Review: Dabigatran does not differ from vitamin K antagonists for mortality or major bleeding

Bloom BJ, Filion KB, Atallah R, Eisenberg MJ. ***Meta-analysis of randomized controlled trials on the risk of bleeding with dabigatran.*** *Am J Cardiol. 2014;113:1066-74.*

Clinical impact ratings: GM ★★★★★★★★ C ★★★★★☆☆ H ★★★★★★☆

Question

What is the relative safety of dabigatran and vitamin K antagonists (VKAs)?

Review scope

Included studies compared dabigatran, 150 mg twice daily, with VKAs alone or low-molecular weight heparin in adults ≥ 18 years of age, and had a treatment duration ≥ 90 days. Outcomes included mortality, major bleeding, and all bleeding.

Review methods

MEDLINE, EMBASE/Excerpta Medica, and Cochrane Library (all to Jun 2013) were searched for randomized controlled trials (RCTs) published in English or French. Reference lists were also searched. 5 multicenter RCTs (n = 20 332, mean age 55 to 71 y), ranging in size from 502 to 18 113 patients, met the selection criteria. 1 RCT comprised patients from 2 other trials included in the review and was excluded from meta-analyses. The remaining 4 RCTs, which included patients treated for atrial fibrillation (AF) (n = 12 334) or venous thromboembolism (VTE) (n = 5132), ranged in size from 236 to 12 098 patients and had follow-up of 84 to 730 days. All trials had low risk for bias as defined by the Cochrane risk for bias tool.

Main results

Meta-analysis showed that groups did not differ for mortality or major bleeding overall or in patients with AF or VTE (Table). Compared with VKAs, patients receiving dabigatran had a reduced risk for any bleeding, overall and in patients with VTE, but not in patients with AF (Table).

Conclusion

Dabigatran does not differ from vitamin K antagonists for mortality or major bleeding.

Dabigatran vs vitamin K antagonists (VKAs)*

Outcomes	Patients	Number of trials (n)	Weighted event rates		At 84 to 730 d	
			Dabigatran	VKAs	RRR (95% CI)	NNT (CI)
Mortality	All	3 (17 230)	5.6%	6.2%	10% (–1 to 20)	NS
	AF	1 (12 098)	7.2%	8.1%	11% (–1 to 21)	NS
	VTE	2 (5132)	1.8%	1.8%	0% (–50 to 33)	NS
Major bleeding	All	3† (17 230)	4.8%	5.2%	8% (–5 to 19)	NS
	AF	1† (12 098)	6.2%	6.6%	6% (–7 to 18)	NS
	VTE	2 (5132)	1.4%	1.8%	24% (–18 to 51)	NS
All bleeding	All	4 (17 466)	24%	31%	23% (7 to 36)	14 (9 to 46)
	AF	2 (12 334)	28%	35%	22% (–27 to 52)	NS
	VTE	2 (5132)	16%	22%	28% (19 to 36)	17 (13 to 25)

**AF = atrial fibrillation; NS = not significant; VTE = venous thromboembolism; other abbreviations defined in Glossary. Weighted dabigatran event rates, RRR, NNT, and CI calculated from control event rates and relative risks in article using a random-effects model.*

†1 trial (n = 236) was excluded from the analysis because it had 0 events in each group.

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Commentary

Direct-acting oral anticoagulants (dabigatran, rivaroxaban, and apixaban) are effective and relatively simple alternatives to warfarin, but are they safe? The new drugs have no antidotes, and their management for major bleeding is uncertain.

The meta-analysis by Bloom and colleagues examined major bleeding rates and mortality in 5 randomized comparisons of dabigatran, 150 mg twice daily, with VKAs: 2 in AF, 2 after acute VTE, and 1 to prevent late recurrence of VTE. Study durations were 6 months after acute VTE and a median of 2 years in AF. Target international normalized ratio for VKAs was 2 to 3.

As in other reviews, rates of major bleeding were similar for dabigatran and VKAs, but dabigatran offers a trade-off: less intracranial (relative risk [RR] 0.4, 95% CI 0.27 to 0.59) and more gastrointestinal bleeding (RR 1.51, CI 1.23 to 1.84) than VKAs.

Strengths of the review by Bloom and colleagues are its excellent methodology and clarity and the independence of analyzed trials from industry sponsors. A limitation is that it considers only the dose of dagibatran approved by the US Food and Drug Administration, 150 mg twice daily, although other countries allow 110 mg twice daily. Also, meta-analysis cannot tell the whole story. Not all major bleeding is clinically equal. A dabigatran study subanalysis (1) and a rivaroxaban review (2) claim fewer deaths from major bleeding with the direct oral anticoagulant than with VKAs. Could major bleeding be less severe with newer agents?

Patients and clinicians need to consider both absolute and relative risks. In the RE-LY study in AF (3), the absolute rates with dabigatran, 150 mg, and VKAs during 2 years were 6.2% and 6.6% for major bleeding, 3.0% and 2.0% for major gastrointestinal bleeding, and 0.6% and 1.4% for intracranial bleeding, respectively. These rates emphasize the importance of patient selection. Dabigatran may be preferred when reducing the incidence of intracranial haemorrhage is a priority, but alternatives may need to be considered for patients with a history of gastrointestinal bleeding.

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References

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