Cardiovascular effect of BCR-ABL TKIs: a meta-analysis and systematic review of arterial and venous occlusive events
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BACKGROUND
High rate of arterial and venous occlusive events were reported with ponatinib during clinical development and serious cases of arterial occlusive disease were also reported with nilotinib. This led to the evaluation of the new generation TKIs.

OBJECTIVES
To determine the risk of arterial and venous occlusive events in patients with Ph+ CML treated with new generation BCR-ABL TKIs in randomized clinical trials.
Stratifications by treatment are performed to provide product specific risk assessment.

METHODS
Literature search
- Screening of scientific articles (PubMed, Scopus, Cochrane library), congress abstracts (ASH, ASCO, ESMO) and clinical trial register (www.clinicaltrials.gov).
- Selection of all randomized clinical trials comparing new generation TKIs versus imatinib in patients with Ph+ CML.

Data collection
- Study and population characteristics
- Arterial occlusive events
- Venous occlusive events

Statistical analysis
- Random-effects (REM) and fixed-effect models (FEM) have been used to analyze the risk of arterial occlusive events and venous occlusive events respectively.
- Effect size measure: odds ratio computing using PETO method.
- Heterogeneity assessment: Cochrane’s Q statistic and I² value.
- One-way sensitivity analysis was performed to assess the robustness.

CONCLUSIONS
- New generation TKIs increased risk of arterial and venous occlusive events compared with imatinib.
- The increased risk of vascular occlusive events associated with new generation BCR-ABL TKIs is primarily driven by thrombotic events occurring at the arterial side.
- Additional investigations are required to assess the underlying pathophysiological mechanisms.
- Appropriate risk minimization measures should be taken/implemented with nilotinib, dasatinib and ponatinib.

RESULTS
- Twelve studies fulfilled the established criteria and were included in the meta-analysis.

Table 1: Absolute risk of arterial and venous occlusive events in patients with CML.

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Venous occlusive events</th>
<th>Arterial occlusive events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>New generation TKIs</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>0.248 (0.00)</td>
<td>0.251 (0.00)</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>0.886 (0.45)</td>
<td>0.606 (0.00)</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>8.929 (0.86)</td>
<td>3.873 (0.34)</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>1/154 (0.65)</td>
<td>0.150 (0.00)</td>
</tr>
<tr>
<td>Overall</td>
<td>123/217 (0.57)</td>
<td>61/194 (0.31)</td>
</tr>
</tbody>
</table>

- Overall, new generation TKIs increase the rate of venous occlusive events (REM ORPETO: 3.26; 95%CI: 1.12 to 9.50), nilotinib (REM ORPETO: 3.60; 95%CI: 2.21 to 5.86) and dasatinib (REM ORPETO: 3.32; 95%CI: 1.37 to 8.01) are associated with higher risk of arterial occlusive events than imatinib.
- No significant difference was found with bosutinib but a trend indicate an increased risk of arterial occlusive events.
- Overall, new generation TKIs increase the rate of venous occlusive events (REM ORPETO: 2.85; 95%CI: 1.04 to 7.78).
- Stratification by treatment for venous analysis demonstrates nonsignificant results due to the low power of the analysis.

LIMITATIONS
- Lack of time-to-event analyses
- Inconsistent report of cardiovascular events in the literature.
- However, the use of a clinical trial register aimed to decrease this heterogeneity, and funnel plots demonstrate no evidences of publication bias. The I² statistic specifies no heterogeneity among studies (data not shown).

DISCLOSURES
François Mullier reports personal fees from Boehringer Ingelheim, Bayer Healthcare and Bristol-Myers Squibb-Pfizer outside the submitted work. Carlos Graux reports personal fees from Novartis, Celgene, and Amgen, outside the submitted work. The other authors have no conflict of interest to disclose.

REFERENCES