Science For A Better Life

Clinical Study Synopsis

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Title	**Treatment and outcomes among patients with atrial fibrillation and acute coronary syndromes in Sweden**
Keywords	ACS, AF, PCI, NOAC, antiplatelet, antithrombotic therapy
Rationale and background	Patients with a history of acute coronary syndrome (ACS) and atrial fibrillation (AF) are at high risk for major adverse cardiovascular events, therefore they are prescribed combination therapy consisting of an anticoagulant and one or more antiplatelet agents, particularly if a percutaneous coronary intervention (PCI) has been conducted. Such drug combinations are associated with increased risk of bleeding complications. In recent years several new non-vitamin K anticoagulants (NOACs) and antiplatelet drugs have been introduced; however, although they have been extensively studied individually, the safety and efficacy of most of the combined regimens have not been evaluated in randomized controlled trials. The recently completed PIONEER AF-PCI trial demonstrated a good safety profile of a regimen containing rivaroxaban [1]; however, the study was not designed to assess the regimen's efficacy. It is important to understand how patients with AF and ACS (including those undergoing PCI) are treated in real-life settings and to determine the outcomes associated with these treatment regimens.
Research question and objectives	This population-based study will describe the real life prescription patterns of antithrombotic drugs in patients with AF and ACS in Sweden, and will evaluate safety and effectiveness endpoints for the most commonly administered treatment regimens. The primary objectives are: • To describe the variety of antithrombotic treatment regimens administered in patients with AF and ACS and to estimate the treatment duration of the most common regimens. • To assess the incidence of bleeding events associated with hospitalization and effectiveness outcomes, including death, in patients with ACS and AF: overall and among subgroups.
Study Design	This is a retrospective cohort study which utilized non-randomized unselected data from nationwide mandatory health registers in Sweden.

Setting	In Sweden all registered oral anticoagulants (OACs; warfarin, dabigatran, rivaroxaban, apixaban, edoxaban) are used in clinical practice. Phenprocoumon can be prescribed under a special license in case of intolerance to other oral anticoagulants. Oral antiplatelet drugs used are acetylsalicylic acid, clopidogrel, ticagrelor, prasugrel and dipyridamol. Ticlopidine was deregistered in 2006, but may still be used under a special license.
Subjects and Study Size, including dropouts	The inclusion period started on 1st December 2011 and included patients up to 1st October 2016. Cohorts were followed up for a minimum of 3 months, thus the inclusion period ended 3 months before the end of the observation period. During the inclusion period, a total of 111,197 individuals were hospitalized with a diagnosis of ACS. Of these individuals, 23,180 also had a diagnosis of AF. After exclusions, 13,275 patients remained in the study cohort, of whom 9,375 did not undergo PCI, 320 had PCI without a stent and 3,580 had PCI with stent implantation during hospitalization.
Variables and Data sources	Detailed descriptive variables including baseline characteristics were captured for the population, including co-medications and comorbidities. CHA2DS2Vasc scores were calculated. Antithrombotic drug combinations, drug strength, treatment duration and most commonly prescribed regimens were identified. Exposure of a certain drug or a drug combination during follow-up was estimated as the number of days the dispensed drug supply would be expected to last if drug adherence was 90%, thus allowing for occasional dropped doses. The assumed dosages were the standard dose for the particular strength of the drug. Patients on non-standard dosing were classified as receiving “other treatment”. For warfarin, where a standard dosing does not exist, an approach based on assessment of refill intervals was employed. To measure safety and effectiveness outcomes the variables indicating the following events were analysed: hospitalization or death with a diagnosis of bleeding; hospitalization for recurrent ACS; revascularization procedure; ischaemic stroke or systemic embolism; death from any cause. Data sources included The Patient register, The Dispensed Drug register, The Cause of Death register and the LISA (longitudinal integration database for health insurance and labour market studies).
Results	There was a great diversity in treatments given to AF patients who experienced ACS-episodes. The most common regimens did not include an oral anticoagulant, in contrast to current national and international guideline recommendations. Dual antiplatlet therapy, the standard treatment for ACS patients without AF, is frequently

	used for AF patients as well. Elderly and frail patients, at high risk for both bleeds and thromboses, generally received less aggressive antithrombotic drug regimens than younger and healthier patients. This complicated the interpretation of outcome data. Differences in bleeding rates between high risk and low risk patients were attenuated by the choice of antithrombotic regimen, while differences regarding ischaemic stroke and reinfarction may have been exaggerated for the same reason. The diversity of regimens made most of the groups including a NOAC too small for valid comparisons of the benefits or risks associated with individual regimens.
Discussion	This study shows that there is no single standard therapy for patients with AF who also have an episode of ACS. There is little or no scientific evidence regarding the benefit or harm for the majority of these regimens. There were clear differences between patients given different regimens; more potent antithrombotic regimens generally were given to younger and healthier patients with lower perceived bleeding risks. Elderly patients with higher perceived bleeding risk were more often given regimens consisting of only antiplatelet drugs and no oral anticoagulation. It was not possible to determine which treatment regimen was better or worse because of selection biases and undocumented reasons why doctors preferred one treatment over the other. The most common treatment among patients with ACS and AF was dual antiplatelet therapy, the standard treatment for ACS patients without AF, indicating that the awareness of the need for oral anticoagulation in this patient population was not adequately recognized by prescribing doctors.
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