Cardiovascular events following vascular endothelial growth factor inhibitor therapy with sunitinib or pazopanib in patients with renal cell carcinoma - a nationwide registry-based follow-up study

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Background: Use of oral vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) with focus on sunitinib and pazopanib approved for treatment of patients with renal cell carcinoma (RCC) may be associated with cardiovascular events. However, there are limited data on the risk related to treatment with sunitinib or pazopanib.

Purpose: The aim of this study was to examine the risk of cardiovascular events in patients with RCC treated with sunitinib and pazopanib compared with age- and sex-matched population control subjects without cancer (1:2 ratio).

Methods: Patients with RCC treated with sunitinib or pazopanib from 2011 through 2018 were identified within the Danish National Patient Registry. Multivariable Cox regression standardized to the age, sex, selected comorbidity and pharmacotherapy distributions of all included subjects were used to derive absolute one-year risks of selected cardiovascular events.

Results: A total of 3,642 patients were included in the analysis, of whom 1,214 had RCC treated with sunitinib or pazopanib, and 2,428 were population control subjects without cancer. Differences in age, sex, prior acute coronary syndrome (ACS), chronic obstructive pulmonary disease, and peripheral artery disease were insignificant (all P>0.05), whereas patients with RCC more frequently had prior hypertension (51.2% vs. 35.2%), diabetes (17.1% vs. 10.3%), and transient ischemic attack (TIA) or stroke (7% vs. 4.5%), all P<0.05. Absolute risk of ACS was 1.4% for patients with RCC vs. 1.0% for controls (P=0.54), stroke/TIA 1.7% vs. 0.8% (P=0.10), and ventricular arrhythmia 0.3% vs. 0.1% (P=0.70). In contrast, risk of hypertension was significantly elevated with 50.7% vs. 41.8% for patients with RCC vs. controls (P<0.001), and this risk was similarly elevated when excluding patients with prior hypertension (30.7% vs. 5.4%, P<0.001). Similarly, risks of atrial fibrillation or flutter (AF) with 5.6% vs. 2.8% (P<0.001) and heart failure (HF) with 0.7% vs. 0.3% (P<0.001) were significantly elevated in patients with RCC versus controls. Risk of venous thromboembolism (VTE) was 5.6% vs. 0.9% (P<0.001) for patients with RCC versus controls. All-cause mortality risk was 40.1% vs. 2.6% (P<0.001). The corresponding relative risks for one-year outcomes are shown in Figure 1.

Conclusions: Patients with RCC treated with sunitinib or pazopanib did not have a significantly higher risk of ACS, stroke/TIA or ventricular arrhythmia when compared to age- and sex-matched controls. In contrast, risks of hypertension, AF, HF, and VTE at 1 year compared with population control subjects were significantly elevated. Risk of HF risk was however limited in absolute numbers and the clinical significance of the evaluated risk of this endpoint as well as other endpoints should be interpreted in the context of a significantly high 1-year mortality risk of around 40% in patients with RCC versus only around 2.5% in population controls.
Figure 1