study, generating hypotheses, interpreting the data, and critically reviewing the paper. LF and EF wrote the first draft of the report. Other members of the writing group were JGK, JCK, PHB, TPL, with support from LvD, RH, KH and EH. LF, KH, JGK and EH had full access to anonymised individual-patient data . The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding

This study was supported by a grant from the Netherlands Organisation for Health Research and Development (ZonMw) on advice from The Dutch Ministry of Health, Welfare and Sport. The sponsor had no involvement in the conduct of the study nor the interpretation of the findings or the writing of the manuscript.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work (except the research grants listed in funding); no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Flinterman, L.E., Kuiper, J.G., Korevaar, J.C., Dijk, L. van, Hek, K., Houben, E., Herings, R., Franken, A.A.M., Graaf, J.P. de, Horikx, A., Janssens, M., Meijer, R., Wijbenga, A., Puijenbroek, E. van, Wolffenbuttel, B.H.R., Links, T.P., Bisschop, P.H., Fliers, E. Impact of a forced dose-equivalent levothyroxine brand switch on plasma TSH; a cohort study, Thyroid: 2020, 30(6), p. 821-828

Ethical approval

The use of electronic health records for research purposes under certain conditions. When these conditions are fulfilled, neither obtaining informed consent from patients nor approval by a medical ethics committee is obligatory for this type of observational studies containing no directly identifiable data (art. 24 GDPR Implementation Act jo art. 9.2 sub j GDPR).

Dissimination plan

The results of this study are integrated in the advice given to GPs in case patients need to change from levothyroxine brand.

Transparency

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Exclusive licences

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Corresponding author

Joke Korevaar, j.korevaar@nivel.nl

Reference list

1. Chaker L, Bianco AC, Jonklaas J, Peeters RP 2017 Hypothyroidism. Lancet 390:1550-1562.
2. Wiersinga WM 2014 Paradigm shifts in thyroid hormone replacement therapies for hypothyroidism. Nat Rev Endocrinol 10:164-174.
3. Fliers E, Demeneix B, Bhaseen A, Brix TH 2018 European Thyroid Association (ETA) and Thyroid Federation International (TFI) joint position statement on the interchangeability of levothyroxine products in EU countries. Eur Thyroid J 7:238-242.
4. Hartman J, Weits G, Rolfes L 2015 A follow-up questionnaire: a successful tool to study topics related to packaging changes of the drug Thyrax in the Netherlands. Drug Saf 38:987 (abstract)
5. Casassus B 2018 Risks of reformulation: French patients complain after Merck modifies levothyroxine pills. BMJ 360:k714
6. Gottwald-Hostalek U, Uhl W, Wolna P, Kahaly GJ 2017 New levothyroxine formulation meeting 95-105% specification over the whole shelf-life: results from two pharmacokinetic trials. Curr Med Res Opin 33:169-174.
7. American Thyroid Association, Endocrin society, American Association of Clinical Endocrinologists 2004 Joint statement on the U.S. Food and Drug Administration's decision regarding bioequivalence of levothyroxine sodium. Thyroid 14:486.

8. Virili C, Giovanella L, Fallahi P, Antonelli A, Santaguida MG, Centanni M, Trimboli P 2018 Levothyroxine therapy : changes of TSH levels by switching patients from tablet to liquid formulation. A systematic review and meta-analysis. Front Endocrinol 9:10.
9. Carswell JM, Gordon JH, Popovsky E, Hale A, Brown RS 2013 Generic and brand-name Lthyroxine are not bioequivalent for children with severe congenital hypothyroidism. J Clin Endocrinol Metab 98:610-617.
10. Walsh JP, Ward LC, Burke V, Bhagat CI, Shiels L, Henley D, Gillet MJ, Gilbert R, Tanner M, Stuckey BG 2006 Small changes in thyroxine dosage do not produce measurable changes in hypothyroid symptoms, well-being, or quality of life: results of a double-blind, randomized clinical trial. J Clin Endocrinol Metab 91:2624-2630.
11. Samuels MH, Kolobova I, Niederhausen M, Janowsky JS, Schuff KG 2018 Effects of altering levothyroxine (L-T4) doses on quality of life, mood, and cognition in L-T4 treated subjects. J Clin Endocrinol Metab 103:1997-2008.

Tables and figures

Table 1: Patient characteristics (per cohort and registry)

	Baseline cohort Nivel (n=2659)	Baseline cohort PHARMO (n=3,479)	Switch cohort Nivel (n=629)	Switch cohort PHARMO (n=575)
% Women	84.9	84.4	83.8	81.2
Mean age (years, SD)	61.8 (16.0)	61.1 (15.7)	66.1 (16.2)	59.4 (17.5)
Mean TSH concentration at first measurement (IU/L, SD)	3.2(6.8)	2.4 (4.0)	2.7 (3.9)	2.8 (3.0)
Mean dose of Thyrax® (µg, SD)	95 (36)	109 (44)	93 (37)	94.9 (43.6)
% of patients using >100µg levothyroxine	16.6	41.4	14.5	32.3
Levothyroxine brand used at second measurement				
Thyrax® (%)	100	100		
Euthyrox (%)			27	39
Teva (%)			70	59
Nycomed (%)			3	1
Thyrofix (%)			0	1

Table 2: Bioequivalence. The table shows the percentage of patients who became hyperthyroid or hypothyroid at the second measurement when the first plasma TSH was within reference in both cohorts per dosage of levothyroxine used

	Thyrax			Switch			Ratio Switch/Thyrax	
		Hyperthyroid	Hypothyroid		Hyperthyroid	Hypothyroid	Hyperthyroid	Hypothyroid
Dose (µg)	N	%	%	N	%	%		
26-50	563	3	15	161	4	12	1.3	0.8
51-75	992	3	13	273	8	9	2.7	0.7
76-100	1.332	8	11	242	33	2	4.1	0.2
101-150	902	13	8	136	55	2	4.2	0.3
151-200	213	19	10	43	77	5	4.1	0.5
>200	51	29	12	6	67	17	2.3	1.4
Total	4.053	8	11	861	26	7	3.2	0.6

Legends

Figura 1a: Thyrax cohort

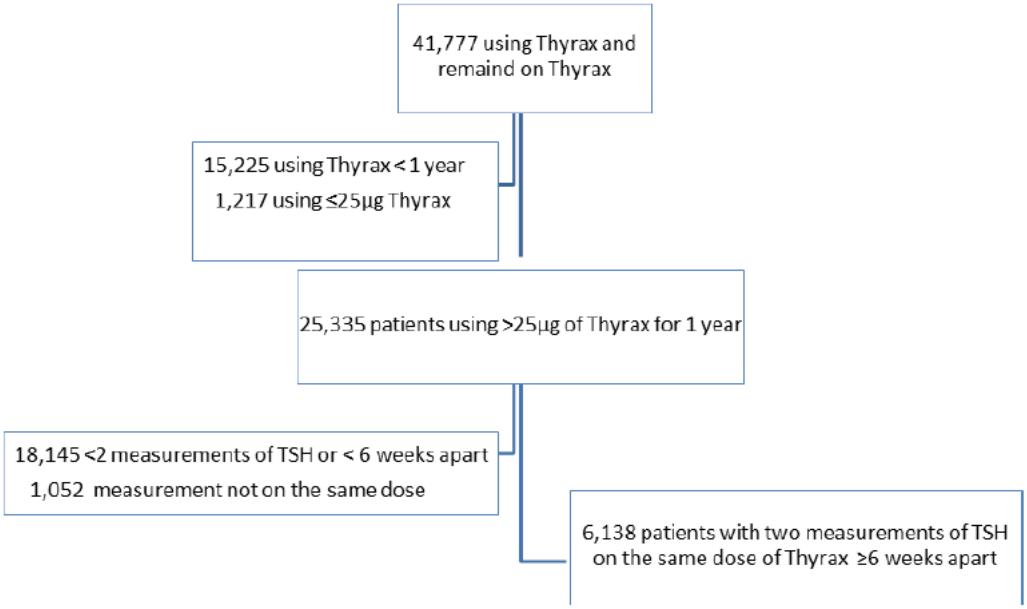

Figure 1b: switch cohort

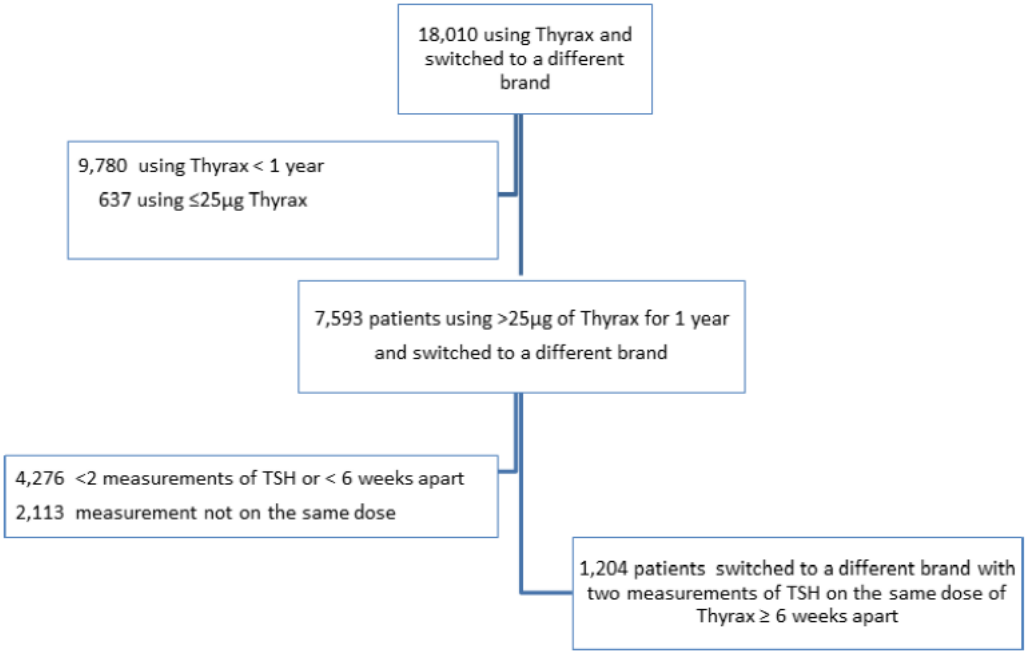

Figure 2a TSH plasma concentration at a second measurement for patients with a TSH within the reference range at the first measurement (panel A: dose <=100µg, panel B: dose >100µg)

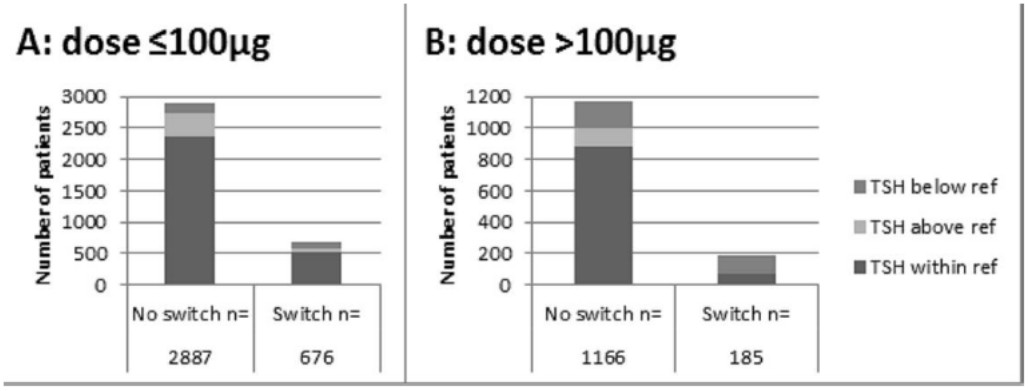

Figure 2b TSH plasma concentration at a second measurement for patients with a TSH above the reference range at the first measurement (panel A: dose <=100µg, panel B: dose >100µg

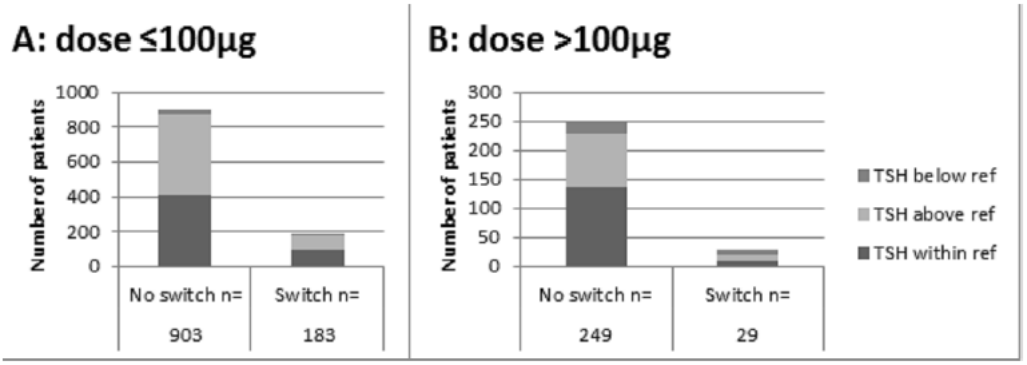

Figure 2c TSH plasma concentration at a second measurement for patients with a TSH below the reference range at the first measurement (panel A: dose <=100µg, panel B: dose >100µg)