

6th NTHC Symposium

Risk of vascular occlusive events with BCR-ABL TKIs in CML

A systematic review and meta-analysis

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

Vascular occlusive events

- **Ponatinib**: arterial and venous occlusive events identified¹
 - Temporal suspension of ponatinib marketing (FDA decision)
 - Early abortion of the phase III clinical trial (EPIC trial)
 - Risk minimization measures²

FDA Drug Safety Communication: FDA asks manufacturer of the leukemia drug Iclusig (ponatinib) to suspend marketing and sales

European Medicines Agency recommends changes in use of leukaemia medicine Iclusig (ponatinib) in order to minimise risk of blood clots

¹Giles, F. J. et al. *Leukemia* **27**(6): 1310-1315.

²EMA. European Medicines Agency recommends changes in use of leukaemia medicine Iclusig (ponatinib) in order to minimise risk of blood clots

Vascular occlusive events

- **Dasatinib**: no vascular occlusive events³
- **Bosutinib**: no vascular occlusive events⁴
- **Nilotinib**: serious cases of PAOD^{5,6}
 - Cardiac and arterial occlusive events included in labeling information

³Food and Drug Administration. "Label information - SPRYCEL."

⁴Food and Drug Administration. "Label information BOSULIF."

⁵Food and Drug Administration. "Label information - TASIGNA."

⁶Quintas-Cardama A., et al. *Clin Lymphoma Myeloma Leuk* **12**(5): 337-340.

Rationales

- TKIs may alter other tyrosine kinases → class effect?⁷
- 2nd generation TKIs: higher efficacy on surrogate outcomes in the treatment of CML

⁷Giles, F. J. et al. (2013). Leukemia **27**(6): 1310-1315.

Question

**Risk of CV occlusive events
associated to new generation
BCR-ABL TKIs in CML?**

Systematic review and Meta-analysis

Literature search:

- Scientific articles: Pubmed, scopus and Cochrane library
- Congress abstracts: ASH, ASCO, ESMO
- Clinical trial register: www.clinicaltrials.gov

Study selection:

- Randomized clinical trials
- Comparing new generation TKIs vs imatinib
- Patients with CML

Systematic review and Meta-analysis

Data collection:

- Study characteristics, population characteristics
- Vascular occlusive events
- (Overall survival and MMR)
- Arterial occlusive events, venous occlusive events

Statistical analysis:

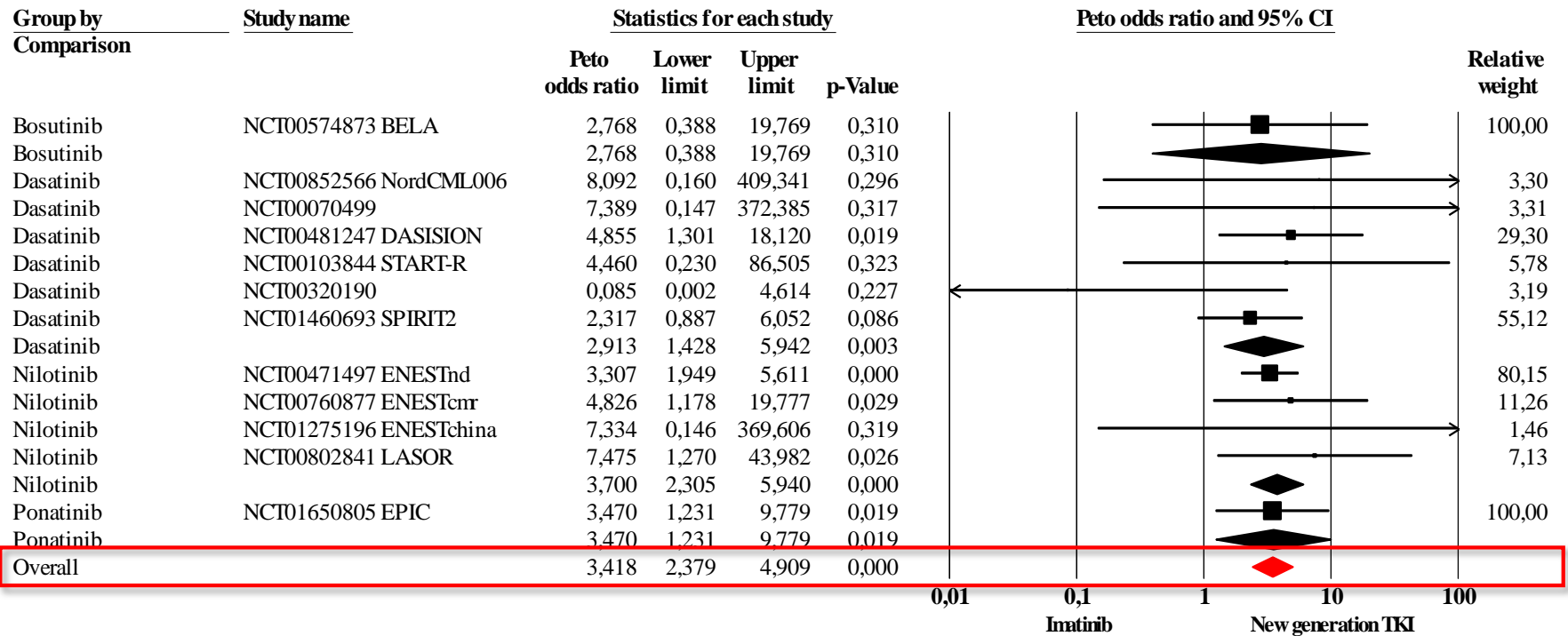
- Random-effects model

Exception: fixed-effect model for venous occlusive events

- Effect size measure: Odds ratio using Peto method

Vascular occlusive events⁸

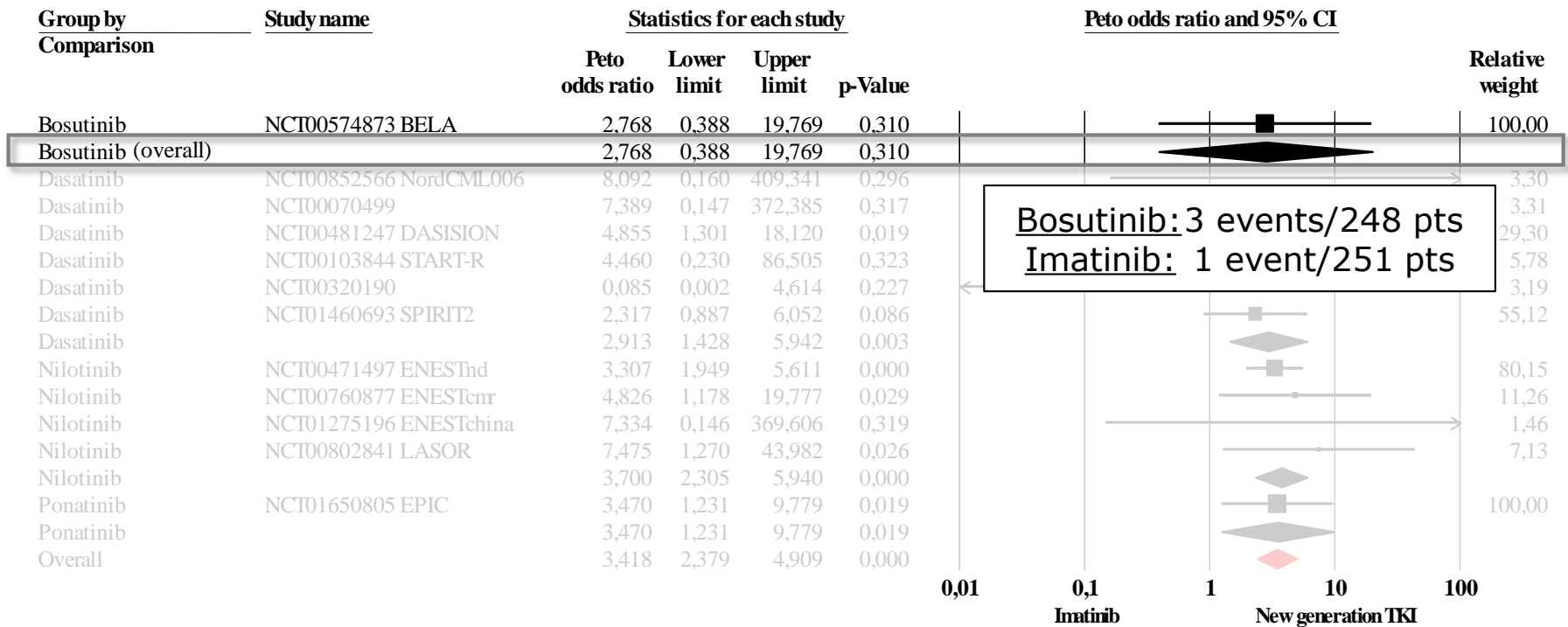
Vascular occlusive events



⁸Douxflis J, Haguët H et al. JAMA Oncol. 2016.

Vascular occlusive events⁸

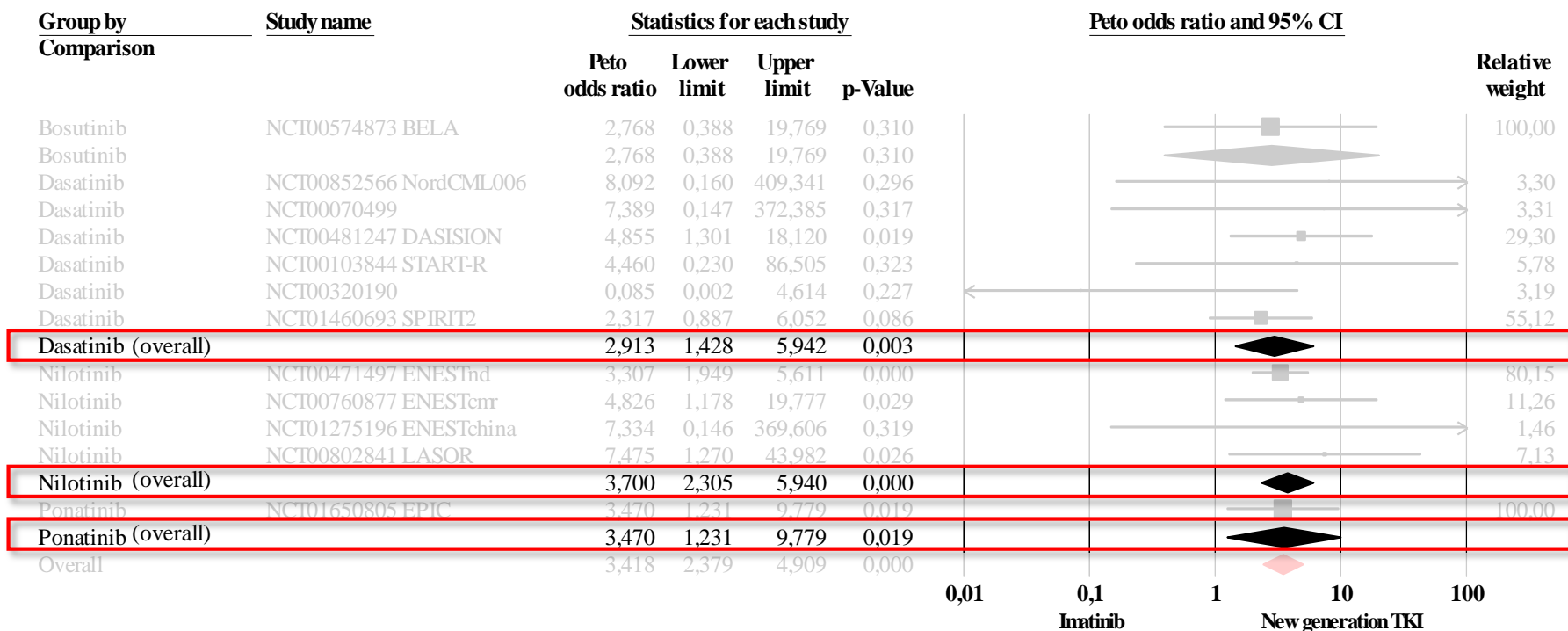
Vascular occlusive events



⁸Douxflis J, Haguët H et al. JAMA Oncol. 2016.

Vascular occlusive events⁸

Vascular occlusive events



⁸Douxflis J, Haguët H et al. JAMA Oncol. 2016.

Limitations

- Lack of individual data
 - Time to event
 - Number of deaths due to VOE
- Lack of homogeneity in evaluation criteria (VOE) between studies^{8,9}

⁸Yang EH, et al. *Future Oncol.* 11(14):1995-8.

⁹Groarke JD, et al. *The New England journal of medicine.* 369(19):1779-81.

Conclusion

- Increased risk of vascular occlusive events with:
 - Ponatinib
 - Nilotinib
 - Dasatinib
 - Trend but nonsignificant risk with bosutinib
- Increased risk of arterial and venous events
 - Predominance of arterial occlusive events
 - Venous occlusive events: lack of statistical power
- Risk minimization measures with dasatinib, nilotinib and ponatinib required

Risk minimization measures

- For ponatinib, the EMA recommends:¹⁰
 - To avoid its use in patients with VOE history
 - To assess the cardiovascular risk factors of all patients and monitor this status
 - Hypertension should be controlled during treatment
 - To monitor evidence of vascular occlusion or thromboembolism and to interrupt treatment if a vascular occlusive event occurs

¹⁰EMA. "European Medicines Agency recommends changes in use of leukaemia medicine Iclusig (ponatinib) in order to minimise risk of blood clots."

Acknowledgments

- Douxfils Jonathan
- Mullier François
- Chatelain Christian
- Graux Carlos
- Dogné Jean-Michel

**Thank you for
your attention!**