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Oral anticoagulation and stroke risk

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Abstract
Background: The risk of ischaemic stroke in patients with atrial fibrillation (AF) and mechanical heart valve (MHV) prostheses can be reduced by oral anticoagulation (OAC), which increases the risk of serious bleeding. The aims of this thesis were [1] to find out how effective and safe warfarin is where treatment quality is high, i.e. Sweden, with proportion of time that patients spend within the therapeutic range (TTR) >70%, [2] whether there is evidence for administering low-molecular-weight heparin (LMWH) during temporary interruptions of OAC (bridging therapy), and whether non-vitamin K-dependent oral anticoagulants (NOACs) as a group, [3] or individually, [4] are more effective and safer than warfarin when used for stroke prevention in patients with AF.
Materials and methods: All four studies were retrospective, based on the Swedish anticoagulation register Auricula, and done with merging of data from some or all of the National Patient Register, the Prescribed Drug Register, the Swedish Stroke Register (Riksstroke), and the Cause of Death Register. In studies 2–4, propensity score matching was performed to obtain treatment groups with similar risk profiles. Outcomes were defined as haemorrhages or thromboses requiring specialist care, or death. Haemorrhages were intracranial, gastrointestinal, or other. Thromboses were ischaemic stroke, systemic embolism, myocardial infarction, or venous thromboembolism (VTE).
Study 1 described all patients on warfarin during 2006–2011, which was before the introduction of NOACs. Study 2 was a cohort study of all patients who had a planned interruption of warfarin during the same period. Study 3 included all 49,011 patients starting OAC for stroke prevention due to AF between 1 July 2011 and 31 December 2014, and study 4 all 64,382 patients with the same indication between 1 January 2013 and 31 December 2015.
Results: Study 1 showed that for the 77,423 patients on warfarin with 217,804 treatment years, TTR was 77.4% for patients with AF, 74.5% with MHV, and 75.9% with VTE. Annual rates of intracranial bleeding were 0.38%, 0.51%, and 0.30%. In study 2, with 14,556 warfarin interruptions, the 30-day risk of a bleeding requiring specialist care was 0.64% for LMWH treated and 0.46% for controls. For patients with VTE as indication for OAC, bleeding rate with LMWH was significantly higher at 0.85% vs. 0.16% (hazard ratio 5.24, 95% confidence interval 1.39–19.77), but with no difference for patients with MHV or AF. The incidence of ischaemic complications was higher in the LMWH bridging group overall and for patients with MHV and AF, but not for patients with VTE. In study 3, for the 12,694 patients starting NOAC (10,392 treatment years) or matched warfarin patients (9,835 treatment years, TTR 70%) due to AF, annual incidence of ischaemic stroke and systemic embolism did not differ between the groups (1.35% vs. 1.58%), but risks of major bleedings and intracranial bleedings were significantly lower: 2.76% vs. 3.61% and 0.40% vs. 0.69%. In study 4, patients on individual NOACs (6,574 dabigatran, 8,323 rivaroxaban, 12,311 apixaban) were compared to 37,174 patients starting warfarin (in total 81,176 treatment years). No NOAC showed any difference in risk of ischaemic stroke or systemic embolism, but there were fewer intracranial bleedings, serious bleedings overall, and deaths for dabigatran and apixaban compared to warfarin. For patients starting rivaroxaban the risk of gastrointestinal bleeding was higher than for matched warfarin counterparts, with no significant differences in other bleeding risks, or mortality.
Conclusions: Swedish warfarin treatment show TTR levels that are high by international standards, correlating to low incidences of ischaemic and haemorrhagic events. LMWH bridging has not been proven beneficial, even for patients with MHV, meaning that bridging in general cannot be recommended. NOACs as a group were safer than high-quality warfarin treatment. Efficacy did not differ, even when comparing individual NOACs to warfarin, but there were fewer bleedings on dabigatran and apixaban. Although not more efficient than warfarin with a high TTR, NOACs should be the recommended first choice for OAC in AF, on the merit of lower bleeding risks.

Keywords
Oral anticoagulation, warfarin, apixaban, dabigatran, rivaroxaban, time in therapeutic range, atrial fibrillation, stroke, bridging, low-molecular-weight heparin

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