**QTC INTERVAL PROLONGATION WITH VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITORS: A SYSTEMATIC REVIEW AND META-ANALYSIS**

G. Sonpavde¹, P.A. Ghatalia¹, Y. Je², M.D. Kaymakcalan³, T.K. Choueiri⁴

¹Medical Oncology, University of Alabama at Birmingham Hospital, Birmingham, AL, USA
²Department of Food and Nutrition, Kyung Hee University, Seoul, KOREA
³Pharmacology, Dana Farber Cancer Institute, Boston, MA, USA
⁴Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA

**Aim:** We performed the first large systematic review and meta-analysis to determine the relative risk (RR) of QTc interval prolongation and serious arrhythmias associated with multi-targeted vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI).

**Methods:** We conducted a trial-level meta-analysis of randomized phase II and III trials comparing arms with and without a US Food and Drug Administration-approved VEGFR TKIs (sunitinib, sorafenib, pazopanib, axitinib, vandetanib, cabozantinib, ponatinib and regorafenib). Analyses were carried out by using Stata/SE version 12.0 software (Stata, College Station, TX). Using extracted data, we calculated relative risks (RRs) and 95% CIs of all-grade and high-grade QTc prolongation in cancer patients assigned to VEGFR TKI vs. controls. To compute a summary incidence and RR, we used fixed-effects models or random-effects models depending on the heterogeneity of trials.

**Results:** 6548 patients from 18 trials evaluating sunitinib, vandetanib, pazopanib and axitinib were eligible. The RR for all grade and high grade QTc prolongation for the TKI vs. no TKI- arms was 8.66 (95% CI 4.92 to 15.2, p < 0.001) and 2.69 (95% CI 1.33 to 5.44, p = 0.006), respectively, with most events being asymptomatic QTc prolongation. 4.4% and 0.83% patients exposed to VEGFR TKI had all grade and high grade QTc prolongation respectively. The sunitinib and vandetanib subgroups were associated with statistically significant risk of QTc prolongation, while pazopanib and axitinib were not. Higher doses of vandetanib were associated with greater risk. The rate of serious arrhythmias including torsade de pointes was not higher with high grade QTc prolongation. The risk of QTc prolongation was independent of the duration of therapy.

**Conclusions:** This meta-analysis shows that VEGFR TKIs are associated with QTc prolongation, although the incidence of high grade events is low (0.83%) and its association with serious arrhythmias is unclear. TKIs relatively selective for VEGFR may have less impact on QTc. Longer duration of therapy did not significantly increase RR, suggesting that early detection may prevent fatal outcomes.

**Disclosure:** G. Sonpavde: Research support and advisory board for Novartis; Advisory board for GSK; Research support from Onyx; T.K. Choueiri: Advisory board: Bayer, Pfizer, GSK, Novartis, Aveo. All other authors have declared no conflicts of interest.