Increased Risk of Atrial Fibrillation After Treatment for Differentiated Thyroid Carcinoma

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Background: Patients with differentiated thyroid carcinoma (DTC) have a favorable prognosis after treatment with thyroidectomy, radioiodine, and TSH suppression. However, treatment is associated with long-term cardiovascular toxicity. The aim of this study was to evaluate whether there is an increased risk of atrial fibrillation (AF) in DTC patients and whether AF occurrence is related to DTC treatment.

Patients and Methods: Incident AF was compared between 518 DTC patients and 1563 matched controls. A cumulative incidence curve was plotted, and competing risk regression analyses with adjustment for all-cause mortality were performed. Within the DTC cohort, associations between time-varying DTC treatment variables and incident AF were analyzed.

Results: For both cohorts, the mean age was 48.6 years (75% of subjects were women). The AF incidence rate was 6.2/1000 person-years for DTC patients and 2.7/1000 person-years for controls. DTC patients had a 2.25-fold (95% confidence interval [CI], 1.40–3.63) and 2.47-fold (95% CI, 1.55–3.95) increased AF risk in crude and fully adjusted analyses, respectively. Within the DTC cohort, the TSH level (which was suppressed in 85.7% of patients) was not associated with AF, whereas a higher cumulative radioiodine dose slightly increased AF risk: subdistribution hazard ratio, 1.04 (95% CI, 1.01–1.08) per 50 mCi (1.85 GBq) increase, after adjustment.

Conclusion: Patients with DTC have an increased AF risk, independent from established AF risk factors. We could not demonstrate a relation between TSH and AF, whereas a higher cumulative radioiodine dose was associated with a slightly increased AF risk. Electrocardiogram screening for AF may be warranted during follow-up of DTC patients to allow early diagnosis and treatment of AF and to prevent its complications. **(*J Clin Endocrinol Metab* 100: 4563–4569, 2015)**

Thyroid carcinoma has a favorable prognosis, with a 5-year relative survival of 98% and an estimated number of 470 020 female thyroid carcinoma survivors for 2014 in the United States (1). Differentiated thyroid carcinoma (DTC), ie, papillary and follicular thyroid carcinoma (2), represents the most common type of thyroid carcinoma, accounting for 97% of cases (1). Standard DTC treatment comprises a total thyroidectomy, a neck lymph node dissection if indicated, and radioiodine (^{131}I) ablation treatment, followed by thyroid hormone suppression therapy (THST). Goals of the latter are to replace patients with thyroid hormone and to lower or suppress the pituitary TSH because TSH may promote growth of residual malignant thyroid cells.

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Abbreviations: AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; DTC, differentiated thyroid carcinoma; ECG, electrocardiogram; IQR, interquartile range; SHR, subdistribution hazard ratio; THST, thyroid hormone suppression therapy.

Since the use of THST for DTC, concerns have raised about possible adverse cardiovascular effects. Several studies endorse these concerns, as cardiac systolic and diastolic dysfunction, decreased arterial elasticity, and prothrombotic effects of THST have been documented in DTC patients (2–5). Moreover, we have recently reported an independent association between lower TSH levels and an increased risk of cardiovascular mortality during long-term follow-up in our DTC cohort (6). Importantly, survivors of DTC are not only faced with an increased risk for cardiovascular mortality, but may also be more susceptible to the development of atrial fibrillation (AF) and its complications, such as stroke. In noncancer patients, it is well known that overt and subclinical hyperthyroidism are associated with an increased risk of AF (7, 8). Even more, clinically euthyroid elderly persons with either a low or low-normal TSH level are at increased risk for AF (9). Studies performed so far on a possible effect of THST on AF risk in DTC patients are hampered by low patient numbers and selection of patients with a low or intermediate DTC risk (10, 11).

Therefore, the primary aim of the present study was to evaluate the long-term risk of AF in a large unselected cohort of DTC patients, taking account of established AF risk factors. Secondary aims were to study whether there is an association between AF and TSH level, and other treatments within the DTC cohort.

Patients and Methods

Study design and population

In this retrospective cohort study, incident AF in patients with DTC was compared to that of controls from a population-based study. The study population consisted of patients previously described in our recent report on cardiovascular and all-cause mortality in DTC patients (6), except that subjects with AF at baseline were excluded (n = 6 DTC patients and 9 controls). In short, all patients diagnosed with DTC in the period from January 1980 to June 2010, treated with a total thyroidectomy and radioiodine ablation therapy in the University Medical Center Groningen (UMCG), were included in the DTC cohort. Data for controls were obtained from the prospective population-based Prevention of REnal and Vascular ENd-stage Disease (PREVEND) study, as previously described (12). For each DTC patient, three controls matched on baseline age (within a range of 2 y) and sex were randomly selected from the Groningen random sample PREVEND cohort, which is an unselected general population sample. Because only subjects between 28 and 75 years old were studied in the PREVEND study, DTC patients aged 26 to 77 years were included. The census dates were January 1, 2009, for the controls and between July 1 and 18, 2012, for DTC patients.

The Institutional Review Board of our hospital approved contacting DTC patients for completion of missing baseline characteristics. According to the Dutch Medical Research Involving Human Subjects Act, no separate approval was needed for retrospective data collection and analysis. Analyses were performed on fully coded data sets.

Treatment and follow-up DTC cohort

Patients with DTC were treated according to our local protocol (13) and the Dutch thyroid carcinoma guideline that was released in 2007 (14). Treatment consisted of a total thyroidectomy and a central or lateral neck lymph node dissection if indicated. Postoperatively, patients were scored according to the fifth or sixth edition of the TNM classification (15, 16). For the current study, a Tx-T2 Nx-N0 Mx-M0 stage corresponded to a low risk; any T3 or N1 tumor to an intermediate risk; and any T4 or M1 tumor to a high risk of recurrence. Four to six weeks after surgery, patients received radioiodine ablation therapy with a dose usually of 50–150 mCi (1.85–5.55 GBq). Patients were generally prepared for radioiodine treatment by endogenous TSH stimulation; recombinant human TSH was only applied in a limited number of cases. Thereafter, patients started with THST that consisted of administration of T_3 during initial treatment and T_4 during follow-up. Until 2007, THST with a TSH target below the lower limit of the reference range was applied to all patients during the entire follow-up. Since then, a TSH in the low-normal range was advised after initial treatment for patients with a low risk of recurrence (14, 17, 18), as a result of the increased recognition of potential adverse effects attributable to THST (2, 4, 5, 19), together with uncertainties about its necessity in patients with a low risk of recurrence (20). For patients with an intermediate and high risk of recurrence, THST with a TSH target of 0.01 to 0.1 mU/L and < 0.01 mU/L, respectively, remained advised for at least several years. The different TSH assays used between 1980 and 2012 have been described previously (6).

Definition of AF

The UMCG is a tertiary referral center. Therefore, DTC patients originate from the entire northern part of The Netherlands. If considered to be disease-free, patients visit the outpatient clinic once yearly; other medical care is often performed in regional hospitals, of which correspondence is available in our institution. AF was defined as AF on an electrocardiogram (ECG) or as diagnosed by a cardiologist from a regional hospital. ECGs were recorded perioperatively and during follow-up on indication. Controls are inhabitants from the city of Groningen, and they visited one of the two hospitals in Groningen for all medical care. For control subjects, AF was defined as AF on an ECG in one of the two hospitals in Groningen or AF recorded on ECGs from the follow-up visits of the PREVEND study that were performed at 3-year intervals (21). For both DTC patients and controls, incident AF was defined as AF occurring in the absence of permanent AF at baseline. For incident AF, no distinction was made between paroxysmal, persistent, permanent, or peri- and postoperative AF or flutter.

Two independent observers manually assessed all ECGs of DTC patients, as well as all ECGs of controls with suspected AF during electronic ECG screening (21). Any identified case of AF was validated by a cardiologist.

Further study definitions and data collection

Baseline was defined as the time of DTC diagnosis or the time of inclusion in the PREVEND study. Survival time was defined as the time from baseline to the first AF event, loss to follow-up, death, or censoring.

For both cohorts, data were collected on the following baseline cardiovascular risk factors: age, sex, smoking behavior, body mass index (BMI), hypertension, hypercholesterolemia, diabetes mellitus, a history of heart failure, and a history of a coronary event. The latter was defined as either a myocardial infarction, coronary disease (defined as unstable angina for DTC patients, and acute or subacute ischemic heart disease for controls), or a coronary intervention (a percutaneous coronary intervention or coronary artery bypass graft). Heart failure was assessed as previously defined (22). Hypertension, hypercholesterolemia, and diabetes mellitus were considered to be present in case of prescribed drug treatment for these conditions. For DTC patients, additional data on TNM staging and tumor histology were obtained. Data were collected by history taking, physical examination, and questionnaires; in addition, the medical record was consulted for patients with DTC.

At the end of follow-up, mortality data for DTC patients were obtained by review of the medical record, and in consultation with the general practitioner in case of an unknown cause of death. Statistics Netherlands (the Dutch institute for population statistics) was consulted for controls. Furthermore, for DTC patients, all TSH values measured during follow-up were collected, as well as data on administered doses of radioiodine, tyrosine kinase inhibitor use, and whether or not patients were treated with external radiotherapy on the neck.

Statistics

Baseline variables were presented as number (percentage), median and interquartile range (IQR), or mean ± SD as appropriate. Missing BMI values were imputed using a regression with age and sex (five times), performed separately for DTC patients and controls.

AF incidence rates were calculated as the number of AF cases per 1000 person-years for both patients with DTC and controls. A cumulative incidence curve was plotted to show the incidence of AF in DTC patients vs controls. Cumulative incidence of AF for both groups was compared with a crude Fine&Gray regression accounting for competing risks from all-cause mortality (23). The crude Fine&Gray competing risk analysis was succeeded by a regression adjusted for age, sex, hypertension, BMI, history of coronary events, and history of heart failure. The covariates adjusted for in this model were chosen based on a previous publication, (24) in which an AF risk score was developed and validated. Subdistribution hazard ratios (SHRs) and 95% confidence intervals (CIs) are reported.

For the secondary aims, baseline and treatment characteristics were compared between DTC patients with and without development of AF during follow-up, using χ^2, nonparametric, and independent samples *t*-tests, as appropriate. Exploratory competing-risks analyses were performed within the DTC cohort on associations between AF and TSH level (cumulative) radioiodine dose, and neck radiotherapy. All treatment characteristics were analyzed as time-varying variables. The geometric mean TSH per follow-up year was calculated as previously described (6). A crude analysis of the association between each treatment modality with AF was succeeded by an adjusted analysis in which variables were inserted that were associated ($P < .10$) with AF in crude analyses. The following variables were eligible: age, sex, hypertension, BMI, history of coronary event, and history of heart failure. For patients with missing BMI, the average BMI of five imputations was used for the latter analysis, due to software limitations of calculating with both time-varying variables and several imputed datasets. In the multivariate analyses, we did not correct for disease stage because we would in part correct for differences in aggressiveness of treatment.

A two-sided *P* value of $< .05$ was considered statistically significant. Software packages STATA version 11.0 (StataCorp) and IBM SPSS for Windows version 22 (IBM) were used for statistical analyses.

Results

Baseline characteristics

A total of 518 DTC patients and 1563 controls were included (Table 1). Mean age was 48.6 ± 14.0 years for DTC patients and 48.6 ± 13.4 years for controls, and 75% of each group were women. BMI was imputed for 100 missing cases (67 DTC patients and 33 controls).

Incident AF

A total of 35 (6.8%) DTC patients developed AF, corresponding to an incidence rate of 6.2 AF cases per 1000 person-years. Of the controls, 42 (2.7%) developed AF; the incidence rate was 2.7 cases per 1000 person-years. Follow-up to AF was median 8.7 (IQR, 4.6–16.2) years for DTC patients, and 10.6 (10.2–10.9) years for controls (Table 2). Of DTC patients, 118 (22.8%) were lost to follow-up after a median follow-up of 8.2 (IQR, 4.2–15.5) years; 293 (18.7%) controls were lost after a median follow-up of 8.8 (5.0–9.8) years. During follow-up, 100 (19.3%) DTC patients and 82 (5.2%) control subjects died. A total of 77 and 70 deaths were a competing event for the primary event of interest, AF, for DTC patients and controls, respectively (see Supplemental Figure 1).

Figure 1 shows that the cumulative incidence of AF was significantly higher in DTC patients as compared to controls (crude competing risks regression $P = .001$). In the crude

Table 1. Baseline Characteristics of Patients With DTC and Controls

	Patients with DTC	Controls
n	518	1563
Age (mean ± SD), y	48.6 ± 14.0	48.6 ± 13.4
Female sex	387 (74.7)	1164 (74.5)
Smoking	118 (22.8)	467 (29.9)
BMI, median (IQR)[a]	25.2 (22.7–28.0)	25.4 (22.9–28.3)
Hypertension	88 (17.0)	175 (11.2)
Hypercholesterolemia	26 (5.0)	53 (3.4)
Diabetes mellitus	22 (4.2)	38 (2.4)
History of coronary event	6 (1.2)	25 (1.6)
History or heart failure	1 (0.2)	1 (0.1)

Data are expressed as number (percentage) unless stated otherwise.

[a] 100 missing values of BMI were imputed (67 missing values of DTC patients, 33 of controls).

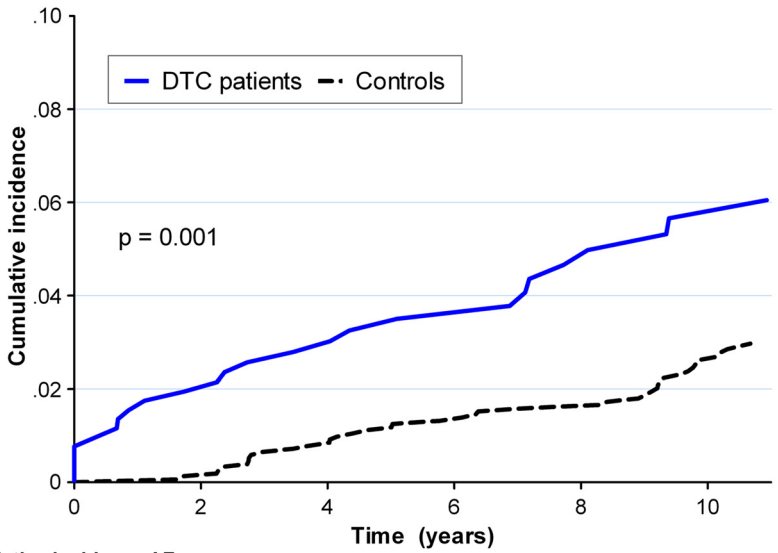
Table 2. Incidence of AF in Patients With DTC and Controls

	Patients With DTC	Controls
n	518	1563
Time at risk, y		
Median (IQR)	8.7 (4.6–16.2)	10.6 (10.2–10.9)
Sum	5646	15 357
Incident AF, n (%)	35 (6.8)	42 (2.7)
Incidence rate, n/1000 person-years	6.2	2.7
All-cause mortality, n (%)	100 (19.3)	82 (5.2)

analysis, DTC patients had a SHR of 2.25 (95% CI, 1.40–3.63) for AF when compared to controls (Table 3). After adjustment for age, sex, hypertension, BMI, and history of coronary event, the AF risk remained significantly higher in DTC patients (SHR, 2.47; 95% CI, 1.55–3.95). The latter analysis was not adjusted for history of heart failure because none of the subjects with AF had heart failure at baseline as documented by medical chart review.

AF within DTC cohort

DTC patients who developed AF (n = 35) were older (mean age, 59.9 ± 10.8 vs 47.7 ± 13.9 y) and had hypertension (49 vs 15%) more often than patients who did not develop AF (n = 483) ($P < .001$ for both). Other baseline and treatment characteristics were similar in both groups (Supplemental Table 1).



Cumulative incidence AF						
DTC	0	.020	.028	.035	.047	.057
Controls	0	.001	.008	.013	.016	.026
Number at risk						
DTC	518	484	434	375	317	279
Controls	1563	1536	1499	1451	1515	1290

Figure 1. Cumulative incidence curve of AF in patients with DTC (blue solid line) vs controls (dashed black line), adjusted for competing risks of all-cause mortality.

The median radioiodine dose in the entire DTC cohort was 200 (IQR, 54–382) mCi (7.4 [IQR, 2.0–14.1] GBq), and a total of 278 patients (54%) received more than one radioiodine treatment. In the majority (85.7%) of DTC patients, the median of geometric mean TSH levels per follow-up year was suppressed (≤0.5 mU/L). An overview of the stratified TSH levels among DTC patients is provided in Supplemental Table 2.

In the crude analysis, TSH level was not significantly related to AF (SHR, 1.21; 95% CI, 0.86–1.72, per 10-fold decrease; Table 4). Results remained unchanged after adjustment for covariates. The radioiodine dose per follow-up year was not related with outcome either (crude SHR, 0.78; 95% CI, 0.50–1.21), whereas the cumulative dose did relate to AF, SHR per 50 mCi (1.85 GBq) increase 1.06 (95% CI, 1.02–1.11). Similar results for both analyses were found after adjustment, with a SHR of 1.04 (95% CI, 1.01–1.08) for each 50 mCi increase in cumulative radioiodine dose. Neck radiotherapy was associated with AF in crude analysis (SHR, 3.14; 95% CI, 1.05–9.38), but the association was lost after adjustment for age and other AF risk factors (SHR, 0.95; 95% CI, 0.25–3.57).

Discussion

The current study shows a 2.5-fold increased risk of AF for patients with DTC as compared to controls, independent from established AF risk factors. Therefore, DTC is an independent predictor for AF next to well-known AF risk factors. We could not demonstrate an association between TSH level and AF within the DTC cohort, whereas a higher cumulative dose of radioiodine was associated with a slightly increased AF risk.

An earlier cross-sectional study assessed AF prevalence in 136 thyroid carcinoma patients (10). Mean age was 52 years, and 10.3% had prevalent paroxysmal or sustained AF, whereas the predicted prevalence for an age- and sex-adjusted general population was 1.0 to 2.0%. A single TSH value measured during follow-up was not different between patients who did and did not develop AF. Furthermore, in a recent study of low- and intermediate-risk DTC patients, 17 of 756 patients (2.3%) developed AF during a median follow-up of 6.5 years (11). The risk of

Table 3. Fine&Gray Regression Models in DTC Patients vs Controls, Adjusted for Competing Risks of All-Cause Mortality

	AF		
	SHR	**95% CI**	***P* Value**
Crude model			
DTC patients vs controls	2.25	1.40–3.63	.001
Adjusted model			
DTC patients vs controls	2.47	1.55–3.95	<.001
Age	1.07	1.05–1.09	<.001
Sex, male vs female	1.63	0.98–2.72	.040
Hypertension, yes vs no	2.11	1.23–3.64	.007
BMI	1.04	0.98–1.10	.170
History of coronary event, yes vs no	1.88	0.76–4.64	.170

AF was similar for patients with a suppressed and nonsuppressed TSH. However, both studies may have been underpowered to find a relation between TSH and AF. In the current study, a large cohort of DTC patients was included together with an age- and sex-matched control group, and we adjusted AF risk for AF risk factors. Moreover, within the DTC cohort, all TSH values measured during follow-up were available, as well as data regarding radioiodine treatment and radiotherapy. The increased AF risk in DTC patients could be confirmed, and similar to these previous studies, no relation between TSH and AF was found.

It is quite surprising though that we did not find a relation between the TSH level and incident AF within the DTC cohort. Given the strong relation between low TSH levels and AF risk in both the general population and patients with subclinical and overt hyperthyroidism (7–9), we expected a lower TSH to be associated with higher AF risk. Moreover, in animal models it has been shown that thyroid hormones can contribute to alterations in cardiac electrophysiology (25, 26). We can only speculate about the reason why we could not find such association in our DTC cohort. It is possible that THST, which was universally applied, serves as a trigger for AF in patients that are prone to AF because of the presence of cardiovascular risk factors, left atrial dilatation, or a genetic susceptibility (27). For these patients, the extent to which the TSH level was suppressed may not be crucial, which may have resulted in loss of a dose-response effect between THST and AF. Thus, we cannot rule out that, due to the near-universal TSH suppression, the range of available TSH levels has been insufficient to detect a relation between TSH and AF. Another explanation could be that other factors may have triggered AF, such as (thyroid) surgery. However, after exclusion of DTC patients (n = 7) who had peri- or postoperative AF, no association was found between TSH and AF either. Another key issue is that when solely T_4 is administered, circulating thyroid hormone levels do not necessarily correlate to tissue T_3 levels (28), which have been proposed to elicit adverse cardiovascular effects when elevated (29). Therefore, it remains uncertain whether the plasma TSH level is an adequate measure for tissue hyperthyroidism.

Of note, higher cumulative radioiodine doses were associated with a slightly increased AF risk. Circulating radioiodine or local uptake of radioiodine by the sodium-iodide symporter, which has been identified in, among others, cardiac tissue (30), can possibly induce a diffuse cardiac inflammation with eventual fibrosis or induce oxidative stress and accelerated cardiovascular aging. Alternatively, there could be an indirect effect, as patients who receive many radioiodine therapies experience several periods of thyroid hormone withdrawal, with concomitant periods of hypothyroidism. The cycling from hypothy-

Table 4. Fine&Gray Regression Models of Associations Between Time-Varying DTC Treatments and AF in Patients With DTC, Adjusted for Competing Risks of All-Cause Mortality

	AF Within DTC Cohort		
	SHR	**95% CI**	***P* Value**
Crude model			
TSH level, per 10-fold decrease	1.21	0.86–1.72	.277
Radioiodine dose, per 50 mCi increase	0.78	0.50–1.21	.271
Cumulative radioiodine dose, per 50 mCi increase	1.06	1.02–1.11	.004
Neck radiotherapy, yes vs no	3.14	1.05–9.38	.040
Adjusted model [a]			
TSH level, per 10-fold decrease	1.01	0.71–1.44	.957
Radioiodine dose, per 50 mCi increase	0.72	0.46–1.11	.138
Cumulative radioiodine dose, per 50 mCi increase	1.04	1.01–1.08	.006
Neck radiotherapy, yes vs no	0.95	0.25–3.57	.935

50 mCi = 1.85 GBq.

[a] Adjusted for covariates that were associated with AF in the crude analyses ($P < .10$); these were age, hypertension, and BMI for all DTC treatment variables analyzed.

roidism to (subclinical) hyperthyroidism may possibly elicit rhythm disturbances. Furthermore, these patients are treated with T_3 for a relatively long time, which possibly triggers AF more easily than T_4 that is prescribed to patients in follow-up. We ruled out that DTC patients that developed AF had a longer follow-up time than DTC patients who did not by comparing follow-up time for patients with and without AF and similar cumulative doses.

The strengths of this study are the large cohort of unselected DTC patients, the use of an even larger cohort of population-based matched controls, the considerable follow-up time, availability of cardiovascular risk factors for all study subjects, and adjustment for competing risks of all-cause mortality in statistical analyses. Furthermore, complete data on tumor characteristics and administered treatments were available for the DTC cohort, and treatment characteristics were analyzed as time-varying variables.

A limitation of the current study is that AF, especially subclinical paroxysmal AF (31), may have been underestimated in both the DTC and PREVEND cohorts due to a surveillance bias. The possible underestimation of AF within the DTC cohort may have influenced the analyses of associations between AF and THST. Furthermore, no echocardiographic data were available, and different TSH assays were used over time (with 9% of follow-up years occurring before 1990, when TSH assays were not sufficiently sensitive to determine the degree of TSH suppression). Additionally, the retrospective and observational design of this study precludes any conclusions about causality between AF and DTC treatment modalities.

It is likely that some of the control subjects used thyroid hormones (although we do not have data about this), and that a few of them may have been oversubstituted, resulting in a higher AF risk in a minor proportion of control subjects. Still, we found a convincingly increased AF risk in patients with DTC as compared to the controls.

AF predisposes to stroke and heart failure, which are accompanied by increased risks of morbidity and mortality (31, 32). Development of AF, and possibly subsequent heart failure, could also contribute to an increased risk of cardiovascular mortality that has been found in patients with DTC (6). Early detection of AF in DTC patients with active case finding using ECG therefore seems justified in an attempt to prevent AF-related complications and reduce symptoms.

In conclusion, patients with DTC have an increased AF risk, independent from established AF risk factors. A relation between the degree of TSH suppression and AF could not be demonstrated, whereas a higher cumulative radioiodine dose was associated with a slightly increased risk of AF. ECG screening for AF may be warranted during follow-up of DTC patients, to allow early diagnosis and treatment of AF and prevent its complications.

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Data are available upon request.

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