Cardiovascular effect of BCR-ABL TKIs: a meta-analysis and systematic review of arterial and venous occlusive events

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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[1] and serious cases of arterial occlusive disease were also reported with nilotinib.[2] 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 leukaemia (CML). The risk was also with dasatinib.[3] 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

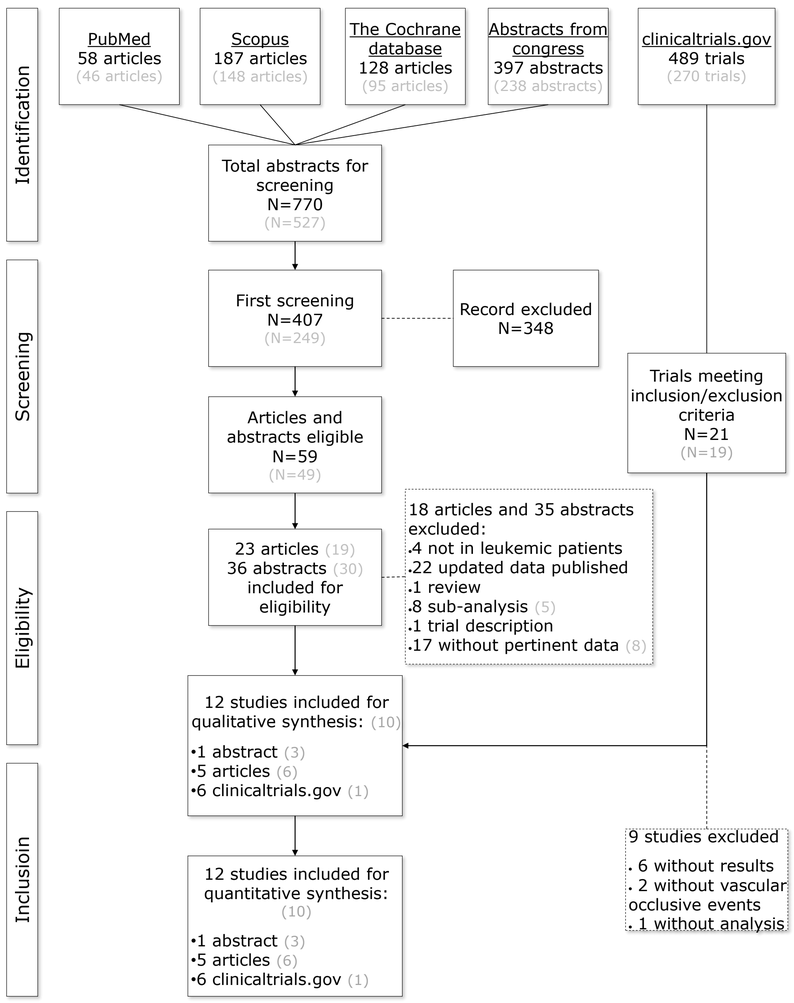
- Study and population characteristics
- Arterial occlusive events
- Venous occlusive events

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^2 value.
- One-way sensitivity analysis was performed to assess the robustness

RESULTS

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.

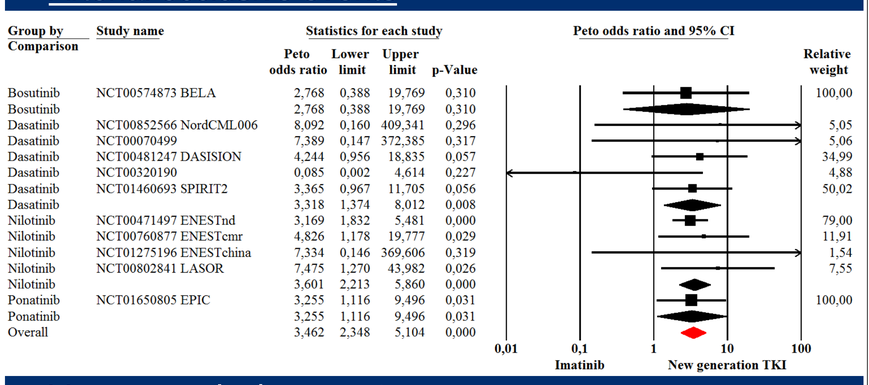
Table 1: Absolute risk of arterial and venous occlusive events in patients with CML.

Treatments	Venous occlusive events		Arterial occlusive events	
	New generation TKIs	Imatinib	New generation TKIs	Imatinib
Bosutinib	0/248 (0.00)	0/251 (0.00)	3/248 (1.21)	1/251 (0.40)
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)
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)**

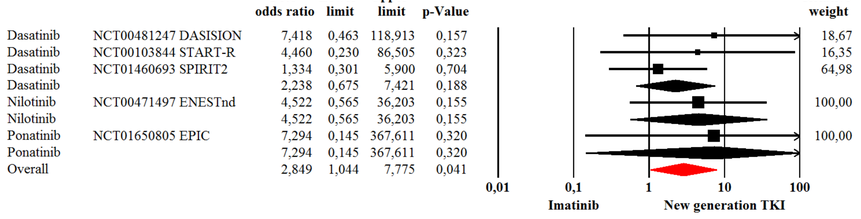
- Overall, 4.47% (99/2,217) of patients developed arterial occlusive events with new generation BCR-ABL TKIs compared with 0.80% (15/1,884) with imatinib (REM OR_{PETO}: 3.46; 95%CI: 2.35 to 5.10).
- Venous occlusive events occurred in only 0.86% (13/2,217) of patients treated with new generation TKIs and in 0.16% (3/1,884) of imatinib-treated patients.

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

Arterial occlusive events



Venous occlusive events



- Ponatinib (REM OR_{PETO}: 3.26; 95%CI: 1.12 to 9.50), nilotinib (REM OR_{PETO}: 3.60; 95%CI: 2.21 to 5.86) and dasatinib (REM OR_{PETO}: 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 OR_{PETO}: 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 I^2 statistic specifies no heterogeneity among studies (data not shown).

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 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.

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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