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

Haguet, Hélène; Mullier, François; Chatelain, Christian; Graux, Carlos; Dogné, Jean-Michel; Douxfils, Jonathan

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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

Hélène Haguet*1, 2, Jonathan Douxfils1, François Mullier2, Christian Chatelain1, Carlos Graux3, Jean-Michel Dogné1 ¹ University of Namur, Department of pharmacy, Belgium ²CHU UCL Namur, Hematology laboratory, Belgium ³CHU UCL Namur, Department of hematology, Belgium

Figure 1. PRISMA (Preferred Reporting Items for

Systematic review and Meta-Analysis) flow

diagram of study selection



Peto odds ratio and 95% CI

Relative

100,00

BACKGROUND

High rate of arterial and venous occlusive events were reported with ponatinib during clinical development¹ 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, ESMO) and clinical trial register

Data collection

- Venous occlusive events

arterial side.

ponatinib.

- Peto method
- Heterogeneity assessment: Cochran's Q statistic and l² value.

CONCLUSIONS

New generation TKIs increased risk of arterial and

venous occlusive events compared with imatinib

associated with new generation BCR-ABL TKIs is

mainly driven by thrombotic events occurring at the

Additional investigations are required to assess the

Appropriate risk minimization measures should be

taken/implemented with nilotinib, dasatinib and

underlying pathophysiological mechanisms.

The increased risk of vascular occlusive events

assess the robustness

Cochrane library), congress abstracts (ASH, ASCO, (www.clinicaltrials.gov)

Selection of all randomized clinical trials comparing new generation TKIs versus imatinib in patients with Ph+ CML.

- Study and population characteristics
- Arterial 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
- One-way sensitivity analysis was performed to

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.

CONTACT INFORMATION

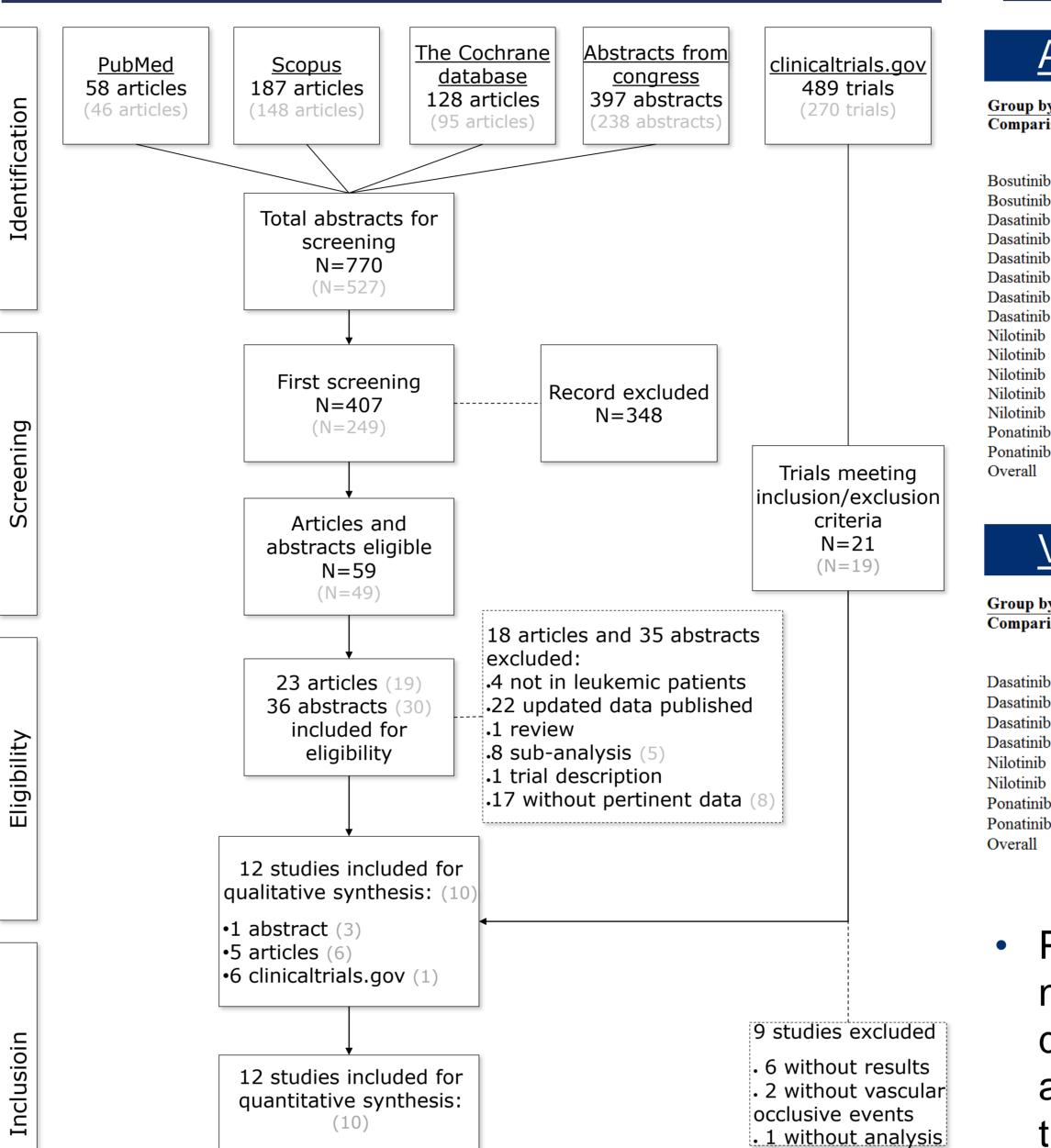
H. Haguet: helene.haguet@gmail.com J. Douxfils: jonathan.douxfils@unamur.be

J-M Dogné: jean-michel.dogne@unamur.be

RESULTS

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

Arterial occlusive events



 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.

•1 abstract (3)

•6 clinicaltrials.gov (1)

5 articles

<u>Treatments</u>	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.

34,99 NCT00481247 DASISION NCT01460693 SPIRIT NCT01275196 ENESTchina NCT01650805 EPIC Ponatinib Ponatinib Overall 3,462 2,348 **Imatinib** New generation TKI Venous occlusive events Peto odds ratio and 95% CI Relative NCT01460693 SPIRIT2 Dasatinil 7,421 100,00 Nilotinib NCT00471497 ENESTnd Nilotinib NCT01650805 EPIC 367.611 0.320 Ponatinib

7,294 0,145 367,611

- Ponatinib (REM OR_{PFTO}: 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.

<u>Limitations</u>

- 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).

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