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# Incidence of thyroid hormone therapy in patients treated with sunitinib or sorafenib: A cohort study

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**Abstract** ***Background:*** Sunitinib and sorafenib can induce serious adverse drug reactions (ADR) such as hypothyroidism. However, the incidence has not been reliably determined in clinical trials.
***Aims:*** To determine incidence rates (IR) and hazard ratios (HR) of thyroid hormone (TH) therapy as a surrogate for sunitinib- and sorafenib-induced clinical hypothyroidism.
***Methods:*** A cohort study was performed using claims data for prescriptions covering >80% of German pharmacies. Patients with a first prescription of sunitinib or sorafenib in the period between June 2006 and December 2007 were followed until incident prescription of any TH (event of interest) or censoring (due to loss to follow-up, discontinuation or switch of therapy, prescription of antithyroid drugs or the end of the study).
***Results:*** One-hundred and seventy eight of 1295 sunitinib patients (13.7%) versus 77 of 1214 sorafenib patients (6.3%) received a TH. IR were 24.2 and 12.1 per 100 person-years, respectively. Unadjusted HR for TH therapy was 2.0 (95% confidence interval (CI) 1.5–2.6) for sunitinib compared to sorafenib and remained significant after adjustment for covariates, i.e. type of prescriber, region, insurance status, type of insurance fund, and relevant co-medication.
***Conclusions:*** Sunitinib- and sorafenib-induced hypothyroidism is a more frequent ADR than currently labelled. Furthermore, patients treated with sunitinib have a two-fold increased risk of requiring TH therapy compared to sorafenib. Patients being treated with sunitinib or sorafenib are, therefore, at risk of thyroid function disturbances and routine monitoring both at baseline and throughout treatment with sunitinib and sorafenib is justified.


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## 1. Introduction

The multi-kinase inhibitors (MKI) sunitinib and sorafenib received approval for the treatment of metastatic and advanced renal cell carcinoma in 2006. Both substances block signal cascades that are activated by the vascular endothelial growth factor (VEGF).[1,2]

From the therapeutic point of view, there has been a great need in developing new treatment options for advanced renal cell carcinoma for a long time as the previous standard treatment with unspecific interferon-α-2a has only a low response rate and is associated with severe adverse drug reactions (ADR).[3]

The efficacy has been proven in advanced and metastatic renal cell carcinoma pivotal trials for both sunitinib and sorafenib.[4,5] Sunitinib has become standard therapy in first-line and sorafenib in second-line treatment of metastatic renal cell carcinoma.[6,7] Furthermore, sunitinib has been approved for the treatment of imatinib-resistant gastrointestinal stromal tumours (GIST) and sorafenib for advanced hepatocellular carcinoma.[8,9]

Frequent ADR of sunitinib and sorafenib are hypertension, fatigue, skin abnormalities, gastrointestinal toxicity, and increased risk of bleeding.[4,5,8–13] However, clinically relevant ADR such as hypothyroidism have been detected in clinical practice, which were not analysed in detail in pivotal trials. Actually, there are several analyses that describe the significance of primary MKI-associated hypothyroidism.[14–25] This resulted in recommendations by the US Food and Drug Administration (FDA) and the Drug Commission of the German Medical Association in 2006 and 2007, respectively, to assess thyroid function before treatment with sunitinib.[26–28]

Hypothyroidism has been observed to occur early as well as late during treatment with sunitinib.[8] The current *Summary of Product Characteristics* (SPC) for sunitinib states a frequency of 2–6% of hypothyroidism observed as an adverse event in phase 3 trials and describes hypothyroidism as ADR as common (1–10%) to very common (>10%).[8] The current SPC for sorafenib states endocrine disorders such as hypo- and hyperthyroidism as uncommon (affects 1–10 users in 1000).[9] Several studies report on hypothyroidism under therapy with sorafenib or sunitinib.[14–25] When analysing the results of these studies, it is necessary to make a difference between thyroid function test abnormalities, subclinical, and clinical hypothyroidism. Thyroid dysfunction means all possible abnormalities of different parameters, e.g. thyroid-stimulating hormone (TSH), free thyroxine (FT4), and triiodothyronine (T3). Subclinical hypothyroidism is defined as a serum TSH-level above the statistically defined upper limit of reference range between 4.5 and 10 mIU/L. Clinical hypothyroidism requiring therapy with a thyroid hormone (TH) (usually levothyroxine) means TSH-values of above 10 mIU/L. The consequences of subclinical thyroid disease (TSH 4.5–10 mIU/L) are minimal and routine treatment is not recommended.[29,30] Therefore, clinical hypothyroidism requiring TH therapy should be the primary event of interest.

While alterations of laboratory values like TSH levels have been reported to occur relatively frequently (in 34–85% of patients treated with sunitinib and 10–68% with sorafenib), the rates of symptomatic hypothyroidism requiring treatment ranged from 14–46% for sunitinib and 3–6% for sorafenib.[14–25] Thus under therapy with sunitinib, the rate of hypothyroidism was uniformly higher than for sorafenib. However, due to the limited numbers of patients (less than 100 in each of these studies) and methodological differences such as setting and follow-up, the variability in incidence of drug-induced hypothyroidism in these studies is substantial. For example, subclinical hypothyroidism occurred in seven of 39 patients (18%) with metastatic renal cell carcinoma during treatment with sorafenib.[19] To the best of our knowledge, no studies are published exploring large, representative databases with regard to sunitinib- or sorafenib-induced hypothyroidism.

## 2. Objectives

In this large cohort study we analysed, therefore, the incidences of initiating thyroid hormone (TH) therapy as a surrogate for clinical hypothyroidism under sunitinib and sorafenib treatment using claims data for ambulatory prescriptions. Specifically, the following questions are to be answered: First, how many patients have received incident TH prescriptions after starting treatment with sunitinib or sorafenib? Second, is there a difference in risk of treatment with TH between patients treated with sunitinib and sorafenib?

## 3. Methods

### 3.1. DAPI database

This study is a retrospective database analysis. The *DAPI* database comprises anonymous claims data of prescribed drugs dispensed at community pharmacies at the expense of the statutory health insurance (SHI) funds. Roughly 90% of Germany's population is insured by this system. The DAPI data cover more than 80% of all community pharmacies' claims data back to the year 2000.

### 3.2. Design

We performed a cohort study comparing two treatment groups, i.e. patients initiating therapy with sunitinib or sorafenib. The first prescription of sorafenib or sunitinib between 1st July 2006 and 31st December 2007 constituted the patients' index prescription, respectively. The primary outcome was the first prescription of a TH according to the World Health Organisation