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White, Richard H

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Review: In older patients with AF or acute VTE, some DOACs reduce thrombotic events and major bleeding

Sharma M, Cornelius VR, Patel JP, Davies JG, Molokhia M. ***Efficacy and harms of direct oral anticoagulants in the elderly for stroke prevention in atrial fibrillation and secondary prevention of venous thromboembolism: systematic review and meta-analysis.*** *Circulation. 2015;132:194-204.*

Clinical impact ratings: GM ★★★★★★☆ HO ★★★★★☆☆ C ★★★★★☆☆ GI ★★★★★★☆ G ★★★★★★☆ H ★★★★★☆☆ N ★★★★★★☆

Question

In older patients with atrial fibrillation (AF) or acute venous thromboembolism (VTE), what are the efficacy and safety of direct oral anticoagulants (DOACs) compared with vitamin K antagonists (VKA)?

Review scope

Included English studies compared DOACs (thrombin inhibitor dabigatran or factor Xa inhibitors apixaban, rivaroxaban, and edoxaban) with a VKA for stroke prevention in patients with AF or for treatment of acute VTE for ≥ 3 months. Primary outcomes were stroke or systemic embolism, recurrent VTE, and major bleeding.

Review methods

MEDLINE, EMBASE/Excerpta Medica, and Cochrane Central Register of Controlled Trials (all to Jun 2014), clinical trial registries, conference proceedings, and reference lists were searched for phase 2 and 3 randomized controlled trials (RCTs). Drug manufacturers, authors, and regulatory bodies were contacted for unpublished subgroup data for patients ≥ 75 years of age. 19 RCTs (n = 102 479; 31 418 patients ≥ 75 y of age; mean age range 54 to 72 y; 47% to 92% men; duration 3 to 34 mo) met selection criteria. 11 were phase 3 trials, and 8 were phase 2; 12 had subgroup data for patients ≥ 75 years of age; all used warfarin as a comparator; and 4 included other VKAs.

Main results

The main results are in the Table. The wide confidence intervals around the number needed to treat may reflect heterogeneity among the studies.

Conclusion

In patients ≥ 75 years of age with atrial fibrillation or acute venous thromboembolism (VTE), direct oral anticoagulants reduce or do not differ from vitamin K antagonists for stroke or systemic embolism, recurrent VTE, or major bleeding.

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For correspondence: Mr. M. Sharma or Dr. M. Mohlokhia, Kings College, London, England, UK. E-mail manujsharma2014@gmail.com; mariam.molokhia@kcl.ac.uk. T3

Commentary

For clinicians to change from prescribing warfarin to DOACs in patients with AF or VTE, the benefits must outweigh the risks. Physicians tend to focus on risks for recurrent VTE, stroke (in patients with AF), and major bleeding, in addition to such other factors as out-of-pocket patient costs and overall quality of life. They may limit use of any anticoagulant in elderly patients based on the fear that patients might fall and have intracranial bleeding; however, the net clinical benefit of anticoagulation in AF may increase with age and has been shown to be greatest for patients ≥ 85 years of age (1).

Sharma and colleagues did a pooled study-level (vs patient-level) meta-analysis to compare the outcomes of DOACs vs VKAs in patients ≥ 75 years of age. They conservatively conclude that DOACs are "at least equal to warfarin" in reducing stroke and recurrent VTE and that the risk for bleeding is "similar" (except for potentially higher gastrointestinal bleeding with dabigatran).

Their conclusions may be understated. The authors note, but do not emphasize, that DOACs reduced intracranial bleeding—one of the outcomes clinicians fear most—by approximately 60% compared with VKAs. Also, the pooled risk for bleeding was lower in patients treated with apixaban or edoxaban.

The absence of an antidote to rapidly reverse DOACs is another major concern for clinicians. Agents designed to reverse the effects of dabigatran and factor Xa inhibitors are under development, but trials with hard clinical outcomes are several years away. Costs may be an issue. Other concerns about use of DOACs in elderly patients include patient adherence (2), inability to monitor the magnitude of anticoagulation, and bleeding in patients with reduced renal function. Additional research and clinical experience that demonstrate both the safety and efficacy of DOACs in elderly patients are required before DOACs replace warfarin in clinical practice.

Richard H. White, MD
University of California, Davis
Sacramento, California, USA

Direct oral anticoagulants (DOACs) vs vitamin K antagonists (VKAs) in patients ≥ 75 y of age with atrial fibrillation or acute venous thromboembolism (VTE)*

Outcomes	Drug	Number of trials (n)	Weighted event rates		At 3 to 34 mo	
			DOAC	VKA	RRR/RRI (95% CI)	NNT (CI)
SSE	Dab, 150 mg	1 (4889)	2.8%	4.2%	RRR 33% (10 to 50)	73 (49 to 250)
	Dab, 110 mg	1 (4772)	3.7%	4.2%	RRR 12% (−17 to 33)	NS
	Rivaroxaban	1 (6164)	4.1%	5.0%	RRR 19% (−2 to 36)	NS
	Apixaban	2 (5746)	2.8%	3.9%	RRR 29% (7 to 47)	89 (55 to 381)
	Edo, 60 mg	1 (5668)	4.9%	5.9%	RRR 18% (−3 to 34)	NS
	Edo, 30 mg	1 (5626)	6.6%	5.9%	RRI 11% (−9 to 36)	NS
Recurrent VTE	Dab, 150 mg	2 (529)	1.2%	1.8%	RRR 34% (−158 to 84)	NS
	Rivaroxaban	2 (1283)	2.3%	3.7%	RRR 37% (−17 to 66)	NS
	Apixaban	1 (749)	1.8%	3.6%	RRR 49% (−20 to 78)	NS
	Edo, 60 mg	1 (1104)	2.5%	5.0%	RRR 49% (6 to 72)	42 (28 to 353)
Major bleeding†	Dab, 150 mg	3 (4726)	9.8%	8.4%	RRI 16% (−3 to 39)	NS
	Dab, 110 mg	1 (4114)	9.2%	9.0%	RRI 3% (−16 to 24)	NS
	Rivaroxaban	4 (7082)	6.4%	6.1%	RRI 4% (−13 to 24)	NS
	Apixaban	2 (6423)	4.9%	7.5%	RRR 35% (22 to 47)	38 (29 to 62)
	Edo, 60 mg	1 (5668)	7.5%	9.1%	RRR 18% (2 to 31)	63 (36 to 603)
	Edo, 30 mg	1 (5626)	4.3%	9.1%	RRR 52% (41 to 60)	22 (19 to 27)

**Dab = dabigatran; Edo = edoxaban; NS = not significant; SSE = stroke or systemic embolism; other abbreviations defined in Glossary. Weighted event rates (for meta-analysis of > 1 trial), RRR, RRI, NNT, and CI calculated from control event rates and odds ratios in article using a fixed-effect model.*

†Major bleeding or any overt bleeding event that led to hospital admission for bleeding, physician-guided treatment, or treatment change.

References

1. **Singer DE, Chang Y, Fang MC, et al.** The net clinical benefit of warfarin anticoagulation in atrial fibrillation. Ann Intern Med. 2009;151:297-305.
2. **Cutler TW, Chuang A, Huynh TD, et al.** A retrospective descriptive analysis of patient adherence to dabigatran at a large academic medical center. J Manag Care Spec Pharm. 2014;20:1028-34.

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