blood advances

TO THE EDITOR:

DOACs in patients with brain cancers: promising but still a long way to go

Michela Giustozzi,[1] Cecilia Becattini,[1] Fausto Roila,[2] Giancarlo Agnelli,[1] and Mario Mandalà[2]

[1]Internal, Vascular and Emergency Medicine–Stroke Unit, University of Perugia, Perugia, Italy; and [2]Unit of Medical Oncology, University of Perugia, Perugia, Italy

We wish to thank Buka and Sutton for their comments on our recently published article.[1] Among the results of our meta-analysis of patients with primary or metastatic brain cancer and VTE, the authors focused their attention on the lower risk of intracranial bleeding (ICH) in patients treated with direct oral anticoagulants (DOACs) than that in those receiving low-molecular weight heparin (LMWH) and advice caution for implementing this finding in the clinical practice. The authors state that these conclusions are driven mainly by Carney's study, which has several limitations including (1) the retrospective design, (2) the patient population, and (3) the potential selection bias.[2] Buka and Sutton concluded that differences in outcomes between DOACs and LMWH are likely to be small in patients with primary brain cancer or brain metastases and therapy should be determined on a case-by-case basis.

We indeed agree with the authors that in patients with primary or metastatic brain cancer and VTE, comparison between DOACs and LMWH requires caution and we are aware that all the 5 included studies have a retrospective design, a limited sample size, and some potential bias, not addressable by specific statistical analyses such as propensity score matching method. Nevertheless, our results seem to support DOACs as a valid option for the treatment of VTE in these patients for the following reasons: (1) the heterogeneity of our meta-analysis was 0%, which means that the variation in study results between studies is low. Moreover, after excluding the findings by Carney et al,[2] the risk of ICH remains lower in patients treated with DOACs than that in those treated with LMWH, although not statistically significant because of the small number of patients included (Relative risk [RR], 0.71; 95% confidence interval [CI], 0.30-1.68); heterogeneity remains 0%. Furthermore, as shown in Table 1, the clinical features of the patients treated with DOACs or with LMWH are similar in all the included studies. Notably, in the study by Carney et al,[2] patients with primary brain cancer or brain metastases treated with DOACs were more likely to have additional risk factors for bleeding than patients treated with LMWH, including concomitant use of aspirin, diagnosis of hypertension or chronic kidney disease. This is somehow reassuring in terms of the safety of DOACs in these patients. Finally, to better investigate this specific topic, we have updated our meta-analysis (since November 2022) on the risk of ICH in patients with primary brain cancer and brain metastases treated with DOACs or LMWH by including 2 newly published studies.[3,4] Both these studies are retrospective, one included both patients with primary brain cancer and brain metastases (a total of 125 patients) and the other only included patients with glioblastoma (a total of 121 patients). Overall, 7 studies on a total of 256 patients treated with DOACs and 423 patients treated with LMWH have now been considered. The risk ratio for ICH in the updated meta-analysis is 0.41 (95% CI, 0.25-0.68) in favor of DOACs, and heterogeneity is 0% (Figure 1). After excluding the findings by Carney et al, the RR is 0.51 (95% CI, 0.26-1.00; I^2, 0%). These results support the safety of DOACs compared with that of LMWH, with regard to reduction of ICH in patients with primary brain cancer and brain metastases treated for VTE.

We recognize that, in the future, a randomized controlled trial comparing LMWH and DOACs in these patients is advocated to investigate the efficacy and safety of these agents. However, because of the fragility of this population, a randomized trial could be difficult to be carried out. Indeed, observational studies, better with prospective design or with a synthetic control arm, could be helpful in this clinical setting.

Submitted 21 November 2022; accepted 23 November 2022; prepublished online on *Blood Advances* First Edition 1 December 2022. https://doi.org/10.1182/bloodadvances.2022009192.

Table 1. Main clinical features of the studies comparing DOACs with LMWH included in our meta-analysis

	Carney				Leader		Dubiski		Lee	
	Primary brain cancer		Brain metastases		Brain metastases		Primary brain cancer		Primary and brain cancer	
	DOACs, n %	LMWH, n %	DOACs, n %	LMWH, n %	DOACs, n %	LMWH, n %	DOACs, n %	LMWH, n %	DOACs, n %	LMWH, n %
Age, (y)	nr	nr	Nr	nr	66	64	65	68	63	62
Male	50	66	48	50	66	51	43	38	56	54
Hypertension	75	23	71	39	49	28	36	38	nr	nr
Chronic kidney disease	5	0	24	4	19	7	nr	nr	19	8
Aspirin	20	9	52	5	5	4	nr	nr	11	13

nr, not reported.

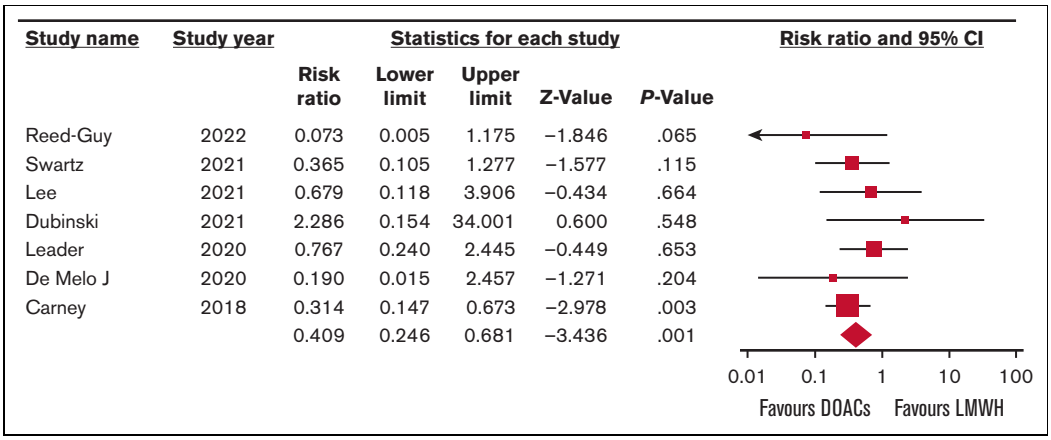

Figure 1. Risk of ICH in patients with primary and metastatic brain cancers treated with DOACs vs LMWH in the updated meta-analysis.

Furthermore, we would like to emphasize that our meta-analysis showed two additional main results: (1) rate of ICH is higher in patients with brain metastases than in patients with primary brain cancer (all ICH, 13% vs 6.4%), and (2) anticoagulation is associated with an increased risk of ICH in patients with primary brain cancer but not in patients with brain metastases. Because decisions around anticoagulation in patients with brain cancer are complex, we believe that our results could help physicians in facing such a challenging clinical situation.

In conclusion, DOACs appear to be safer than LMWH with a 60% risk reduction of ICH in patients with primary brain cancer and brain metastases. This warrants future research, and the jury is in the process of making the final decision.

Contribution: M.G., C.B., F.R., G.A., and M.M. analyzed the data and wrote the paper.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: M.G., 0000-0002-8033-4945; C.B., 0000-0002-8343-4888; M.M., 0000-0001-8846-8959.

Correspondence: Mario Mandalà, Unit of Medical Oncology, University of Perugia, Santa Maria della Misericordia Hospital, Perugia, Italy; email: mario.mandala@unipg.it.

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