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

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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 leukemia (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

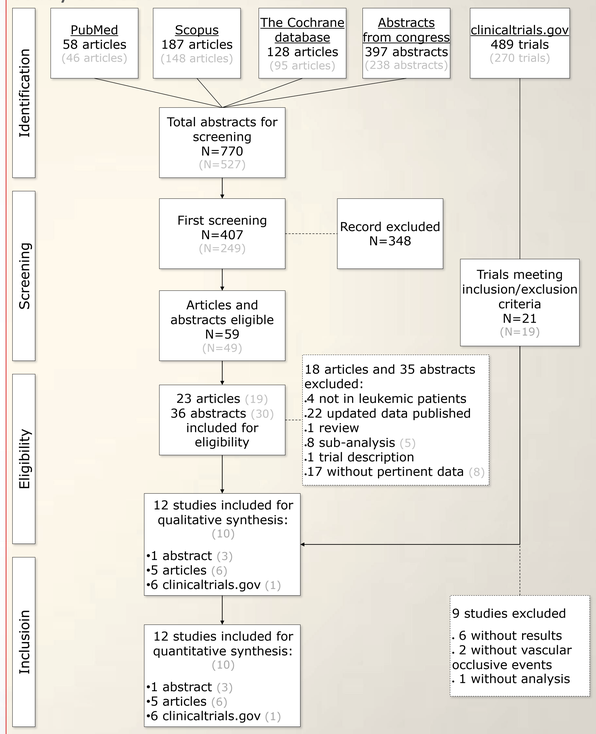
- Study and population characteristics
- Arterial occlusive events
- Venous occlusive events

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.

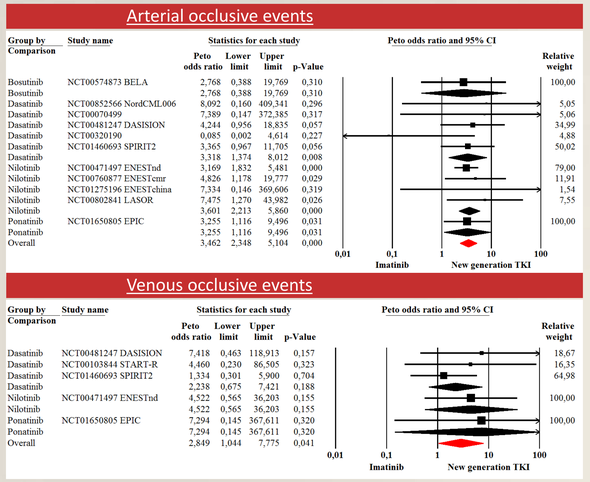
RESULTS

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.

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_{PETO}: 2.85; 95%CI: 1.04 to 7.78) and arterial (REM OR_{PETO}: 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.

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_{PETO}: 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^2 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.

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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.

REFERENCES

1. Giles FJ, Mauro MJ, Hong F, Ortmann CE, McNeill C, Woodman RC, et al. Rates of peripheral arterial occlusive disease in patients with chronic myeloid leukemia in the chronic phase treated with imatinib, nilotinib, or non-tyrosine kinase therapy: a retrospective cohort analysis. Leukemia. 2013;27(6):1310-5.

2. Quintás-Cardama A, Kantarjian H, Cortes J. Nilotinib-associated vascular events. Clinical lymphoma, myeloma & leukemia. 2012;12(5):337-40.

3. Douxfils J, Haguet H, Mullier F, Chatelain C, Graux C, Dogné JM. Association Between BCR-ABL Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia and Cardiovascular Events, Major Molecular Response, and Overall Survival: A Systematic Review and Meta-analysis. JAMA oncology. 2016.