

New Oral Anticoagulants in the Management of VTE

Stavros K Kakkos, Ioannis A Tsolakis

Stavros K Kakkos, Ioannis A Tsolakis, Department of Vascular Surgery, University Hospital of Patras, Patras, 26504, Greece
Correspondence to: Stavros K Kakkos, MD, MSc, PhD, RVT, Department of Vascular Surgery, University Hospital of Patras, Patras, 26504, Greece.

Email: kakkos@upatras.gr

Telephone: +30-2613-603406 Fax: +30-2613-603360

Received: January 2, 2015

Accepted: February 1, 2015

Published online: April 30, 2015

ABSTRACT

The advent of the new oral anticoagulants (NOAs) for the treatment and long-term (secondary) prevention of venous thromboembolism has been viewed as a revolution in patient care. Not only because the NOAs offer a simple solution compared to the traditional treatment with vitamin K antagonists with similar effectiveness and no need for dose monitoring, but more importantly because NOAs have first less bleeding complications, second very few drug and no food interactions, third no heparin-induced thrombocytopenia has been reported and last but not least two of them (rivaroxaban and apixaban) can be started as monotherapy. These facts are outlined by this Editorial.

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Key words: Venous thromboembolism; New oral anticoagulants; Vitamin K antagonists

Kakkos SK, Tsolakis IA. New Oral Anticoagulants in the Management of VTE. *International Journal of Hematology Research* 2015; 1(1): 4-6 Available from: URL: <http://www.ghrnet.org/index.php/ijhr/article/view/1006>

EDITORIAL

The new oral anticoagulants (NOAs) dabigatran, rivaroxaban,

apixaban and edoxaban have emerged not only as an effective treatment for venous thromboembolism (VTE) but also as a safe alternative to traditional management, i.e. heparin (usually low molecular weight heparin administered subcutaneously) followed by oral vitamin K antagonists (VKAs). Dabigatran is a factor IIa (thrombin) inhibitor, while rivaroxaban, apixaban and edoxaban are all factor Xa inhibitors. Six randomized-controlled trials (RCTs) have compared NOAs with heparin/VKA^[1-6]; four of them were double-blind trials. Four additional double-blind RCTs had as subject secondary prevention of VTE with three trials comparing a NOA with placebo and the fourth one comparing directly warfarin with dabigatran^[4,6,7].

The authors have recently published a systematic review and meta-analysis of all studies on NOAs in VTE management^[8]. Almost 38,000 patients were included and significant safety advantages were identified with no compromise of effectiveness. Apart from any difference in these two major outcome measures, there are several additional aspects that make NOAs different from VKAs.

NOAs, unlike heparins, fondaparinux and VKAs, are direct inhibitors of factor IIa or Xa, which could explain their more predictable results. Indeed all VKAs have a narrow therapeutic window that necessitates frequent INR measurements to carefully titrate their dose and to prevent recurrent VTE or bleeding in case of sub-therapeutic or supra-therapeutic INR, respectively. The same applies for the intravenous administration of heparin during the first days of VTE management. On the other hand, NOAs do not require any laboratory test to determine their dose, which is fixed. Therefore there is no cost for INR measurement in addition to any indirect costs (travelling etc) and patient inconvenience.

NOAs are quickly absorbed by the GI tract and their relatively short half-life time (usually less than 10-15 hours) does not necessitate bridging (with heparin or low molecular weight heparin) before surgical operations, for switching of anticoagulant treatments or during initial treatment with rivaroxaban or apixaban. However, two NOAs (dabigatran and edoxaban) require initial use of a conventional parenteral anticoagulant to be co-administered with the NOA for several days. The remaining two NOAs (rivaroxaban and apixaban) are administered as monotherapy. Unlike VKAs that interact with a very large number of drugs, the list of drugs that

interact with the NOAs is limited. Similarly, there are no known food interactions for NOAs, while VKA action is altered by any change in the amount of food that contains vitamin K (e.g. green vegetables etc). Rivaroxaban in particular should be taken with food to increase its bioavailability. Heparin-induced thrombocytopenia (HIT) has not been reported to occur after use of the NOAs.

One point that requires special attention is renal function, because dose reduction might be necessary in patients with moderate to severe impairment of renal function and there is a contraindication in very severe impairment, always based on glomerular filtration rate (GFR) estimation and the product SPC. Monitoring of GFR at regular intervals would help dose modification or change to VKAs, as appropriate in case of deterioration of renal function. An additional area of active research is the development of a specific antidote^[9], to be used in case of bleeding or the need for urgent surgery, where specific recommendations have been suggested^[10].

In the acute setting, NOAs are equally effective with VKAs in preventing recurrent symptomatic DVT (1.1% vs 1.3% with the use of VKA, RR 0.89, 95% CI 0.75-1.05, $p=0.16$) and also pulmonary embolism (PE), according to a recent meta-analysis^[8]. On subgroup analysis, factor Xa inhibitors and also NOAs not requiring initial parenteral anticoagulation (rivaroxaban and apixaban) were associated with a reduced risk of recurrent DVT compared to VKAs with the difference being statistically significant (RR 0.77, 95% CI 0.60-0.99, $P=0.04$ and RR 0.67, 95% CI 0.47-0.94, $p=0.02$, respectively).

In the same meta-analysis major bleeding occurred less often

with NOAs (1.08% vs 1.73% for VKAs, RR 0.63, 95% CI 0.51-0.77, $p<0.00001$, Figure 1A) and so did clinically relevant non-major bleeding (8.5% vs 6.6% for NOAs, RR 0.74, 95% CI 0.59-0.93, $p=0.01$)^[8]. Additionally, fatal bleeding occurred less often with NOAs (0.09% vs 0.18% for VKAs, RR 0.51, 95% CI 0.26-1.01, $p=0.05$, Figure 1B). This improved safety profile of NOAs is evident also in trials on atrial fibrillation, where NOAs are associated with a reduced rate of intracranial bleeding, which has a high fatality rate^[11].

The single RCT (RE-MEDY) that compared dabigatran with warfarin concluded that dabigatran was not inferior to warfarin (recurrent VTE 1.8% vs 1.3% for warfarin, $p=0.01$ for noninferiority), however major or clinically relevant bleeding occurred less frequently with dabigatran (RR 0.54, 95% CI 0.41 to 0.71)^[7].

In three secondary prevention trials, comparing the NOAs with placebo^[4,6,7], as expected the former reduced significantly pooled VTE recurrence rates at the expense of an increased clinically-relevant non-major bleeding, but not major bleeding^[8]. Surprisingly, pooled all-cause mortality rate was reduced to 0.41% with NOAs vs 0.86% with placebo (RR 0.38, 95% CI 0.18-0.79, $p=0.009$)^[8].

Nevertheless NOAs and particularly rivaroxaban are considered as a cost-effective alternative to warfarin, given the equal effectiveness and reduced bleeding rates^[12].

In conclusion, compared to VKAs, NOAs are not only effective but also safer regarding bleeding rates, which makes them suitable for long-term secondary prevention of VTE, as also shown by the corresponding trials. Because of their favorable characteristics and the above facts, NOAs are expected to simplify the management of VTE.

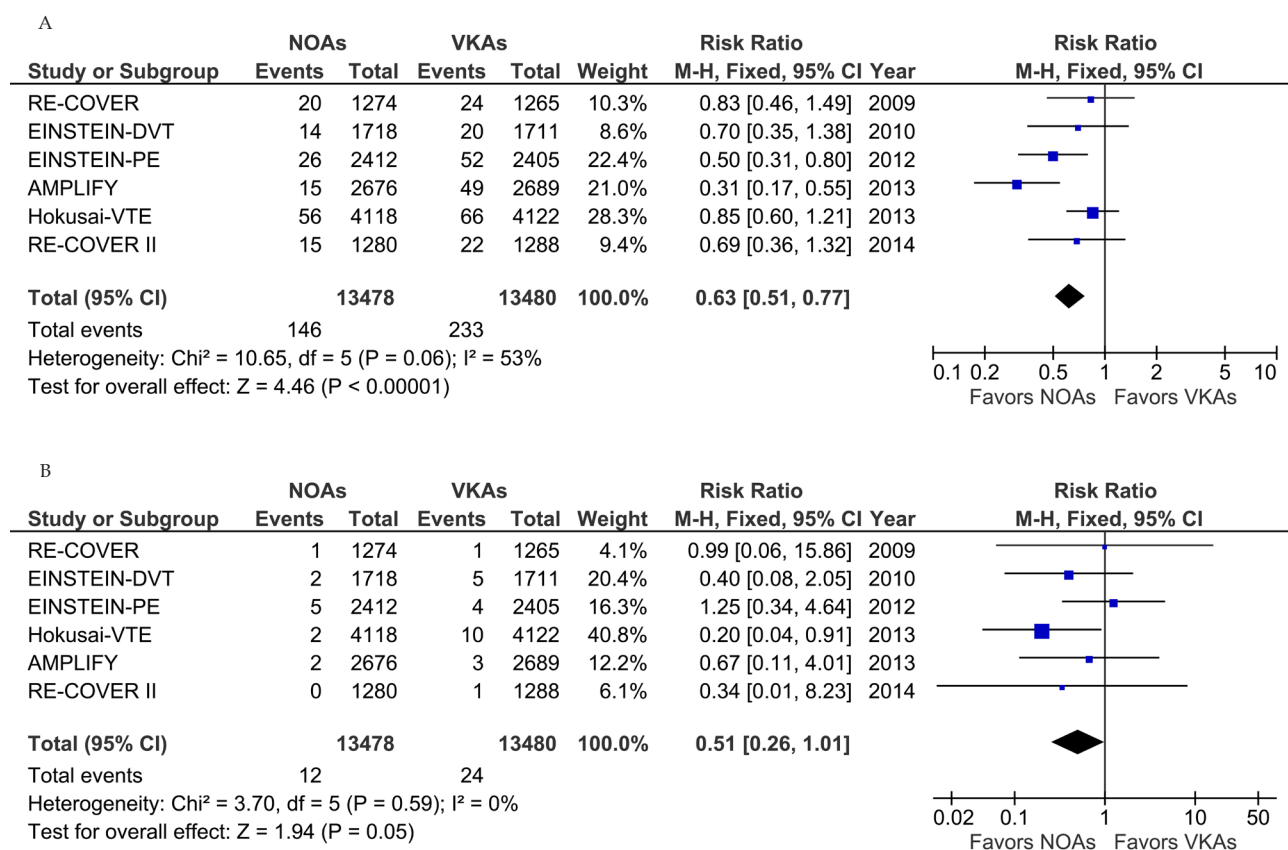


Figure 1 A: Safety of NOAs in the treatment of VTE. Major bleeding rates fell from 1.73% with VKAs to 1.08% with NOAs; B: while fatal bleeding rates approached statistical significance in favor of NOAs. Reproduced from reference 8, with permission from the publisher Elsevier.

CONFLICT OF INTERESTS

The Author has no conflicts of interest to declare.

REFERENCES

- 1 Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009; **361**(24): 2342-2352.
- 2 The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; **363**(26): 2499-2510
- 3 The EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012; **366**(14): 1287-1297
- 4 Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI, for the AMPLIFY Investigators. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. *N Engl J Med* 2013; **369**: 799-808
- 5 The Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013; **369**(15): 1406-1415
- 6 Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, Christiansen AV, Friedman J, Le Maulf F, Peter N, Kearon C. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation* 2014; **129**(7): 764-772
- 7 Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, Kvamme AM, Friedman J, Mismetti P, Goldhaber SZ. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med* 2013; **368**(8): 709-718
- 8 Kakkos SK, Kirkilelis GI, Tsolakis IA. Efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of phase III trials. *Eur J Vasc Endovasc Surg* 2014; **48**(5): 565-575
- 9 Lu G, DeGuzman FR, Hollenbach SJ, Karbarz MJ, Abe K, Lee G, Luan P, Hutchaleelaha A, Inagaki M, Conley PB, Phillips DR, Sinha U. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. *Nat Med* 2013; **19**(4): 446-451
- 10 Majeed A, Schulman S. Bleeding and antidotes in new oral anticoagulants. *Best Pract Res Clin Haematol* 2013; **26**(2): 191-202.
- 11 Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014; **383**(9921): 955-962
- 12 Seaman CD, Smith KJ, Ragni MV. Cost-effectiveness of rivaroxaban versus warfarin anticoagulation for the prevention of recurrent venous thromboembolism: A U.S. perspective. *Thromb Res* 2013; **132**(6): 647-651.

Peer reviewer: Yuri V. Bobryshev, PhD, School of Medical Sciences, Faculty of Medicine, University of New South Wales, NSW 2506 Kensington, Sydney, Australia.