BCR-ABL Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia: A Systematic Review and Meta-Analysis on the Risk of Cardiovascular Events, Major Molecular Response and Overall Survival

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BCR-ABL tyrosine kinase inhibitors in chronic myeloid leukemia: a systematic review and meta-analysis on the risk of cardiovascular events, major molecular response and overall survival

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Background

A high incidence of arterial events including peripheral artery occlusive diseases (PAOD) has been observed with ponatinib during the clinical development.[1] This brought the Food and Drug Administration (FDA) to include a boxed warning indicated that 8% of patients treated by ponatinib experienced serious arterial thrombosis.

Serious cases of PAOD were also reported in CML patients treated with nilotinib in clinical trials and in post-marketing experience.[2] However, these reports were not considered conclusive, due to the small number of patients and the retrospective design.[3] To date, no signal of increased risk of vascular thrombosis and embolism was found in clinical trials with imatinib and dasatinib. However, some cases were reported post-marketing.

Objectives

- To assess the risk of vascular occlusive events with novel generation BCR-ABL TKI (i.e. bosutinib, dasatinib, nilotinib and ponatinib) in CML patients compared with imatinib.
- Stratifications by BCR-ABL TKI are performed to provide product specific risk assessment.
- Data on the overall survival and the MMR were also extracted to provide global benefit-risk evaluation.

Methods

Literature search

- The research of randomized clinical trials was performed for bosutinib, dasatinib, nilotinib and ponatinib.
- Systematic trial research from inception until November 21, 2014
- Only randomized clinical trials that compared a novel generation of BCR-ABL TKI versus standard of care (i.e. imatinib) were included.
- Restriction to the subgroup analysis of clinical trials that involved leukemic patients

Statistical analysis:

- Fixed-effect model
- Odds ratio using the Peto method
- One-way sensitivity analysis for robustness
- Heterogeneity: Cochran's Q statistic and I^2

Results

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

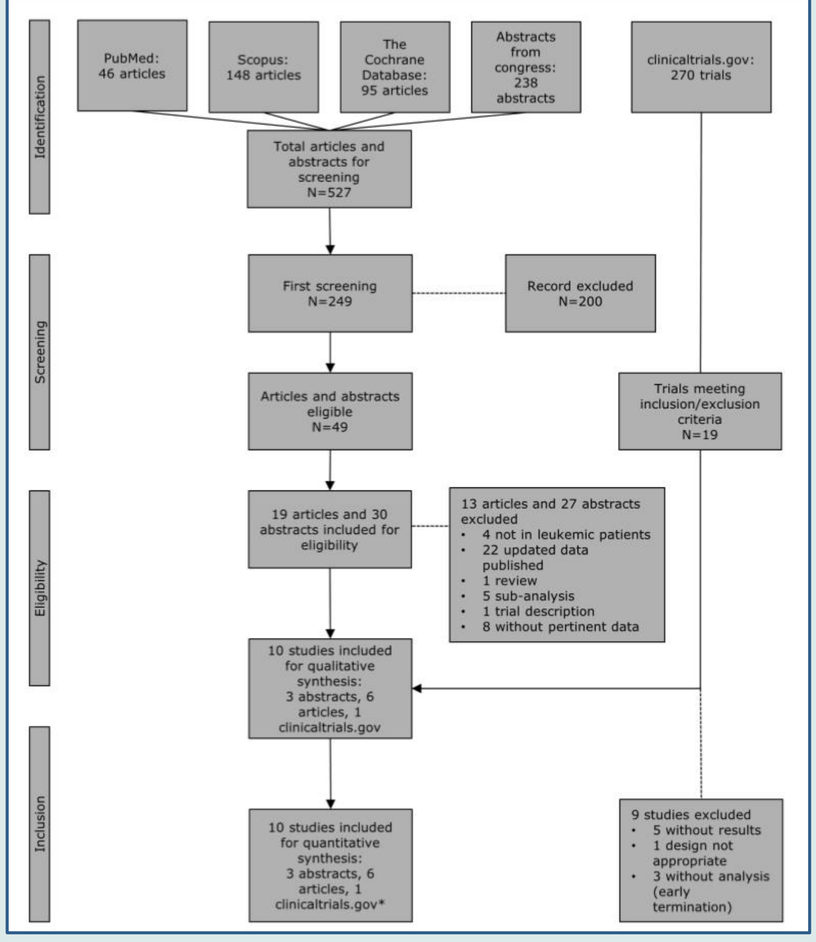
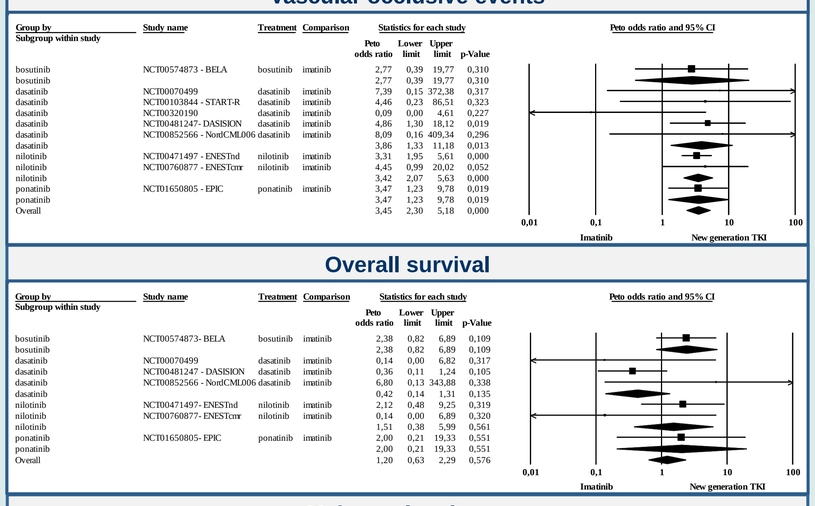


Figure 2: Forest plot of the included studies for the risk of myocardial infarction, major bleedings and all-cause mortality (Fixed effect model analyses)

Vascular occlusive events

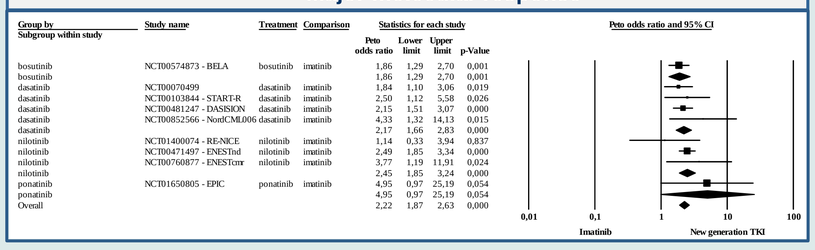


Group by Subgroup within study	Study name	Treatment	Comparison	Peto odds ratio	Lower limit	Upper limit	p-Value
bosutinib	NCT00574873 - BELA	bosutinib	imatinib	2,77	0,39	19,77	0,310
bosutinib				2,77	0,39	19,77	0,310
dasatinib	NCT00070499	dasatinib	imatinib	7,39	0,15	372,38	0,317
dasatinib	NCT00103844 - START-R	dasatinib	imatinib	4,46	0,23	86,51	0,323
dasatinib	NCT00320190	dasatinib	imatinib	0,09	0,00	4,61	0,227
dasatinib	NCT00481247- DASISION	dasatinib	imatinib	4,86	1,30	18,12	0,019
dasatinib	NCT00852566 - NordCML006	dasatinib	imatinib	8,09	0,16	409,34	0,296
dasatinib				3,86	1,33	11,18	0,013
nilotinib	NCT00471497 - ENESTnd	nilotinib	imatinib	3,31	1,95	5,61	0,000
nilotinib	NCT00760877 - ENESTcmr	nilotinib	imatinib	4,45	0,99	20,02	0,052
nilotinib				3,42	2,07	5,63	0,000
ponatinib	NCT01650805 - EPIC	ponatinib	imatinib	3,47	1,23	9,78	0,019
ponatinib				3,47	1,23	9,78	0,019
Overall				3,45	2,30	5,18	0,000

Overall survival

Group by Subgroup within study	Study name	Treatment	Comparison	Peto odds ratio	Lower limit	Upper limit	p-Value
bosutinib	NCT00574873- BELA	bosutinib	imatinib	2,38	0,82	6,89	0,109
bosutinib				2,38	0,82	6,89	0,109
dasatinib	NCT00070499	dasatinib	imatinib	0,14	0,00	6,82	0,317
dasatinib	NCT00481247 - DASISION	dasatinib	imatinib	0,36	0,11	1,24	0,105
dasatinib	NCT00852566 - NordCML006	dasatinib	imatinib	6,80	0,13	343,88	0,338
dasatinib				0,42	0,14	1,31	0,135
nilotinib	NCT00471497- ENESTnd	nilotinib	imatinib	2,12	0,48	9,25	0,319
nilotinib	NCT00760877- ENESTcmr	nilotinib	imatinib	0,14	0,00	6,89	0,320
nilotinib				1,51	0,38	5,99	0,561
ponatinib	NCT01650805- EPIC	ponatinib	imatinib	2,00	0,21	19,33	0,551
ponatinib				2,00	0,21	19,33	0,551
Overall				1,20	0,63	2,29	0,576

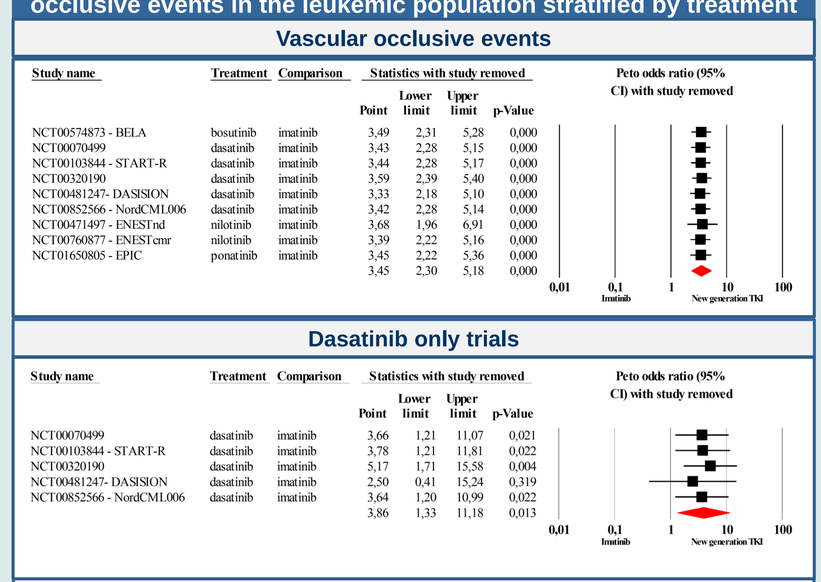
Major molecular response



Group by Subgroup within study	Study name	Treatment	Comparison	Peto odds ratio	Lower limit	Upper limit	p-Value
bosutinib	NCT00574873 - BELA	bosutinib	imatinib	1,86	1,29	2,70	0,001
bosutinib				1,86	1,29	2,70	0,001
dasatinib	NCT00070499	dasatinib	imatinib	1,84	1,10	3,06	0,019
dasatinib	NCT00103844 - START-R	dasatinib	imatinib	2,50	1,12	5,58	0,026
dasatinib	NCT00481247 - DASISION	dasatinib	imatinib	2,15	1,51	3,07	0,000
dasatinib	NCT00852566 - NordCML006	dasatinib	imatinib	4,33	1,32	14,13	0,015
dasatinib				2,17	1,66	2,83	0,000
nilotinib	NCT01400074 - RE-NICE	nilotinib	imatinib	1,14	0,33	3,94	0,837
nilotinib	NCT00471497 - ENESTnd	nilotinib	imatinib	2,49	1,85	3,34	0,000
nilotinib	NCT00760877 - ENESTcmr	nilotinib	imatinib	3,77	1,19	11,91	0,024
nilotinib				2,45	1,85	3,24	0,000
ponatinib	NCT01650805 - EPIC	ponatinib	imatinib	4,95	0,97	25,19	0,054
ponatinib				4,95	0,97	25,19	0,054
Overall				2,22	1,87	2,63	0,000

Figure 3: One-way sensitivity analysis of the risk of vascular occlusive events in the leukemic population stratified by treatment

Vascular occlusive events

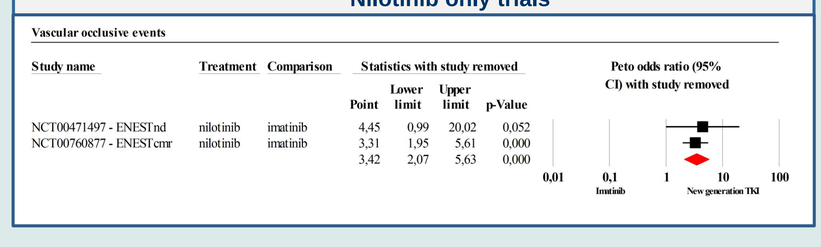


Study name	Treatment	Comparison	Statistics with study removed: Point	Lower limit	Upper limit	p-Value
NCT00574873 - BELA	bosutinib	imatinib	3,49	2,31	5,28	0,000
NCT00070499	dasatinib	imatinib	3,43	2,28	5,15	0,000
NCT00103844 - START-R	dasatinib	imatinib	3,44	2,28	5,17	0,000
NCT00320190	dasatinib	imatinib	3,59	2,39	5,40	0,000
NCT00481247- DASISION	dasatinib	imatinib	3,33	2,18	5,10	0,000
NCT00852566 - NordCML006	dasatinib	imatinib	3,42	2,28	5,14	0,000
NCT00471497 - ENESTnd	nilotinib	imatinib	3,68	1,96	6,91	0,000
NCT00760877 - ENESTcmr	nilotinib	imatinib	3,39	2,22	5,16	0,000
NCT01650805 - EPIC	ponatinib	imatinib	3,45	2,22	5,36	0,000
			3,45	2,30	5,18	0,000

Dasatinib only trials

Study name	Treatment	Comparison	Statistics with study removed: Point	Lower limit	Upper limit	p-Value
NCT00070499	dasatinib	imatinib	3,66	1,21	11,07	0,021
NCT00103844 - START-R	dasatinib	imatinib	3,78	1,21	11,81	0,022
NCT00320190	dasatinib	imatinib	5,17	1,71	15,58	0,004
NCT00481247- DASISION	dasatinib	imatinib	2,50	0,41	15,24	0,319
NCT00852566 - NordCML006	dasatinib	imatinib	3,64	1,20	10,99	0,022
			3,86	1,33	11,18	0,013

Nilotinib only trials



Vascular occlusive events

Study name	Treatment	Comparison	Statistics with study removed: Point	Lower limit	Upper limit	p-Value
NCT00471497 - ENESTnd	nilotinib	imatinib	4,45	0,99	20,02	0,052
NCT00760877 - ENESTcmr	nilotinib	imatinib	3,31	1,95	5,61	0,000
			3,42	2,07	5,63	0,000

References

[1] Gainor JF, Chabner BA. Ponatinib: Accelerated Disapproval. The oncologist. 2015.

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Discussion

Dasatinib, nilotinib and ponatinib are associated with a higher rate of vascular occlusive events compared to imatinib. Even if the results are not statistically significant with bosutinib, there is a trend toward an increased risk of vascular occlusive events. However, little is known about the exact incidence of vascular occlusive events in long-term TKI-treated patients with CML and about factors predisposing for vascular occlusive events development. Several case-reports, retrospective and prospective studies analysed the correlations between pre-existing risk factors and arterial occlusive disease occurrence and demonstrated that arterial occlusive events develop predominantly in patients with one or more risk factors (hypertension, diabetes, hyperlipidaemia, obesity, smoking and prior vascular disease) prior to TKI treatment (i.e. nilotinib and ponatinib). The MMR at one year is achieved by almost twice as many patients when using the novel generation TKI. However, the improvement of overall survival is not achieved at this data lock point, i.e. 1 year.

The cardiovascular risk is likely to be dose-related. However, the currently available data on the dose-efficacy and dose-toxicity relationship are not sufficient to make a formal recommendation on dose reduction, and there is a risk that lower doses might have reduced efficacy. Safety and efficacy data concerning dose reduction following major cytogenetic response (MCyR) have been included in the EU-SmPC of Iclusig® (ponatinib). A dose-ranging study in patients with chronic phase CML is currently recruiting to determine the optimal starting dose of ponatinib and characterise the safety and efficacy of ponatinib following dose reduction after achieving MCyR (OPTIC trial - NCT02467270). Such risk minimization measures are not yet implemented with the other TKI of interest, i.e. dasatinib and nilotinib, with whom the risk of vascular occlusive events is clearly identified.

Conclusions

This meta-analysis demonstrates a significant increase in the rate of vascular occlusive events associated with the use of dasatinib, nilotinib and ponatinib compared to imatinib. However, even if no statistical significance was found for bosutinib, a trend was also depicted. Dasatinib, nilotinib and ponatinib should be associated with frequent cardiovascular monitoring and an intensive support of comorbidities. Ponatinib should be reserved for patients with advanced disease or patients with the T315I mutation, or when others treatments cannot be used. Further dose-ranging studies are required to define the dose regimen of each BCR-ABL TKI that will provide the best benefit-risk profile. Finally, monitoring the response at the individual level is of utmost importance to reduce the risk of vascular occlusive events while keeping the benefit in term of MMR.

Disclosure

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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