Chapter 4
Conclusions

The number of available NOACs has provided clinicians with a greater range of options for the management of patients with thromboembolic disorders. Recently, two meta-analyses compared the efficacy and safety of the NOACs in stroke prevention in patients with AF [1] and the prevention of recurrent venous thromboembolism (VTE) [2]. These meta-analyses were the first to include data for all four NOACs studied in pivotal phase III studies for these indications.

In the meta-analysis of patients with AF, this included all 71,683 patients from the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 studies; in total 42,411 patients received a NOAC and 29,272 patients received warfarin. Treatment with NOACs was associated with a 19 % decrease in the risk of stroke compared with warfarin (relative risk 0.81, 95 % CI 0.73–0.91; $P < 0.0001$) (Fig. 4.1).

In patients treated with NOACs, there was a significant reduction in all-cause mortality (relative risk 0.90, 95 % CI 0.85–0.95; $P = 0.0003$) and intracranial bleeding (relative risk 0.48, 95 % CI 0.39–0.59; $P < 0.0001$), however an increase in gastrointestinal bleeding was noted (relative risk 1.25, 95 % CI 1.01–1.55; $P = 0.043$). Low-dose NOAC regimens exhibited similar rates of stroke and systemic embolic events to warfarin (relative risk 1.03, 95 % CI 0.84–1.27; $P = 0.74$), with a more favorable bleeding profile (relative risk 0.65, 95 % CI 0.43–1.00; $P = 0.05$) but were associated with significantly

E. Shantsila, G. YH Lip, *Non-Vitamin K Antagonist Oral Anticoagulants: A Concise Guide*,
DOI 10.1007/978-3-319-25460-9_4,

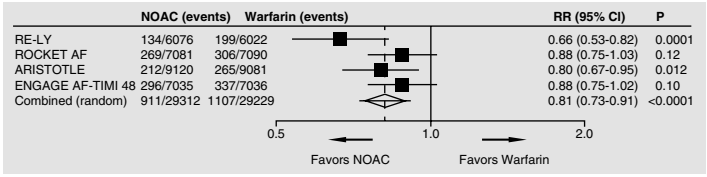

FIGURE 4.1 Stoke or systemic embolic events. *CI* confidence interval, *NOAC* non-VKA oral anticoagulants, *RR* relative risk (Reproduced with permission from Ruff et al. [1])

more ischemic strokes (relative risk 1.28, 95 % CI 1.02–1.60; P = 0.045). NOACs were associated with a favorable risk-benefit profile compared with warfarin, having demonstrated significant reductions in stroke, intracranial hemorrhage and mortality and similar rates of major bleeding. The safety and efficacy outcomes of NOACs in AF are consistent across a wide range of patients.

A similar meta-analysis based on phase III trials comparing NOACs to VKAs in 24,455 patients with VTE was performed, which included five studies, RE-COVER, EINSTEIN-DVT, EINSTEIN-PE, AMPLIFY and Hokusai-VTE. The risk ratios for VTE, fatal pulmonary embolism and overall mortality for NOACs vs VKAs were 0.88 (95 % CI 0.74–1.05), 1.02 (95 % CI 0.39–5.96), and 0.97 (95 % CI 0.83–1.14), respectively (Fig. 4.2).

With regards to safety the risk ratio of major bleeding was 0.60 (95 % CI 0.41–0.88) and fatal bleeding 0.36 (95 % CI 0.15–0.87). Compared with VKAs, in the treatment of VTE NOACs have comparable efficacy with a significantly lower risk of bleeding complications.

4.1 Future Directions

The number of NOACs that have been approved or are under clinical development reflects the huge clinical demand for such medicines and the desire of the pharmaceutical industry to respond to the as yet unmet needs of patients.

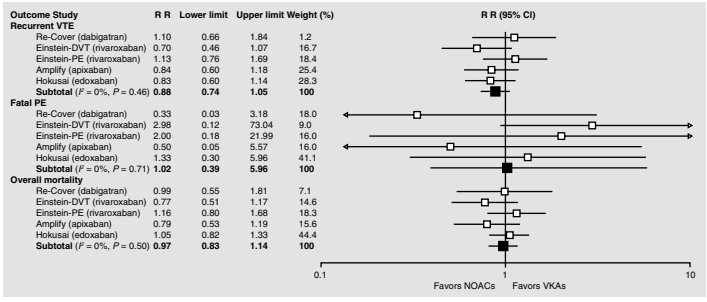

FIGURE 4.2 Efficacy outcomes of non-VKA oral anticoagulants (NOACs) vs vitamin K antagonists (VKAs) in phase III prevention of venous thromboembolism (VTE) studies. *CI* confidence interval, *PE* pulmonary embolism, *RR* relative risk (Reproduced with permission from van der Hulle et al. [2])

Four NOACs, the direct thrombin inhibitor dabigatran etexilate and the direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban, have already successfully completed phase III trials for indications requiring long-term anticoagulation. These drugs largely correspond to the requirements of an ideal anticoagulant. Furthermore, as they all participate in late stages of the coagulation cascade, their inhibition allows disruption of both the intrinsic and the extrinsic pathways; their high antithrombotic efficacy stems from this 'double' action.

References

1. Ruff CT, Giugliano RP, Braunwald E, et al. 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;383:955–62.

2. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost. 2014;12:320–8.