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# Meta-analysis of the risks of arterial and venous occlusive events with new generation BCR-ABL TKIs in patients with chronic myeloid leukemia

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## BACKGROUND

High rate of arterial and venous occlusive events were reported with ponatinib during clinical development<sup>1</sup> and serious cases of arterial occlusive disease were also reported with nilotinib.<sup>2</sup> This led to the evaluation of the vascular safety profile of new generation BCR-ABL TKIs through a meta-analysis that confirmed the increased risk of vascular occlusive events with ponatinib and nilotinib compared with imatinib in chronic myeloid leukemia (CML). The risk was also with dasatinib.<sup>3</sup> However, distinction between arterial of venous events was not assessed.

## 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.

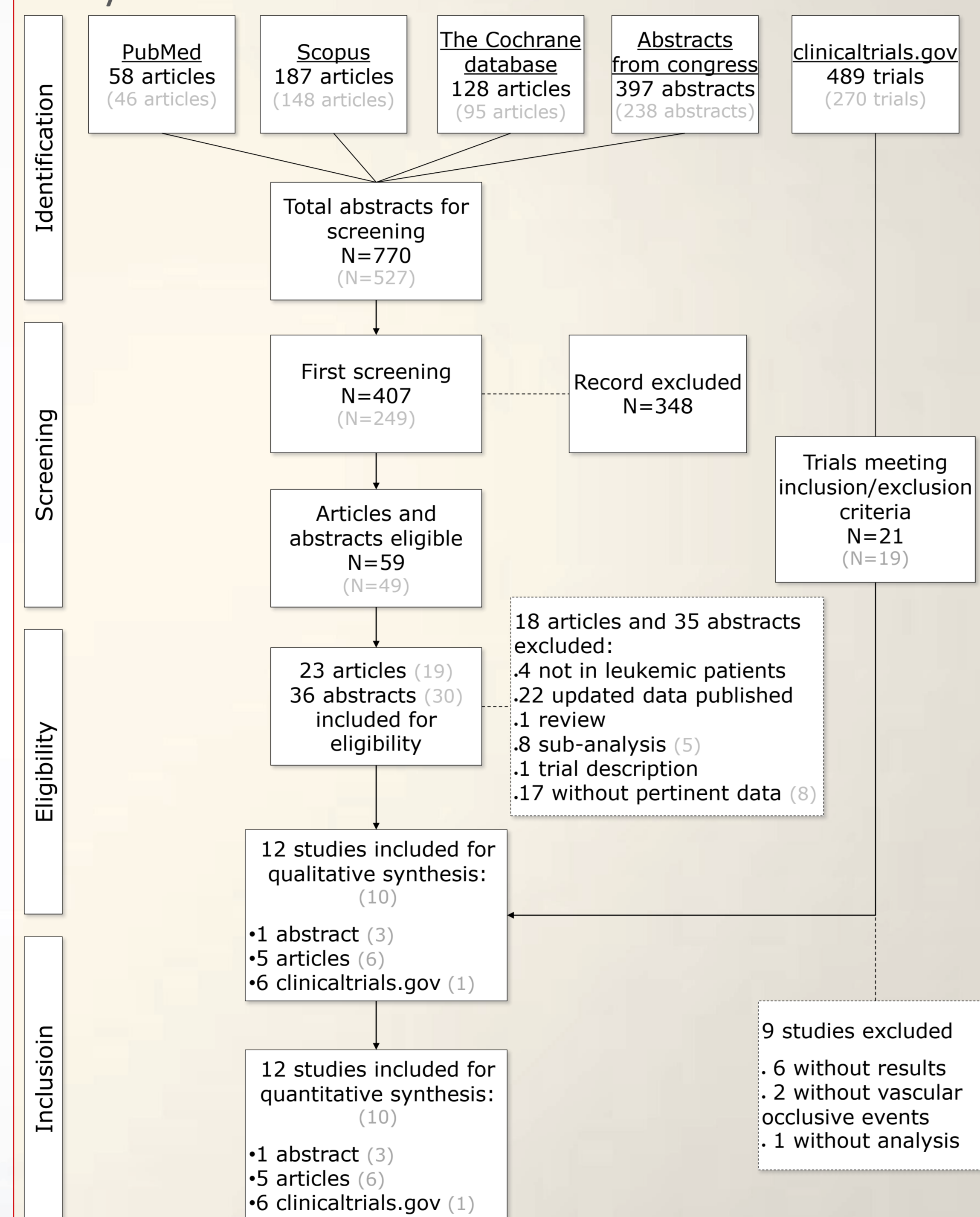
### Data collection

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

### Statistical analysis

- Random- (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: Cochran's Q statistic and I<sup>2</sup> value.
- One-way sensitivity analysis was performed to assess the robustness.

**Figure 1.-** PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis) flow diagram of study selection



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

## DISCLOSURES

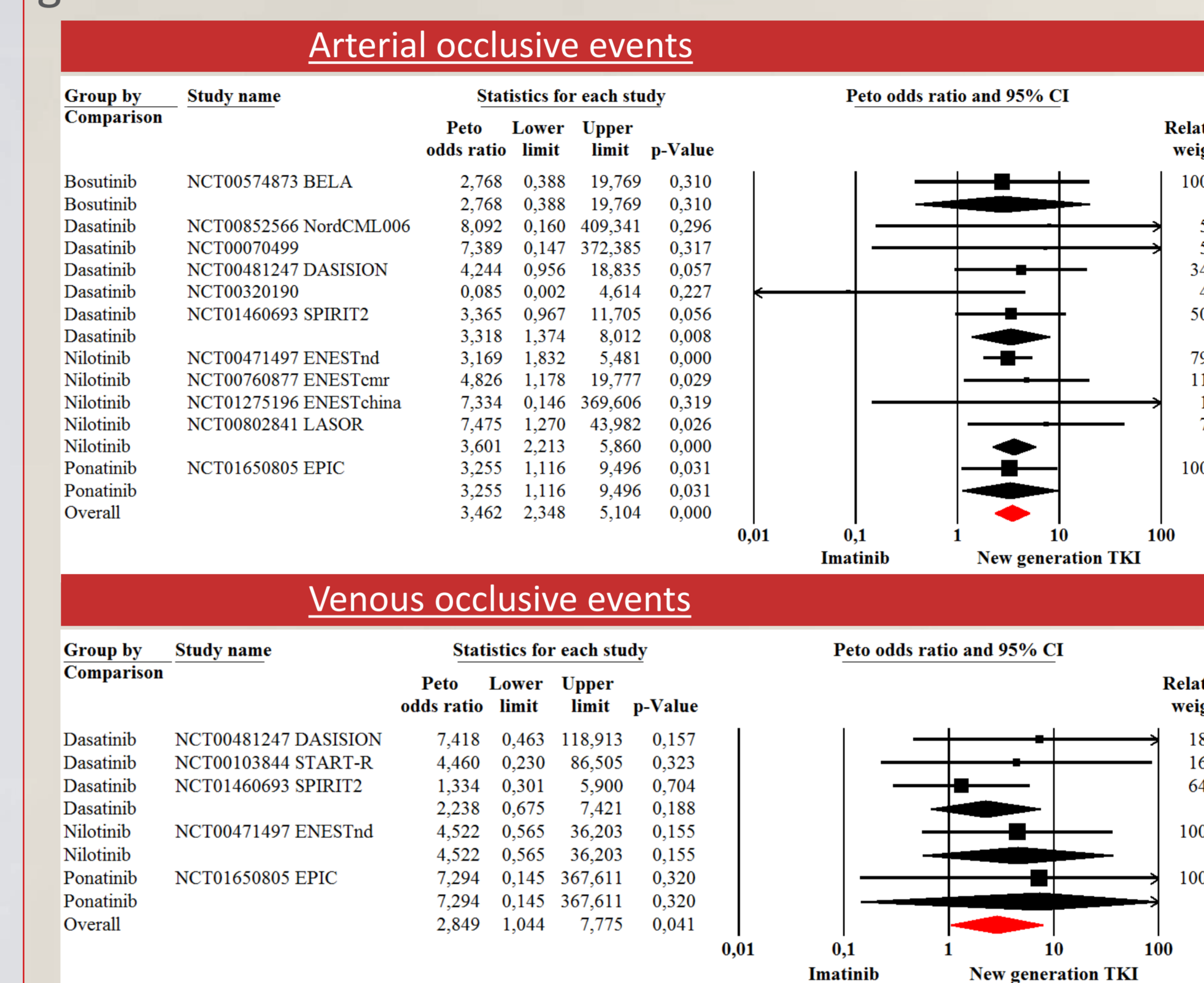
François Mullier reports personal fees from Boehringer Ingelheim, Bayer Healthcare and Bristol-Myers Squibb-Pfizer outside the submitted work. Carlos Graux reports personal fees from Novartis, Celgene, and Amgen, outside the submitted work. The other authors have no conflict of interest to disclose.

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## RESULTS

**Figure 2.-** Forest plots of arterial and venous occlusive events in patients with Ph+ CML treated with new generation TKIs versus imatinib.



- Overall, new generation TKIs increase the rate of venous (FEM OR<sub>PETO</sub>: 2.85; 95%CI: 1.04 to 7.78) and arterial (REM OR<sub>PETO</sub>: 3.462; 95%CI: 2.35 to 5.10) occlusive events.
- Ponatinib, nilotinib and dasatinib 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.
- Stratification by treatment for venous analysis demonstrates nonsignificant results due to the low power of the analysis.

## 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 TKIs is mainly 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.

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

| Treatments | Venous occlusive events |               | Arterial occlusive events |                |
|------------|-------------------------|---------------|---------------------------|----------------|
|            | New generation TKIs     | Imatinib      | New generation TKIs       | Imatinib       |
| Nilotinib  | 4/886 (0.45)            | 0/608 (0.00)  | 69/886 (7.79)             | 7/608 (1.15)   |
| Dasatinib  | 8/929 (0.86)            | 3/873 (0.34)  | 16/929 (1.72)             | 4/873 (0.46)   |
| Bosutinib  | 0/248 (0.00)            | 0/251 (0.00)  | 3/248 (1.21)              | 1/251 (0.40)   |
| Ponatinib  | 1/154 (0.65)            | 0/152 (0.00)  | 11/154 (7.14)             | 3/152 (1.97)   |
| Overall    | 13/2217 (0.59)          | 3/1884 (0.16) | 99/2217 (4.47)            | 15/1884 (0.80) |

- Overall, 4.47% (99/2,217) of patients developed arterial occlusive events with new generation BCR-ABL TKIs compared with 0.80% (15/1,884) with imatinib (REM OR<sub>PETO</sub>: 3.46; 95%CI: 2.35 to 5.10).
- Venous occlusive events occurred in only 0.59% (13/2,217) of patients treated with new generation TKIs and in 0.16% (3/1,884) of imatinib-treated patients.

## 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 I<sup>2</sup> statistic specifies no heterogeneity among studies (data not shown).

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