Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials
Choueiri TK, Schutz FA, Je Y, Rosenberg JE, Bellmunt J

CRD summary
The authors concluded that treatment of cancer patients with vascular endothelial growth factor receptor tyrosine kinase inhibitors (sunitinib and sorafenib) was associated with a significant increase in the risk of arterial thromboembolic events. Given the potential for bias and the unclear quality of the included trials, the reliability of the authors' conclusion is uncertain.

Authors' objectives
To assess the incidence and relative risk of arterial thromboembolic events with the clinical use of sunitinib and sorafenib (multi-targeted tyrosine kinase inhibitor agents) in cancer patients.

Searching
PubMed (from January 1966 to July 2009) was searched for studies published in the English language only. Search terms were reported. Abstracts presented at the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) meetings (between January 2004 and July 2009) were scanned. Updated manufacturer's package inserts of the approved agents (sunitinib and sorafenib) were handsearched.

Study selection
Eligible study designs included phase II and III clinical trials, expanded access programs, and prospective clinical trials. Eligible trials were of patients with cancer assigned to treatment with sorafenib or sunitinib, with safety data available for arterial thromboembolic events. Phase I trials were excluded.

Adverse outcomes considered as arterial thromboembolic events included arterial thrombosis, cerebral infarct, cerebral ischaemia, cerebrovascular accident, myocardial infarction, and myocardial ischaemia.

In all included trials, patients had adequate organ function, coagulation and haematological function. Patients with uncontrolled hypertension or clinically significant cardiovascular or cerebrovascular events or disease during the preceding 12 months were generally excluded from the trials. Patient malignancies assessed included renal cell cancer, hepatocellular cancer, gastrointestinal stromal tumour, non–small cell lung cancer, and neuroendocrine tumour; the median progression-free survival ranged between 2.8 to 10.2 months. Most of the trials reported cardiac ischaemia or infarction as an adverse outcome. The median age of included patients ranged between 56 and 69 years (where reported).

Drug doses and schedules were: sunitinib, 50 mg orally once daily on a four-weeks-on/two-weeks-off schedule; sorafenib, 400 mg orally twice daily. The median treatment duration ranged between 1.7 to 10.1 months (where reported).

Reviewers independently selected studies for inclusion; the authors did not state how disagreements were resolved.

Assessment of study quality
The authors did not state that they assessed study validity.

Data extraction
Data on the number of arterial thromboembolic events and the number of patients receiving vascular endothelial growth factor receptor tyrosine kinase inhibitors were extracted from the safety profile to calculate the incidence of arterial thromboembolic events and corresponding 95% confidence intervals (CIs).

For studies with comparative arms in which patients were assigned to sorafenib or sunitinib versus controls in the same trial, data on the proportion of patients with adverse outcomes were extracted to calculate relative risks (RRs) of arterial
thromboembolic events and corresponding 95% confidence intervals. The half-integer correction method was used to calculate relative risks and variance in one trial that reported zero events in the control arm.

Two reviewers independently extracted data according to the Quality of Reporting of Meta-Analyses (QUORUM) guidelines; disagreements were resolved by consensus.

**Methods of synthesis**

Pooled incidence, relative risks and corresponding 95% confidence intervals were calculated using random-effects (DerSimonian and Laird) or fixed-effects (weighted with inverse variance) models based on the heterogeneity of the included trials. Statistical heterogeneity was assessed using Cochran Q test and $I^2$ statistic.

Subgroup analyses assessed underlying malignancy or tyrosine kinase inhibitor agents used.

Meta-regression was performed assessing underlying malignancy or tyrosine kinase inhibitors as potential effect modifiers.

Publication bias was assessed using funnel plots, and by Begg's and Egger's tests.

**Results of the review**

Ten trials were included in the review (n=10,255 patients, range 40 to 4,185).

**Incidence of arterial thromboembolic events**: The overall incidence of sunitinib- and sorafenib-associated arterial thromboembolic events in cancer patients was 1.4% (95% CI 1.2 to 1.6; Cochran Q $p=0.159$, $I^2=31.0%$; n=9,387 patients, 10 trials). There was no significant difference in the incidence of arterial thromboembolic events between: sorafenib versus sunitinib trials ($p=0.35$); renal cell cancer versus non-renal cell cancer patients ($p=0.71$); phase II versus phase III versus expanded access programs ($p=0.23$).

**Risks of arterial thromboembolic events**: Compared with controls, sorafenib or sunitinib were associated with significantly greater risk for developing arterial thromboembolic events (RR 3.03, 95% CI 1.25 to 7.37; Cochran Q $p=0.53$, $I^2=0%$; n=1,857 patients, three trials).

**Stratified analyses**: Stratifying by underlying malignancy revealed a relative risk of arterial thromboembolic events of 6.0 (95% CI 1.35 to 26.66) for renal cell cancer patients compared with a relative risk of 2.08 (95% CI, 0.69 to 6.29) for non-renal cell cancer patients. Stratifying by tyrosine kinase inhibitors used revealed a relative risk of arterial thromboembolic events of 3.1 (95% CI 1.22 to 7.85) for sorafenib-treated patients compared with a relative risk of arterial thromboembolic events of 2.39 (95% CI, 0.12 to 49.4) for sunitinib-treated patients. No significant differences were found between groups stratified by underlying malignancy ($p=0.46$) or drug type ($p=0.89$).

No evidence of publication bias was found for the incidence or relative risks of arterial thromboembolic events.

**Authors' conclusions**

Treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitors (sunitinib and sorafenib) was associated with a significant increase in the risk of arterial thromboembolic events.

**CRD commentary**

The review addressed a clearly stated question. One relevant database was searched for English-only publications, increasing the likelihood of language bias. Efforts were made to search for unpublished studies, reducing the likelihood of publication bias. Study selection and data extraction were conducted in duplicate, reducing the risk of reviewer error and bias.

Trial quality assessment was not performed, so the quality of the included evidence was unclear. Statistical methods used to combine trial results appeared appropriate and were justified.
The reliability of the authors' conclusion is uncertain given a number of weaknesses in the review (potential for language bias, unclear quality of included trials).

Three of the authors disclosed financial links with various pharmaceutical companies (including the manufacturers of sunitinib and sorafenib evaluated in the review).

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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