The parathyroid glands are usually 4 delicate structures 3 to 4 mm in size and located close to the thyroid gland. Their function is to maintain calcium (Ca) homeostasis by producing the parathyroid hormone (PTH). Unfortunately, these organs are at risk of damage during thyroid surgery, potentially resulting in postoperative hypoparathyroidism (hypoPT). HypoPT is one of the most common complications after total or completion thyroidectomy and is in most patients caused by accidental damage or resection of parathyroid glands or impaired blood supply.1,4 Immediate clinical signs of hypoPT due to hypocalcemia are perioral numbness, muscle cramps, and paresthesia, as well as severe seizures and cardiac arrhythmias in rare instances. In the case of persistent hypoPT, patients are at risk for kidney complications, impaired quality of life, and increased mortality rates.3-5 Transient hypoPT (parathyroid function restores within the first year after surgery) occurs in up to 19% to 38% of patients after total or completion thyroidectomy.6 Patients with hypoPT beyond this period are usually classified as having persistent hypoPT.7-9 Data from high-volume single centers show frequencies of persistent hypoPT less than 5%. A single-center study from Sweden and a Korean case series published a 1.9% and 1.5% incidence rate, respectively.6,10 Another single-center study from Austria and a French multicenter study showed even lower incidences of 1.2% and 1.0%, respectively.11,12 However, recent registries and nationwide multicentric studies reported much higher frequencies.2,13,14

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higher incidence rates. A Swedish population-based study reported a persisting hypoPT rate of 14.5%, and a Spanish multicenter nationwide study reported an even higher incidence rate of 16.7%. The British Association of Endocrine and Thyroid Surgeons (BAETS) reported a 7.3% rate in their fifth national audit, and a survey from the Thyroid Cancer Alliance yielded a 13.8% rate. This variety in reported incidence rates might be partially explained by the absence of an international standardized definition for persistent hypoPT, differences in case mix, and underreporting of this complication. Despite the fact that there is substantial literature on the incidence of hypoparathyroidism, uniform diagnosis and treatment guidelines are still lacking. We hypothesized that the incidence of hypoparathyroidism in the literature is underestimated because there are no diagnostic guidelines, and national registries and multicenter studies demonstrate substantially different outcomes compared with single-center studies.

In the Netherlands, nearly a decade ago, centralization of complex health care and (oncological) thyroid care was introduced. Centralization is defined as the reorganization of health care services into fewer specialized units. Correspondingly, surgical procedures for high-risk thyroid cancer, large goiters, and repeated thyroid surgery, for example, are predominantly conducted in academic centers. Within this framework, and because most studies, to our knowledge, include single-center studies or national registries, this study evaluates the real-life incidence of postoperative, persistent hypoPT after total or completion thyroidectomy in a tertiary academic patient population. In addition, the effect of different definitions regarding hypoparathyroidism is assessed. The outcome of this study has the potential to refine the informed consent procedure in specialized centers and provide a stepping stone for further collaborations that aim to reduce complication rates and establish uniform treatment protocols.

Methods

Study Design and Study Participants
This is a retrospective, 1-year, multicenter cohort study of patients undergoing a total or completion thyroidectomy in 7 university hospitals (of 8) in the Netherlands during 2016. All 8 university hospitals were invited to participate in this study, of which 7 responded to the invitation. Oncological thyroid care in the Netherlands is centralized, and patients who require extensive thyroid surgery, such as for advanced cancer or large goiters, mainly undergo their procedures in university hospitals. Patients eligible for inclusion were 18 years or older and underwent a total or completion thyroidectomy for any diagnosis. Patients were excluded if (1) they were known to have preoperative parathyroid disease (eg, hyperparathyroidism) or used active vitamin D (Dv) for another indication, (2) follow-up data were unavailable, or (3) the patient underwent reoperation in the central neck compartment within 1 year after total or completion thyroidectomy.

Surgical Procedure
Total or completion thyroidectomy was performed by endocrine surgeons in university hospitals in the Netherlands. One hospital performed robot-assisted transaxillary thyroidectomies in 2016. All other hospitals performed the surgery via a Kocher incision over the thyroid parallel to the skin folds. Thyroidectomy procedures were performed in the same standardized manner by ligation of the superior vessels and mobilization of the upper pole followed by the capsular dissection technique with respect to the parathyroid glands. The inferior vessels were ligated after identifying the recurrent laryngeal nerve. Incidentally resected parathyroid glands were autotransplanted into the sternocleidomastoid muscle. A central (level VI) or lateral (levels IIA, III, IV, and Vb) lymph node dissection (cervical lymph node dissection [CLND] and lateral lymph node dissection [LLND]) was performed when indicated (eg, preoperative suspicion of lymph node metastasis).

Key Points

Question What is the incidence of postoperative, persistent hypoparathyroidism after total or completion thyroidectomy in a university hospital patient population?

Findings In this cohort study of 200 Dutch patients, the risk of persistent hypoparathyroidism after total or completion thyroidectomy was 15% in patients who were referred to university hospital centers.

Meaning The study results suggest that the high rate of persistent hypoparathyroidism warrants efforts to reduce this complication rate, and the use of uniform evidence-based treatment guidelines could enable comparison of interventions.

Ethics
Data obtained from patient records were anonymously stored using study-specific patient codes in a password-protected database. The protocol had been approved by the Medical Ethics Committee Rotterdam, and informed consent was waived. The study used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data Collection and Definition
Medical health records were reviewed to determine the patient’s age and sex, the indication, extent and outcome of surgery, the length of hospital stay, and additional postoperative treatment. Data on Ca and Dv supplementation at discharge, 6 months after surgery, and 1 year after surgery were collected. We chose a clinical and pragmatic definition of persistent hypoPT as requiring Dv with or without Ca longer than 1 year after surgery. We believe that this definition reflects those patients who have a markedly low amount or lack of PTH levels because it is well known that patients with hypoPT require active Dv supplementation (with or without Ca) to absorb Ca because of the markedly low amount or lack of PTH levels. Therefore, this definition approximates the true incidence of persistent hypoPT. Parathyroid hormone levels are not routinely assessed in participating hospitals and are therefore not included in this article.
Postoperative Hypocalcemia Supplementation Protocols

Each hospital had its own Ca supplementation protocol (eTable in the Supplement). In one of the participating hospitals, a prophylactic Ca supplementation protocol was used during 2016. However, as stated in this center’s Ca protocol, Ca supplementation was discontinued 2 weeks postoperatively, if possible (eTable in the Supplement). Two hospitals initiated Ca supplementation when serum Ca levels were lower than 8.4 mg/dL (to convert to mmol/L, multiply by 0.25) and all other hospitals when the serum Ca levels were less than 8.8 mg/dL. The initial daily dose of calcium carbonate varied between 1500 mg and 3000 mg. In 4 hospitals, active Dv analogues were administered when serum Ca levels were less than 8 mg/dL and in 1 hospital when serum Ca levels were less than 8.4 mg/dL. Another hospital administered Dv with Ca supplements, and another if persisting hypocalcemia (Ca <8.8 mg/dL) was seen during the first postoperative day. All hospitals adjusted the dosage based on serum Ca levels. Target serum Ca levels were within the lower normal range in all hospitals (Table 1). Three hospitals explicitly stated that weaning could be initiated when normocalcemia or Ca levels greater than 8.8 mg/dL were reached. In the case of severe hypocalcemia, an endocrinologist was consulted. All hospitals left weaning of supplementation at the discretion of the endocrinologist at the outpatient clinic.

Statistical Analysis

Data were analyzed using descriptive statistics. Categorical variables are displayed as count and percentage. Continuous variables with normal distribution or abnormal distribution are displayed by mean (SD) or median (IQR), respectively. Differences between groups were evaluated with an effect size metric of absolute difference, and the precision of the effect size metric was measured with 95% CI.17 Statistical analyses were performed using IBM SPSS, version 25.0.

Results

Study Population and Baseline Characteristics

Of the 224 adult patients who underwent a total or completion thyroidectomy, 200 (89.3%) were included in this study. Demographic characteristics and clinical data of the final study cohort are summarized in Table 1. The median age of our final study cohort was 49.0 (IQR 37.0-62.0) years, and 143 (71.5%) were women. The reason for surgery was carcinoma for 138 (69.2%), Graves disease for 33 (16.5%), and multinodular goiter for 17 patients (8.5%), and 12 (6.0%) had other indications.

Surgery and Additional Postoperative Treatment

In total, 135 patients (67.5%) underwent a total thyroidectomy (TTx) and 65 patients (32.5%) a completion thyroidectomy; 4 patients (2.0%) underwent robot-assisted transaxillary thyroidectomy. Of the 135 patients who underwent a TTx, 128 patients (94.8%) underwent a TTx alone without a CLND or LLND. A CLND alone was performed in 34 patients (17.0%), and a CLND and LLND was performed in 38 patients (19.0%). In patients who underwent a TTx (n = 135), 27 (20.0%) developed postoperative persistent hypoPT, while the rate was 4.6% for the 65 patients who underwent a completion thyroidectomy (difference, 15.4%; 95% CI, 7.0%-23.9%). Among the 38 patients who underwent a CLND and LLND, the rate of postoperative hypoPT was 26.3%, while the rate was 12.4% for the 162 patients who did not differ (difference, 14.0%; 95% CI, −0.9% to 28.9%). The mean (SD) length of hospital stay in patients with a diagnosis of postoperative persistent hypoPT was 6.7 (3.7) days; this was 3.5 days (95% CI, 2.2-4.8 days) longer than in patients without hypoPT (Table 2).

In total, 119 patients (59.7%) received postoperative radiiodine (RAI) therapy. In these patients, the rate of persistent hypoPT was 10.1%, and the rate among the 81 who did not receive RAI was 22.2% (difference, 12.1%; 95% CI, −22.7% to
−1.6%). Postoperative radiotherapy of the neck was performed in 6 patients (3.0%), of whom 0 developed persistent hypoPT vs a hypoPT rate of 15.5% in the 194 patients who did not receive radiotherapy (difference, 15.5%; 95% CI, −20.6% to −10.4%). Reoperation for postoperative bleeding was performed for 12 patients, of whom 2 (16.7%) developed persistent hypoPT; in patients who did not undergo a reoperation, 28 (14.9%) developed persistent hypoPT (difference, 1.8%; 95% CI, −19.9% to 23.5%) (Table 2).

### Table 2. Procedural Characteristics and Outcomes Stratified by the Presence of Persistent HypoPT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study population (n = 200)</th>
<th>No. of hypoPT (n = 30)</th>
<th>Rate of hypoPT (%)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroidectomy</td>
<td>Total 135 27 20.0</td>
<td>15.4% (7.0 to 23.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Completion 65 3 4.6</td>
<td>11.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLND</td>
<td>Positive 34 7 20.6</td>
<td>6.7 (-7.9 to 21.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative 166 23</td>
<td>13.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLND and LLND</td>
<td>Positive 38 10</td>
<td>26.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative 162 20</td>
<td>12.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization, mean (SD, d)</td>
<td>3.7 (3.6) 6.7 (3.7)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAI</td>
<td>Positive 119 12</td>
<td>10.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative 81 18</td>
<td>22.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT neck</td>
<td>Positive 6 0 0 15.5 (-20.6 to -10.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative 194 30</td>
<td>15.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reoperation for bleeding</td>
<td>Positive 12 2</td>
<td>16.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative 188 28</td>
<td>14.9</td>
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</tbody>
</table>

Table 3. Postoperative Ca and Dv Supplementation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>At discharge (%</th>
<th>6 Months postsurgery</th>
<th>1 Year postsurgery</th>
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<tr>
<td>Ca only</td>
<td>78 (39.0)*</td>
<td>21 (10.5)</td>
<td>13 (6.5)</td>
</tr>
<tr>
<td>Dv only</td>
<td>1 (0.5)</td>
<td>4 (2.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>CaDv</td>
<td>55 (27.5)</td>
<td>32 (16.0)</td>
<td>29 (14.5)</td>
</tr>
<tr>
<td>Dv or CaDv</td>
<td>56 (28.0)</td>
<td>36 (18.0)</td>
<td>30 (15.0)</td>
</tr>
<tr>
<td>Ca and/or Dv</td>
<td>134 (67.0)</td>
<td>57 (28.5)</td>
<td>43 (21.5)</td>
</tr>
</tbody>
</table>

Postoperative Ca and Dv Supplementation

The rate of persistent hypoPT in this cohort was 15.0% (30 patients). The range of incidence of persistent hypoPT across the 7 participating hospitals was 5.6% to 26.9%, and there was no meaningful difference in the incidence of persistent hypoPT between the hospitals. At discharge, 78 patients (39.0%) received postoperative Ca supplementation only (of whom 31 patients [39.7%] received a prophylactic), 1 patient (0.5%) Dv supplementation only, and 55 patients (27.5%) Ca and Dv (CaDv) supplementation (Table 3). One year after surgery, 13 patients (6.5%) received Ca supplementation only, 1 (0.5%) Dv only, and 29 (14.5%) CaDv supplementation (Table 3).

### Table 3. Postoperative Ca and Dv Supplementation

<table>
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<tr>
<th>Treatment</th>
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</table>

Discussion

This study assessed the real-life incidence of postoperative persistent hypoPT in patients who were referred to university hospital centers in the Netherlands and found that persistent hypoPT, defined as the need for Dv with or without Ca supplementation that persists at least 1 year after surgery, occurred in 15.0% of the participants after total or completion thyroidectomy. This number compares unfavorably with data from high-volume single centers that reported incidences of less than 5% (the definition of hypoPT ranged from Dv or CaDv supplementation 6 months post surgery to serum levels of intact PTH <15 pg/mL [to convert to ng/L, multiply by 1] for at least 1 year)\(^8\),\(^10\),\(^11\) and is considerably higher than reported by the BAETS fifth national audit (7.3%, with a definition of hypoPT as the need for treatment with CaDv supplementation 6 months postoperatively).\(^14\) However, it is similar to data from a multicenter study (16.7%, with a definition of hypoPT as the need for treatment with Ca or Dv 12 months after surgery)\(^7\) and a survey from the Thyroid Cancer Alliance (13.8%, with a definition of hypoPT as low blood Ca levels 1 year after surgery).\(^9\)
More recently, a Swedish nationwide study reported a 12.5% risk of persistent hypoPT after TTx (definition of hypoPT as the need for Ca and/or Dv more than 12 months after surgery).13 These numbers reflect the discrepancy in incidence rates between single-center studies and national registries, which can partially be explained by the use of different definitions for hypoPT. Mehanna et al18 demonstrated that the rate of persistent hypoPT varied between 0% to 4.4% depending on the definition. This finding was confirmed in our study cohort, with a persistent hypoPT incidence varying from 14.5% (CaDv 1 year postsurgery) to 28.5% (Ca and/or active Dv 6 months postsurgery) depending on the definition used.18

The incidence of persistent hypoPT in this cohort warrants a closer look. In this study, only university hospital centers participated, where oncological thyroid care is centralized and mainly extensive thyroid surgeries are performed, as they serve as referral centers in the Netherlands for advanced cancers and large goiters. This challenging case mix could be 1 reason for the high incidence of persistent hypoPT, a possible explanation that is supported by the literature in which higher rates of persistent hypoPT were seen after more extensive surgery and lymph node dissections.7,10,20 Moreover, thyroid malignancy and Graves disease are risk factors for persistent hypoPT.11,21,22 Because 77.0% of TTx performed in this cohort were to treat thyroid cancer or Graves disease and for 17.0% a CLND alone and 19.0% a CLND and LLND were performed, this might explain the high incidence of persistent hypoPT. This contrasts with the Swedish study from Almqquist et al18 in which 19.3% of TTx were performed for thyroid cancer and a study from Bergenfelz et al23 in which all cancers were excluded. Both studies reported a persistent hypoPT incidence rate below 5%.8,23 Other studies have also reported higher rates of persistent hypoPT after more extensive surgery and lymph node dissections.12,18,19 When excluding patients who underwent CLND or LLND, the incidence rate of postoperative persistent hypoPT decreased to 10.2%. This suggests that hypoPT reflects extensive disease. The number of cases overall that qualified for inclusion was not large. However, we assume this had a limited effect because all centers also perform many hemithyroidectomies, redo surgeries, neck dissections, and parathyroidectomies (>100-150 neck surgeries per hospital), rendering the necessary expertise to save parathyroid glands during thyroid surgery.

Reported hypoPT incidence rates in the literature may be inaccurate because of loss to follow-up. In line with this assertion, 25% of patients do not have long-term data on CaDv replacement in the BAETS audit; therefore, the hypoPT rate may be underrated.14 The BAETS study focuses on a national audit in which nonacademic centers also participated, probably reflecting less complex surgical cases. Our definition assumes that physicians have attempted to decrease Dv supplementation doses within 1 year after surgery. It is hypothesized that oncologic trajectories are intensive because of thyroid hormone withdrawal and RAI therapy, leading to maintaining the initial supplementation regimen to protect patients from new interventions. Therefore, patients may use unnecessary supplementation, which may be followed by a higher incidence of persistent hypoPT. However, we do not have data to support this assumption.

Despite persistent hypoPT being such a common complication, we lacked uniformity in definition and treatment. With this study, we intended to emphasize the problem of high incidence rates and large variations among guidelines and local hospital protocols. However, there was no meaningful difference in the incidence of hypoPT between the hospitals. Efforts should be made to reduce this complication rate and use national uniform diagnostic and treatment guidelines to enable comparison of interventions. An international consensus for the definition of persistent hypoPT after thyroid surgery and the development of reliable registration systems can serve national and international benchmarking purposes that aim for improved quality for patients who are treated with total or completion thyroidectomy. Furthermore, new techniques that aim to decrease hypoPT after thyroid surgery should be investigated and implemented. Recently, Benmiloud et al12 showed that the use of near-infrared autofluorescence during TTx lowered the temporary postoperative hypocalcemia rate from 22% to 9%. However, it did not aid in decreasing the rate of persistent hypoPT (corrected Ca level <8.0 mg/dL 6 months after surgery), which was only 1%. Intraoperative parathyroid gland angiography with indocyanine green (ICG) has also been proposed to prevent postoperative hypoPT. Vidal For tuny et al24 showed that ICG angiography obviates the need for Ca supplementation and postoperative measurement of Ca and PTH 10 days after surgery in patients with at least 1 well-perfused parathyroid gland on ICG angiography.24 Although promising, the clinical value of ICG angiography in preventing persistent hypoPT is undetermined. Other ways to decrease the incidence of hypoPT could be centralization of thyroid surgery to high-volume centers25 and hesitancy in performing a TTx.26-28 Patients should be informed realistically regarding the complication rate of total or completion thyroidectomy in the context of the gain in the oncological outcome and should be informed about alternative treatments. Lastly, we should focus on refining surgical techniques and continuously incorporating these in surgical training programs.

Limitations
This study is a nonrandomized, retrospective study, and despite the care of data collection and the use of clear inclusion criteria, some degree of observation bias cannot be ruled out. Although this study was performed in university hospitals in the Netherlands, we believe the results of this study are generalizable to institutions who also perform fewer than 100 to 150 specialized and complex head and neck surgeries per year, comprising an average of 30 total and completion thyroidectomies. The heterogeneity in surgical techniques, such as sealing devices within the different centers, is a limitation of this study. The definition of persistent hypoPT was based on the use of Dv supplementation, and serum Ca or PTH levels were not considered. However, PTH levels may not be the optimal criterion to define hypoPT because Lončar et al30 showed that in 6 of 14 patients who could not discontinue Ca supplementation 1 year after surgery, PTH levels were within the normal range. Additionally, a recent study showed that the incidence
of persistent hypoPT was 18.7%, with a definition of PTH concentrations less than the normal range for more than 12 months. This may indicate that the definition based on CaDv supplementation does not necessarily result in a higher incidence of persistent hypoPT compared with a definition based on PTH values. A recent systematic review found 20 different definitions in 89 articles, emphasizing the need for uniform diagnosis and treatment guidelines. Only if measurements are used universally can we study the incidence of postoperative hypoparathyroidism and identify which practices need to improve and how to do so. Furthermore, serum magnesium, phosphate, and Dv levels were not collected. Therefore, the severity of parathyroid deficiency could not be quantified. However, this was not the goal of our study, and we believe that if hypomagnesaemia was the cause of hypocalcemia, it would have been corrected by the experienced endocrinologists during the first year after surgery and not have any association with the incidence of persistent hypoPT. However, this is an assumption and a possible limitation of this study. Also, no data on discontinuing medication were collected, as this is not routinely described in medical health records and not standardized in local protocols. Lastly, data on parathyroid glands in situ and autotransplantation were not available, which are shown to be significantly associated with persistent hypoPT.

Conclusions

This cohort study describes the real-life incidence of hypoPT after total or completion thyroidectomy in the setting of centralized thyroid care in a highly selected population undergoing extensive thyroid surgery. These data provide a better understanding of the magnitude of this postoperative complication and enable more realistic information for patients who are undergoing extensive and complex thyroid surgery. Efforts should be made to reduce this complication rate and use national uniform treatment guidelines to enable comparison of interventions.

ARTICLE INFORMATION

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Author Contributions: The principal investigators (Drs van Ginhoven and Kruijff) had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Ms Lončar and Neltes contributed equally to this work and are co-first authors. Drs van Ginhoven and Kruijff contributed equally to this work and share last authorship.

Concept and design: Lončar, Neltes, Engelsman, Vriens, Bouvy, Kruijff, van Ginhoven.
Acquisition, analysis, or interpretation of data: Lončar, Neltes, Dickhoff, Engelsman, Schepers, Vriens, Bouvy, Kruijff.
Drafting of the manuscript: Lončar, Neltes, Vriens, Kruijff.
Critical revision of the manuscript for important intellectual content: Dickhoff, Engelsman, Schepers, Vriens, Bouvy, Kruijff, van Ginhoven.
Statistical analysis: Lončar, Neltes.
Administrative, technical, or material support: Lončar, Neltes, Bouvy, Vriens.
Supervision: Engelsman, Schepers, Vriens, Bouvy, Kruijff, van Ginhoven.

Conflict of Interest Disclosures: None reported.

Data Sharing Statement: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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