Time-in-therapeutic-range defined warfarin and standard dose direct oral anticoagulants in atrial fibrillation: Ischemic stroke, intracranial hemorrhage and death in a nationwide registry study

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Background and aims: Direct oral anticoagulants (DOACs) have almost replaced warfarin in stroke prevention of patients with atrial fibrillation (AF). However, little is known whether DOACs are more efficacious or safer than warfarin having information on time-in-therapeutic-range (TTR) in the warfarin-treated patients.

Methods: The Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) is a nationwide study of AF patients combining data from several Finnish health care registers. We analyzed all new-onset AF patients from 2011 to 2018 with available laboratory data.

The rates of ischemic stroke (IS), intracranial hemorrhage (ICH) and mortality during oral anticoagulation (OAC) use were analyzed until maximum follow-up of 730 days. Confounding factors by baseline characteristics as well as medications were taken into account by an inverse probability of treatment weighted analysis. For warfarin users, TTR was calculated and patient quartiles by TTR were assigned. The rates of IS, ICH and mortality in TTR quartiles for warfarin users were compared to standard dose dabigatran (150 mg bd.), apixaban (5mg bd.) and rivaroxaban (20mg od.).

Results: Altogether, 73 469 new-onset AF patients with OAC therapy (50.4 % male, mean age 73.0 years, 43 548 on warfarin, with mean TTR 66% and median TTR 72%) were followed for 76 546 patient years (py).

The rate of IS among patients with standard dose DOACs was 0.73/100 py for dabigatran (n=4 545), 1.05/100 py for apixaban (n=12 426) and 0.83/100 py for rivaroxaban (n=12 950). In the TTR quartiles of patients on warfarin, rates of IS were 3.5, 1.8, 1.2 and 0.74/100 py from the lowest (mean TTR 32%) to the highest quartile (mean TTR 90%), respectively. The weighted rates of IS were 1.3, 1.1 and 0.87/100 py for dabigatran, apixaban and rivaroxaban, and for warfarin from the lowest to the highest quartile: 3.2, 1.7, 1.2 and 0.7/100 py.

The respective rates of ICH were 0.47, 0.62 and 0.67/100 py for dabigatran, apixaban and rivaroxaban, and for warfarin from the lowest to the highest quartile: 3.6, 0.99, 0.51 and 0.32/100 py. The weighted rates of ICH were 0.70, 0.65 and 0.73/100 py for dabigatran, apixaban and rivaroxaban, and for warfarin from the lowest to the highest quartile: 3.4, 0.96, 0.51 and 0.30/100 py.

For mortality, the raw incidence rates were 1.2, 2.8 and 2.1/100 py for dabigatran, apixaban and rivaroxaban, and for warfarin from the lowest to the highest quartile: 16.5, 5.3, 2.3, and 1.5/100 py. The weighted rates of mortality were 1.6, 2.9, and 2.6, for dabigatran, apixaban and rivaroxaban, and for warfarin from the lowest to the highest quartile: 14.6, 4.8, 2.0, and 1.3/100 py.

The Figures provide cumulative incidence of IS and total mortality (crude rates) of the analyzed OAC groups.

Conclusions: The rates of IS, ICH and mortality were highest among patients on warfarin in the two lowest TTR quartiles, whereas the differences between high TTR groups and standard dose DOACs were only modest.
Cumulative incidence of ischemic stroke

Cumulative mortality rate