Changes in the Etiology of Acute Limb Ischemia in the DOAK Era — A Retrospective, Single-Center Cohort Study at Augsburg University Hospital

NCT Number: not yet assigned

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Study Protocol

1. Responsibilities
The principal investigator is Yvonne Gosslau,MD, PhD managing senior physician at the Department of Vascular and Endovascular Surgery at the Augsburg University Hospital.

2. Data Source
The data used were obtained from the Department of Vascular Surgery at the Augsburg University Hospital. The study includes patients who were hospitalized during the period from January 1, 2006, to December 31, 2010 (pre-DOAK era) and from January 1, 2012, to December 31, 2018 (DOAK era) were treated as inpatients for acute limb ischemia (ICD-10: I74.0–I74.3, I74.9) and documented atrial fibrillation (ICD-10: I48.0–I48.9). Cases are identified through an automated query of the ORBIS hospital information system based on the specified ICD-10 diagnoses; cases involving aneurysms or dissections (ICD-10: I71.X) are excluded. Consent from hospital management to use this data has been obtained.

3. Scientific Background
Acute limb ischemia (ALI) is a vascular emergency associated with significant morbidity and mortality. Recent epidemiological studies have shown, since 2015, a significant decline in the incidence of ALI, which coincides with the widespread introduction of direct oral anticoagulants (DOACs) beginning in 2011/2012. For example, Jarosinski et al. documented, using the U.S. National Inpatient Sample, a decline in the incidence of ALI from 7.16 to 4.16 per 100,000 person-years between 2006 and 2020, although this decline did not reach statistical significance until 2015. A population-based Austrian analysis confirmed this trend with a decrease in hospitalized ALI cases of approximately 50% between 2009 and 2023 (from 27.2 to 13.6 per 100,000 person-years).
In randomized controlled trials, DOACs have been shown to be effective in patients with atrial fibrillation compared to warfarin in reducing systemic embolisms, with a risk reduction of approximately 48–52%. Multivariable analyses also suggest that anticoagulation initiated prior to hospital admission is associated with a significantly reduced amputation rate as well as reduced mortality.
To date, however, there have been no studies that use clinical rather than purely code-based criteria to analyze changes in the etiological distribution - embolic versus thrombotic - of ALI before and after the introduction of DOACs. Registry-based studies typically rely on ICD codes, which do not distinguish between embolic and thrombotic causes. This distinction is, however, highly clinically relevant, as cardioembolic ALI in patients with atrial fibrillation can be prevented primarily through adequate anticoagulation, whereas thrombotic ALI in patients with peripheral arterial disease (PAD) is caused by different pathomechanisms. The present study therefore investigates whether the proportion of embolic acute limb ischemia in patients with atrial fibrillation changed significantly between the pre-DOAC era (2006–2010) and the DOAC era (2012–2018) at a university vascular center.

4. Endpoints, Outcomes, and Hypotheses
The primary hypothesis is that the proportion of cardioembolic ALI in patients with atrial fibrillation is significantly lower in the DOAK era (2012–2018) than in the

pre-DOAK era (2006–2010). The secondary hypotheses postulate that, following the introduction of DOACs, there is a trend toward a gradual decline in embolic ALI, that the relative proportion of thrombotic ALI is trending upward, and that prehospitalization DOAC therapy, when compared to vitamin K antagonists or no anticoagulation is associated with lower rates of cardioembolic ALI.
The primary endpoint of the study is the proportion of cardioembolic ALI events in the pre-DOAC era compared to the DOAC era. Secondary endpoints include the proportion of thrombotic ALI events, the chosen treatment modality (embolectomy versus endovascular therapy), the in-hospital amputation rate, and the in-hospital mortality rate.

5. Biometrics

The case number estimate is based on empirical data from large vascular centers, according to which approximately 20–30 cases of ALI are expected annually in patients with atrial fibrillation. Over the entire 12-year observation period, therefore, approximately 250–400 cases are expected, of which an estimated 125–200 are of classic embolic origin. Assuming a decrease in the embolic proportion from 60% to 40% (corresponding to an effect size h of 0.40), at a significance level of $\alpha = 0.05$ and a power of 0.80, a minimum sample size of $n = 98$ per group is required; this is significantly exceeded by the estimated total number of cases.
For descriptive statistics, the analytical methods used—depending on the distribution—include the mean and standard deviation or the median and interquartile range for continuous variables, as well as absolute and relative frequencies for categorical variables. Baseline characteristics are compared using the t-test or the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables; the assumption of normal distribution is first tested using the Shapiro-Wilk test. To analyze the temporal trend, a segmented regression analysis in the form of an interrupted time series analysis (Interrupted Time Series) is performed, with quarters defined as time points. For multivariate adjustment of the binary outcome measures etiology, amputation, and mortality, logistic regression is applied, adjusting for age, sex, comorbidities (diabetes mellitus, renal insufficiency, peripheral arterial disease), and anticoagulation status; the results are presented as adjusted odds ratios with 95% confidence intervals. Sensitivity analyses include a subgroup analysis limited exclusively to patients with documented atrial fibrillation, exclusion of unclear cases by restricting the analysis to unambiguously embolic or thrombotic cases, and stratification by type of anticoagulation (none versus vitamin K antagonist versus DOAC). The significance level is set at $\alpha = 0.05$ (two-sided).