Intern Emerg Med (2015) 10:3–4
DOI 10.1007/s11739-014-1160-x

DEBATE

Restarting oral anticoagulants after intracerebral hemorrhage: pros

George Ntaios

Received: 13 October 2014 / Accepted: 14 November 2014 / Published online: 28 November 2014

Restarting anticoagulants after an intracerebral hemorrhage (ICH) is one of the challenges that no physician feels happy to face: the available evidence is very weak to support any strong suggestion. Unfortunately, this is a rather frequent scenario given the large number of patients who are treated with anticoagulants, and the fact that intracerebral hemorrhage is not a rare complication of anticoagulants. Given the lack of any relevant randomized controlled trial, one needs to weigh the thromboembolic risk against the risk for re-bleeding to reach a clinical decision. Obviously, the long-term thromboembolic risk depends on the underlying condition with the most frequent causes being atrial fibrillation (AF), mechanical valves and venous thromboembolism (VTE). Moreover, one should keep in mind that a post-ICH patient is frequently bed-ridden, which further increases the risk for VTE regardless of and in addition to the underlying condition that initially required treatment with anticoagulants. On the other hand, the risk of ICH recurrence seems to be associated with ICH location [1], age [2], apolipoprotein E ε2 or ε4 alleles [3] and presence of microbleeds on T2*-weighted gradient-echo MRI [4].

Unfortunately, there are no randomized data available to guide our decision about reinitiating anticoagulation when encountering a patient with anticoagulant-associated ICH. Only a few observational studies have investigated whether reinitiation or avoidance of anticoagulants is the preferable strategy. Recently, the CHIRONE study shows that the rate of ICH recurrence after reinitiation of vitamin-K antagonists is 2.56 per 100 patient-years during a median follow-up of 16.5 months, (of which, only 0.4 cases per 100 patient-years were fatal) [5]. Of note, there was no hemorrhage outside the central nervous system during the follow-up of 778 patient-years [5]. A recent report by the Registry of the Canadian Stroke Network shows that re-initiation of warfarin after ICH does not increase mortality or bleeding in patients with high thrombotic risk [6]. In similar, another single-center study in 52 patients who survived a warfarin-associated ICH shows that there is no statistically significant difference in outcome between patients who restart warfarin and patients who do not [7]. Of note, the rate of recurrent ICH after reinstitution of warfarin therapy is numerically lower than the rate of recurrent thromboembolic events in patients who do not restart warfarin therapy [7].

Of course, one should be very cautious when trying to draw conclusions from these studies given the inherent limitations of any observational non-randomized study. This is also reflected in the Guidelines of the European Stroke Organization about the management of spontaneous ICH in which no specific evidence-based suggestion is made due to the very low quality of available data [8]. But still, these are the best data available and at the bottom line, any inferences need to be drawn from these data. And these data imply that the risk for ICH recurrence in patients who reinitiate warfarin is not higher than the thromboembolic risk in those who do not reinitiate warfarin.

Nevertheless, our choice about our warfarin-associated ICH patients may finally be even more straightforward in the era of the new oral anticoagulants: during recent years, four new oral anticoagulants were launched based on a series of large randomized controlled trials. Apixaban, dabigatran, edoxaban and rivaroxaban were all shown to be at least as effective as warfarin for primary and secondary stroke prevention in patients with AF [9–14], as well as for

G. Ntaios (✉)
Department of Medicine, Larissa University Hospital, School of Medicine, University of Thessaly, Biopolis, 41110 Larissa, Greece
e-mail: gntaios@med.uth.gr

extended treatment of VTE [15–19]. Importantly, the huge advantage of these drugs against warfarin is their excellent safety profile: they are all associated with a large reduction of bleeding risk, and in particularly ICH risk [13, 14], which provides further support to the strategy of reinitiating anticoagulation in an anticoagulant-ICH patient, in particular using one of these new agents. Unfortunately, one should keep in mind that this is the case for patients with AF or VTE, but not for patients with mechanical heart valves, for whom dabigatran was recently shown to be associated with worse outcome compared to warfarin [20].

Hopefully, more evidence-based suggestions may become possible when the ongoing RESTART trial (www.RESTARTtrial.org) is completed. Until then, current data show that there is weak evidence that reinitiation of anticoagulants in patients with warfarin-associated ICH does not increase mortality and bleeding risk, and in this context, they argue in favor of restarting anticoagulants in these patients. Moreover, the substitution of warfarin by one of the new oral anticoagulants seems to further enhance the safety of this strategy for patients with AF or VTE, but not for patients with mechanical valves.

Needless to say, of course, that the patient should definitely be a part of the decision process after being thoroughly informed about all potential risks and strategies.

Conflict of interest None.

References

1. Bailey RD, Hart RG, Benavente O, Pearce LA (2001) Recurrent brain hemorrhage is more frequent than ischemic stroke after intracranial hemorrhage. Neurology 56:773–777
2. Vermeer SE, Algra A, Franke CL, Koudstaal PJ, Rinkel GJ (2002) Long-term prognosis after recovery from primary intracerebral hemorrhage. Neurology 59:205–209
3. O'Donnell HC, Rosand J, Knudsen KA et al (2000) Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. N Engl J Med 342:240–245
4. Greenberg SM, Eng JA, Ning M, Smith EE, Rosand J (2004) Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. Stroke J Cereb Circ 35:1415–1420
5. Poli D, Antonucci E, Dentali F et al (2014) Recurrence of ICH after resumption of anticoagulation with VK antagonists: CHIRONE study. Neurology 82:1020–1026
6. Claassen DO, Kazemi N, Zubkov AY, Wijdicks EF, Rabinstein AA (2008) Restarting anticoagulation therapy after warfarin-associated intracerebral hemorrhage. Arch Neurol 65:1313–1318
7. Yung D, Kapral MK, Asllani E, Fang J, Lee DS, Investigators of the Registry of the Canadian Stroke N (2012) Reinitiation of anticoagulation after warfarin-associated intracranial hemorrhage and mortality risk: the Best Practice for Reinitiating Anticoagulation Therapy After Intracranial Bleeding (BRAIN) study. Can J Cardiol 28:33–39
8. Steiner T, Al-Shahi Salman R, Beer R et al (2014) European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. Int J Stroke 9:840–855
9. Connolly SJ, Ezekowitz MD, Yusuf S et al (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 361:1139–1151
10. Giugliano RP, Ruff CT, Braunwald E et al (2013) Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 369:2093–2104
11. Granger CB, Alexander JH, McMurray JJ et al (2011) Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 365:981–992
12. Patel MR, Mahaffey KW, Garg J et al (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 365:883–891
13. Ntaios G, Papavasileiou V, Diener HC, Makaritsis K, Michel P (2012) Nonvitamin-K-antagonist oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack: a systematic review and meta-analysis of randomized controlled trials. Stroke J Cereb Circ 43:3298–3304
14. Ruff CT, Giugliano RP, Braunwald E et al (2014) Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 383:955–962
15. Agnelli G, Buller HR, Cohen A et al (2013) Apixaban for extended treatment of venous thromboembolism. N Engl J Med 368:699–708
16. Buller HR (2014) Edoxaban versus warfarin for venous thromboembolism. N Engl J Med 370:80–81
17. Investigators E, Bauersachs R, Berkowitz SD et al (2010) Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 363:2499–2510
18. Investigators E-P, Buller HR, Prins MH et al (2012) Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 366:1287–1297
19. Schulman S, Kearon C, Kakkar AK et al (2013) Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 368:709–718
20. Eikelboom JW, Connolly SJ, Brueckmann M et al (2013) Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 369:1206–1214