Timing of anticoagulation after acute ischemic stroke in patients with atrial fibrillation

by

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Abstract

Patients with atrial fibrillation (AF) and ischemic stroke are at high risk for stroke recurrence. Early anticoagulation may reduce the risk of recurrent events but is usually avoided due to the risk of hemorrhagic transformation (HT). The risk of HT is based on historical data from an older generation of anticoagulants. Recently, four direct oral anticoagulants (DOACs) have demonstrated a lower risk of intracranial hemorrhagic complications compared to older anticoagulants. However, in the pivotal phase III DOAC trials, AF patients were excluded within 7-30 days of an acute ischemic stroke (or up to 6 months for severe/disabling strokes). In patients with AF-related ischemic stroke, we aimed 1) To assess the safety of early DOAC initiation, 2) To identify clinical, imaging and RNA transcript predictors of HT, and 3) To determine the current practices on the timing of DOAC initiation.

Chapter 1 reviews the risk of recurrent ischemic stroke and HT in patients with AF, pathophysiology, classification, predictors, natural history and outcomes of HT, and discusses the studies of early anticoagulation after AF-related ischemic stroke.

Chapter 2 is a prospective study of patients with AF treated with dabigatran within 14 days of transient ischemic attack (TIA)/ minor ischemic stroke. Our results demonstrated that early dabigatran treatment did not precipitate symptomatic HT after minor stroke, and recurrent ischemic stroke as an outcome may be more common and important than HT.

Chapter 3 is a prospective study of patients with AF treated with apixaban within 14 days of TIA/ ischemic stroke regardless of the size and severity. We found that early apixaban treatment did not precipitate symptomatic HT after stroke. All HT identified on neuroimaging were asymptomatic. Recurrent ischemic events were clinically symptomatic.

Chapter 4 is a design for a randomized controlled trial (RCT) with an associated registry, which has actually begun at University of Alberta Hospital. A sample size of 150 patients with AF-related ischemic stroke is planned to be randomized 2:1 within five days of symptom onset to early (≤5 days, n=100) or delayed (6-14 days, n=50) edoxaban initiation. By conducting this RCT, we aimed to demonstrate the safety of edoxaban initiation within five days of AF-related stroke, and establish clinical, imaging and RNA transcript predictors of HT.

Chapter 5 is an international electronic survey with practice-related demographic and clinical questions related to the timing of DOAC initiation. Our results showed that decisions related to the timing of DOAC initiation varied globally and the variability in clinical practice will continue until RCTs are completed.

Chapter 6 is a pooled analysis of six studies of DOAC initiation within 14 days of ischemic stroke. Our analysis revealed that DOAC initiation within 48 hours after ischemic stroke was not associated with increased incident HT risk and that recurrent ischemic events were common and associated with poor outcomes.

Chapter 7 is an interim analysis of the RCT that is described in chapter 4. We demonstrated that initiating edoxaban within five days of ischemic stroke onset was not associated with an increased risk of symptomatic or incident radiographic HT.

By using clinical and systematic brain imaging data at baseline and following DOAC initiation, this thesis demonstrates that early DOAC initiation after ischemic stroke is not associated with an increased risk of HT. Baseline asymptomatic HT is associated with larger infarct volumes, and DOAC initiation does not appear to increase the risk of symptomatic HT. Incident radiographic HT on follow-up imaging could represent the natural history in the

evolution of the infarct and does not appear to independently influence the functional outcomes. This may suggest that incident radiographic HT may be a useful objective performance criterion if systematic serial post-randomization imaging is included in the design. Finally, this thesis reveals that recurrent ischemic events are common, clinically symptomatic, and appear to affect functional outcomes. This observation suggests that recurrent ischemic stroke will be the more common clinical outcomes of interest in the RCTs; however, risk of symptomatic HT remains an important consideration as even a slight increase in frequency may outweigh any benefits of early anticoagulation. This thesis supports the need for further trials of DOAC timing after AF-related stroke, and our data might be useful for designing and calculating sample size requirements for future trials.

Preface

The research presented in this dissertation, has been published, will be published, or is currently under peer-review.

Chapter 1 and chapter 8 of this thesis have been published in a peer-review journal as *Anas Alrohimi, Glen Jickling, Brian Buck, and Ken S Butcher. Timing of anticoagulation after acute ischemic stroke in patients with atrial fibrillation. Can J Neurol Sci. 2022 Jun 28:1-12.*

Chapter 2 of this thesis has been published in a peer-review journal as *Alrohimi A, Ng K, Dowlatshahi D, Buck B, Stotts G, Thirunavukkarasu S, et al. Early dabigatran treatment after transient ischemic attack and minor ischemic stroke does not result in hemorrhagic transformation. Can J Neurol Sci. 2020:1-22.*

Chapter 3 of this thesis has been published in a peer-review journal as *Alrohimi A, Buck B, Jickling G, Shuaib A, Thirunavukkarasu S, Butcher KS. Early apixaban therapy after ischemic stroke in patients with atrial fibrillation. J Neurol. 2021;268(5):1837-46.*

Chapter 4 of this thesis has been published in a peer-review journal as *Alrohimi A, Jickling G, Jeerakathil T, Shuaib A, Khan K, Kate M, et al. Protocol for LASER: A Randomized Evaluation and an Associated Registry of Early Anticoagulation With Edoxaban After Ischemic Stroke in Patients With Atrial Fibrillation. Front Neurol. 2021;12:645822.*

Chapter 5 of this thesis will be submitted to a peer-review journal as *Alrohimi A, Kate M, Thirunavukkarasu S, Jeerakathil T, Jickling G, Shuaib A, Buck B, Butcher KS. Timing of Anticoagulation After Ischemic Stroke in Patients with Atrial Fibrillation: An international survey.*

Chapter 6 of this thesis has been accepted for publication in a peer-review journal as *Alrohimi A, Rose AZ, Burgin WS, et al. Risk of Hemorrhagic Transformation with Early Use of Direct Oral Anticoagulants after Acute Ischemic Stroke: A Pooled Analysis of Prospective Studies and Randomized Trials.*

Chapter 7 of this thesis is an interim analysis of an ongoing randomized controlled trial.

Chapter 8 of this thesis is discussion and future directions

The research projects, of which this thesis is a part, received the following research ethics approvals from the University of Alberta Research Ethics Board:

1. Project Name "Canadian Pradaxa Acute Stroke/TIA Safety Study (CPASS)", No. Pro00044395, December 16, 2013.
2. Project Name "Rivaroxaban Acute Stroke Safety (RASS) Study", No. Pro00044168, January 24, 2014
3. Project Name "Dabigatran Following Transient Ischemic Attack and Minor Stroke (DATAS) II", No. Pro00047362, December 16, 2014
4. Project Name "Eliquis Acute Stroke Safety Evaluation (EASSE)", No. Pro00065217, December 23, 2016.
5. Project Name "Lixiana Acute Stroke Evaluation Registry (LASER)", No. Pro00080630, June 11, 2018

Dedication

This PhD dissertation is dedicated first and foremost to the greatest women and man in my life, my mother and father. Thank you for teaching me how to hold a pencil. Thank you for always holding a special place in your heart for me. Thank you so much for everything! Words can hardly describe my thanks and appreciation to you. You have been my source of inspiration, support, and guidance. You have taught me to be unique, determined, to believe in myself, and to always persevere. Thank you for your unwavering love and support along this journey I have taken. I love you both always and forever. To my sisters and brother, thank you for your everlasting love and warm encouragement throughout my studies. Without your support, I wouldn't have accomplished this.

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List of abbreviations

AF: Atrial fibrillation

HT: Hemorrhagic transformation

CI: Confidence interval

HAEST: The Heparin in Acute Embolic Stroke Trial

LMWH: Low molecular weight heparin

IST: The International Stroke Trial

UFH: Unfractionated heparin

HR: Hazard ratio

PH: Parenchymal hemorrhage

HI: hemorrhagic infarction

BBB: Blood-Brain Barrier

ROS: Reactive oxygen species

MMP: Matrix metalloproteinases

ECASS: European Cooperative Acute Stroke Study

IVH: Intraventricular hemorrhage

SAH: Subarachnoid hemorrhage

SDH: Subdural hemorrhage

HBC: Heidelberg Bleeding Classification

NIHSS: National Institutes of Health Stroke Scale

LVO: large vessel occlusion

IA: intra-arterial

IV: Intra-venous

EVT: Endo-Vascular Thrombectomy

BP: Blood pressure

LDL: Low- density lipoprotein

CSF: Cerebrospinal fluid

CT: Computed Tomography

ASPECTS: Alberta Stroke Program Early CT Score

CTA: Computed Tomography Angiography

CTP: Computed Tomography Perfusion

CBF: Cerebral Blood Flow

CBV: Cerebral Blood Volume

MTT: Mean Transit Time

TTP: Time to peak

SWI: Susceptibility weighted imaging

MRI: Magnetic Resonance Imaging

DWI: Diffusion Weighted Imaging

ADC: Apparent diffusion coefficient

FLAIR: Fluid Attenuated Inverse Recovery

HARM: Hyperintense acute reperfusion marker

CMB: Cerebral microbleed

DSA: Digital subtraction angiography

RNA: Ribonucleic acid

OR: Odds Ratio

aOR: adjusted Odds Ratio

VKA: Vitamin K Antagonists

DOAC: Direct oral anticoagulants

RCT: Randomized controlled trial

TIA: Transient Ischemic Attack

INR: International normalized ratio

ICH: Intracerebral hemorrhage

SAMURAI: The Stroke Acute Management with Urgent Risk-factor Assessment and Improvement study

RAF: The early Recurrence and cerebral bleeding in patients with Acute ischemic stroke and atrial Fibrillation study

VISTA: Virtual International Stroke Trials Archive

CROMIS-2: The Clinical Relevance Of Microbleeds In Stroke-2 study

Triple AXEL: Acute Stroke With Xarelto to Reduce Intracranial Hemorrhage, recurrent Embolic Stroke, and hospitaL stay

AHA/ASA: American Heart Association/American Stroke Association

EHRA-ESC: European Heart Rhythm Association of the European Society of Cardiology

OPC: Objective Performance Criteria

NINDS: The National Institute of Neurological Disorders and Stroke

SITS-MOST: The Safe Implementation of Thrombolysis in Stroke-Monitoring Study

IST-3: The third International Stroke Trial

ASA: Aspirin

DVT: Deep venous thrombosis

PE: Pulmonary embolism

CPASS: Canadian Pradaxa Acute Stroke Safety Study

NCT: The National Clinical Trial

eGFR: Estimated glomerular filtration rate

mRS: modified Rankin Scale

MoCA: Montreal Cognitive Assessment

EQ-5D: EuroQol-5 Dimension

CCI: Charlson Co-morbidity Index

VAS: Visual Analog Scale

DICOM: Digital Imaging and Communications in Medicine

SAE: Serious adverse events

IQR: Interquartile range

TIMING: Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation: a Prospective Multicenter Registry-based Non-inferiority Randomized Controlled Clinical Trial

ELAN: Early Versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients With Atrial fibrillation

START: Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation

OPTIMAS: OPtimal TIming of Anticoagulation After Acute Ischemic Stroke

EASSE: Eliquis Acute Stroke Safety Evaluation

ARISTOTLE: The Apixaban for Reduction In STroke and Other ThromboembоLic Events in atrial fibrillation

DATAS II: Dabigatran in Acute Transient Ischemic Attack and minor Stroke II trial

RAF-NOACs: The Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non–Vitamin-K Oral Anticoagulants study

NOACISP: The 'Novel Oral Anticoagulants in Ischemic Stroke Patients' registry

LASER: Lixiana Acute Stroke Evaluation Registry

AREST: Apixaban for Early Prevention of Recurrent Embolic Stroke and Hemorrhagic Transformation

SD: Standard Deviation

tPA: Tissue Plasminogen Activator

BID: Twice a day

ENGAGE AF-TIMI 48: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation - Thrombolysis in Myocardial Infarction 48

REDCap: Research Electronic Data Capture

CrCl: Creatinine Clearance

COVID-19: Corona Virus Disease - 2019

RT-PCR: Reverse Transcription Polymerase Chain Reaction

SAIHF: The Servier Alberta Innovation Health Fund

QUICR: Quality Improvement & Clinical Research

HSFC: Heart and Stroke Foundation of Canada

CIHR: Canadian Institutes of Health Research

ECG: Electrocardiography

AVM: Arteriovenous malformation

RASS: Rivaroxaban Acute Stroke Safety Study

N/A: Not applicable

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

Chapter 1

Timing of anticoagulation after acute ischemic stroke in patients with atrial fibrillation

Patients with atrial fibrillation (AF) and ischemic stroke are at high risk for stroke recurrence. Early anticoagulation may reduce the risk of recurrent events but is usually avoided due to the risk of hemorrhagic transformation (HT). Current guidelines are based on empiric expert opinion. The assumed risk of HT is based on historical data from an older generation of anticoagulants. The direct oral anticoagulants (DOACs) have demonstrated lower risk of intracranial hemorrhage compared to older anticoagulants. However, the optimal timing of DOAC initiation after AF-related ischemic stroke has remained an area of clinical equipoise, as the pivotal phase III trials did not include patients in the early period after ischemic stroke. Multiple prospective studies and a few smaller randomized controlled trials evaluating the safety and efficacy of early versus delayed DOAC initiation have been completed. These studies have reported promising results of early DOAC initiation after acute ischemic stroke. However, a standardized documentation of HT rates on follow-up imaging with objective assessment criteria is missing from most of these studies. Larger randomized trials of early versus delayed DOAC are ongoing. In this article, we review the risk of recurrent ischemic stroke and HT in patients with AF, pathophysiology, classification, predictors, natural history and outcomes of HT, and discuss the studies of early anticoagulation after AF-related ischemic stroke.

1.1 Atrial fibrillation and ischemic stroke

Atrial fibrillation (AF) is a major risk factor for ischemic stroke, associated with 3 to 5-fold increased risk.[1] The rate of AF-associated ischemic stroke has tripled over the last few decades and it is predicted to continue increasing in the future.[2] It is established that patients with AF who have suffered an ischemic stroke are at high risk for recurrence and require long-term anticoagulation. The risk of recurrent ischemic stroke ranges from 0.5 % to 1.3% per day within the first 14 days after the index event based on retrospective observational studies.[3] AF-related ischemic stroke is disabling in 60% and fatal in 20% of cases.[4] A European epidemiological observational study demonstrated cardioembolic ischemic stroke is associated with the highest recurrence rate (22%; 95% CI 14 – 30) and lowest 2-year survival (55%; 95% CI 0.47 – 0.63) compared to other etiologies.[5] In patients with acute ischemic stroke and either known or newly diagnosed AF the usual practice is to bridge with an antiplatelet agent until the patient is anticoagulated.[6, 7] The timing of OAC initiation is often highly variable and opinion rather than evidence based. While earlier anticoagulation may reduce early recurrent ischemic stroke, it may also increase the risk of hemorrhagic transformation (HT), a serious early complication of ischemic stroke. Predictors of recurrent ischemic stroke in patients with AF include atrial thrombus, left atrial enlargement, left ventricular dysfunction, older age, larger infarct volume, and increasing CHA_2DS_2-VASc score, which is a clinical stroke risk score for patients with AF that includes heart failure, hypertension, age, diabetes mellitus, prior ischemic stroke, female sex, and other vascular diseases.[8-11] Most of these predictors are of limited use in informing the timing of anticoagulation, as they are also associated with an increased risk of HT. The competing rationales for early versus late anticoagulation make the optimal timing of anticoagulation after an ischemic stroke a persisting area of clinical equipoise.

1.2 Hemorrhagic transformation

HT is a spectrum of ischemia-related brain hemorrhage, which varies from subtle heterogenous leakage of blood within the infarction to extensive hemorrhage within and beyond the infarction with and without mass effect.[12] HT can lead to clinical deterioration from increasing edema, mass effect, intraventricular extension, and hydrocephalus and ultimately can result in death.[13]

1.2.1 Pathophysiology

Understanding the mechanism of HT is a key element for predicting, preventing, treating, and prognosticating HT. The entire pathophysiology is still unclear. However, breakdown of the blood-brain barrier (BBB) is an essential component in the development of HT in ischemic stroke.[14, 15] BBB disruption results from a series of cellular, metabolic, and inflammatory events led by reduction in energy and failure in the Na+-K+ ATPase activity, causing injuries to cerebral endothelial cells and impairment in autoregulation of the cerebral blood vessels.[16, 17] It has also been suggested that the BBB disruption is time-dependent, and that the mechanism of early HT ($\leq$ 24 hours) may be different than the late HT (> 24 hours).[18] Reactive oxygen species (ROS), blood derived matrix metalloproteinases (MMP)–9, and the brain derived MMP–2 may play critical roles in the mechanism of early HT. On the other hand, multiple factors could contribute to the late HT. This includes brain derived MMP–9, MMP–3, inflammatory responses, vascular remodeling processes, and other proteases.[18]

1.2.2 Classification

Classification of HT is based on two components, the radiographic features of the hemorrhage and associated clinical changes. The term hemorrhagic infarction (HI) has emerged

to describe subtle or confluent heterogenous blood within the infarcted tissue without mass effect. The term parenchymal hematoma (PH) describes the extensive homogamous hematoma within and beyond the infraction borders with mass effect.[19, 20] In 1999, Fiorelli et al proposed the European Cooperative Acute Stroke Study (ECASS) classification system, which includes two subtypes of HI (HI1; small petechiae along the margins of the infarct, and HI2; confluent petechiae within the infarcted area but no space-occupying effect) and two subtypes of PH (PH1; hematoma in 30% or less of the infarcted area with some slight space-occupying effect, and PH2; hematoma in more than 30% of the infarcted area with substantial space-occupying effect).[21] The ECASS criteria do not clearly differentiate between PH within the area of infarction and PH remote from the infarction, nor do they include other types of hemorrhages such as intraventricular hemorrhage (IVH), subarachnoid hemorrhage (SAH), and subdural hemorrhage (SDH). The Heidelberg Bleeding Classification (HBC) is a classification tool to grade HT that expands beyond the ECASS system by including and categorizing these previously non-classified hemorrhages.[22] The single standard definition of symptomatic HT in ischemic stroke has yet to emerge. As a result, variability in how HT is defined in stroke studies has impacted the reporting rate of symptomatic HT and makes comparing rates of HT between studies challenging. [22-27]

1.2.3 Risk of hemorrhagic transformation after acute ischemic stroke

Most of the older studies on HT in patients with acute ischemic stroke were of limited sample size and/or study design, or derived from studies on thrombolysis. Additionally, the reported rates of HT after ischemic stroke are variable in different studies. This variability could be related to the differences in study design, the included populations, the definitions of HT, type and frequency of imaging, timing and sequence of scan used, and method of assessing and

defining clinical worsening. The reported incidence of HT is up to 70% in autopsy studies.[28-31] On the other hand, the incidence of HT in CT studies was variously reported over the last four decades, from few to 43% of consecutive patients. [12, 30-35]. A more recent large prospective study that examined the risk of early HT in patient with acute ischemic stroke by using systematic brain CT at baseline and 5 ± 2 days after stroke onset was conducted.[36] Early HT in patients with acute ischemic stroke, including both AF and non-AF related infarcts, was observed to be about 9% within 5 to 7 days from the index event and, of these HT events, 3.2% were PH. The early Recurrence and cerebral bleeding in patients with Acute ischemic stroke and atrial Fibrillation (RAF) study was a prospective observational study which specifically examined the risk of HT in patients with AF-related ischemic stroke. The rate of HT was found to be higher, 13%; 8.8% HI and 4.2% PH.[8] A recent combined analysis from two large observational studies included 2183 patients and found that HT occurred in 11% on repeated imaging, with 3.1% of these being PH. [37] The reported incidence of HT varies based on type of study, type and frequency of imaging, and sequence of scan used.

1.2.4 Clinical Predictors of HT

Several clinical factors have been described in association with development of HT. Recognizing these clinical variables might be helpful for clinicians to anticipate and stratify the risk of HT in individual patients. However, it is unknown if early anticoagulation in the presence of these clinical parameters further increases the risk of new and/or progressive HT. The size of infarction is independently associated with HT. [38] Larger ischemic infarct volume is associated with mass effect and vascular compression, both of which increase vascular permeability and therefore HT risk. Higher National Institutes of Health Stroke Scale (NIHSS) scores indicates severe stroke and larger infarct which increase the risk of HT. [39] Further, cardioembolic stroke

and AF-related ischemic stroke tend to be severe and related to large vessel occlusion (LVO).[40] Compared to other subtypes, cardioembolic stroke associated with AF has been associated with the highest risk of HT.[41] Additionally, hyperglycemia may worsen the BBB disruption by inducing systemic stress and enhancing circulating factors that damage BBB which increases the risk of HT.[42-44] The effect of high blood pressure (BP) on the risk of HT has been documented, especially in patients with larger infarcts who received thrombolytic therapy.[45] High BP is considered an modifier of the risk of HT through its interaction with other predictors.[41] Another factor was found to be associated with HT is high body temperature in the first 24 hours after stroke onset.[46, 47] Moreover, low-density lipoprotein (LDL) cholesterol level with and without statin has correlated with the risk of HT. [48, 49] Finally, reperfusion therapies, including thrombolysis and endovascular therapy are all associated with an increased rate of HT. [41, 50-54] However, a recent prospective observational study has shown that acute reperfusion therapies using thrombolysis and/or EVT prior to initiating anticoagulation did not influence the risk of recurrent ischemic stroke(s) and HT.[55]

1.2.5 Radiographic Predictors of HT

Non-contrast computed tomography (CT)/ CT angiography (CTA)/ CT perfusion (CTP).

Early ischemic changes, including loss of grey– white matter differentiation, hypodensity (hypoattenuation) of brain parenchyma, presence of edema or mass effect, and low Alberta Stroke Program Early CT Score (ASPECTS) of ≤ 7 on baseline CT scan appear to increase the risk of HT.[56-59] Another CT marker associated with HT is the hyperdense middle cerebral artery sign.[60] Patients with hyperdense middle cerebral artery sign, LVO, poor collateral flow, lower clot burden scores, and severe hypoperfusion with large core in CTP tend to have severe stroke and early ischemic changes, and thus, higher risk of HT.[61-63]

Magnetic Resonance Imaging (MRI). MRI is more sensitive than CT for detection of HT after acute ischaemic stroke,[64, 65] especially with adding the susceptibility weighted imaging (SWI), which is highly accurate in detecting blood products. A low volumetric apparent diffusion coefficient (ADC) and large diffusion weight imaging (DWI) on baseline MRI are associated with an increased risk of HT.[45, 66-68] Additionally, multiple radiological markers in MRI have been associated with HT including poor fluid suppression on fluid-attenuated inversion recovery (FLAIR) from extravasation of contrast into CSF leading to hyperintensity of the CSF space, which has been labelled Hyperintense Acute Reperfusion Marker (HARM),[69] sulcal hyperintensity on FLAIR,[70] parenchymal enhancement on post-contrast T1,[71-73] signs of disrupted BBB.[74, 75], and finally, cerebral microbleeds (CMBs). A recent meta-analysis has shown that patients with ≥5 CMBs are at higher risk of hemorrhage than those with fewer or no CMBs- patients with <5 CMBs (2.48%; 95% CI 1.2 – 6.2; p= 0.001).[76] At this point, however, MRI screening is not routinely performed prior to initiation of anticoagulation and this finding has not changed clinical practice.

1.2.6 Serological Biomarkers

Matrix metalloproteinases (MMPs). Several studies have demonstrated that increased expression of MMP-9 is associated with an increased risk of HT after reperfusion.[77-79] Similar studies have shown that elevated MMPs correlates with disrupted BBB and HT in experimental stroke models regardless of whether or not thrombolysis is received. This observation is likely secondary to the fact that MMP has the potential to degrade the basal lamina of the vascular endothelium.[80] However, the role of MMPs in the setting of anticoagulant-associated bleeding is unknown.

Leukocyte RNA. Inflammation and immune response after ischemic stroke may also influence the risk of HT by promoting peripheral leukocytes activation, adhesion, migration, and potentially BBB disruption.[81, 82]. Preliminary data suggest the risk of HT in patients with stroke can be stratified by RNA expressed in circulating leukocytes within 3 hours of stroke onset. A panel of 6 genes associated with subsequent HT has been identified.[18, 83] Of note, these data are driven from patient with early HT after thrombolysis, thus the role of leukocyte RNA in the setting of anticoagulation related bleeding remains unclear.

1.2.7 Natural history and outcomes of hemorrhagic transformation

HT is part of the spectrum of ischemia-related brain hemorrhage associated with a wide range of clinical significance. Most studies of the significance of HT come from thrombolysis trials. The relationship between PH-2 and clinical and functional outcomes has been established, but this is not the case for HI-1, HI-2, and PH-1.[84] A retrospective study indicated that any PH independently predicted mortality at day 30 and day 90.[13] . Conversely, a post hoc analysis of European Cooperative Acute Stroke Study I (ECASS I) indicated that only PH-2 was associated with an increased risk of neurological deterioration at 24 hours (OR 18.0; 95% CI 6.0 – 56.0) and 90 day mortality (OR 11.4; 95% CI 3.7 – 36.0).[21] Another post hoc analysis of the ECASS II study demonstrated that PH-2 was associated with approximately 50% mortality.[85] This analysis and others revealed that HI-1 and HI-2 were not associated with unfavourable outcomes.[21, 85, 86] Similarly, another prospective study assessed the outcomes of early HT after ischemic stroke, and found that only PH was independently associated with a higher risk of mortality and functional disability.[36] Conversely, a more recent prospective study revealed that both PH (OR 1.79; 95% CI 1.00 – 3.27; p=0.05) and HI (OR 1.75; 95% CI 1.21 – 2.53; p=0.003) were

associated with death and disability.[37] However, quantifying the impact of HT, especially HI, on functional outcome is challenging as the independent contribution of HT to clinical worsening remains uncertain [87], and evidence from high quality studies is lacking.

1.3 Early anticoagulation after atrial fibrillation-related ischemic stroke

Older studies focused on heparins for early anticoagulation, perhaps due to its rapid onset of action compared with Vitamin K Antagonists (VKA) which can take several days to reach to therapeutic level. However, in the last decade, four direct oral anticoagulants (DOACs) have been demonstrated to have a lower long-term risk of intracranial hemorrhagic complications compared to older anticoagulants, and these are now the standard of care for stroke prevention in non-valvular AF.[88-91] In a meta-analysis, DOACs were associated with a 52% significant reduction of intracranial hemorrhage compared to warfarin.[92] In the following sections, we discuss studies of anticoagulation initiation within 14 days of an ischemic stroke or transient ischemic attack.

1.3.1 Early heparin initiation after acute ischemic stroke

Among patients who were not on any antithrombotic therapy in The International Stroke Trial (IST), 4.9% developed recurrent ischemic events within two weeks of the index stroke onset.[93] A dose-dependent reduction in the recurrent ischemic strokes was noted in the unfractionated heparin (UFH) groups, but that benefit was offset by an increase in HT. A meta-analysis indicated that initiating LMWH withing 24-72 hours after ischemic stroke (regardless of the mechanism) for 7-30 days was associated with no reduction in recurrent ischemic stroke rates, but a trend to more symptomatic HT, and a significant increase in major extracranial bleeding.[94] The Heparin in Acute Embolic Stroke Trial (HAEST) compared LMWH and aspirin initiation within 30 hours of stroke onset. Recurrent ischemic events within 14 days of the index

stroke occurred 7.5% and 8.5% in patients that received LMWH and aspirin, respectively.[95] Starting LMWH within 30 hours of AF-related ischemic stroke was associated with an increased rate of symptomatic HT and extracranial hemorrhage.[95] A meta-analysis of seven trials of parenteral anticoagulants (UFH, LMWH, heparinoids) started within 48 hours of acute cardioembolic stroke indicated recurrent ischemic events within 7-14 days were similar to those in patients treated with aspirin or placebo (3.0% vs. 4.9%; OR 0.68; 95% CI 0.44 – 1.06; p=0.09), but symptomatic HT was more frequent (2.5% vs 0.7%; OR 2.89; 95% CI 1.19 – 7.01; p=0.02), (Figure 1). [96]

1.3.2 Early Vitamin K antagonist initiation after acute ischemic stroke

Randomized controlled trials (RCTs) and observational studies of early anticoagulation after stroke, including patients initiated on VKA and DOACs, are summarized in Table 1. Data from RCTs evaluating the timing of VKA initiation after ischemic stroke in patients with AF are limited. The Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) study was a prospective observational study of initiating anticoagulant after stroke/TIA in patients with AF.[97] A total of 650 patients were started on warfarin at a median of 3 days after stroke/TIA onset. There was no reported ICH prior to hospital discharge, however, systematic neuroimaging was not performed. The early Recurrence and cerebral bleeding in patients with Acute ischemic stroke and atrial Fibrillation (RAF) study was a prospective observational study.[8] VKA alone was initiated in 37% of patients, with another 36% started on LMWH therapy before receiving VKA. Timing of anticoagulation was at the discretion of the treating physician, varying from 1 to 90 days after stroke. The optimal net clinical benefit of composite outcomes for anticoagulation initiation was 4 to14 days after stroke onset. Conversely, data from 1644 patients in the Virtual International Stroke Trials Archive (VISTA) indicated that

early VKA initiation, within 2-3 days after stroke onset, was associated with lower recurrent ischemic events without an increase in symptomatic ICH.[98] Finally, The Clinical Relevance Of Microbleeds In Stroke-2 (CROMIS-2) study assessed the effect of oral anticoagulant timing in patients with AF and stroke.[99] Timing of anticoagulation was determined by the treating physicians and then retrospectively dichotomized into early (0-4 days) and late (≥ 5 days or never started) groups. Of 1355 patients prescribed an oral anticoagulant, 26% started early and 74% started late. Both groups had similar rates of recurrent ischemic events and ICH. Most patients (65%) were treated with warfarin, and 24% received bridging heparin therapy.

1.3.3 Early direct oral anticoagulants initiation after acute ischemic stroke

RCTs and observational studies of early anticoagulation after stroke, including patients initiated on VKA and DOACs, are summarized in Table 1. In the pivotal phase III DOAC trials, more than 70,000 patients were randomized; however, patients were not eligible immediately after ischemic stroke (exclusion ranged from 7 to 30 days after onset).[88-91] Moreover, among all the randomized patients, only 30% had previous stroke or TIA and the number of patients randomized early after stroke has never been published, but is likely to be small.[92] DOACs are now the standard of care for stroke prevention in AF patients.[6, 7] The optimal timing after ischemic stroke is a highly relevant clinical question, given the anticoagulant effect of these drugs begins within hours of administration.[100]

Randomized studies of early DOAC use post stroke: There are only three published randomized trials assessing the safety of early DOAC administration after ischemic stroke. The Triple AXEL (Acute Stroke With Xarelto to Reduce Intracranial Hemorrhage, recurrent Embolic Stroke, and hospitaL stay) compared rivaroxaban (n=101) to warfarin (n=94) initiation within 5 days of cardioembolic stroke (Median NIHSS score of 2 in both arms).[101] This study revealed

similar recurrent ischemic stroke and HT rates in both groups. Incident radiographic HT detected on follow up MRI was seen in 49.5% and 54.5% of patients receiving rivaroxaban and warfarin respectively. The higher frequency of HT compared to previous studies is likely related to the higher sensitivity of MRI for petechial bleeding. The DATAS II trial (Dabigatran in Acute Transient Ischemic Attack and minor Stroke) randomized 305 patients *without AF* to dabigatran or aspirin within 72 hours of mild ischemic symptom onset.[102] There were no symptomatic HT events in either group, but asymptomatic HT detected with MRI was reported in 7.8% of the dabigatran group and 3.5% of the aspirin group (relative risk 2.22, [0.79, 6.21]). More recently, the Apixaban for Early Prevention of Recurrent Embolic Stroke and Hemorrhagic Transformation (AREST) trial randomized patients to apixaban or warfarin, but the timing of initiation was according to the infarct size. [103] The study was stopped early in 2019, after 91 patients had been randomized as DOACs have become the standard of care for most patients with AF-related stroke. One case of symptomatic HT occurred in the warfarin group. Incident radiographic HT was detected in 12.2% and 10.6 % of the apixaban and warfarin groups respectively. Recurrent ischemic events were more common in both the apixaban (14.6%) and warfarin (19.2%) groups.

Prospective, non-randomized studies of early DOAC use post stroke: The SAMURAI study included a total of 466 patients who were started on DOAC at a median of 4 days after stroke/TIA onset.[97] In those patients, the recurrent stroke/systemic embolism rate was 2.84% and the rate of major bleeding was 1.1% at day 90.[104] The Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non–Vitamin-K Oral Anticoagulants (RAF-NOACs) study examined 1127 patients, 80% of whom received DOAC within 15 days of stroke.[105] Recurrent ischemic events within 90 days occurred in 2.8%

of patients, which was more common than the symptomatic cerebral bleeding rate of 1.6%. However, the lack of serial imaging may have led to an under-estimation of the rate of asymptomatic HT. The 'Novel Oral Anticoagulants in Ischemic Stroke Patients' (NOACISP) registry did not report an increased risk of symptomatic HT or recurrent stroke in 100 patients initiated on DOAC within 7 days of stroke onset.[106] In another study, the risk of recurrent stroke and hemorrhagic complication was found to be similar in patients with anterior and posterior circulation infarcts.[107] Symptomatic HT rate was higher in this cohort (4.2% and 3.7% in the anterior and posterior circulation respectively), and potentially explained by the fact that warfarin and/or bridging heparin prior to DOAC administration was used.

Prospective studies including systematic brain imaging following OAC initiation post-stroke have generally been smaller. By using serial MRI pre and post treatment, a prospective assessment of the safety of rivaroxaban initiation at a median of 3 days after AF-related ischemic stroke demonstrated that asymptomatic petechial HT was common at baseline (25/60) and remained clinically silent despite immediate treatment with rivaroxaban.[108] A recent prospective, multi-center registry of dabigatran initiation within 14 days of acute minor ischemic stroke/TIA (NIHSS≤3) onset in patients with AF has also been published.[109] A total of 101 patients (median NIHSS score was 1) were enrolled. The median time to from ischemic symptom onset to dabigatran initiation was two days and this was not associated with any symptomatic HT, but asymptomatic HT evident on systematically acquired follow-up CT was seen in 6% of patients. Another recent prospective study of apixaban initiation within 14 days of TIA/ acute ischemic stroke regardless the size and severity has been completed.[110] A total of 100 patients (median NIHSS score was 4) were included. The median time to from ischemic symptom onset to apixaban initiation was two days and this was not associated with any

symptomatic HT, but incident radiographic HT evident on systematically acquired follow-up CT was seen in 3% of patients. Recurrent ischemic events occurred in 13 patients, 4 of which were associated with severe disability and 4 with mortality. One prospective study included 120 patients with AF-related stroke who received either DOAC or heparin/warfarin, 80% of which treated within 14 days.[111] HT occurred in 27%, including 7% whom developed a parenchymal hematoma, but the majority of these were related to warfarin with/without heparin. A more recent study of 147 patients treated with DOAC within 7 days, HT was seen in 8 patients (asymptomatic in 7, and symptomatic in 1).[112] Another small MRI-based prospective study of 41 patients was completed.[113] Median NIHSS and time from onset to DOAC initiation were 3 and 2 days, respectively. Incident asymptomatic HT was observed in 11 patients, all of which were asymptomatic.

1.4 Guidelines statements and current practice

Current guidelines are inconsistent and provide limited advice with respect to the timing of DOAC initiation after AF-related ischemic stroke.[6, 7, 114-118] The European Heart Rhythm Association of the European Society of Cardiology (EHRA-ESC) endorsed the "1–3–6–12 days rule", which recommends timing of anticoagulation based on clinical severity and infarct size, but neither are well defined.[114] The 2021 guidelines of the American Heart Association/American Stroke Association (AHA/ASA) recommend starting oral anticoagulation immediately after TIA and 2-14 days after the index event for ischemic stroke.[7] In the same guideline statement, a delay in initiation beyond 14 days is recommended for patients considered to be at high risk of HT. Bridging therapy with heparins is considered a class III recommendation against (harm) in the ESC guidelines.[115] An online survey indicated that 95% of physicians in the UK were uncertain when to start oral anticoagulation after cardioembolic stroke.[119]

1.5 Objectives and scope of dissertation

1.5.1 Research rationale and significance

The optimal timing of anticoagulation initiation after AF-related ischemic stroke remains a longstanding and unresolved clinical conundrum that is commonly encountered by physicians. The concern of worsening or causing HT has led physicians to delay anticoagulation; however, the clinical significance of HT associated with early anticoagulation and its contribution to clinical worsening remain uncertain. Despite being the standard of care for stroke prevention in non-valvular AF for over a decade, there has been a paucity of data related to the safety of initiating DOACs within 14 days in patients with AF-related ischemic stroke. Additionally, the rates of HT associated with early DOAC initiation is unknown. A standardized documentation of HT rates on follow-up imaging is missing from most studies of early anticoagulation. Symptomatic HT remains difficult outcome to predict. Although asymptomatic HT is of questionable clinical significance, it likely shares a common pathophysiological pathway with larger symptomatic HT.[12, 18] In the lack of high quality evidence, one way to overcome the barrier of paucity of safety data associated with early DOAC initiation is to assess the HT rates as Objective Performance Criteria (OPC). OPC are values that are driven from historical controls, but they have turned out to be an adequate design for comparing safety or effectiveness endpoints. OPC have been used to define safety standards and are an important part of the medical device development pipeline.[109-111] Asymptomatic HT can be a useful objective evaluation criterion when assessing the effect of early versus delayed DOAC initiation. Systematic collection of HT rates constitutes OPC. These criteria may be important surrogate markers for symptomatic HT, where the expected absolute number of cases is likely to be low.

1.5.2 Research objectives

The objectives of this research are:

1. To demonstrate the feasibility and safety of early DOAC initiation by using dabigatran therapy within 14 days of TIA or minor ischemic stroke in patients with AF.
2. To demonstrate the feasibility and safety of early DOAC initiating by using apixaban therapy within 14 days of TIA or ischemic stroke regardless of the size and severity in patients with AF & to provide an estimate of the incidence of asymptomatic HT.
3. To design an RCT to demonstrate the safety of early DOAC initiation by using edoxaban early (≤5 days) vs. delayed (6-14 days) after AF-related ischemic stroke & to identify clinical, imaging and RNA transcript predictors of HT.
4. To evaluate the global variation and establish current practices on the timing of DOAC initiation after AF-related ischemic stroke to help facilitate the design of clinical trials in this area.
5. To provide an estimate of the incidence of incident radiographic HT associated with DOAC initiation within 48 hours vs > 48 hours in the post-stroke period as well as the rate of recurrent ischemic stroke.
6. To provide an estimate of the incidence of incident radiographic HT, symptomatic HT, and recurrent ischemic stroke of patients with AF randomized to early (≤5 days) or delayed (6-14 days) edoxaban initiation.

Table 1.1. Studies of early initiation of oral anticoagulants after Atrial Fibrillation-related ischemic stroke.

Study	N	NIHSS and infarct size	Median time from onset to anticoagulation initiation	Follow up period	HT	Recurrent ischemic events
Randomized controlled trials of early DOAC initiation post stroke						
AREST trial [103]	88 (41 received apixaban)	Mean NIHSS 6.5; (29.3% TIA, 29.3% small, 41.5% medium)	Stratified based on infarct size and agent (apixaban vs. warfarin)	CT/MRI at day 14 and day 180	**Symptomatic:** 2.1% (warfarin) and 0% (apixaban) **Asymptomatic:** 10.6% (warfarin) and 12·2% (apixaban, p=0.82)	19.2% (warfarin) and 14·6% (apixaban, p=0.58)
The Triple AXEL trial [101]	195 (95 received rivaroxaban)	Median NIHSS 2; Median infarct volume 2.6 ml	2 days	MRI at week 4	**Symptomatic:** None (both groups) **Asymptomatic:** 28.7% (warfarin) and 31·6% (rivaroxaban, p=0.50)	1.1% (warfarin) and 1·1% (rivaroxaban, p>0.99)
DATAS II* [102]	305 (153 received dabigatran)	Median NIHSS 1; Median infarct volume 1.0 ml	1 day	MRI at day 30	**Symptomatic:** None (both groups) **Asymptomatic:** 3.5% (ASA) and 7·8% (dabigatran) (RR, 2.3; 95% CI 0.78 – 6.9)	2.7% (ASA) and 3.9% (dabigatran) (RR, 1.49; 95% CI 0.41 – 5.39)
Observational studies including systematic brain imaging following early DOAC initiation post stroke						
Alrohimi, et al [109]	101 (All received dabigatran)	Median NIHSS 1; Median infarct volume 0 ml	2 days	CT at day 7	**Symptomatic:** None **Asymptomatic:** 6 (6%)	4 (4%)
Alrohimi, et al [110]	100 (All received apixaban)	Median NIHSS 4; Median infarct volume 4.0 ml	2 days	CT at day 7	**Symptomatic:** None **Asymptomatic:** 3 (3%)	13 (13%)
A.I. Al Bakr, et al [111]	120 (37 received DOAC)	Median NIHSS 7; (46% small, 54% large)	No overall median reported. 80% within 14 days of stroke onset	CT scan at 3 – 6 months	32 (27%), including 8 (7%) who developed a parenchymal hematoma, but the majority of these were related to warfarin with/without heparin.	5 (4.2%): All were not on DOAC
Gioia et al [108]	60 (All received rivaroxaban)	Median NIHSS 2; Median infarct volume 7.9 ml	3 days	MRI at day 7	**Symptomatic:** None **Asymptomatic:** 8 (13.3%)	2 (3.3%)
M. Cappellari et al [112]	147 (All received DOAC)	Mean NIHSS 8.2; (54% small, 22% medium, 24% large, 15% posterior circulation)	3·3 days (≤3 days for 97 patients; ≤7 days for all patients)	CT scan at day 7	**Symptomatic:** 1 patient (0.7%) **Asymptomatic:** 7 patients (4.7%)	None

K. Shibazaki et al [113]	41 (All received DOAC)	Median NIHSS 3	2 days	MRI at week 2	**Symptomatic:** None **Asymptomatic:** 31%	None
Observational studies without systematic brain imaging following early DOAC initiation post stroke						
SAMURAI -NVAF study [104]	1137 (475 received DOAC)	Median NIHSS 4; (29.9% small, 56.3% medium, 13.8% large)	4 days	3 months	0.32% (warfarin) and 0.22% (DOAC)	2.58% (warfarin) and 2.82% (DOAC) (aHR, 1.12; 95% CI 0.50 – 2.47)
RAF-NOACs study [105]	1127 (All received DOAC)	Mean NIHSS 8; (41% small, 33% medium, 22% large)	No overall median reported 80% within 15 days of stroke onset	3 months	1.6%	2.8%
NOACISP registry [106]	204 (155 received DOAC)	Median NIHSS 4; No information on infarct size	5 days (≤7 days for 100 of DOAC-treated patients)	3 – 6 months	1 patient (1.3%/y), who was in the warfarin group	6 patients (7.7%/y), 2 received DOAC ≤ 7 days (5.1%/y) vs 2 received DOAC > 7 days (9.3%/y) (p=0.53) and 2 in the warfarin group (11.3%/y)
CROMIS-2 study [99]	1355 (475 received DOAC)	Median NIHSS 4; (8% small, 18% large)	11 days (≤4 days for 358 of patients)	3 months	0.6%/y (combined DOAC and warfarin)	5.7%/y (combined DOAC and warfarin)
RAF study [8]	1029 (93 received DOAC)	Mean NIHSS 9.2; (37% small, 36% medium, 27% large)	8·5 days for DOAC, 12·1 days for warfarin	3 months	77 events (7.6%)	37 (3.6%) symptomatic HT
Abdul-Rahim et al [98]	1300 (none received DOAC)	Median NIHSS 14; No information on infarct size	2 days	3 months	30 events (2.3%)	107 events (8.2%)
Paciaroni et al [107]	473 (314 received DOAC)	Mean NIHSS 6.8; (75.5% has lesion size > 1.5 cm)	12.3 days	3 months	20 events (4.2%)	18 events (3.8%)
Macha et al [126]	243 (All received DOAC)	Median NIHSS 5; (17% small or TIA, 70% medium, and 13% large)	From 1·7 days for small infarct or TIA to 6·7 days for large infarcts (≤7 days for of DOAC-treated patients)	In hospital	**Symptomatic:** 1 (0.4%) **Asymptomatic:** 2 (0.8%)	No information on recurrent ischemic events
Deguchi et al [127]	300 (186 received DOAC)	Median NIHSS 7; No information on infarct size	3 days for DOAC and 7 days for warfarin	In hospital	**Symptomatic:** None **Asymptomatic:** 2 warfarin treated patients (1.4%)	None

N, number; NIHSS, National Institutes of Health Stroke Scale; HT, hemorrhagic transformation; DOAC, direct oral anticoagulant; TIA, transient ischemic attack; CT, computed tomography; MRI, magnetic resonance imaging; ASA, aspirin; RR, relative risk; aHR, adjusted hazard ratio; cm, centimeter

* Patients without atrial fibrillation

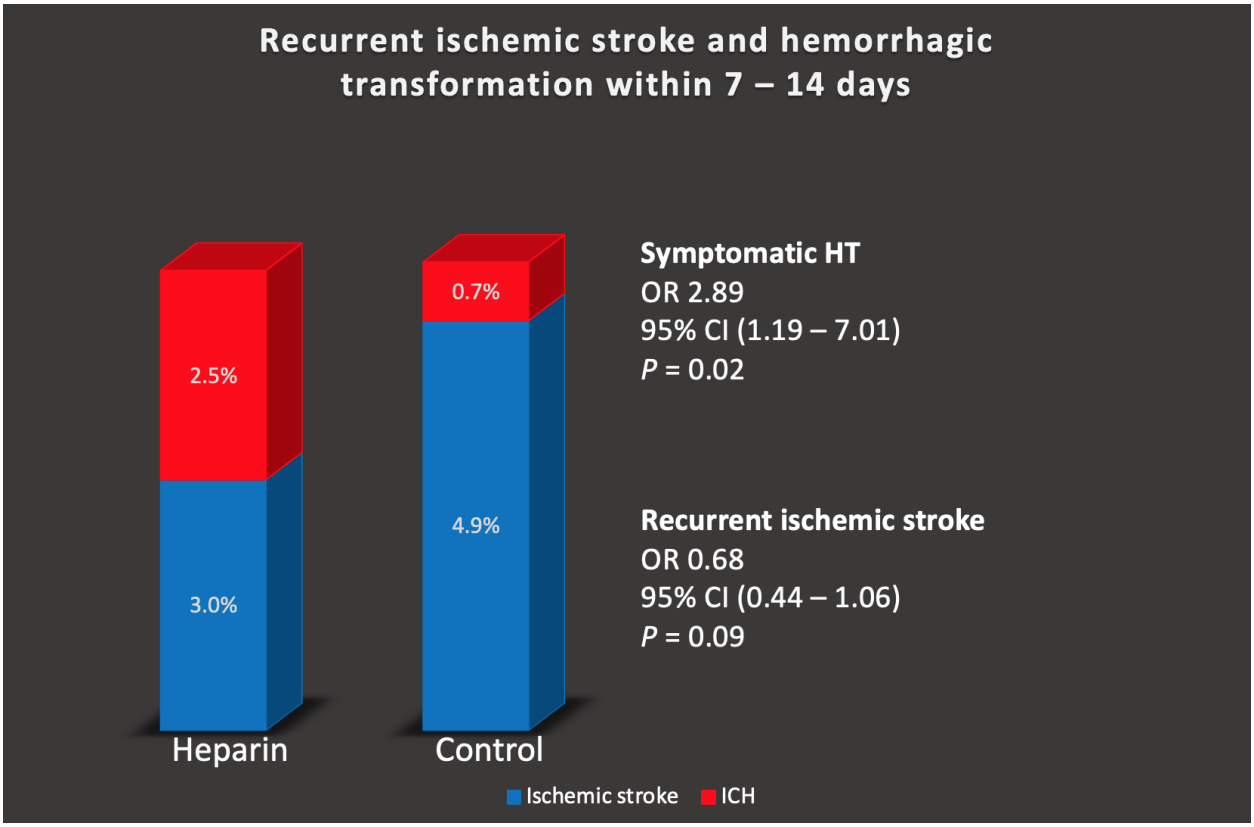

Figure 1.1. Absolute event rates of recurrent ischemic stroke and symptomatic HT associated with early LMWH after acute ischemic stroke

HT, hemorrhagic transformation; ICH, intracerebral hemorrhage; LMWH, low molecular weight heparin

1.6 References

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Chapter 2

Early dabigatran treatment after transient ischemic attack and minor ischemic stroke does not result in hemorrhagic transformation

Running title: Canadian Pradaxa Acute Stroke Safety Study (CPASS)

2.1 Abstract

Objectives: The optimal timing of anticoagulation after ischemic stroke in Atrial Fibrillation (AF) patients is unknown. Our aim was to demonstrate the feasibility and safety of initiating dabigatran therapy within 14 days of TIA or minor stroke in AF patients.

Patients and Methods: A prospective, multi-centre registry (NCT02415855) in patients with AF treated with dabigatran within 14 days of acute ischemic stroke/TIA (NIHSS≤3) onset. Baseline and follow up CT scans were assessed for hemorrhagic transformation (HT) and graded by using European Cooperative Acute Stroke Study (ECASS) criteria.

Results:101 patients, with a mean age of 72.4±11.5 years were enrolled. Median infarct volume was 0 ml. Median time from index event onset to dabigatran initiation was 2 days, and median baseline NIHSS was 1. Pre-treatment HT was present in 7 patients. No patients developed symptomatic HT. On the day 7 CT scan, HT was present in 6 patients (one progressing from baseline HI1). Infarct volume was a predictor of incident HT (OR=1.063 [1.020–1.107], P<0.003). All 6 (100%) patients with new/progressive HT were functionally independent (mRS=0-2) at 30 days, which was similar to those without HT (90%, p=0.422). Recurrent ischemic events occurred within 30 days in 4 patients, two of which were associated with severe disability and death (mRS 5 and 6, respectively).

Conclusions: Early dabigatran treatment did not precipitate symptomatic HT after minor stroke. Asymptomatic HT was associated with larger baseline infarct volumes. Early recurrent ischemic events may be clinically more important.

Keywords Atrial fibrillation, Ischemic stroke, Hemorrhagic transformation, Dabigatran, Cardioembolic stroke, Intracerebral hemorrhage

2.2 Introduction

Patients with atrial fibrillation (AF) who have suffered a transient ischemic attack (TIA) or ischemic stroke are at high risk for recurrence and require long-term anticoagulation. The risk of recurrent stroke (3-20%) within the first two weeks after stroke/TIA is clinically important.[1, 2] The optimal timing of anticoagulation after an ischemic stroke however remains controversial. Previous trials of have demonstrated that anticoagulation in acute stroke patients is associated with reduced early stroke recurrence rates, but these benefits are offset by a comparable increase in the rate of symptomatic hemorrhagic transformation (HT).[3, 4] An individual patient level meta-analysis reported that the hemorrhagic complication rate associated with low-molecular weight heparin within 14 days of ischemic stroke was 0.8%.[5] Similarly, early warfarin use in stroke patients without AF is associated with a significant increase in the rate of HT (relative risk 1.93, 95% CI 1.27-2.94).[6]

Dabigatran is a direct oral anticoagulant (DOAC), approved for the prevention of ischemic stroke in patients with AF. Dabigatran is associated with a lower risk of intracranial hemorrhagic complications than warfarin in patients with chronic AF without recent stroke.[7] There are limited data related to the use of dabigatran within 14 days of stroke. All safety data related to dabigatran comes from trials that excluded patients within 14 days of stroke and 3 days of a TIA. This is precisely the period when stroke patients are at highest risk of recurrent events and most likely to derive benefit from anticoagulation. Based on the limited data, Canadian Stroke Best Practice guidelines recommend basing the timing of anticoagulation on clinical severity and infarct size, but neither are well defined.[8] This recommendation is based on expert consensus that was proposed by European Heart Rhythm Association and has not been defined by randomized clinical trial evidence.[9] The question of optimal timing of oral anticoagulation

after ischemic stroke is frequently encountered in clinical practice. The guidance in this matter has been based largely on expert opinion and clinical experience, along with serial imaging.

2.3 Aims

The overall aim of this study was to demonstrate the feasibility and safety of initiating dabigatran therapy within 14 days of TIA or minor ischemic stroke in AF patients. We systematically assessed prospectively collected CT scan images for evidence of HT.

2.4 Methods

The Canadian Pradaxa Acute Stroke Safety (CPASS) study was an investigator-initiated prospective, multicenter, open label, single arm phase IV study (clinicaltrials.gov registration NCT02415855).

2.4.1 Study population

Patients with documented non-valvular atrial fibrillation (newly or previously diagnosed) with acute TIA (defined as acute focal neurological deficits, with complete resolution of symptoms within 24 h of onset) or mild ischemic stroke (National Institutes of Health Stroke Scale (NIHSS) score ≤3) were enrolled. Study investigators approached patients after the treating physician's decision to treat with dabigatran within 14 days of stroke/TIA, independent of the registry. Informed consent was obtained from the patient or substitute decision maker in all cases prior to enrolment. The research protocol was approved by our local Human Research Ethics Board. Patients were excluded if they had acute or chronic renal failure (estimated glomerular filtration rate (eGFR) <30 ml/min), known hypersensitivity to dabigatran or potential medical interactions with dabigatran therapy, and/or significant ongoing systemic bleeding risk.

2.4.2 Dabigatran Therapy

The dabigatran dose was determined by the treating physician, based on age and renal function. Patients with an estimated glomerular filtration rate 30-50 ml/min and/or age ≥ 80 years received 110 mg twice a day. All other patients received 150 mg twice a day.

2.4.3 Clinical Assessments

All study participants were followed for 30 days after dabigatran initiation. A NIHSS score was assessed, by certified study personnel at baseline, 7 and 30 days after enrolment. Functional outcome was assessed with a modified Rankin Scale (mRS) at baseline, 7, and 30 days. Montreal Cognitive Assessments (MoCA) were performed at baseline, day 7 and day 30 and quality of life was assessed with the EuroQol-5 Dimension (EQ-5D) and Visual Analog Scale (VAS). The Charlson Co-morbidity Index (CCI) was calculated at baseline.

2.4.4 Imaging Procedures and Analysis

All patients had a non-contrast CT scan at baseline (within 24 hours from study recruitment) and at 7±2 days after enrolment using a non-contrast CT scan. In the event of clinical deterioration, CT scans were repeated.

Anonymized dicom CT data were analyzed centrally. Baseline and recurrent infarct volumes were measured using planimetric techniques (Analyze 11.0, Biomedical Imaging Resource, Mayo Clinic).[10] Any HT seen at baseline and day 7 was graded using European Cooperative Acute Stroke Study (ECASS) criteria: Hemorrhagic Infarction Type 1 (HI1; small petechiae along the margins of the infarct), Hemorrhagic Infarction Type 2 (HI2; confluent petechiae within the infarcted area but no space-occupying effect), Parenchymal Hemorrhage Type 1 (PH1; blood clots in 30% or less of the infarcted area with some slight space-occupying

effect) or Parenchymal Hemorrhage Type2 (PH2; blood clot in more than 30% of the infarcted area with substantial space-occupying effect). [11]

2.4.5 Endpoints

The primary endpoint was symptomatic HT, defined as PH2 associated with a ≥4-point increase in NIHSS score within 30 days of initiating dabigatran therapy. Secondary outcomes included any HT at day 7, systemic hemorrhagic complications, and recurrent ischemic stroke within 30 days of enrolment. Serious adverse events (SAE) within the study period were recorded using standardized event, resolution and association codes, and reported to the local Human Research Ethics Boards and Health Canada.

2.4.6 Sample Size and Statistical Analysis

The study was an open label registry not powered to demonstrate safety or efficacy. A sample of 100 patients was planned in order to obtain initial estimates of the frequency of symptomatic and asymptomatic HT. Given the lack of published data with respect to dabigatran in this population, the maximum acceptable rate of symptomatic HT was considered 2%. This was based on a meta-analysis of low molecular weight heparin treatment in acute stroke, indicating the absolute symptomatic HT rate ranged from 2.4% to 2.9%.[12] An a priori stopping rule therefore governed study continuation; enrolment would be halted immediately and permanently if ≥ 2 symptomatic HT events occurred.

All statistical analyses were performed using the Statistical Package for Social Sciences version 23.0.0 (IBM SPSS Statistics Inc, 2015, Armonk, NY, USA). Differences between groups were assessed using independent t-tests for parametric data, Mann-Whitney-U tests for non-parametric data. Pearson's correlation coefficients were used to estimate the relationship between

time to dabigatran initiation and infarct volume. The five-digit health state in EQ-5D, was calculated using preference weights, as described previously.[13]

2.4.7 Role of the Funding Source

The trial was an Investigator Initiated Study, funded by Boehringer – Ingelheim. The study sponsor was 'The Governors of the University of Alberta'. The protocol was written by the Principal Investigator (KB) and reviewed by the Boehringer – Ingelheim global medical team prior to funding. Boehringer – Ingelheim had no role in study design, data collection, analysis, interpretation, or manuscript preparation. Additional support was provided by the Canada Research Chairs Program and the Heart and Stroke Foundation of Alberta, Northwest Territories and Nunavut. The authors had full access to all data in the study and had final responsibility for the presentation of results.

2.5 Results

2.5.1 Baseline Characteristics

Between December 2013 and February 2018, a total of 101 patients (65% male) were enrolled at 3 Canadian stroke centres (Figure 2.1). Patient characteristics are summarized in Table 2.1. At the time of treatment initiation, median (IQR) NIHSS 1 (0-2) and the median (IQR) infarct volume was 0 (0 – 7.43) ml.

The median (IQR) time from onset to first dabigatran dose was 2 (1-5) days for all patients (Figure 2.2). The majority of patients (64%) received dabigatran 150 mg twice a day, and the remainder received 110 mg twice a day. The number of days between symptom onset and dabigatran initiation was directly correlated with the infarct volume ($r=0.49$, $P<0.0001$). An acute infarct was visible on CT in 48 (48%) of patients, and the most common location was cortical (35%). Evidence of previous infarction was seen on baseline CT in 30 (30%) patients.

2.5.2 Dabigatran Compliance and Follow-up

During the follow-up period, two patients withdrew consent prior to the follow up CT scan at day 7. Two patients withdrew consent after the day 7 assessment. One patient died within 7 days of enrolment as a consequence of recurrent ischemic stroke and concomitant systemic emboli. A CT scan was not obtained in four patients at day 7. A follow-up CT scan was obtained in 95 patients at a median (IQR) of 7 (5 – 8.5) days after dabigatran initiation. One patient was non-compliant on dabigatran therapy at day 7 and developed a recurrent ischemic event. The remaining patients were compliant at day 7 and 30.

2.5.3 Baseline Hemorrhagic Transformation

On baseline CT, HT was present in 7 patients (7%). Of these, 4 patients had HI1 and 3 patients had HI2 (Table 2.1). In 3 of these 7 patients, the petechial hemorrhage completely resolved by day 7, despite treatment with dabigatran (Figure 2.3). In 3 patients the HT grade did not change at day 7. A single patient developed asymptomatic progression from HI1 to HI2 (Figure 2.3).

Median (IQR) infarct volume in patients with baseline HT was 31.2 (27.8 – 47.5) ml, which was larger than patients without HT 0 (0 – 5.1) ml ($p<0.0001$). Dabigatran initiation in patients with baseline HT was delayed to 5 (4.5 – 9) days, which was significantly longer than in patients without baseline HT (2 (1 – 5) days, $p<0.0001$; Table 2.1). The relationship between infarct volume, baseline and incident HT, recurrent ischemic events and time to dabigatran initiation is illustrated in Figure 2.4.

2.5.4 Incident Hemorrhagic Transformation

No patients developed symptomatic HT or asymptomatic PH at any point. The total number of patients with incident HT by day 7 was 6 (6%). Clinically silent, but new HI1 was seen in 4 patients, and a single patient developed asymptomatic progression from HI1 to HI2. Another patient developed incident asymptomatic HI2 (Figure 2.3). Patients with incident HT had larger median (IQR) baseline infarct volume 27.3 (13 – 48.5) ml, than those without (HT 0 (0 – 5.4) ml, $p<0.0001$; Table 2.1). The only predictor of incident HT was infarct volume (OR=1.063 [1.020–1.107], $P<0.003$).

2.5.5 Recurrent Ischemic Events

Recurrent ischemic events occurred within 30 days in 4 patients (Table 2.1). One of these patients also developed fatal systemic emboli 3 days after dabigatran initiation. All ischemic events occurred within 10 days of dabigatran initiation. There were no predictors of recurrent ischemic stroke.

2.5.6 Clinical Outcomes

All 6 patients with incident HT were functionally independent (mRS=0-2) at 30 days, which was similar to the good outcome rates seen in those without HT (90%, p=0.422). Conversely, 2 of the 4 patients with recurrent ischemic events were dead or severely disabled (mRS=5) by day 30. There were no systemic bleeding complications or other serious adverse events were reported within the study period.

2.6 Discussion

These data support the safety of initiating dabigatran in AF patients early after TIA or minor ischemic stroke. Even in cases where HT was present prior to anticoagulation, dabigatran did not result in symptomatic HT. In contrast to HT, which was always clinically silent, early

recurrent ischemic events were always clinically evident and resulted in clinical disability/death in half the cases. Recurrent ischemic events occurred within 10 days of the index event, suggesting there is a cost to delaying anticoagulant therapy.

There are limited published data related to the safety of early anticoagulation with dabigatran after cardioembolic stroke or TIA. There are several retrospective analyses of AF management in acute stroke that describe early anticoagulation, primarily with heparin, and/or warfarin. [3-6] A meta-analysis of heparin/low molecular weight heparin/heparinoids suggested that early anticoagulation with these agents in cardioembolic stroke is harmful, due to increased rates of symptomatic HT.[3] Conversely, a more recent meta-analysis suggested that recurrent ischemic stroke is more common than symptomatic HT within 90 days and that early antithrombotic therapy (antiplatelets and anticoagulants were combined) may be beneficial.[14]

The DOACs have all been shown to safer than warfarin with respect to intracranial hemorrhage in patients with chronic AF.[15] The DOACs specifically target single steps in the coagulation cascade, whereas warfarin impairs production of multiple pro-factors. This may theoretically make DOACs safer in the acute stroke setting but given the multifactorial and incompletely understood pathogenesis of HT, this is highly speculative.

Four prospective observational studies of early anticoagulation after stroke, included some patients initiated on a DOAC. The Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) study was a prospective observational study of anticoagulant decision making in patients admitted to hospital with stroke/TIA and AF.[16] A total of 1116 patients were started on warfarin (n=650, median 3 days) or a DOAC (n=466, median 4 days) after stroke/TIA onset. Although there were no reports of intracerebral hemorrhage prior to hospital discharge, systematic neuro-imaging after anticoagulation initiation

was not performed. At 90 days, the recurrent stroke/systemic embolism rate was 2.84% and the rate of major bleeding was 1.1% in the DOAC treated patients.[17] The early Recurrence and cerebral bleeding in patients with Acute ischemic stroke and atrial Fibrillation (RAF) study was a similar prospective observational study performed in 1092 patients that included 93 patients treated with a DOAC.[18] Timing of anticoagulation was at the discretion of the treating physician, varying from 1 to 90 days, and 24% of patients were never anticoagulated. The recurrent ischemic stroke rate was 7.6% risk, and symptomatic cerebral hemorrhage occurred in 3.6% of patients by day 90. Analysis of data from the Clinical Relevance Of Microbleeds In Stroke-2 (CROMIS-2) study assessed the effect of oral anticoagulant timing in patients with AF and stroke.[19] The time to treatment was determined by the investigators and retrospectively dichotomized into early (0-4 days) and late (≥ 5 days or never started) periods. Of 1355 patients prescribed an oral anticoagulant, 358 patients (26%) were started early and 997 (74%) were started late. Recurrent ischemic stroke and intracranial hemorrhage rates were similar between the two groups. The majority of patients (65%) were treated with warfarin, rather than a DOAC. Finally, one single centre registry of anticoagulation practice patterns in cardioembolic stroke indicated that 65% of 155 patients prescribed a DOAC after stroke were initiated within 7 days of onset and that this was not associated with increased risk of symptomatic HT or recurrent stroke.[20] Once again, however, systematic imaging was not part of this registry.

Previous assessments specific to the safety of DOAC initiation in acute cardioembolic stroke have largely been limited to retrospective and small prospective studies. One single centre study reported no symptomatic HT or recurrent stroke in 41 patients treated with DOACs at a median of 2 (IQR 5) days after onset.[21] Our group previously reported a prospective assessment of the safety of rivaroxaban initiation at a median of 3 (IQR 5) days after

cardioembolic stroke symptom onset.[22] Using serial MRI pre and post treatment, we determined asymptomatic petechial HT was common at baseline (25/60), and remained clinically silent despite immediate treatment with rivaroxaban.

One randomized evaluation of rivaroxaban versus warfarin within 5 days of cardioembolic stroke has been published (Triple AXEL; Acute Stroke With Xarelto to Reduce Intracranial Hemorrhage, recurrent Embolic Stroke, and hospitaLstay).[23] Rivaroxaban (n=101) and warfarin (n=94) were associated with similar recurrent ischemic stroke and intracranial haemorrhage rates. Asymptomatic HT on MRI performed at 4 weeks was seen in 49.5% and 54.5% of patients receiving rivaroxaban and warfarin respectively. The higher rates of HT than seen in our study were most certainly related to the higher sensitivity of MRI for petechial bleeding, rather than differences between anticoagulants. As in our study, most patients had mild stroke symptoms (median NIHSS score of 2 in both groups).

In the present study, we observed that the infarct volume was the only predictor of asymptomatic HT after anticoagulation. In addition, clinicians delayed dabigatran initiation in patients with larger infarcts, irrespective of the presence or absence of HT. A similar pattern was observed in the RAF study,[18] reflecting common clinical practice patterns and expert recommendations.[24] Symptomatic HT after anticoagulation is an infrequent event, making it difficult to predict, but thrombolysis related HT as previously been associated with infarct volume.[25] The practice of delaying anticoagulation in patients with large lesions due to concerns that they are more prone to symptomatic HT appears reasonable at present. The absolute risk of HT and the optimal timing in individual patients remains unknown, however.

Ultimately, the risk/benefit ratio of early versus delayed anticoagulation in AF patients with stroke will remain an area of clinical equipoise until randomized trials are completed. The

only randomized trial of early dabigatran versus aspirin published to date was completed in patients without AF.[26] Several trial protocols have been published or registered.[27] Patients in these trials are randomized to a DOAC, initiated as early as 48 hours and up to 4 days after onset, or delayed to 5-10 days. The primary outcome is the composite of recurrent ischemic stroke and symptomatic HT. These include the TIMING (Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation: a Prospective Multicenter Registry-based Non-inferiority Randomized Controlled Clinical Trial, NCT02961348)[28], ELAN (Early Versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients With Atrial fibrillation, NCT03148457), START (Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation, NCT03031928) trials and OPTIMAS (OPtimal TIming of Anticoagulation After Acute Ischemic Stroke, NCT03759938).

Few limitations of our study are important to mention. This non-randomized study does not provide definitive evidence for the safety of early anticoagulation after cardioembolic stroke or TIA. Cardioembolic stroke is often associated with moderate to severe deficits and larger infarct volumes. Based on our study design, these patients were systematically excluded. Caution with respect to early dabigatran use in these patients is therefore still warranted. Low rates of the events, both recurrent ischemic stroke and hemorrhagic transformation seen as a limitation.

2.7 Conclusions

Using prospective clinical and CT scans data, early anticoagulation with dabigatran after TIA and minor cardioembolic stroke is safe and is not associated with symptomatic hemorrhage. Asymptomatic HT is associated with larger baseline infarct volumes. Evidence of baseline petechial or confluent hemorrhagic transformation (HI1 or HI2) on CT scan at the time of dabigatran initiation does not appear to increase the risk of symptomatic HT after minor stroke/TIA. Early recurrent ischemic events may be clinically more important. This observation provides reassurance that current practice patterns are safe, but conclusive evidence will require a larger sample size.

Table 2.1. Characteristics of patients with/without baseline Hemorrhagic Transformation

	All patients (n=101)	**Patients with baseline HT (n=7)**	**Patients without baseline HT (n=94)**	**Patients with incident HT (n=6)**	**Patients with recurrent ischemic events (n=4)**
Mean±SD Age, years	72.4±11.5 years	71.6±9.3 years	72.4±11.7 years	70±5 years	78.8±14.2 years
Male, n (%)	65 (65%)	5 (71%)	60 (65%)	4 (67%)	2 (50%)
Median (IQR) CHA_2DS_2-VASc score	5 (3-6)	4 (3.5-4.5)	5 (3-6)	4 (3 – 6)	4.5 (3.5 – 5.5)
HAS-BLED score, median (IQR)	2 (2-3)	2 (2-3.5)	2 (2-3)	2.5 (2 – 3)	3 (2.5 – 3.5)
Median (IQR) Infarct volume (ml)	0 (0 – 7.43)	31.2 (27.8 – 47.5)	0 (0 – 5.1)	27.3 (13 – 48.5)	2 (1.5 – 3.5)
Infarct location					
Cortical, n (%)	35 (35%)	5 (71%)	30 (32%)	6 (100%)	3 (75%)
Subcortical, n (%)	10 (10%)	2 (29%)	8 (9%)	0 (0%)	1 (25%)
Posterior fossa, n (%)	3 (3%)	0 (0%)	3 (3%)	0 (0%)	0 (0%0
No lesion, n (%)	53 (52%)	0 (0%)	53 (56%)	0 (0%)	0 (0%)
Median (IQR) baseline NIHSS	1 (0-2)	2 (1-2)	1 (0-2)	1 (1 – 2)	2 (1 – 3)
Median (IQR)day 30 NIHSS	0 (0-1)	1 (0.5-1)	0 (0-1)	0 (0-1)	0 (0-8)
Median (IQR) baseline mRS	0 (0-0)	1 (0-2)	0 (0-0)	0 (0-0)	0.5 (0-1.5)
Median (IQR) day 30 mRS	1 (0-2)	2 (1-2)	1 (0-2)	2 (2-2)	3.5 (1.5-5.5)
Median (IQR) baseline CCI	4 (2-5)	3 (3-4.5)	4 (2-5)	3 (3-4)	5.5 (3.5-6)
Median (IQR) baseline MoCA	24.5 (21.25-26)	24.5 (21-26)	24.5 (21-26)	23 (22-24)	24.5 (19-26)
Median (IQR) day 30 MoCA	25 (23-27.5)	24.5 (21-28)	25 (23-27)	27 (26-28)	25 (23-27.5)
Mean (SD) EQ-5D index score at day 30	0.876±0.11	0.91±0.11	0.87±0.11	0.84±0.01	0.82±0.01
Mean (SD) EQ-5D VAS score at day 30	71.8±18.3	69.75±24.6	72±18.1	75±7	72.5±3.5
Median (IQR)Time to dabigatran initiation (Days)	2 (1-5)	5 (4.5-9)	2 (1-5)	6 (2-9)	2 (1.5 – 3.5)

CHA_2DS_2-VASc Score, congestive heart failure, hypertension, age, diabetes mellitus, stroke (doubled), vascular disease, age, and sex category (female); HAS-BLED Score, hypertension, abnormal renal/ liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; IQR, Interquartile Range; HT, hemorrhagic transformation; NIHSS, National Institute of Health Stroke Scale; mRS, Modified Rankin Scale; CCI, Charlson Comorbidity Index; MoCA, Montreal Cognitive Assessment; EQ-5D, EuroQol-5 Dimension; VAS, Visual Analog Scale.

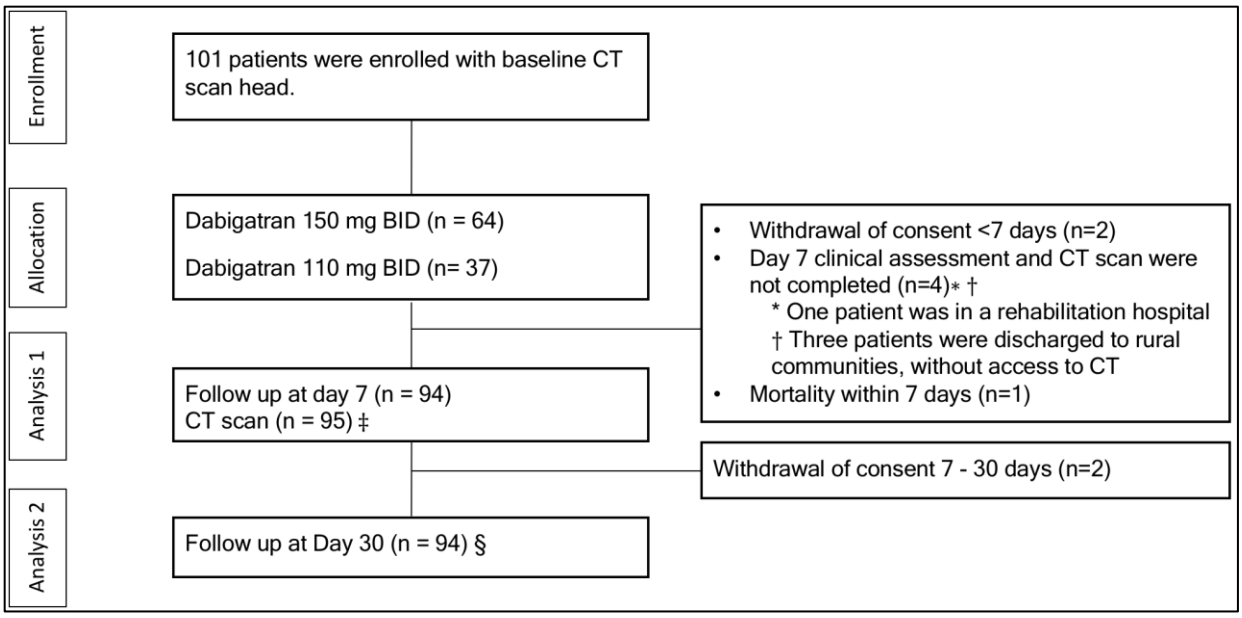

Figure 2.1. Consort diagram of enrollment, allocation, follow-up, and outcomes.

The intention-to-treat population included all the patients who were enrolled in this study. All study participants were followed for 30 days after dabigatran initiation. Day 7 follow-up included clinical assessment and CT scan, while day 30 included clinical assessment. ‡ One patient died within 7 days of enrolment as a consequence of recurrent ischemic stroke and concomitant systemic emboli, CT scan was repeated and included in the analysis. § Four patients whom clinical assessment and CT scan were not completed at day 7 follow-up, returned for their day 30 follow-up.

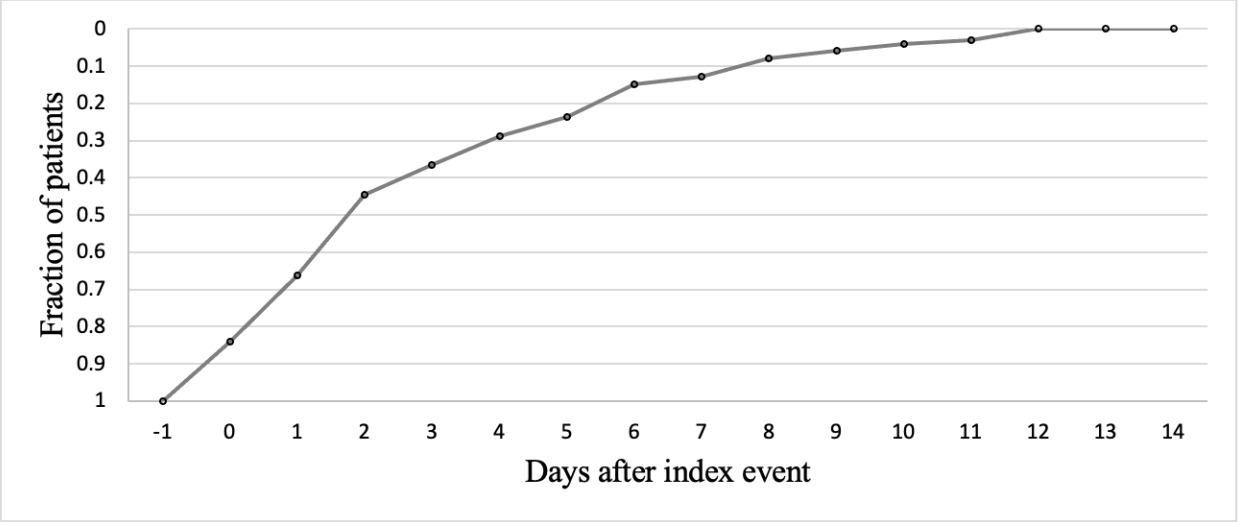

Figure 2.2. Time from ischemic stroke/TIA onset to dabigatran initiation in all patients. Patients initiated on day 0 received their first dose on the day of the index event. The median time to dabigatran initiation was 2 days.

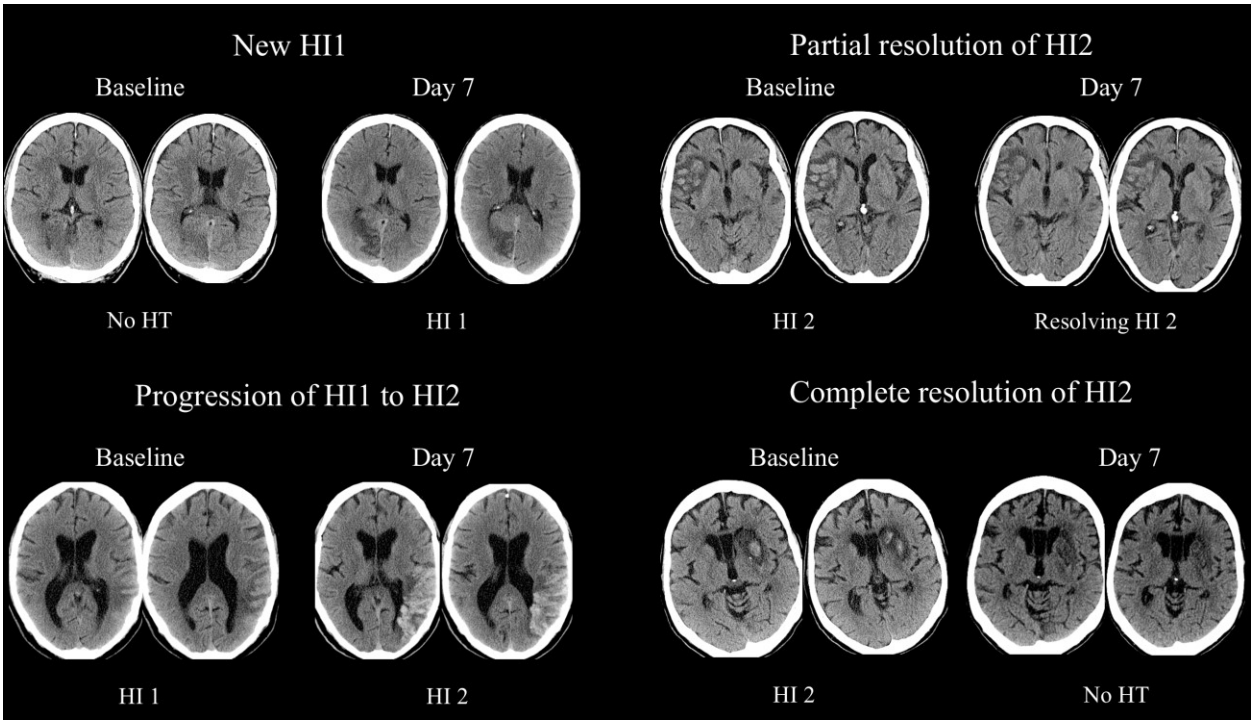

Figure 2.3. Examples of asymptomatic incident (new/progressive) and resolving HT observed after dabigatran initiation.

Hemorrhagic Infarction Type 1 (HI1) was defined as small petechiae along the margins of the infarct, and Hemorrhagic Infarction Type 2 (HI2) as confluent petechiae within the infarcted area but no space-occupying effect.

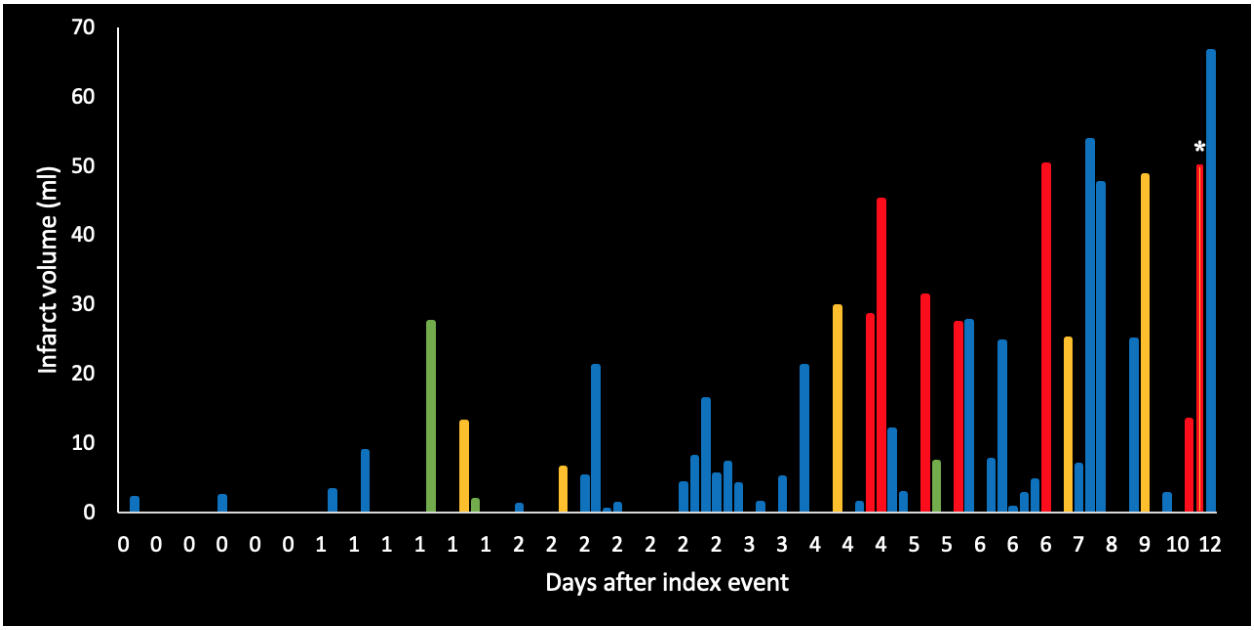

Figure 2.4. Relationship between baseline infarct volume and time from symptom onset to first dabigatran dose.

Blue bars: No HT. Red bars: Baseline HT. Yellow bars: Incident HT at day 7. Green bars: Recurrent ischemic events. * Patient with baseline HI1 that progressed to HI2 at day 7.

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Chapter 3

Early apixaban therapy after ischemic stroke in patients with atrial fibrillation

Running title: Eliquis Acute Stroke Safety Evaluation (EASSE)

3.1 Abstract

Background: The optimal timing of anticoagulation after stroke in patients with atrial fibrillation (AF) is unknown. We aimed to objectively assess the rate of radiological hemorrhagic transformation (HT) associated with early anticoagulation.

Patients and methods: A prospective, open label study (NCT04435418) of patients with AF treated with apixaban within 14 days of ischemic stroke/TIA onset was conducted. Baseline and follow-up CT scans were assessed for HT and graded using European Cooperative Acute Stroke Study (ECASS) criteria. The primary endpoint was symptomatic HT. Incident HT rates were assessed as Objective Performance Criteria.

Results: One-hundred AF stroke patients, with a mean age of 79±11 years were enrolled. Median infarct volume was 4 (0.5–10.75) ml. Median time from index event onset to apixaban initiation was 2 (1–6) days, and median baseline NIHSS was 4 (1–9). Asymptomatic HT on baseline imaging was present in 15 patients. Infarct volume (OR= 1.1, [1.02–1.12], P <0.0001) and NIHSS (OR= 1.11, [1.03–1.20], P =0.007) were both associated with baseline HT. No patients developed symptomatic HT or systemic hemorrhage. Incident asymptomatic HT was seen on follow-up CT scan in 3 patients. Patients with incident HT were functionally

independent (mRS=0-2) at 90 days. Recurrent ischemic events occurred within 90 days in 13 patients, 4 of which were associated with severe disability (mRS 3-5) and 4 with death.

Discussion: Early apixaban treatment did not precipitate symptomatic HT after stroke. All HT was asymptomatic identified on imaging. Recurrent ischemic events were common and clinically symptomatic.

Conclusions: Symptomatic HT rates are likely to be low in randomized trials of DOAC initiation post-stroke. Recurrent ischemic stroke may be the major clinical outcome. These data may be used as expected event rates when calculating sample size requirements for future safety/efficacy trials of early versus late DOAC initiation after AF-related stroke.

Keywords Atrial fibrillation, Ischemic stroke, Hemorrhagic transformation, Apixaban, Cardioembolic stroke, Intracerebral hemorrhage

3.2 Introduction

Patients with atrial fibrillation (AF) and ischemic stroke are at high risk for recurrence and require long-term anticoagulation. The optimal timing of anticoagulation after cardioembolic ischemic stroke is unknown and there are competing rationales for early versus delayed initiation of therapy. Early anticoagulation will reduce the risk of recurrent ischemic events, but also may increase the frequency of hemorrhagic transformation (HT). Retrospective, observational studies indicate that the risk of recurrent ischemic events in the first 14 days after ischemic stroke in patients with AF ranges from 0.5 % to 1.3% per day.[1] Older anticoagulants were avoided in acute stroke, as they were associated with a comparable increase in the risk of HT.[2-4] In the last decade, direct oral anticoagulants (DOACs) including apixaban have become the standard of care for stroke prevention in non-valvular atrial fibrillation patients.[5, 6]

The Apixaban for Reduction In STroke and Other ThromboembоLic Events in atrial fibrillation (ARISTOTLE) trial demonstrated significantly lower ICH rates associated with long-term use of this DOAC, relative to warfarin.[7] Patients were not eligible for randomization within 7 days of ischemic stroke or transient ischemic attack (TIA), however. Although 20% of patients had a prior history of stroke/TIA, the number of patients randomized early is unknown, but likely low as most investigators were not stroke specialists. The contraindications section of the product monograph states apixaban should not be used in patients with 'lesions or conditions at increased risk of clinically significant bleeding, e.g., recent cerebral infarction (ischemic or hemorrhagic)'.[8] The Canadian Stroke Best Practice guidelines recommend timing of anticoagulation based on clinical severity and infarct size, as seen on CT scan, but neither are well defined.[5] This guideline statement is based on expert opinion originally included in the European Heart Rhythm Association recommendations, but neither are based on randomized

evidence.[9] The incidence of objectively defined HT associated with early apixaban initiation is unknown. We therefore completed a prospective, open label study of apixaban initiation within 14 days of an ischemic stroke/TIA. The study aim was to provide an estimate of the incidence of sub-clinical HT associated with apixaban initiation in this post-stroke period. Serial imaging was used to objectively assess the rate of sub-clinical HT after apixaban initiation.

3.3 Methods

Eliquis Acute Stroke Safety Evaluation (EASSE) was an investigator-initiated prospective, open label, single arm phase IV study (clinicaltrials.gov registration NCT04435418).

3.3.1 Study population

Patients with documented non-valvular AF (newly or previously diagnosed) with acute TIA (defined as acute focal neurological deficits, with complete resolution of symptoms within 24 hours of onset) or ischemic stroke, irrespective of infarct volume or clinical severity were enrolled. The decision to treat with apixaban and the timing of initiation was at the attending physicians' discretion, independent of enrolment in EASSE. Informed consent was obtained from the patient or substitute decision maker in all cases prior to enrolment. The research protocol was approved by our local Human Research Ethics Board.

3.3.2 Apixaban Therapy

Apixaban dose was determined by the treating physician, based on age, weight and renal function as per the product monograph.[8] Patients with two of the following: Age >80, weight <60 kg, and creatinine ≥133 mmol/l, received 2.5 mg twice a day. All other patients received 5 mg twice a day.

3.3.3 Clinical Assessments

The study period was 90 days after apixaban initiation. A National Institute of Health Stroke Scale (NIHSS) score was assessed, by certified study personnel at baseline, 7 and 90 days after enrolment. Functional status was assessed with the modified Rankin Scale (mRS) at baseline (pre-morbid), 7 and 90 days. Montreal Cognitive Assessments (MoCA) were performed at baseline, and day 90 (versions A and B). Quality of life was assessed with the EuroQol-5 Dimension (EQ-5D) and Visual Analog Scale (VAS) at day 90.

3.3.4 Imaging Procedures and Analysis

All patients had a non-contrast CT scan at baseline (within 24 hours from study recruitment) and at 7±2 days after apixaban initiation. In the event of clinical deterioration, CT scans were repeated.

Anonymized dicom CT data were analyzed centrally. Baseline and recurrent infarct volumes were measured using planimetric techniques (Analyze 11.0, Biomedical Imaging Resource, Mayo Clinic).[10] Any HT seen at baseline and day 7 was graded using European Cooperative Acute Stroke Study (ECASS) criteria: Hemorrhagic Infarction Type 1 (HI1; small petechiae along the margins of the infarct), Hemorrhagic Infarction Type 2 (HI2; confluent petechiae within the infarcted area but no space-occupying effect), Parenchymal Hemorrhage Type 1 (PH1; hematoma in 30% or less of the infarcted area with some slight space-occupying effect) or Parenchymal Hemorrhage Type2 (PH2; hematoma in more than 30% of the infarcted area with substantial space-occupying effect).[11] Incident HT seen on follow-up CT scan is defined as new or progressive HT.

3.3.5 Endpoints

The primary endpoint was symptomatic HT, defined as PH2 associated with a ≥4-point increase in NIHSS score within 90 days of initiating apixaban therapy. Secondary outcomes included any HT at day 7, systemic hemorrhagic complications, and recurrent ischemic events within 90 days of enrolment. Serious adverse events (SAE) within the study period were recorded using standardized event, resolution and association codes, and reported to the local Human Research Ethics Board.

3.3.6 Sample Size and Statistical Analysis

A sample of 100 patients was planned in order to obtain estimates of the frequency of asymptomatic HT associated with early apixaban initiation. The maximum acceptable rate of symptomatic HT was considered 2%, based on a meta-analysis of low molecular weight heparin treatment in acute stroke, indicating the absolute symptomatic HT rate ranged from 2.4% to 2.9%.[12] An *a priori* stopping rule governed study continuation; enrolment would be halted immediately and permanently if ≥ 2 symptomatic HT events occurred. Incident radiological HT rates were assessed as Objective Performance Criteria.[13-15]

All statistical analyses were performed using the Statistical Package for Social Sciences version 23.0.0 (IBM SPSS Statistics Inc, 2015, Armonk, NY, USA). The primary analysis was intention-to-treat, irrespective of compliance. Linear regression was used to assess the relationship between time to apixaban initiation and infarct volume after log transformation of both variables. Functional outcome at 90 days was dichotomized as independent (mRS score 0-2) and dependent group (mRS score 3-6). The distribution of independent outcomes in patients with/without recurrent ischemic events and HT was assessed with Pearson's Chi-Square tests.

The five-digit health state in EQ-5D, was calculated using the Canadian preference weights, as described previously.[16]

3.4 Results

3.4.1 Baseline Characteristics

Between March 2017 and September 2019, a total of 100 patients (51% female) were enrolled. At the time of apixaban initiation, median (IQR) NIHSS was 4 (1–9) and infarct volume was 4 (0.5–10.75) ml. Baseline clinical and imaging characteristics are summarized in Table 3.1.

3.4.2 Patient Follow-up

One patient withdrew consent prior to the follow up CT scan at day 7 (Figure 3.1). One patient withdrew consent after the day 7 assessment. Nine patients died after the day 7 assessment. Four of the deaths were secondary to recurrent ischemic stroke and/or concomitant systemic emboli. Other deaths were unrelated to HT or systemic bleeding. A CT scan was not obtained in eight patients at day 7. A follow-up CT scan was obtained in 92 patients at a median (IQR) of 7 (5 – 8.5) days after apixaban initiation.

3.4.3 Apixaban Treatment

The median (IQR) time from onset to first apixaban dose was 2 (1-6) days. The majority of patients (79%) received apixaban 5 mg twice a day, and the remainder received 2.5 mg twice a day. The number of days between symptom onset and apixaban initiation was directly correlated with infarct volume (R=0.256 [0.165, 0.347], p<0.0001; Figure 3.2). An acute infarct was visible on CT in 78 (78%) of patients, most commonly in a cortical location (59%). Evidence of previous infarction was seen on baseline CT in 18 (18%) patients.

3.4.4 Hemorrhagic Transformation (HT)

Baseline CT revealed HT, *prior to initiation of apixaban*, in 15 patients (15%). The HT was graded as HI1 in nine patients, HI2 in five and PH1 in a single patient. Median (IQR) infarct volume in patients with baseline HT (47 (27 – 72) ml) was larger compared to those without HT (2 (0 – 8) ml; $p<0.0001$). Univariate logistic regression indicated infarct volume (OR= 1.1, [1.02–1.12], $p<0.0001$) and NIHSS (OR= 1.11, [1.03–1.20], $p=0.007$) were both associated with baseline HT. Linear regression indicated that the presence of HT on baseline images was associated with a delay in apixaban initiation (R=4.059 [2.41, 5.71], $p<0.0001$). Median time to apixaban initiation in patients with baseline HT was 6 (5 – 9.5) days after onset, which was longer than in those without baseline HT 2 (1 – 5) days, $p<0.001$.

The primary outcome of symptomatic HT was not seen in any patients after initiation of apixaban (Table 3.2). No patients developed a new parenchymal hematoma after initiation of apixaban. Incident asymptomatic HT on the day 7 CT scan (Objective Performance Criteria) was seen in 3 patients (3%; Figure 3.3). New HI1 was seen in 2 patients and another patient with baseline HI1, developed asymptomatic progression to HI2 on the day 7 CT. In 5 of the remaining 14 patients with baseline HT, the petechial hemorrhage completely resolved by day 7, despite treatment with apixaban. In eight patients with baseline HT, the grade did not change on the day 7 scan, and one patient with HI2 improved to HI1 on the follow up scan.

3.4.5 Systemic Hemorrhagic Complications

There were no systemic bleeding complications or other serious adverse events reported within the study period.

3.4.6 Recurrent Ischemic Events

Recurrent ischemic events occurred within 90 days in 13 patients (13%). Of these 13 patients, 11 experienced recurrent ischemic strokes (Figure 3.4). Five events occurred within 7 days of apixaban initiation, and six more between day 7 and day 90. Two patients suffered peripheral arterial ischemic events. In 2/13 (15%) patients with recurrent ischemic stroke, the apixaban dose was 2.5 mg twice daily. Baseline NIHSSS, infarct volume, and left atrial index volume did not predict recurrent ischemic events.

3.4.7 Clinical Outcomes

All 3 patients with incident HT were functionally independent (mRS 0-2) at 90 days. The presence of HT at any time was not associated with functional outcome (OR=1.9, [0.66, 5.4], p=0.23; Figure 3.5). At 90 days, 8/13 (62%) patients with recurrent ischemic events were functionally dependent (mRS 3-6). The proportion of patients who were independent at day 90 was not related to recurrent ischemic events, however (OR=2.75, [0.83, 9.1], p=0.89).

3.5 Discussion

These data provide objective evidence of the rate of HT associated with early apixaban treatment in ischemic stroke patients with AF. Incident HT developed in 3% of patients, none of whom were symptomatic. Early recurrent ischemic events occurred in 13% of patients, all of whom were symptomatic.

The lack of a comparator group and small sample size are the primary weaknesses of this study. These non-randomized data do not provide definitive evidence for the safety of early apixaban initiation after ischemic stroke or TIA in patients with AF. However, the results are hypothesis generating only, but do provide estimates of the sub-clinical HT rate that may be useful in the design, particularly sample size and power calculations, of future randomized

clinical trials of early versus delayed anticoagulation after cardioembolic ischemic stroke. Careful and systematic collection of HT rates constitute Objective Performance Criteria, that have been used to define safety standards and are an important part of the medical device development pipeline.[13-15] These criteria may be important surrogate markers even in larger trials, where the absolute number of symptomatic HT cases is likely to remain low. A final limitation of the study is the mild to moderate stroke severity case mix, which may make our results less applicable to those with large infarcts.

Randomized studies of early DOAC use post stroke: There are two published randomized trials designed to evaluate the safety of early DOAC administration after ischemic stroke. The Triple AXEL (Acute Stroke With Xarelto to Reduce Intracranial Hemorrhage, recurrent Embolic Stroke, and hospitaL stay) compared rivaroxaban to warfarin initiation within 5 days of cardioembolic stroke.[17] Rivaroxaban (n=101) and warfarin (n=94) were associated with similar recurrent ischemic stroke and intracranial hemorrhage rates. Asymptomatic HT detected on magnetic resonance imaging (MRI) 4 weeks post-stroke was seen in 49.5% and 54.5% of patients receiving rivaroxaban and warfarin respectively. The higher frequency of HT in that study relative to ours, likely relates to the higher sensitivity of MRI for petechial bleeding rather than the different anticoagulants studied. Most patients in Triple AXEL had mild stroke symptoms (median NIHSS score of 2 in both groups). More recently, the DATAS II trial (Dabigatran in Acute Transient Ischemic Attack and minor Stroke) randomized 305 patients *without AF* to dabigatran or aspirin within 72 hours of ischemic symptom onset.[18] There were no symptomatic HT events in either group, but asymptomatic HT detected with MRI was reported in 7.8% of the dabigatran group and 3.5% of the aspirin group (relative risk 2.22, [0.79, 6.21]). As in Triple AXEL, DATAS II patients had relatively mild clinical deficits and small

infarcts. In addition, the apparent safety of dabigatran in this non-cardioembolic stroke population cannot be extrapolated to patients with AF and larger cardioembolic infarcts.

Prospective, non-randomized studies of early DOAC use post stroke: There are nine prospective studies of the safety of early oral anticoagulation after ischemic stroke that included at least some patients treated with a DOAC.[19-27] Most studies included patients treated with one of the available DOACs or warfarin and very few included systematic imaging follow-up. The Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) study which was a prospective observational study of initiating anticoagulant after stroke/TIA in patients with AF.[19] Warfarin (n=650) or a DOAC (n=466) were started a median of 3 and 4 days after stroke/TIA onset respectively. There were no intracerebral hemorrhages prior to hospital discharge, but unlike our study, systematic neuroimaging was not performed. In patients treated with a DOAC, the recurrent stroke/systemic embolism rate was 2.84% and the rate of major bleeding was 1.1% at day 90.[28] The Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non–Vitamin-K Oral Anticoagulants (RAF-NOACs) study evaluated 1127 patients, 80% of whom received therapy within 15 days of stroke.[20] The remaining 20% were treated within 90 days. Ischemic embolic events within 90 days were higher than symptomatic cerebral bleeding at rates 2.8% and 1.6%, respectively. However, the lack of systematic imaging may have led to under-estimation of the rate of HT. The 'Novel Oral Anticoagulants in Ischemic Stroke Patients' (NOACISP) registry reported that 65% of 155 patients prescribed a DOAC after stroke had treatment initiated within 7 days of onset and that this was not associated with increased risk of symptomatic HT or recurrent stroke.[21] The Clinical Relevance Of Microbleeds In Stroke-2 (CROMIS-2) study assessed the effect of oral anticoagulant timing in patients with AF and stroke.[22] As in our

study, the time to treatment was determined by the treating physicians and then retrospectively dichotomized into early (0-4 days) and late (≥ 5 days or never started) periods. Of 1355 patients prescribed an oral anticoagulant, 358 patients (26%) started early and 997 (74%) started late. Both groups had similar recurrent ischemic stroke and intracranial hemorrhage rates. The majority of patients (65%) were treated with warfarin, rather than a DOAC, and 24% received bridging heparin therapy. A recent prospective demonstrated similar rates of recurrent stroke and hemorrhagic complications in anterior and posterior circulation stroke patients.[23] A higher symptomatic hemorrhagic event rate (4.2% and 3.7% in the anterior and posterior circulation respectively) may have been related to the use of warfarin and/or bridging heparin prior to DOAC administration. Bridging prior to DOAC administration has recently been associated with a high risk of symptomatic HT in a pooled registry analysis.[29]

Prospective studies including systematic brain imaging following OAC initiation post-stroke have generally been smaller. A prospective assessment of the safety of rivaroxaban initiation at a median of 3 (IQR 5) days after cardioembolic stroke symptom onset demonstrated comparable results to the present study.[24] Serial MRI pre and post treatment, demonstrated asymptomatic petechial HT was common at baseline (25/60), and remained clinically silent despite immediate treatment with rivaroxaban. A more recent prospective, multi-center registry of dabigatran initiation within 14 days of acute minor ischemic stroke/TIA (NIHSS≤3) onset in patients with AF has also been published.[25] A total of 101 patients (median infarct volume was 0 ml and median baseline NIHSS was 1) were enrolled. The median time to from ischemic symptom onset to dabigatran initiation was two days and this was not associated with any symptomatic HT, but asymptomatic HT evident on systematically acquired follow-up CT was seen in 6% of patients. Two other small prospective observational studies utilizing systematic

imaging after oral anticoagulation in cardioembolic stroke patients have been published. In one study of 120 patients, HT occurred in 32 patients, 8 of whom developed a parenchymal hematoma, but the majority of these were related to warfarin with/without heparin.[26] In contrast, in another study of patients treated with DOAC within 7 days of stroke, only asymptomatic HT was seen (16/147) on a one-week follow-up CT scan.[27] The asymptomatic HT (16/147) and recurrent ischemic stroke rates (0/147) were both low.

In the present study, infarct volume was associated with asymptomatic HT at baseline. The time to initiate apixaban therapy was longer in patients with larger infarcts, irrespective of the presence or absence of HT. This treatment pattern has been previously reported [26, 30], reflecting common clinical practice patterns that are based on expert opinion.[31] Infarct volume has been previously reported as a predictor of HT post thrombolysis[32] and incident asymptomatic HT after early dabigatran post-stroke.[25] Incident HT associated with early anticoagulation is relatively infrequent and appears to be clinically silent in most cases, making it difficult to accurately predict. The practice of delaying anticoagulation in patients with large lesions due to concerns that they are more prone to symptomatic HT appears reasonable at present. The absolute risk of HT and the optimal timing in individual patients remains unknown however, and we suggest early follow-up imaging after DOAC initiation to assess for asymptomatic HT should be included as Objective Performance Criteria in all future studies of anticoagulant timing.

Ongoing studies: Until randomized controlled trials for the safety and efficacy of early versus delayed anticoagulation after ischemic stroke in patients with AF are completed, the question of optimal timing to start anticoagulation will remain an area of clinical equipoise. Several trial protocols have been published and/or registered.[33-35] Patients in these trials are randomized to a

DOAC, initiated as early as 48 hours and up to 5 days after onset, or delayed to 6-14 days. The primary outcome in these trials is the composite of recurrent ischemic stroke and symptomatic HT. Many of these trials stratify DOAC initiation timing, based on clinical severity. Objective performance criteria for bleeding rates may be helpful in the interpretation of results from these forthcoming studies. Ongoing trials include LASER (Lixiana Acute Stroke Evaluation Registry, NCT03494530), TIMING (Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation: a Prospective Multicenter Registry-based Non-inferiority Randomized Controlled Clinical Trial, NCT02961348)[34], ELAN (Early Versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients With Atrial fibrillation, NCT03148457), START (Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation, NCT03021928) trials, OPTIMAS (OPtimal TIming of Anticoagulation After Acute Ischemic Stroke, NCT03759938) and AREST (Apixaban for Early Prevention of Recurrent Embolic Stroke and Hemorrhagic Transformation, NTC02283294).

3.6 Conclusions

The results of this pilot study suggest symptomatic HT rates are likely to be low in randomized trials of DOAC initiation post-stroke, but sub-clinical HT may be a useful objective performance criterion if systematic serial post-randomization imaging is included in the design. Finally, our results suggest that the more common clinical outcomes of interest in these trials will be recurrent ischemic stroke, rather than HT, although the latter remain important as even a slight increase in frequency may out-weight any benefits of early anticoagulation. These results support the need for further trials of DOAC timing after AF-related stroke.

3.7 Acknowledgments

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Table 3.1. Baseline Patient Characteristics

	Apixaban (n=100)
Mean ± SD, age	79±11
Female	51 (51%)
IV-tPA (%) / EVT (%)	11% / 11%
IV-tPA and EVT (%)	7%
Known AF (%) / New diagnosis of AF (%)	81% / 19%
Apixaban dose: 5 mg twice a day 2.5 mg twice a day	79% 21%
Median (IQR) Infarct volume (ml)	4 (0.5 – 10.75)
Median (IQR) time from index event onset to apixaban initiation (days)	2 (1 – 6)
Mean ± SD, Baseline BP	142±20 / 79±16
Median (IQR) Baseline NIHSS	4 (1 – 9)
Median (IQR) Pre-morbid mRS	0 (0 – 1)
Imaging characteristics	
Cortical lesion(s) (%) *	59%
Subcortical lesion(s) (%) †	15%
Multiple infarcts (%)	4%
No visible infarct (%)	22%
Previous infarct(s) (%)	18%

SD, standard deviation; IV-tPA, intravenous tissue plasminogen activator; EVT, endovascular thrombectomy; AF, atrial fibrillation; IQR, Interquartile Range; BP, blood pressure; NIHSS, National Institute of Health Stroke Scale; mRS, Modified Rankin Scale. *Cerebellar lesions were considered cortical lesions. † Brainstem lesions were considered subcortical lesions

Table 3.2. Primary and secondary outcomes

	Apixaban (n=100)
Primary outcome	
Symptomatic HT (PH2)	0/100
Secondary outcomes	
New parenchymal hemorrhage (PH1 or asymptomatic PH2)	0/100
Systemic hemorrhagic complication(s)	0/100
Recurrent ischemic event(s)	13/100
Ischemic stroke(s)	11/13
Transient ischemic attack	0/13
Systemic ischemic event(s)	2/13
Clinical outcomes	
Median (IQR) day 90 mRS	2 (0 – 3)
Median (IQR) day 90 NIHSS	1 (0 – 3)
Median (IQR) day 90 MoCA	23 (18 – 25)
Median (IQR) day 90 EQ-5D index score	0.808 (0.701 – 1.00)
Median (IQR) day 90 EQ-5D VAS score	70 (56 – 80)

HT, hemorrhagic transformation; PH, parenchymal hemorrhage; IQR, Interquartile Range; mRS, Modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; MoCA, Montreal Cognitive Assessment; EQ-5D, EuroQol-5 Dimension; VAS, Visual Analog Scale.

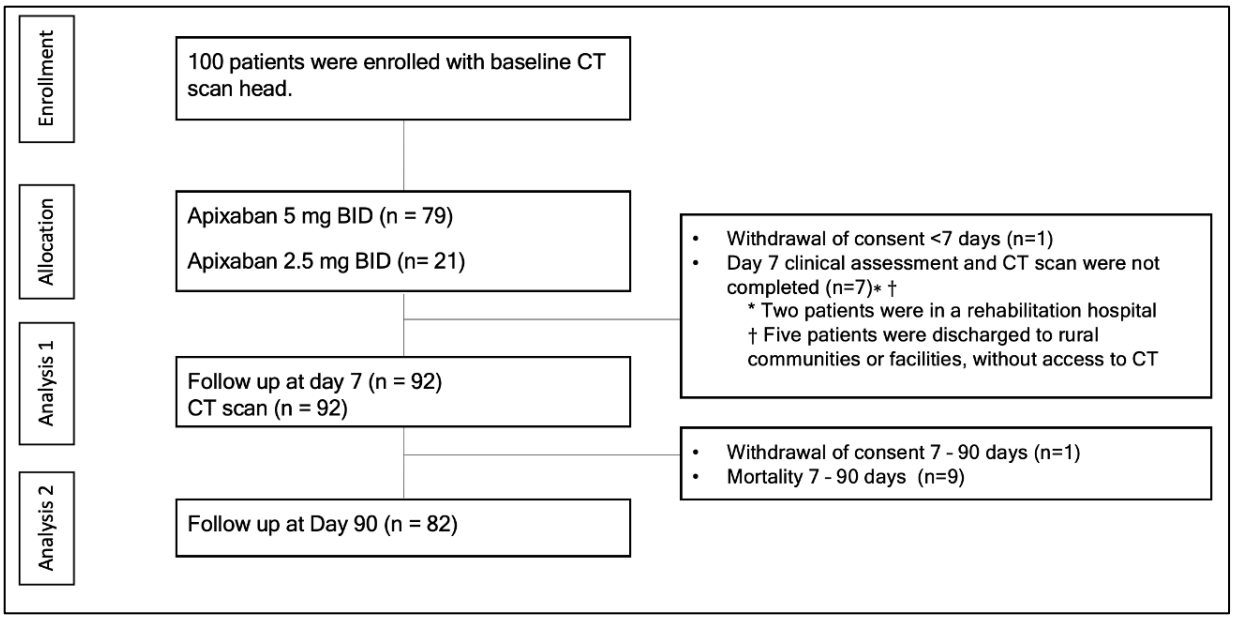

Figure 3.1. Consort diagram of enrollment, allocation, follow-up, and outcomes.

Day 7 follow-up included clinical assessment and CT scan, while day 90 included clinical assessment. CT, computed tomography; BID, twice a day

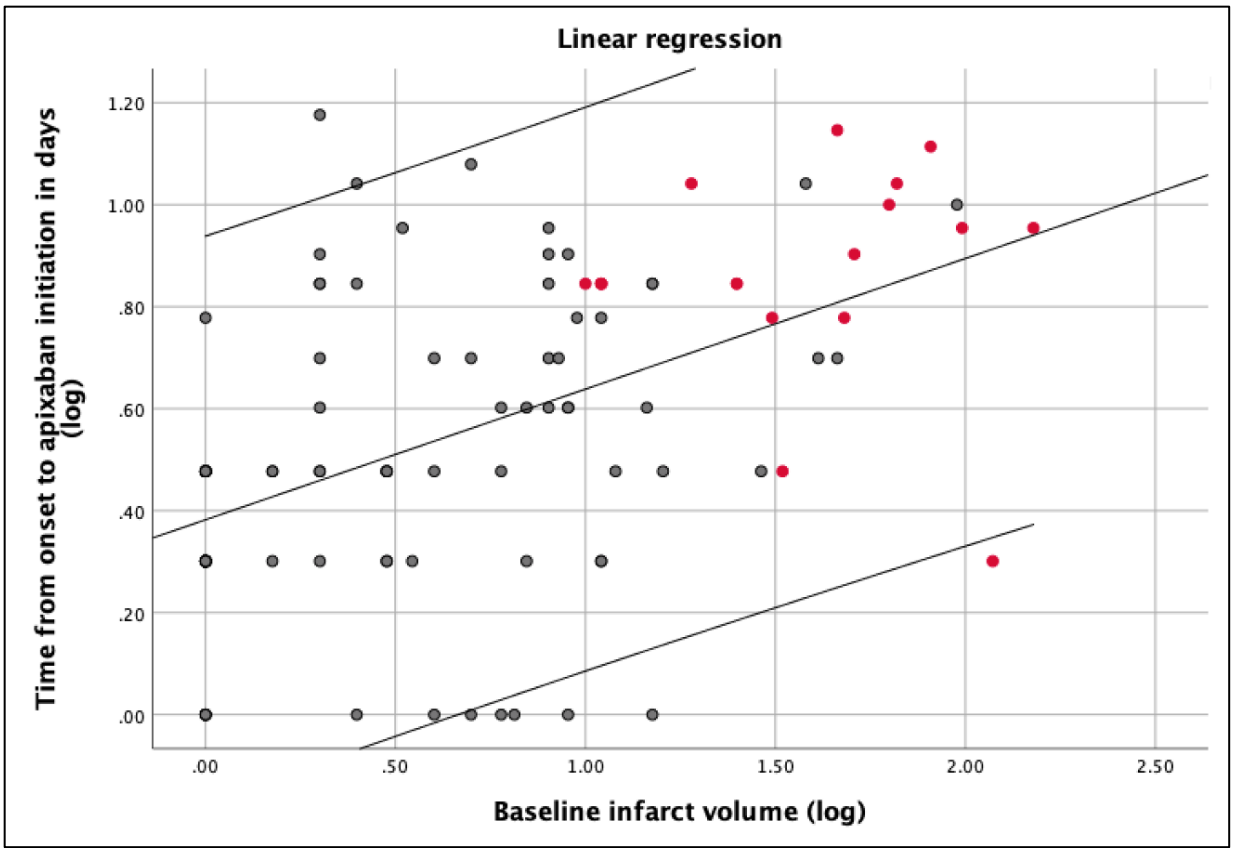

Figure 3.2. The relationship between the time of onset to apixaban initiation and baseline infarct volume.

The number of days between stroke onset and initiation of apixaban was associated with baseline infarct volume (R=0.256, [0.165, 0.347], p<0.0001), reflecting physician practice patterns. Red dots represent patients with baseline HT.

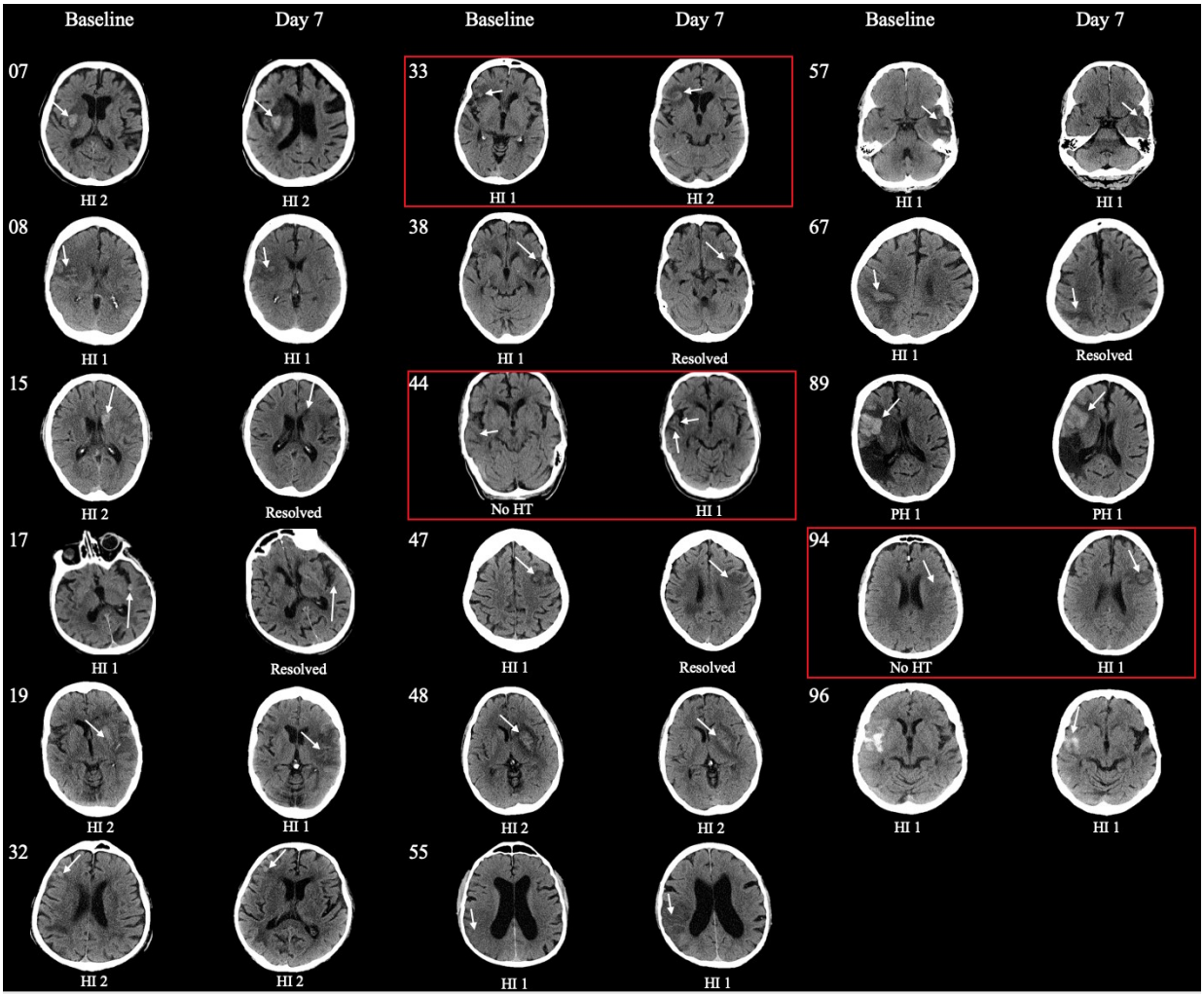

Figure 3.3. All cases of hemorrhagic transformation (HT) seen in the study (none were symptomatic).

Hemorrhagic Infarction Type 1 (HI1) was defined as small petechiae along the margins of the infarct, Hemorrhagic Infarction Type 2 (HI2) as confluent petechiae within the infarcted area but no space-occupying effect, and Parenchymal Hemorrhage Type 1 (PH1) as hematoma in <30% of the infarcted area with some slight space-occupying effect. Squares indicate incident HT.

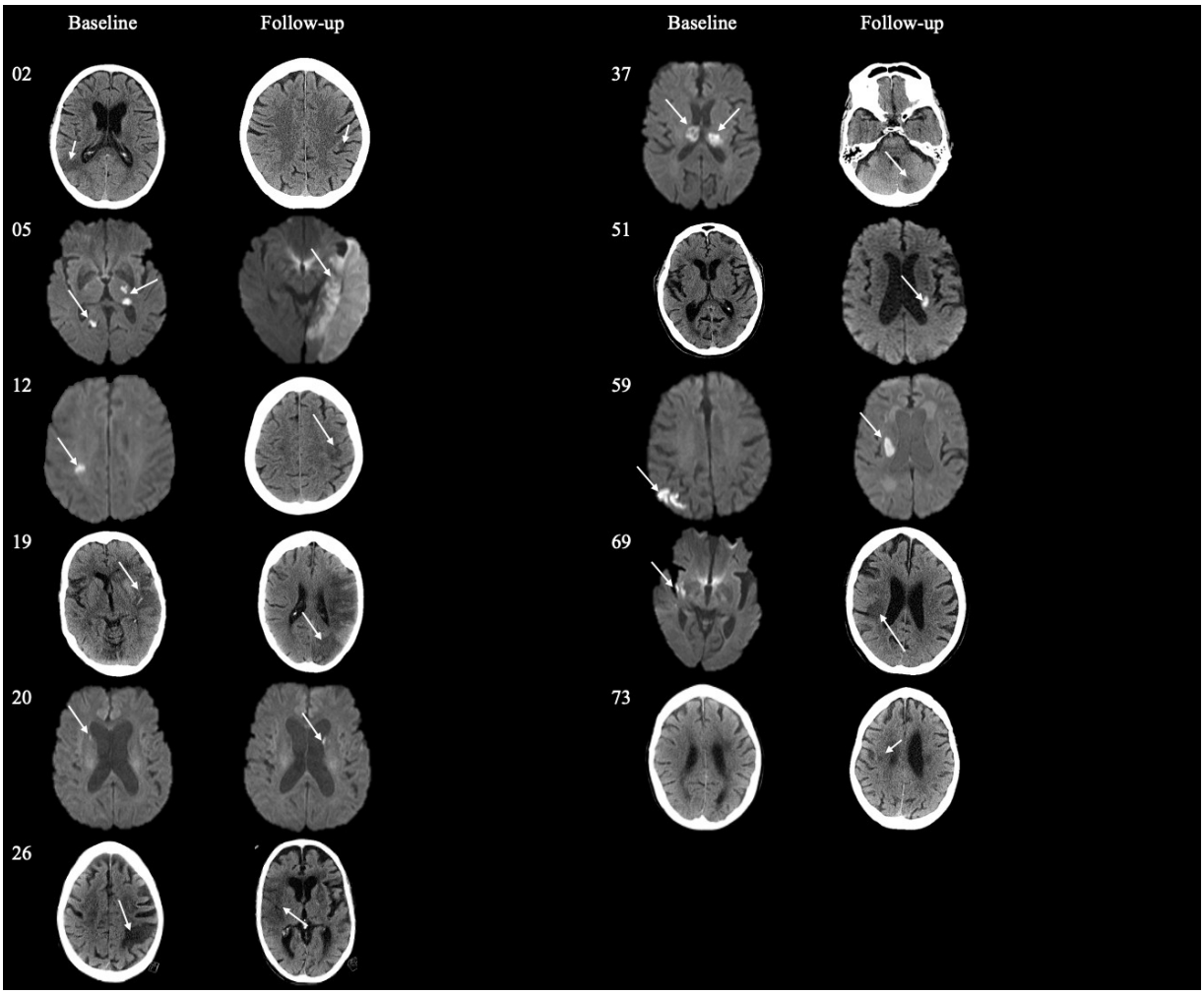

Figure 3.4. All recurrent ischemic infarcts seen in the study (all were symptomatic).

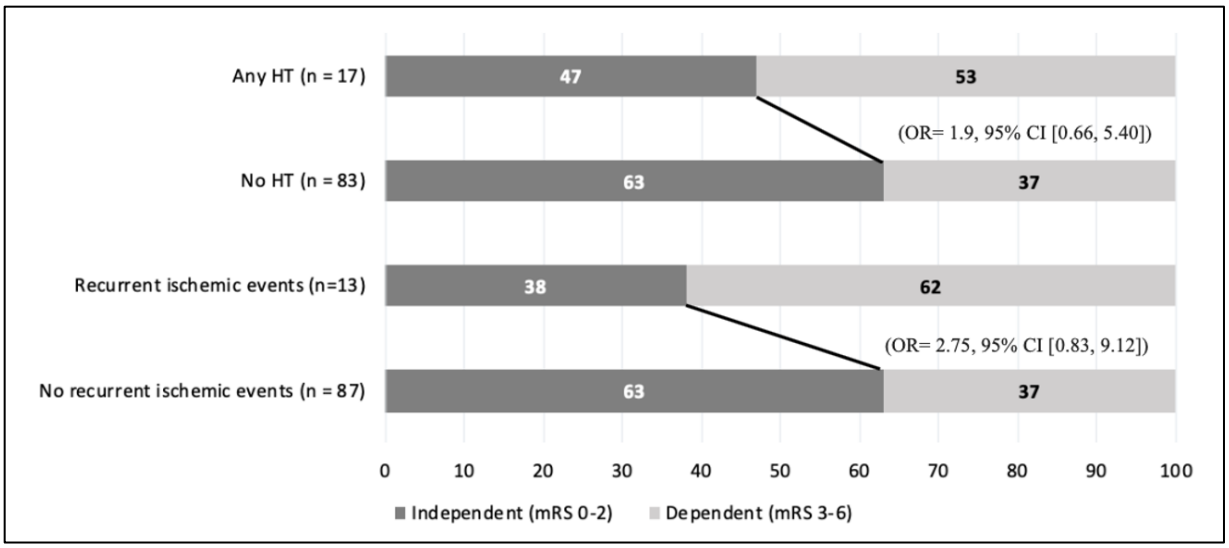

Figure 3.5. Day 90 functional outcomes in patients with/without hemorrhagic transformation (HT) and patients with/without recurrent ischemic events.

The proportion of patients who were independent at day 90 was not associated with HT or recurrent ischemic events. Any HT includes baseline and incident HT. mRS, modified Rankin Scale; OR, odds ratio; CI, confidence interval.

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Chapter 4

Protocol for LASER: A randomized evaluation and an associated registry of early anticoagulation with edoxaban after ischemic stroke in patients with atrial fibrillation

Running title: Lixiana Acute Stroke Evaluation Registry (LASER)

4.1 Abstract

Background: The optimal timing of anticoagulation after stroke in patients with atrial fibrillation (AF) is unknown.

Aim and hypothesis: Our primary aim is to demonstrate the safety of edoxaban initiation within five days of AF related stroke. Our secondary aim is to determine predictors of hemorrhagic transformation (HT) after cardioembolic stroke. We hypothesize that the rate of radiological HT will not be increased in patients starting edoxaban within five days of cardioembolic stroke, relative to those in whom initiation is delayed. We hypothesize that the risk of HT in patients treated with edoxaban can be predicted using RNA expressed in leukocytes at time of stroke.

Methods and design: LASER (Lixiana Acute Stroke Evaluation Registry**)** is a randomized controlled trial with an associated registry (clinicaltrials.gov NCT03494530). One hundred and fifty patients with ischemic stroke and AF will undergo baseline Computed Tomography (CT) scan and will be randomized 2:1 within five days of symptom onset to early (≤5 days, n=100) or delayed (6-14 days, n=50) edoxaban initiation. Participants will undergo clinical assessment and repeat CT at 7 days and clinical assessment to 90 days.

Study outcomes: The primary outcome is the rate of incident radiological HT. Secondary outcomes include symptomatic HT, recurrent ischemic stroke, recurrent sub-clinical infarcts on follow up CT, systemic hemorrhagic complication rate, National Institute of Health Stroke Scale and modified Rankin Scale at day 7 and 90, mortality within 90 days, quality of life assessments at day 90, and predictors of HT, including RNA expression by 6 pre-selected candidate genes.

Discussion: Event rates for both HT and recurrent ischemic events, in patients treated with early versus delayed edoxaban initiation are unknown. The primary study endpoint of LASER is an objective performance criterion relevant to clinical decision making in cardioembolic stroke patients. This study will provide data required for a definitive safety/efficacy study sample size power calculation.

4.2 Introduction

The optimal timing of anticoagulation after ischemic stroke is an area of clinical equipoise. It is clearly established that patients with atrial fibrillation (AF) who develop ischemic stroke are at high risk for recurrence and require long-term anticoagulation. Previous studies have reported that starting older anticoagulants within 48 hours after acute ischemic stroke is associated with a reduction in the rate of recurrent ischemic events, but that is offset by an increased risk of hemorrhagic transformation (HT).[1-3] More recently, four direct oral anticoagulation (DOACs) have shown a lower risk of intracranial hemorrhagic complications compared to older anticoagulants, and they are now the standard of care for long-term stroke prevention in non-valvular AF.[4-7] In the pivotal phase III DOAC trials, patients were not eligible for randomization as early as 7 days and up to 30 days after ischemic stroke. Current stroke guidelines are inconsistent regarding the timing of DOAC initiation and recommendations are based on expert opinion only.[8-10]

Edoxaban is one of the DOACs approved for the prevention of ischemic stroke in patients with AF.[7] Patients within 30 days of ischemic stroke were excluded from the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation - Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial. As with other DOACs, there are no randomized data related to the use of edoxaban early after ischemic stroke. The optimal timing of DOAC initiation is unknown and a clinical problem commonly encountered by stroke physicians. Even less is understood about the timing of anticoagulation after HT, asymptomatic or otherwise, has occurred.

Symptomatic HT remains difficult to predict. Although clinical severity and infarct volume appear to increase HT risk [11, 12], the association is highly inconsistent. Novel

biomarkers would be useful in determining DOAC timing. Preliminary data suggest the risk of HT in patients with stroke can be stratified by RNA expressed in circulating leukocytes within 3 hours of stroke onset. A panel of 6 genes associated with subsequent HT has been identified.[13, 14]

The primary aim of the Lixiana Acute Stroke Evaluation Registry (LASER) is to demonstrate the safety of edoxaban initiation within five days of cardioembolic stroke. Secondary aims include identification of clinical, imaging and RNA transcript predictors of HT. We hypothesize that edoxaban initiation within five days of ischemic stroke will not be associated with increased HT rates, relative to patients in whom anticoagulation is delayed. Serial imaging using Computed Tomography (CT) will be utilized to determine the rate of radiological HT after edoxaban initiation. Incident radiological HT rates will be assessed as objective performance criteria for the safety of early versus delayed edoxaban initiation.[15-17] We also hypothesize that RNA expressed in leukocytes at time of stroke can stratify risk of HT in patients treated with edoxaban. We will assess the rate of recurrent ischemic stroke, but recognize any differences between groups will be hypothesis generating only due to the small trial sample size.

4.3 Methods

4.3.1 Study design

LASER is a randomized controlled, parallel-group, two-arm, assessor-blinded trial with an associated registry (clinicaltrials.gov NCT03494530). Patients with previously known or newly diagnosed AF-related ischemic stroke will be randomized 2:1 to early (≤5 days) or delayed (6-14 days) edoxaban initiation (Figure 4.1). Ischemic stroke will be defined as evidence of acute focal cerebral infarction confirmed on CT/MRI and/or focal hypoperfusion/vessel

occlusion on multimodal CT, or by sudden focal and objective neurological deficits (i.e. NIHSS ≥ 1) of presumed ischemic origin persisting > 24 hours. Informed consent will be obtained from the patient or substitute decision maker in all cases prior to enrolment. The research protocol has been approved by our local Human Research Ethics Board.

4.3.2 Patient Population

One hundred fifty patients from a Comprehensive Canadian Stroke Center will be enrolled. Eligible patients will be randomized within five days of symptom onset after baseline CT. Inclusion and exclusion criteria are shown in Table 4.1.

Patients with spontaneous parenchymal hemorrhage (PH) (European Cooperative Acute Stroke Study (ECASS) grade PH1 or PH2 on the baseline CT will not be eligible for randomization.[18] These patients will be included in the registry portion of LASER and follow-up will be identical to that in the trial. The timing of edoxaban initiation in these patients will be at the discretion of the treating physician.

4.3.3 Randomization

Eligible patients will be randomized 2:1 following open label simple randomization procedure to early (≤5 days) or delayed (6-14 days) edoxaban initiation via a centralized web-based randomization process, Research Electronic Data Capture (REDCap, Vanderbilt university).[19, 20] After randomization to early or delayed arms, the decision to time the edoxaban initiation within the specific arm will be at the treating physician's discretion.

The rationale for the specific timing of treatment, within the randomization window, will also be recorded by surveying the treating physician in each case.

4.3.4 Treatment

Randomized patients will be treated with edoxaban 60 mg once daily. The edoxaban dose will be reduced to 30 mg once daily if any of the following characteristics are present at the time of randomization or during the study: estimated creatinine clearance (CrCl) of 30 to 50 ml per minute using Cockcroft-Gault Equation or body weight ≤ 60 kg. Prior to edoxaban initiation, all patients will be treated as per the clinical standard of care using antiplatelet(s) and anticoagulation for deep venous thrombosis (DVT) prophylaxis. Any antithrombotic therapy prior to randomization will be recorded.

4.3.5 Clinical assessment

All randomized patients will be followed for 90 days after edoxaban initiation. A National Institute of Health Stroke Scale (NIHSS) score will be assessed at baseline, 7 and 90 days after edoxaban initiation. Functional outcome will be assessed with a modified Rankin Scale (mRS) score at baseline, 7 and 90 days after edoxaban initiation. Montreal Cognitive Assessment (MoCA) will be performed at baseline, and day 90 after edoxaban initiation. Functional outcome at 90 days will be dichotomized as favourable (mRS score 0-2) and unfavourable (mRS score 3-6). Quality of life will be assessed with the EuroQol-5 Dimension (EQ-5D) and Visual Analog Scale (VAS) at day 90.

4.3.6 Standardized image acquisition and central analysis

In addition to diagnostic imaging, all patients will have a baseline CT prior to randomization and follow up CT 7±2 days after edoxaban initiation. Therefore, all patients will have a minimum of two scans (diagnostic and pre-randomization). In the event of clinical deterioration, CT scans will be repeated. In patients treated with thrombolysis and/or

endovascular thrombectomy, a 24-hour post-treatment CT will be used as the baseline study prior to randomization.

4.3.7 Imaging Protocol

The original LASER protocol included MRI acquisition in all patients. Following diagnostic CT, all patients were to undergo MRI including diffusion-weighted imaging (DWI to assess the acute infarct volume), Fluid Attenuated Inverse Recovery (FLAIR to assess chronic infarct and white matter ischemic change volumes) and susceptibility weighted imaging (SWI to assess for acute HT and chronic cerebral microbleeds) prior to randomization.

Shortly after trial initiation, however, COVID-19 restrictions limited access to research MRI protocols. The protocol was therefore amended and both baseline and day 7 imaging will be performed using non-contrast, axial CT.

All CT scans will be assessed by two independent raters, blinded to treatment group, for the presence, number and total volume of regions with infarction. Infarct volumes will be measured using planimetric techniques (Analyze 11.0, Biomedical Imaging Resource, Mayo Clinic).[21] Any HT, as well as other intracranial hemorrhage, seen at baseline and day 7 will be graded using the Heidelberg Bleeding Classification (HBC).[22] Incident HT seen on follow-up CT scan is defined as new or progressive HT. Progressive HT will be defined as any increase in the severity grade between the baseline and follow-up scan. Two raters will rate the HT using the Heidelberg criteria.

4.3.8 RNA Analysis

A blood sample will be drawn into a PAXgene tube for RNA analysis at the time of the baseline CT. RNA will be isolated and measured by RNA sequencing and reverse transcription

polymerase chain reaction (RT-PCR). Genes different between patients who develop HT compared to those without HT will be identified by analysis of variance adjusted for covariates as previously described [13, 14]. A prediction model will be developed using the identified genes. The ability of the developed gene model to predict HT will be compared to other factors associated with HT including age, stroke severity, infarct volume.

4.4 Study outcomes

The primary study endpoint is the rate of incident (new or progressive) radiological HT. The secondary endpoint is the rate of symptomatic HT, defined as intracerebral hemorrhage within and beyond infarcted brain tissue with PH >1/3 the volume of the ischemic infarct (Class 2 in HBC) associated with clinical deterioration (worsening of NIHSS score by ≥ 4 points) within 30 days of treatment initiation.[18, 22] Other secondary endpoints are recurrent ischemic stroke within 90 days of randomization, recurrent sub-clinical infarcts on follow up CT at 7±2 days post edoxaban initiation, systemic hemorrhagic complication rate within 90 days of randomization, NIHSS at day 7 and 90, mRS score at day 7 and 90, favourable mRS at day 90, and mortality within 90 days, quality of life at 90 days assessed by (EQ-5D) and Visual Analog Scale (VAS), and ability of leukocyte RNA to predict HT.

4.5 Sample size estimates

Based on previous open label studies of DOAC use in acute stroke, the rate of symptomatic HT is likely to be nil, which is why we have made this a secondary endpoint. We have previously demonstrated the rate of asymptomatic HT in serial imaging studies to be as lower as 3% in CT-based studies [23, 24] and up to 13% in MRI based studies.[25] There are no data related to the difference in asymptomatic HT rates in patients randomised to early versus late

DOAC initiation. Our aim is to determine the event rates in these two groups with reasonable precision.

A sample size of 150 patients, randomized 2:1 (≤5 days:6-14 days) will allow detection of an asymptomatic hemorrhage rate of 3% (95% CI 0.6-8.5%) in the early treatment arm (n=100) and 4% (95% CI 0.5-13.7%) in the late treatment arm (n=50). Thus, we will have confidence interval width of a maximum of 13.7%, allowing enough precision to demonstrate the safety of early treatment. The rationale for adopting a 2:1 randomization approach is to increase the precision around the estimate of safety in the early treatment arm, without substantively losing power.

4.6 Statistical analysis

The primary analysis will be intention-to-treat, irrespective of edoxaban compliance. The primary endpoint of incident HT rates (and 95% CIs) in the early vs delayed groups will be calculated. Crude rates will be adjusted only if there are baseline imbalances in stroke severity (NIHSS), infarct volume or HT at baseline. Unadjusted differences in proportions between the two groups will be tested using a Fisher's exact test. Univariate linear and logistic regression analyses will be used to assess potential relationships between CT and clinical factors including age, clinical severity (NIHSS score), history of diabetes/glucose level, hypertension/blood pressure, bridging anti-thrombotic therapy, thrombolysis or endovascular thrombectomy and HT risk.

Confirmed genes will be used to create a linear discriminant analysis prediction model to stratify risk of HT. The model will be assessed by 10-fold leave one out cross-validation. Using logistic regression, the gene prediction of HT will be compared to clinical factors used to stratify

risk of HT in stroke including age, stroke severity, blood pressure, glucose, thrombolysis as we have previously described [13, 14].

4.7 Discussion

This randomized controlled trial (RCT) is the first step in advancing the knowledge of the safety of early versus delayed anticoagulation after ischemic stroke in patients with AF. In our pilot safety studies with rivaroxaban, dabigatran and apixaban we observed low rates of symptomatic HT when these DOACs were initiated within 14 days of symptom onset.[23-25] While encouraging with respect to the safety of early DOAC initiation, these studies are far from definitive. Several trial protocols have been published and/or registered for the safety and efficacy of early versus delayed anticoagulation after ischemic stroke in patients with AF.[26-28] Patients in these trials are randomized to DOAC initiation as early as 24 hours and up to 5 days after onset, or delayed initiation 6-14 days. The primary endpoint in these trials is the composite of recurrent ischemic stroke and symptomatic HT. Patient allocation to the treatment arms in most of these trials is determined by stroke severity and/or size. Ongoing trials include TIMING (Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation: a Prospective Multicenter Registry-based Non-inferiority Randomized Controlled Clinical Trial, NCT02961348)[27], ELAN (Early Versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients With Atrial fibrillation, NCT03148457), START (Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation, NCT03031928) trials, OPTIMAS (OPtimal TIming of Anticoagulation After Acute Ischemic Stroke, NCT03759938) and AREST (Apixaban for Early Prevention of Recurrent Embolic Stroke and Hemorrhagic Transformation, NTC02283294).

Edoxaban is the newest drug in the DOAC class. Although equipoise exists with respect to timing of initiation of all the DOACs, a design utilizing all four drugs introduces additional confounding factors. A novel aspect of this RCT is to identify RNA transcript as well as clinical and imaging predictors of HT after AF related stroke. If a biomarker of HT risk can be identified, it may be useful in guiding anticoagulation timing after acute cardioembolic stroke. A standardized documentation of HT rates on follow-up CT as objective assessment criteria will be employed in this study. This method is missing from most studies of early anticoagulation.

Number of limitations of our design deserve mention. First, the amended protocol limits follow-up imaging to CT, making it highly likely that we will under-estimate the true rate of recurrent sub-clinical infarcts. Second, this trial is not powered to detect differences in clinical outcomes, including symptomatic HT and recurrent infarction. Third, dichotomization at 5 days leaves a considerable discretionary range within which clinicians can initiate edoxaban. In cases where the period of equipoise is narrower, i.e. day 0 vs day 2-3, this may be relevant. Stratified randomization can address this to an extent, but as we are assessing radiological HT event rates, a more pragmatic approach was chosen for this trial.

4.8 Trial status

Enrolment of patients started in November 2018 and study completion is estimated in December 2021. Protocol version 4.0 was approved on 14 January 2021.

4.9 Conclusions

Objective evaluation criteria such as systematically acquired imaging assessment of HT is required to understand the true effect of DOAC timing. These data are critical to developing future efficacy trials. Accurate and objective predictors of HT, including novel biomarkers, will also help refine future trial inclusion/exclusion criteria.

4.10 Ethics statements

This protocol was approved by University of Alberta Human Research Ethics Committee. The patients/participants or substitute decision maker will provide written informed consent to participate in this study.

4.11 Study organization and funding

This study is funded by a grant from the Alberta Innovates Technologies Futures and the University Hospital Foundation in partnership with Servier Canada (the Servier Alberta Innovation Health Fund (SAIHF)). LASER is also supported by infrastructure provided by the Quality Improvement & Clinical Research (QUICR) CRIO grant. Dr. Butcher holds a New South Wales Health Senior Cardiovascular Scientist award. Dr. Jickling has salary and grant support from HSFC and CIHR.

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Table 4.1. Study inclusion and exclusion criteria

Inclusion criteria
1. Male or female patients
2. ≥ 18 years of age
3. Ischemic stroke, diagnose and enrol ≤5 days from symptom onset*
4. AF (paroxysmal or persistent), confirmed with ECG/Holter monitor, or by history (clinical documentation of previous AF must be provided)
5. Informed consent
Exclusion criteria
1. Acute or chronic renal failure, defined as eCrCl <30 ml/min (Cockcroft Gault formula)
2. Known hypersensitivity to edoxaban
3. Any significant ongoing systemic bleeding risk, or recent major surgery
4. Recent past history or clinical presentation of ICH, SAH, AVM, aneurysm, or cerebral neoplasm
5. Hereditary or acquired hemorrhagic diathesis
6. Stroke mimics
7. HT with a grade of PH1 or PH2 on baseline or screening CT†
8. Any condition that, in the judgment of the investigator(s), could impose hazards to the patient if study therapy is initiated

* Ischemic stroke is defined as evidence of acute focal cerebral infarction confirmed on CT/MRI and/or focal hypoperfusion/vessel occlusion on multimodal imaging, or by sudden focal and objective neurological deficits (i.e. NIHSS ≥ 1) of presumed ischemic origin persisting > 24 hours.

† eligible for registry

AF, atrial fibrillation; ECG, electrocardiography; eCrCl, estimated creatinine clearance; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; AVM, arteriovenous malformation; HT, hemorrhagic transformation; PH, parenchymal hemorrhage; CT, computed tomography

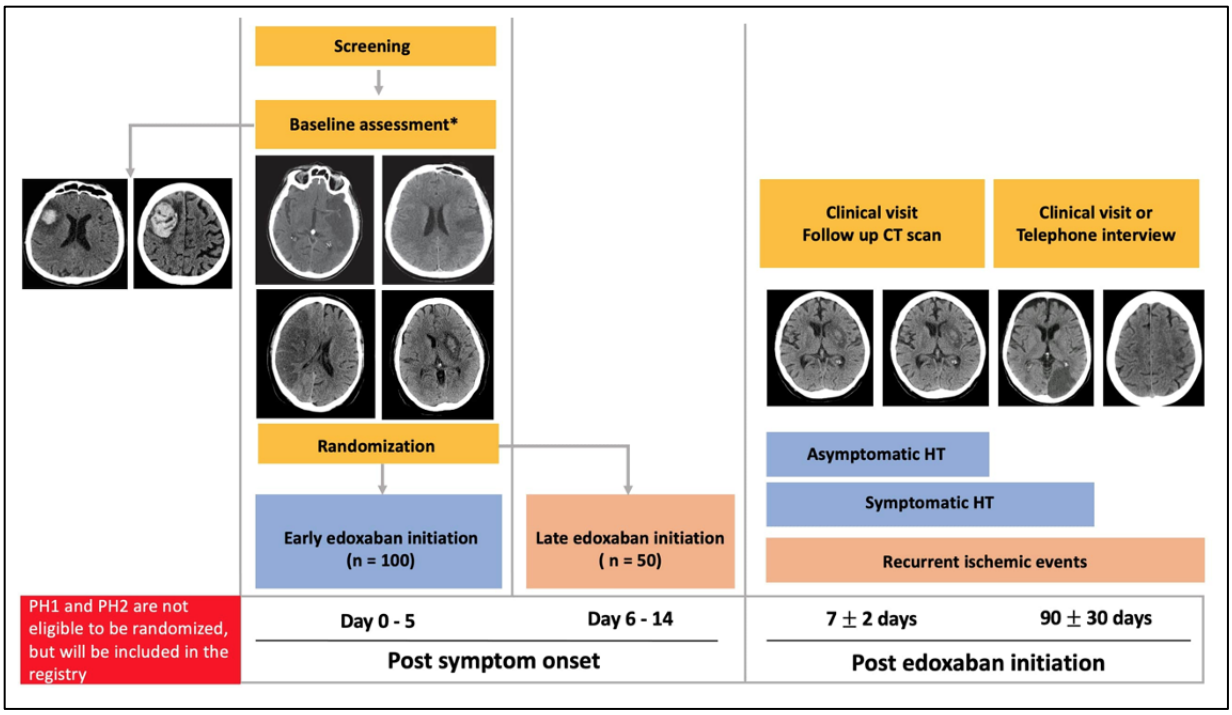

Figure 4.1. Randomized trial and registry schema.

PH, parenchymal hematoma; CT, computed tomography; HT, hemorrhagic transformation

* All stroke severities, infarction sizes and HT (Hemorrhagic infarction type 1 and Hemorrhagic infarction type 2) are eligible for randomization

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Chapter 5

Timing of Anticoagulation After Ischemic Stroke in Patients with Atrial Fibrillation: An international survey

5.1 Abstract

Introduction: The timing of direct oral anticoagulant (DOAC) after atrial fibrillation (AF)-related stroke is unknown. Most guidelines are inconsistent and based on expert opinion. We conducted a survey to evaluate the global practice patterns of this common clinical scenario.

Methods: We used an electronic survey with practice-related demographic and clinical questions of 10 cases with different stroke severities and sizes: transient ischemic attack, small, medium, large, and strokes with hemorrhagic infarction (HI) and parenchymal hematoma (PH).

Results: A total of 242 clinicians from 21 countries completed at least one clinical scenario. The majority of the respondents were from Australia (36.4%) or Canada (22.7%). Stroke-specific sub-specialty training was self-reported in 82.2% of the respondents. Median (IQR) time spent dedicated to stroke patient care/research was 70 (60) % of total working hours. Only 14% of responding clinicians reported current participation in a randomized trial of DOAC initiation timing after AF-related stroke. Stroke size, severity, and the grade of hemorrhage if present seem to be determinants of the decisions. Lack of consensus was observed in moderate stroke, multi-territory infarcts, large stroke, and in the presence of HT. The majority of respondents would be willing to randomize patients with different stroke sizes and severities with/without HT in a clinical trial of early versus delayed initiation of DOAC after AF-related stroke.

Conclusions: Decisions related to the timing of DOAC initiation after AF-related stroke vary globally. The variability in clinical practice will continue until randomized controlled trials are completed.

5.2 Introduction

Patients with atrial fibrillation (AF) and ischemic stroke are at high risk for recurrence and require long-term anticoagulation. The optimal timing of direct oral anticoagulant (DOAC) initiation after ischemic stroke is an area of clinical uncertainty. Early anticoagulation may reduce the risk of recurrent ischemic stroke, but may also increase the risk of hemorrhagic transformation (HT). Older anticoagulants were associated with a comparable increase in the risk of HT.[1-3] However, in the last decade, four DOACs have been demonstrated to have a rapid onset of action and a lower risk of intracranial hemorrhagic complications compared to older anticoagulants, and they are now the standard of care for stroke prevention in non-valvular AF.[4-7] In a meta-analysis, DOACs were associated with a 52% significant reduction of intracranial hemorrhage compared to warfarin.[8] More than 70,000 patients were randomized in the pivotal phase III DOAC trials, however, patients were not eligible for randomization as early as 7 days and up to 30 days after ischemic stroke. Current guidelines are inconsistent and not based on high-quality evidence, and recommendations are based on expert opinion only.[9-11] In routine clinical practice, the decision to time DOAC initiation after AF-related stroke is commonly encountered by physicians. The lack of data from clinical trials in this population has created considerable uncertainties and wide practice variability. By conducting this survey, we aimed to evaluate the global variation and establish current practices on the timing of DOAC initiation after acute ischemic stroke in patients with AF. Establishing the practice pattern would highlight the need for higher quality trials and evidence-based guidelines and help design of clinical trials in this area.

5.3 Methods

A survey was created online to improve response and facilitate dissemination using a centralized web-based, Research Electronic Data Capture (REDCap, Vanderbilt university).[12, 13] Responses were obtained between September 14, 2020, and November 14, 2020. E-mail addresses from each respondent were requested to avoid duplicated responses. The survey offered no incentives or honorariums to participants. The survey was piloted, reviewed, and then circulated. The survey consisted of 10 clinical vignettes with baseline with/without follow-up scans for patients with different stroke severities and sizes: transient ischemic attack (TIA), small, medium, large, and strokes with hemorrhagic infarction (HI) and parenchymal hematoma (PH). The first five questions demonstrated demographic information of responders. Additional two questions explored whether clinicians interpret their own scans to make the decision and whether they are actively randomizing patients in trials in this area. In each clinical scenario, the patient had AF, no contraindications for anticoagulation, and scenarios were consistent except for thrombolysis, endovascular thrombectomy (EVT), size and severity of stroke, and presence of baseline HT. In each scenario, responders were asked to give their opinion on the optimal time to start DOAC, bridging therapy prior DOAC initiation, whether re-imaging pre and post DOAC is required, whether equipoise exists, and the earliest and latest times they would be willing to randomize patients to start DOAC in a potential clinical trial. Descriptive statistics were produced to describe responses.

5.4 Results

5.4.1 Demographics

A total of 242 clinicians from 21 countries completed at least one clinical scenario. The majority of the respondents were from Australia (36.4%) or Canada (22.7%). Neurology was the most common speciality among respondents at 74.3%. Stroke specific sub-specialty training was self-reported in 82.2% of the respondents. Median (interquartile range, IQR) time spent dedicated to stroke patient care/research was 70 (60) % of total working hours. Most respondents (84%) were practicing independently. The majority of respondents (88%) reported relying on their own visual assessment of brain images when making decisions related to DOAC timing, rather than a radiology report. Only 14% of responding clinicians reported current participation in a randomized trial of DOAC initiation timing after AF-related stroke. A total of 10 clinical scenarios of patients with different stroke severities and sizes with/without baseline HT were provided as in table 5.1 and 5.2 to determine the current practices.

5.4.2 Timing of DOAC initiation in different stroke severities and sizes with/without baseline HT

Case 1 (pontine stroke). A total of 25% of respondents reported that they would initiate DOAC immediately, and the remaining preferred to delay DOAC initiation with median (IQR) 4 (4) day (Table 5.1; Figure 5.1). The majority (81%) agreed that the equipoise in this scenario exists as shown in table 5.2. The median days for the earliest and the latest acceptable times to randomize patients with pontine stroke to start DOAC in a clinical trial were 2 (2) and 7 (7) days, respectively as demonstrated in table 5.2 and figure 5.2(a) and (b).

Case 2 & 9 (large stroke with HI 1). There was a consensus among the respondents (98-99%) to delay DOAC initiation in those scenarios for 9-10 (7) days (Table 5.1; Figure 5.1). Most

respondents (69-75%) reported that clinical uncertainty is demonstrated in these two scenarios (Table 5.2). The median days for the earliest and the latest acceptable times to randomize patients with large stroke and HI1 to start DOAC in a clinical trial were 6 (4) and 14 (7) days, respectively as demonstrated in table 5.2 and figure 5.2(a) and (b).

Case 3 (mild stroke). The majority of clinicians (88%) would start DOAC immediately, and the remaining reported a delay for 2 (2) days (Table 5.1; Figure 5.1). Almost half of the respondents (53%) have agreed that there is an equipoise related to the decision-making in this case (Table 5.2). The median days for the earliest and the latest acceptable times to randomize patients with mild stroke to start DOAC in a clinical trial were 1 (0) and 5 (4) days, respectively as demonstrated in table 5.2 and figure 5.2(a) and (b).

Case 4 (moderate stroke). Most physicians in this survey (92%) would delay starting DOAC for a median of 5 (4) days (Table 5.1; Figure 5.1) with 91% agreed about the equipoise nature of the clinical decision (Table 5.2). The median days for the earliest and the latest acceptable times to randomize patients with moderate stroke to start DOAC in a clinical trial were 3 (2) and 10 (7) days, respectively as demonstrated in table 5.2 and figure 5.2(a) and (b).

Case 8 (TIA). Almost 90% of the respondents would start DOAC immediately in TIAs and the remaining would wait for 1 (0) day (Table 5.1; Figure 5.1). Most respondents (62%) do not think there is equipoise, and they would be concerned about the safety of delaying DOAC initiation (Table 5.2). Among those who are willing to randomize patients with TIA, the median days for the earliest and the latest acceptable times to randomize patients with TIA to start DOAC in a clinical trial were 1 (0) and 3.5 (4) days, respectively as demonstrated in table 5.2 and figure 5.2(a) and (b).

Case 10 (multi-territory infarcts). The majority of respondents (84%) would delay DOAC initiation for 5 (4) days in patients with multi-territory infarcts (Table 5.1; Figure 5.1). The majority of respondents (90%) agreed that there an equipoise related to the decision to time DOAC initiation in this scenario (Table 5.2). The median days for the earliest and the latest acceptable times to randomize patients with multi-territory infarcts to start DOAC in a clinical trial were 3 (3) and 12 (7) days, respectively as demonstrated in table 5.2 and figure 5.2(a) and (b).

5.4.3 Timing of DOAC initiation in patients with stroke and PH or subarachnoid hemorrhage (SAH)

Case 5 (moderate stroke and PH2). All responders reported that they currently delay DOAC initiation to 14 (7) days in patients with baseline PH2 (Table 5.1; Figure 5.3). Most respondents (70%) reported that clinical uncertainty is demonstrated related to the time of DOAC initiation exists in this case (Table 5.2). However, 28% of responders would be concerned about initiating DOAC early. The median days for the earliest and the latest acceptable times to randomize patients with PH2 to start DOAC in a clinical trial were 7 (9) and 21 (16) days, respectively as demonstrated in table 5.2 and figure 5.4(a) and (b).

Case 6 (moderate stroke with HI1 and SAH). Almost all respondents (98%) described that they currently delay DOAC initiation in patients who developed post EVT moderate stroke with HI1 and SAH to 7 (5) days (Table 5.1; Figure 5.3). Most respondents (77%) agree that there is an equipoise related to the time of DOAC initiation in this case and would be willing to randomize patients to a clinical trial (Table 5.2). The median days for the earliest and the latest acceptable times to randomize such patients to start DOAC in a clinical trial were 5 (4) and 14 (9) days, respectively as demonstrated in table 5.2 and figure 5.4(a) and (b).

Case 7 (moderate stroke with PH1). The majority of clinicians (98.5%) would currently delay DOAC initiation in patients with PH1 to 7 (5) days (Table 5.1; Figure 5.3). The optimal timing of DOAC initiation in such patients is unknown as reported by 77% of respondents (Table 5.2). The median days for the earliest and the latest acceptable times to randomize patients with PH1 to start DOAC in a clinical trial were 5 (4) and 14 (9) days, respectively as demonstrated in table 5.2 and figure 5.4(a) and (b).

5.5 Discussion

This international online survey amongst clinicians revealed that the optimal timing of DOAC initiation after acute ischemic stroke in patients with AF is an area of clinical equipoise, commonly encountered by physicians. The results indicated that a clinical trial to answer this clinical question is needed. The lack of consensus was demonstrated in patients with moderate stroke, multi-territory infarcts, large stroke, and in the presence of HT. There was a relative consensus amongst physician in initiating DOAC early after TIA and mild stroke. Clinicians tend to delay DOAC initiation in patients with larger infarcts, irrespective of the presence or absence of HT. This practice pattern has been documented previously[14-16], and is consistent with expert recommendations.[17] This practice pattern is also relevant to ongoing trials of DOAC initiation after AF-related stroke as patients' allocation to the treatment arms in some of these trials is determined by infarct volume/size [18](ELAN, NCT03148457) and/or includes groups with broad initiation time windows of several days, extending up to 14 days after symptom onset.[19, 20](OPTIMAS, NCT03759938) This form of stratification by stroke size or where the decision to time the treatment at the treating physician's discretion, even in the context of randomization, may play a role in introducing a bias. The current practices have been formed by older low-quality evidence from pre-DOAC era. This has been further influenced by the current guidelines, which provide

limited advice concerning the timing of DOAC initiation and their recommendations are based on expert opinion only.

Physicians were also surveyed about the earliest and latest acceptable times to randomize patients with different stroke severities and sizes to receive DOAC in a clinical trial. There was an observed variability amongst clinicians in answering such questions. This further highlights the need for a clinical trial in this area. Thrombolysis and/or EVT did not influence the decision-making on the timing of DOAC, but rather stroke size, severity, and the grade of hemorrhage if present. This is consistent with a recent prospective observational study, which has shown that acute reperfusion therapies did not influence the risk of recurrent ischemic stroke(s) and HT.[21] Ultimately, the optimal timing of DOAC initiation after AF related-stroke will remain a clinical equipoise until randomized trials assessing the safety and efficacy of early versus delayed DOAC are completed.[18-20, 22] Ongoing trials include LASER (Lixiana Acute Stroke Evaluation Registry, NCT03494530), TIMING (Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation: a Prospective Multicenter Registry-based Non-inferiority Randomized Controlled Clinical Trial, NCT02961348), ELAN (Early Versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients With Atrial fibrillation, NCT03148457), START (Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation, NCT03021928) trials, and OPTIMAS (OPtimal TIming of Anticoagulation After Acute Ischemic Stroke, NCT03759938). Patients in these trials are randomized to a DOAC, initiated as early as 48 hours and up to 5 days after onset, or delayed to 6-14 days. The primary outcome in these trials is the composite of recurrent ischemic stroke and symptomatic HT. While these trials will advance the field, the broad randomization windows and the

stratification by stroke size may leave some clinical equipoise and also facilitate the continuation of current practices based on expert opinion.

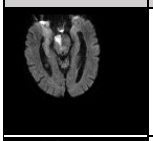
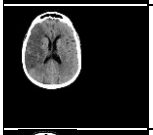
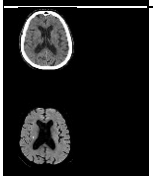
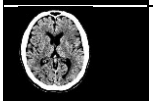
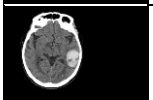
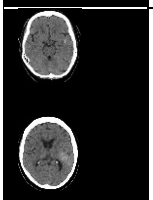
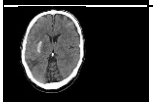
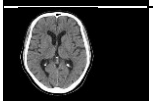
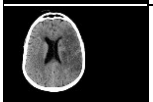
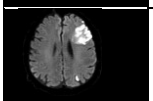
5.6 Conclusions

This international online survey of clinicians showed that decisions related to the timing of DOAC initiation after AF-related stroke lack of consensus globally. The results suggest this area will remain a clinical equipoise until randomized trials assessing the safety and efficacy of early versus delayed DOAC are completed.

5.7 Acknowledgments

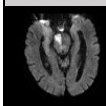
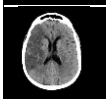
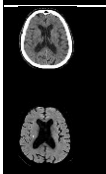
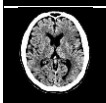
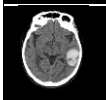
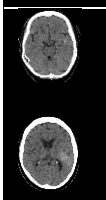
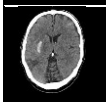
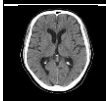
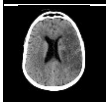
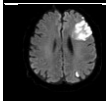
AA thanks King Saud University and the Saudi Arabian Ministry of Education for Residency and Fellowship funding. AA thanks The University of Alberta Hospital Foundation and the Neuroscience and Mental Health Institute for the Neurology Fellowship Award.

Table 5.1. Current practices of DOAC initiation after ischemic stroke in patients with atrial fibrillation

Imaging Results	Imaging Time (h)	NIHSS	n	No Delay to DOAC	Delay prior to DOAC	Re-image prior to DOAC	Median (IQR) Days to Initiate	Bridging Therapy Prior to DOAC Initiation	Re-image Post DOAC Initiation
	20	12	242	61 25.2%	93 38.4%	88 36.4 %	4 (1-14) IQR 4	175 72.3%	30 12.4%
	30	19	235	2 0.9%	37 15.7%	196 83.4%	10 (1-30), IQR 7	206 87.7%	87 37.0%
	5, 23	0	232	205 88.4%	19 8.2%	8 3.4%	2 (1-14) IQR 2	66 28.4%	11 4.7%
	12	10	230	18 7.8%	88 38.2%	124 53.9%	5 (1-14) IQR 4	190 82.6%	59 25.7%
	24	10	225	1 0.4%	13 5.8%	211 93.8%	14 (1-31), IQR 7	105 47.7%	122 54.2%
	48	12	223	4 1.8%	17 7.6%	202 90.6%	7 (1-31) IQR 5	151 67.7%	109 48.9%
	25	10	221	3 1.4%	16 7.2%	202 91.4%	7 (1-28) IQR 5	135 61.1%	105 47.5%
	3	0	219	196 89.5%	7 3.2%	16 7.3%	1 (1-3), IQR 0	35 16.0%	26 11.9%
	30	19	218	4 1.8%	25 11.5%	189 86.7%	9 (1-30), IQR 7	178 81.7%	163 74.8%
	25	10	217	34 15.7%	63 29.0%	120 55.3%	5 (1-21) IQR 4	152 70.0%	68 31.3%

DOAC, direct oral anticoagulants; h, hours; NIHSS, National Institutes of Health Stroke Scale; n, number*;* IQR, interquartile range

Table 5.2. Equipoise and Randomization Tolerances

Imaging Results	Imaging Time (h)	NIHSS	n	Equipoise	No Equipoise: Early initiation unsafe	No Equipoise: Delay unsafe	Median (IQR) Earliest Randomization Day	Median (IQR) Latest Randomization Day
	20	12	242	195 80.6 %	13 5.4%	34 14.1%	2 (1-10), IQR 2	7 (3-30), IQR 7
	30	19	235	162 68.9%	70 29.8%	3 1.3%	6(1-14), IQR 4	14 (3-30), IQR 7
	5, 23	0	232	122 52.6%	1 0.43%	109 47.0%	1 (1-7), IQR 0	5 (3-30), IQR 4
	12	10	230	210 90.9%	11 4.8%	9 3.9%	3 (1-21), IQR 2	10 (3-30), 7
	24	10	225	158 70.2%	63 28.0%	4 1.8%	7 (1-31), IQR 9	21 (3-31), IQR 16
	48	12	223	172 77.1%	46 20.6%	5 2.2%	5 (1-14), IQR 4	14 (3-31), IQR 9
	25	10	221	171 77.4%	47 21.3%	3 1.4%	5 (1-21), IQR 4	14 (3-31), IQR 9
	3	0	219	82 37.4%	2 0.9%	135 62%	1 (1-7), IQR 0	3.5 (3-30), IQR 4
	30	19	218	163 74.8%	51 2.4%	4 1.8%	6 (1-21), IQR 4	14 (3-30), 7
	25	10	217	195 89.9%	11 5.1%	11 5.1%	3 (1-14), IQR 3	12 (3-30), IQR 7

H, hours; NIHSS, National Institutes of Health Stroke Scale; n, number; IQR, interquartile range

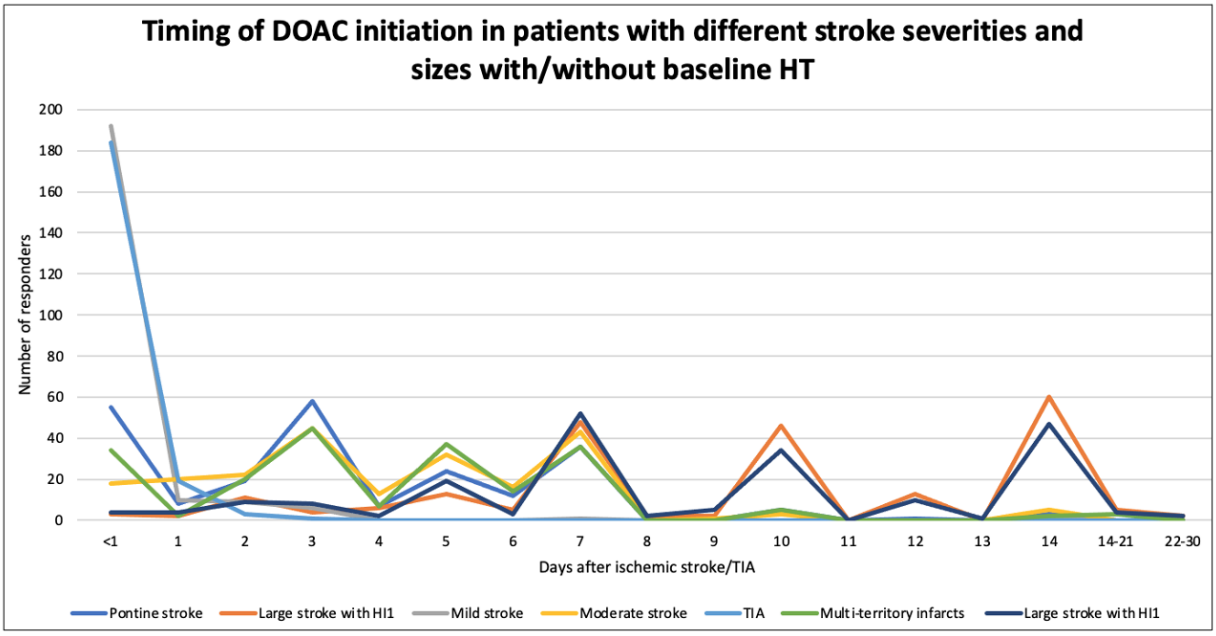


Figure 5.1. Response analysis of current practices related to timing of DOAC initiation in different stroke severities and sizes with/without baseline HT.

DOAC, direct oral anticoagulants; HT, hemorrhagic transformation; HI, hemorrhagic infarction; TIA, transient ischemic attack

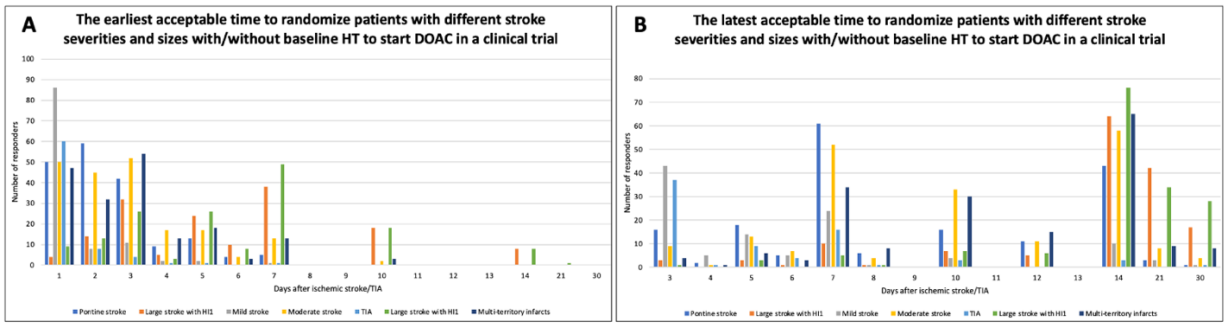


Figure 5.2. The earliest (A) and the latest (B) acceptable times to randomize patients with different stroke severities and sizes with/without baseline HT to start DOAC in a clinical trial. DOAC, direct oral anticoagulants; HT, hemorrhagic transformation; HI, hemorrhagic infarction; TIA, transient ischemic attack

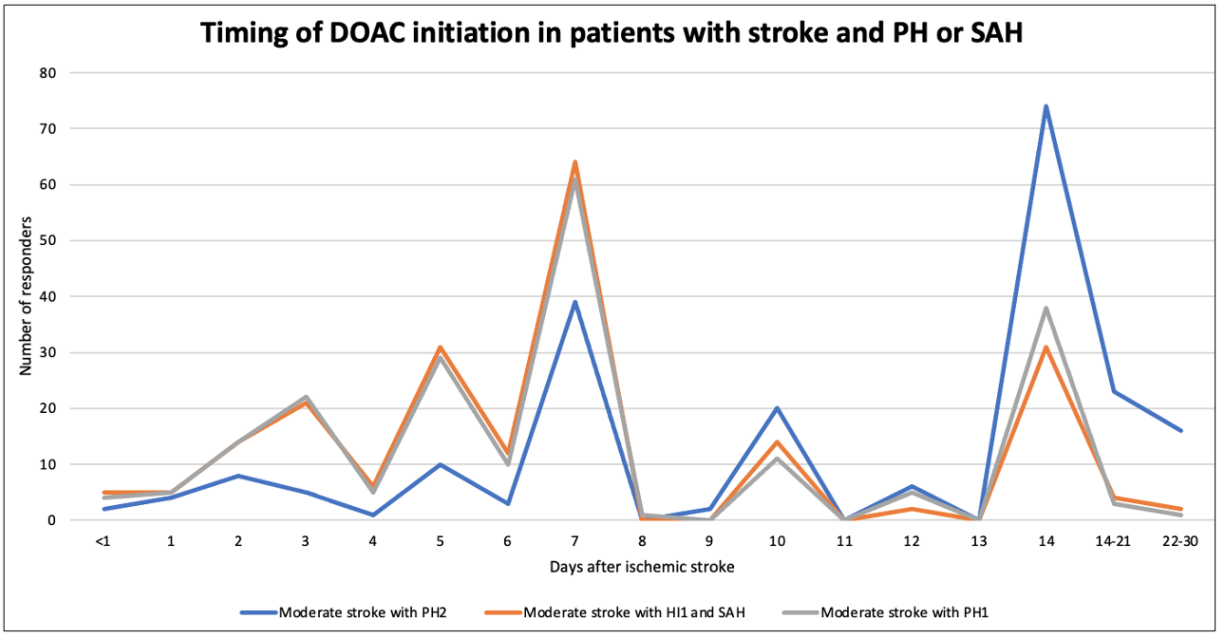


Figure 5.3. Response analysis of current practices related to timing of DOAC initiation in patients with stroke and PH or SAH.

DOAC, direct oral anticoagulants; PH, parenchymal hemorrhage; SAH, subarachnoid hemorrhage

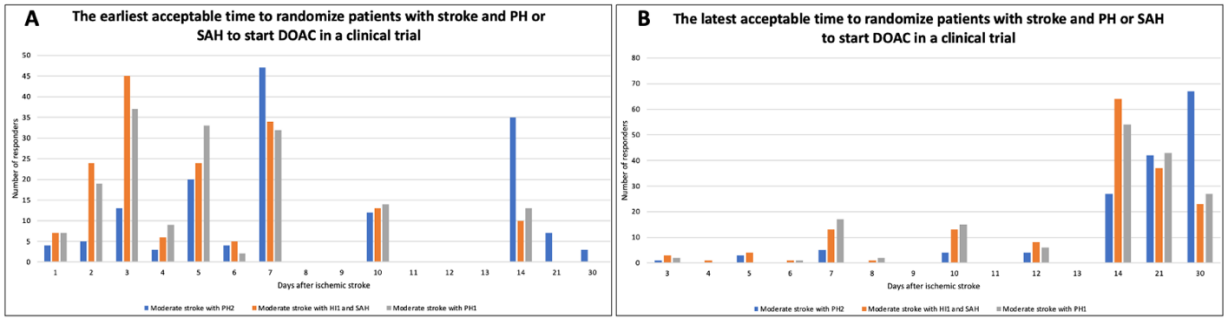


Figure 5.4. The earliest (A) and the latest (B) acceptable times to randomize patients with stroke and PH or SAH to start DOAC in a clinical trial.

DOAC, direct oral anticoagulants; PH, parenchymal hemorrhage; SAH, subarachnoid hemorrhage

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Chapter 6

Risk of Hemorrhagic Transformation with Early Use of Direct Oral Anticoagulants after Acute Ischemic Stroke: A Pooled Analysis of Prospective Studies and Randomized Trials

6.1 Abstract

Introduction: The risk of hemorrhagic transformation (HT) in the early phase of acute ischemic stroke (AIS) remains unknown, leading to potential unnecessary delays in initiation of anticoagulation for secondary stroke prevention. We sought to assess the rate of HT associated with direct oral anticoagulant (DOAC) initiation within and beyond 48 hours after AIS, using a pooled analysis of available published data.

Methods: A pooled analysis of 6 studies (4 prospective observational blinded outcome studies and 2 randomized trials) of DOAC initiation within 14 days of AIS or transient ischemic attack (TIA) was conducted. The primary endpoint was incident radiographic HT on follow-up imaging. Secondary endpoints included symptomatic HT, new parenchymal hemorrhage, recurrent ischemic events, extracranial hemorrhage, mortality within the study period, and follow-up modified Rankin Scale score. The results were reported as odds ratio (OR) and hazard ratio (HR) with 95% confidence interval (CI).

Results: We evaluated 509 patients; median infarct volume was 1.5 (0.1-7.8) ml, and median National Institutes of Health Stroke Scale was 2 (0-3). Incident radiographic HT was seen on follow-up scan in 34 (6.8%) patients. DOAC initiation within 48 hours from index event was not associated with incident HT (adjusted OR 0.67, [0.30 – 1.50] P=0.32). No patients developed

symptomatic HT. Conversely, 31 (6.1%) patients developed recurrent ischemic events, 64% of which occurred within 14 days. Initiating DOAC within 48 hours of onset was associated with a non-significant reduction in the risk of recurrent ischemic events (HR 0.42, [0.17 – 1.008] *P*=0.052). In contrast to HT, recurrent ischemic events were associated with poor functional outcomes (OR=6.8, [2.84 – 16.24], p<0.001).

Conclusions: DOAC initiation within 48 hours after stroke was not associated with increased risk of HT yet did reveal a strong non-significant trend towards decrease in ischemic events. Both recurrent ischemic events and incident HT occurred relatively at similar rates. Unlike HT, however, recurrent ischemic events were associated with poor outcomes.

6.2 Introduction

In the immediate management of patients with acute ischemic stroke (AIS) or transient ischemic attack (TIA), who require direct oral anticoagulant (DOAC), the optimal timing of initiation of this medication remains unknown. Early DOAC use may reduce the risk of recurrent ischemic events but may also provoke hemorrhagic transformation (HT). For some of the older-generation anticoagulants, such as heparin and warfarin, the reduction in recurrent ischemic risk, when initiated acutely after AIS, were comparable to the risk of HT.[1-3] However, the newer-generation anticoagulants, such as the DOAC class, pose a 52% lower risk of intracranial hemorrhagic complications compared to vitamin K antagonists,[4] and are now the preferred agents (standard of care) for stroke prevention in non-valvular atrial fibrillation (AF).[5, 6] In the pivotal phase III DOAC trials in AF subjects, patients were excluded if they were within 7 to 30 days of an AIS (or up to 6 months if the stroke was severe and disabling).[7-10] Current guidelines provide limited advice with respect to the timing of DOAC initiation and recommendations are based on expert opinion.[11-13] The incidence of HT associated with early DOAC initiation is unknown. Standardized documentation of HT rates on follow-up imaging as objective assessment criteria is not included in most studies of early anticoagulation initiation post-AIS. However, systematic collection of HT rates can help establish Objective Performance Criteria (OPC) for anticoagulation timing studies in AIS.[14-16]

HT represents a spectrum of ischemia-related brain hemorrhage. Although asymptomatic HT is of questionable clinical significance, it likely shares a common pathophysiological pathway with larger symptomatic HT,[17, 18] making it a useful objective evaluation criterion when assessing the effect of earlier versus later DOAC initiation. These criteria may be important surrogate markers even in larger trials, where the absolute number of symptomatic HT

cases is likely to remain low. Recently, we completed 4 prospective, single treatment arm, blinded outcome studies and 2 randomized controlled trials (RCTs) of DOAC initiation within 14 days of an AIS or TIA. Serial imaging with Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI) were used to determine the rate of incident radiological HT after DOAC initiation. Incident radiological HT rates were assessed as the OPC, which is most relevant to the safety of early DOAC initiation. In all studies, the rates of recurrent ischemic stroke were assessed as secondary endpoints. We conducted a pooled analysis of the 6 studies in order to provide an estimate of the incidence of incident radiological HT associated with DOAC initiation before versus after 48 hours post-stroke as well as the rate of recurrent ischemic stroke.

6.3 Methods

6.3.1 Study design

A pooled analysis of patients from 4 prospective, single treatment arm, blinded outcome studies and 2 multicentre RCTs was conducted. All trials assessed DOAC initiation within 14 days of AIS/TIA: 4 studies in patients with AF, and 2 studies in patients without AF. Main inclusion and exclusion criteria for each study are summarized in Table 1. Ethical approval was obtained at participating sites for all included trials, and informed consent was obtained from the patient or substitute/proxy decision-maker prior to enrolment.

6.3.2 Data extraction and clinical assessments

We extracted data on age, sex, type and dose of DOAC (all were appropriately dosed as per guidelines[5, 6]), time of the index stroke onset, baseline National Institutes of Health Stroke Scale (NIHSS), pre-morbid Modified Rankin Scale (mRS), time from index event onset to

DOAC initiation, systemic hemorrhage, symptomatic HT, recurrent ischemic events, mortality during the study period, and last follow-up NIHSS and mRS.

6.3.3 Imaging Procedures and Analysis

All patients had a non-contrast CT and/or MRI at baseline (within 24 hours from study recruitment) and at 7±2 days after DOAC initiation. In the event of neurologic deterioration, brain imaging was repeated.

Anonymized DICOM CT/MRI data were analyzed centrally by two raters (AA and KB). Baseline and recurrent infarct volumes as continues variables were measured using planimetric techniques (Analyze 11.0, Biomedical Imaging Resource, Mayo Clinic).[19] All HT was graded centrally at baseline and day 7 using the European Cooperative Acute Stroke Study (ECASS) criteria: Hemorrhagic Infarction Type 1 (HI1; small petechiae along the margins of the infarct), Hemorrhagic Infarction Type 2 (HI2; confluent petechiae within the infarcted area but no space-occupying effect), Parenchymal Hemorrhage Type 1 (PH1; hematoma in 30% or less of the infarcted area with some slight space-occupying effect) or Parenchymal Hemorrhage Type 2 (PH2; hematoma in more than 30% of the infarcted area with substantial space-occupying effect).[20] Incident HT seen on follow-up CT scan and/or MRI was defined as new HT or progression to more severe grade HT.

6.3.4 Outcomes

The primary endpoint of the pooled analysis was incident radiological HT on follow-up imaging. Secondary endpoints included symptomatic HT, new parenchymal hemorrhage (PH1 or

asymptomatic PH2), recurrent ischemic events, extracranial hemorrhage, mortality within the study period, and final mRS score.

6.3.5 Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences version 28.0.0 (IBM SPSS Statistics Inc, 2015, Armonk, NY, USA). Unless stated otherwise, quantitative (numerical) and qualitative (categorical) data in baseline patient characteristics were summarized as median (interquartile range, IQR) and proportions, respectively. Multivariable linear regression models were used to examine the relationship between baseline variables (age, NIHSS, baseline infarct volume, baseline HT) and the number of days between symptom onset and DOAC initiation, after log transformation of non-normally distributed data. Multivariable logistic regression models were used to assess the relationship between the number of days between symptom onset and DOAC initiation as a continuous measure and the risk of incident HT and recurrent ischemic events. The risk of incident HT and recurrent ischemic events was also compared in two groups, based on the median (IQR) time from index event to DOAC initiation. The results were reported as OR with 95% confidence interval (CI). A time-to-event analysis was used for the recurrent events in patients receiving DOAC $\leq$ 48 hours vs. $>$ 48 hours with the use of Kaplan–Meier survival curves. The difference between two groups was estimated as a hazard ratio with a 95% CI, which was derived with the use of a Cox proportional-hazards model after adjusting for age, stroke severity, infarct volume. Functional outcome at 90 days was dichotomized as independent (mRS score 0-2) and dependent group (mRS score 3-6). We analyzed the dichotomous functional outcomes using logistic regression and we reported the results as OR and adjusted OR with 95% CI. All tests were two-tailed, and p-value < 0.05 was considered statistically significant.

6.4 Results

6.4.1 Baseline Characteristics

Between March 2012 and September 2019, a total of 509 patients (58% men) were enrolled into 6 studies (Table 1) (CPASS[21] = 101, EASSE[22] = 100, RASS[23] = 60, DATAS[24] = 53, DATAS II[25] [dabigatran arm] = 154, and AREST[26] [apixaban arm] = 41). The 6 studies assessed initiation of 3 different DOACs within 14 days of AIS/TIA in patients with and without AF: apixaban, dabigatran, and rivaroxaban. At the time of DOAC initiation, median (IQR) NIHSS was 2 (0 – 3) and infarct volume was 1.5 (0.1 -7.8) ml. Patients characteristics for each trial are summarized in Table 2.

6.4.2 Patient Follow-up

Of the 509 enrolled patients, imaging outcome data were available in 470. The CONSORT diagram illustrates the details of enrollment, allocation, follow-up, and outcomes (Figure 1). Fifteen patients died during the study follow-up period, but only one within 7 days of enrollment. Five deaths, including the one within 7 days of enrollment, were secondary to recurrent ischemic stroke and/or concomitant systemic emboli. The other deaths were secondary to other causes, unrelated to HT or systemic bleeding.

6.4.3 DOAC Treatment

The median (IQR) time from onset to first DOAC dose was 2 (1 – 4) days. The majority of patients (75%) received the standard (full) dose of DOAC, consistent with prescribing guidelines.[5, 6] Larger baseline infarct volume (β=0.365, [0.126, 0.270], $p<0.001$), older age

(β=0.201, [0.002, 0.009], p<0.001), and higher NIHSS score (β=0.185, [0.063, 0.282], p=0.002) were independently associated with a greater number of days between symptom onset and DOAC initiation.

6.4.4 Baseline Hemorrhagic Transformation (HT)

Baseline HT, prior to initiation of DOAC, was observed in 50 patients (10% [7% – 12%]). The HT was graded as HI1 in 34 patients, HI2 in 15 and PH1 in a single patient. Median (IQR) infarct volume in patients with baseline HT (28 (12 – 50) ml) was larger compared to those without HT (1 (0 – 5) ml; p<0.0001). Infarct volume (adjusted OR= 1.08, [1.06–1.1]) was significantly associated with baseline HT. Median time to DOAC initiation in patients with baseline HT was 5 (2 – 8) days after onset, which was longer than in those without baseline HT 1 (1 – 3) days, p<0.001. Other types of intracranial hemorrhage (subarachnoid, subdural, epidural) were not observed on baseline images prior to initiation of DOAC.

6.4.5 Outcomes: Incident Hemorrhagic Transformation

Of the 509 enrolled patients, imaging outcome data were available in 470. The primary outcome of incident radiographic HT on the day 7 scan was observed in 34 patients (6.8% [5% – 9%]). Incident (de novo) HT was seen in 27 (79%) patients on the day 7 scan (23 HI1 and 4 HI2). In addition, 7 (20%) patients exhibited progression of baseline HI1 to HI2 on the day 7 scan. No patients developed a symptomatic hemorrhage, new parenchymal hematoma (PH1 or PH2) or other types of intracranial hemorrhage after DOAC initiation.

Infarct volume was the only variable associated with incident HT (OR 1.018, [1.006 – 1.030]). After adjusting for age, NIHSS, and infarct volume, the number of days between symptom onset and DOAC initiation as a continuous measure was not associated with incident HT (adjusted OR 1.11, [0.99 – 1.24]). The risk of incident HT was further calculated to assess the difference between patients who were initiated on a DOAC $\leq$ 48 hours vs. $>$ 48 hours. DOAC initiation within 48 hours from index event onset was not associated with incident HT (adjusted OR 0.63, [0.29 – 1.35]; Table 3).

6.4.6 DOAC comparison

After adjusting for infarct volume and stroke severity, the rates of asymptomatic HT were similar for patients prescribed rivaroxaban, apixaban and dabigatran (OR 1.3, [0.80 – 2.1]).

6.4.7 Recurrent Ischemic Events

Recurrent ischemic events occurred in 31 patients (6.1% [4% – 8%]). Of these 31 patients, 27 (87%) experienced recurrent ischemic strokes, 2 (6.5%) isolated systemic emboli causing limb ischemia, and 2 (6.5%) TIAs.

The majority of recurrent ischemic events (n=20, 64%) occurred within 14 days of initial symptom onset. The median time to recurrent stroke was 18 (7.25 – 35.5) days in those whose DOAC was initiated within 48 hours from onset and 10 (5 – 26) days in those whose DOAC was started after 48 hours (p=0.18). After adjusting for age, NIHSS, and infarct volume, the number of days between symptom onset and DOAC initiation was not associated with recurrent ischemic events (adjusted OR 1.04, [0.91 – 1.18]). Initiating DOAC within 48 hours of onset was not

associated with a reduction of recurrent ischemic events (OR 0.42, [0.17 – 1.04]). The estimated number need to treat with initiating DOAC within 48 hours to prevent recurrent stroke was 18-19 and 41 for mortality. There was a non-statistical significant reduction of recurrent ischemic events between patients who were initiated on a DOAC $\leq$ 48 hours vs. $>$ 48 hours as demonstrated in Cox Proportional Hazards Regression Analysis (Figure 2). On a secondary analysis limited to patients with AF, initiating DOAC within 48 hours did not significantly decrease ischemic events (adjusted hazard ratio, 0.49 (95%CI, 0.16 – 1.48), p=0.20)

6.4.8 Clinical Outcomes

Incident HT was not associated with functional outcome (OR=0.41, [0.12 – 1.40], adjusted OR=0.28, [0.07 – 1.20]), or mortality (OR=2.16, [0.47 – 9.98], adjusted OR=1.94 [0.37 – 10.06]; Figure 3). Conversely, recurrent ischemic events were associated with a higher probability of poor functional outcomes (OR=7.32, [3.43 – 15.64], adjusted OR=6.80 [2.84 – 16.24]), as well as elevated mortality (OR=8.85, [2.82 – 27.77], adjusted OR=5.86 [1.71 – 29.10]).

6.5 Discussion

In this pooled analysis of patients started on a DOAC after mild to moderate AIS or TIA, incident HT was seen in 6.8% of patients, none of which were symptomatic. Infarct volume was the only variable associated with both baseline and incident HT. Even in cases where HT was present at baseline (10%), DOAC initiation within 48 hours was not associated with symptomatic HT. Initiation of a DOAC within 48 hours of ischemic stroke onset was not associated with an increased risk of incident radiographic HT when adjusted for age, NIHSS, and infarct volume. These results support the safety of earlier DOAC initiation in patients with TIA, mild and

moderate stroke. The underrepresentation of larger infarcts in this analysis may make our results less generalizable to patients with hemispheric or cortical strokes.

Earlier recurrent ischemic events occurred in 6.1% of patients (4.9% of whom had AF), all of whom were symptomatic. Of all the recurrent ischemic events, 64% occurred in the first 14 days, suggesting the risk of ischemic events is highest earlier after the index event. In contrast to HT, which was clinically silent, recurrent ischemic events were symptomatic and associated with poor functional outcomes. Infarct volume was the only predictor of both baseline HT prior to anticoagulation and incident HT after anticoagulation. Clinicians delayed DOAC initiation in patients with larger infarcts, irrespective of the presence or absence of HT. This practice pattern has been documented previously[27], and is consistent with expert recommendations.[28] This inherent bias is also relevant to some of the ongoing trials of DOAC timing after AF-related stroke, where randomization is stratified by infarct volume or size.[29][ELAN, NCT03148457] Our analysis identified that clinicians also delayed DOAC initiation in older patients and those with higher NIHSS scores. Our data suggests that perhaps that delay for these three subgroups is unnecessary, but further research would be required to confirm this.

Symptomatic HT after anticoagulation is an infrequent event but is also clearly associated with increased clinical severity and larger infarct volumes.[30, 31] The low event rate makes it difficult to predict and also complicates studies aimed at risk stratification of patients with AF-related stroke. These data might be useful to help design future trials of safety and efficacy of even earlier DOAC use post-AIS. Documentation of asymptomatic HT requires systematic pre- and post-treatment imaging, but the timing of the latter is highly variable in clinical practice and

uncommonly performed in studies to-date. This likely reflects the additional burden and cost of additional imaging without incremental benefit (in the absence of clinical neurological deterioration). Only one RCT [32], and 3 small prospective observational studies have included systematic serial imaging in AF-related stroke patients.[33-35] The Triple AXEL (Acute Stroke with Xarelto to Reduce Intracranial Hemorrhage, Recurrent Embolic Stroke, and Hospital Stay) study, utilised MRI to assess HT after rivaroxaban or warfarin initiation within 5 days of AF-related stroke.[32] Follow-up MRI demonstrated asymptomatic HT in a higher proportion of patients than other studies (49.5% and 54.5% of patients receiving rivaroxaban and warfarin respectively), reflecting the higher sensitivity of MRI for petechial bleeding.

In the Apixaban for Early Prevention of Recurrent Embolic Stroke and Hemorrhagic Transformation (AREST) trial, which was included in our analysis, patients were randomized to apixaban or warfarin, and the only case of symptomatic HT occurred in the warfarin group[26]. Incident radiological HT was observed in 12.2% and 10.6% of the apixaban and warfarin groups respectively. In AREST, the timing of initiation of apixaban was stratified based on stroke size: day 0–3 for TIA, day 3–5 for small-sized AIS (<1.5 cm), and day 7–9 for medium-sized AIS (1.5 cm or greater but less than a full territory of brain cortex), versus initiation of warfarin at 1 week post-TIA, or 2 weeks post-AIS.[26] The study was terminated prematurely in 2019, after updated guidelines favored DOACs over warfarin for AF-related stroke.[5, 7-10] The overall AREST results, similar to Figure. 2 in this pooled analysis, suggest that the greatest risk to patients with AF-related stroke is a recurrent ischemic event, rather than HT.

This pooled analysis has a number of limitations, including the lack of a comparator group, small sample size, and pooling CT and MRI data. Indeed, the effect of current practice patterns is evident in the fact that larger infarcts were started on DOACs later than those with small or no visible infarcts. Mild-to-moderate stroke severity patients are over-represented in this analysis, limiting the ability to confirm the safety of earlier DOAC initiation in patients with larger infarcts.

Ultimately, the optimal timing of anticoagulation after AF-related ischemic stroke remains unknown until randomized trials assessing the safety and efficacy of earlier versus later DOAC are completed, analyzed, published, and presented – a process that could take years.[29, 36-38] Ongoing trials include LASER (Lixiana Acute Stroke Evaluation Registry, NCT03494530), TIMING (Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation: a Prospective Multicenter Registry-based Non-inferiority Randomized Controlled Clinical Trial, NCT02961348), ELAN (Early Versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients With Atrial fibrillation, NCT03148457), START (Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation, NCT03021928) trials, and OPTIMAS (OPtimal TIming of Anticoagulation After Acute Ischemic Stroke, NCT03759938), the enrollment of which have decelerated because of the COVID-19 pandemic "Stay at Home" orders displacing the stroke mantra of "Time Is Brain" which resulted in lower stroke census in hospitals and less opportunity to participate in research.[39] Regardless, patients in these ongoing trials are randomized to (and started on) DOAC as early as 48 hours and as late as 14 days, with the primary outcome typically the composite of recurrent ischemic stroke and symptomatic HT. Although these trials lack

systematic imaging post-initiation, most objectively-defined radiographic HT is asymptomatic, making this a reasonable and cost-saving approach. Nevertheless, any clinical changes warrant urgent repeat imaging and these findings assessed as part of the final analysis.

6.6 Conclusions

In this pooled analysis of 4 prospective studies and 2 randomized trials involving patients with mild and moderate ischemic stroke, DOAC initiation within 48 hours was not associated with increased risk of HT yet did demonstrate a strong non-significant trend towards decrease in ischemic events. Our results suggest that earlier recurrent ischemic events portend a poorer prognosis and are of greater clinical concern than HT in these patients.

6.7 Acknowledgments

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Table 6.1. Main inclusion and exclusion criteria for each study

CPASS	EASSE	RASS	DATAS	DATAS II	AREST
Inclusion criteria					
Male/female patients ≥ 18 years of age	Male/female patients ≥ 18 years of age	Male/female patients ≥ 18 years of age	Male/female patients ≥ 18 years of age	Male/female patients ≥ 18 years of age	Male/female patients ≥ 18 years of age
TIA/Acute Ischemic Stroke* (NIHSS ≤ 3)	TIA/Acute Ischemic Stroke*	TIA/Acute Ischemic Stroke* (NIHSS < 9)	TIA/Acute Ischemic Stroke* (NIHSS ≤ 3)	TIA/Acute Ischemic Stroke* (NIHSS ≤ 9)	TIA/Acute Ischemic Stroke*
AF	AF	AF	AF was an exclusion	AF was an exclusion	AF
Enrolled and initiated on therapy within 14 days of onset	Enrolled and initiated on therapy within 14 days of onset	Enrolled and initiated on therapy within 14 days of onset	Enrolled and initiated on therapy within 24 hours of onset	Randomized and initiated on therapy within 72 hours of onset	Diagnosed within 48 hours of symptom onset
Exclusion criteria					
eGFR <30 ml/min	eGFR <30 ml/min	eGFR <30 ml/min	eGFR <30 ml/min	eGFR <30 ml/min	eGFR <30 ml/min
Hypersensitivity to dabigatran	Hypersensitivity to apixaban	Hypersensitivity to rivaroxaban	Hypersensitivity to dabigatran	Acute DWI lesion volume ≥25 mL	Large ischemic stroke (including any brain stem stroke)
Prior treatment with DOAC	Prior treatment with DOAC	Prior treatment with DOAC	Prior treatment with DOAC	Contraindication to dabigatran or aspirin	Contraindication to anticoagulation
Any significant ongoing intracranial or extracranial bleeding risk, or recent major surgery	Any significant ongoing intracranial or extracranial bleeding risk, or recent major surgery	Any significant ongoing intracranial or extracranial bleeding risk, or recent major surgery	Any significant ongoing intracranial or extracranial bleeding risk, or recent major surgery	Any significant ongoing intracranial or extracranial bleeding risk, or recent major surgery	Any significant ongoing intracranial or extracranial bleeding risk, or recent major surgery
PH1 or PH2 on baseline CT	PH1 or PH2 on baseline CT	PH1 or PH2 on baseline CT	PH1 or PH2 on baseline CT	planned carotid endarterectomy/stent within 30 days or life expectancy <90 days	Any HT on baseline scan
		Contraindications to MRI	Contraindications to MRI	Contraindications to MRI	
			Thrombolysis or endovascular therapies	Thrombolysis or endovascular therapies	

* Ischemic stroke is defined as evidence of acute focal cerebral infarction confirmed on CT/MRI and/or focal hypoperfusion/vessel occlusion on multimodal imaging, or by sudden focal and objective neurological deficits (i.e NIHSS ≥ 1) of presumed ischemic origin persisting > 24 hours. TIA, transient ischemic attack; NIHSS, National Institute of Health Stroke Scale; AF, atrial fibrillation; ECG, electrocardiography; eGFR, *estimated Glomerular*

Filtration Rate; DWI, diffusion-weighted imaging; DOAC, Direct Oral Anticoagulant; PH, parenchymal hemorrhage; CT, computed tomography; MRI, magnetic resonance imaging

Table 6.2. Baseline characteristics

	CPASS	EASSE	RASS	DATAS	DATAS II	AREST	Pooled data
Trial characteristics							
Sample size	101	100	60	53	154	41	509
DOAC	Dabigatran	Apixaban	Rivaroxaban	Dabigatran	Dabigatran	Apixaban	
Follow-up period	30 days	90 days	90 days	90 days	90 days	180 days*	
Imaging modality	CT	CT	MRI	MRI	MRI	CT/MRI	
Patient characteristics							
Mean ± SD, age	72.4 ± 11.5	79±11	73.5 ± 13.2	66 ± 11.8	65 ± 13.3	72.6 ± 14.9	70.9± 13.4
Male	65%	49%	67%	60%	60%	37%	58%
Full DOAC dose	64%	79%	64%	79%	82%	76%	75%
Median infarct volume, ml (IQR)	0 (0-7.2)	4 (0.5 – 10.75)	7.9 (1.5 – 14.75)	0.8 (0.3 – 2.4)	1 (0.1 – 3.3)	6.7 (2.8 – 17.5)	1.5 (0.1 – 7.8)
Median time from index event onset to DOAC initiation, days (IQR)	2 (1-5)	2 (1-6)	3 (1.5-6)	0.8 (0.5 – 0.9)	1 (1 – 2)	4 (3 – 7)	2 (1 – 4)
Median baseline NIHSS (IQR)	1 (0-2)	4 (1 – 9)	2 (0-4)	1 (0 – 2)	1 (0 – 2)	3 (1 – 8.5)	2 (0 – 3)
Median Pre-morbid mRS (IQR)	0 (0 – 0)	0 (0 – 1)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	2 (0 – 3)	0 (0 – 1)
Baseline HT	7/101 (7%)	15/100 (15%)	25/60 (45%)	2/53 (4%)	1/154 (0.5%)	0/41 (0%)	50/509 (10%)

HT, hemorrhagic transformation; PH, parenchymal hemorrhage; IQR, Interquartile Range; mRS, Modified Rankin

Scale; NIHSS, National Institute of Health Stroke Scale

Table 6.3. Primary and secondary outcomes

	DOAC ≤ 48 hours (n=239)	DOAC > 48 hours (n=265)	Odds ratio * (95% CI)	p value
Primary outcome				
Incident radiological HT	12/239 (5%)	22/265 (8.3%)	0.63 (0.29 – 1.35)	0.24
Secondary outcomes				
Symptomatic HT (PH2)	0/235 (0%)	0/227 (0%)		
New parenchymal hemorrhage (PH1 or asymptomatic PH2)	0/235 (0%)	0/227 (0%)		
Extracranial hemorrhage	0/235 (0%)	0/227 (0%)		
Recurrent ischemic event(s)	8/239 (3.3%)	23/265 (8.7%)	0.42 (0.17 – 1.04)	0.06
Independent functional outcome (mRS 0-2)	189/239 (79.1%)	184/265 (69.4%)	0.82 (0.45 – 1.46)	0.50
Mortality	4/239 (1.7%)	11/265 (4.1%)	0.91 (0.25 – 3.4)	0.90

*Adjusted for age, NIHSS, and infarct volume.

DOAC, direct oral anticoagulants; CI, confidence interval; HT, hemorrhagic transformation; PH, parenchymal hemorrhage; mRS, Modified Rankin Scale; NIHSS

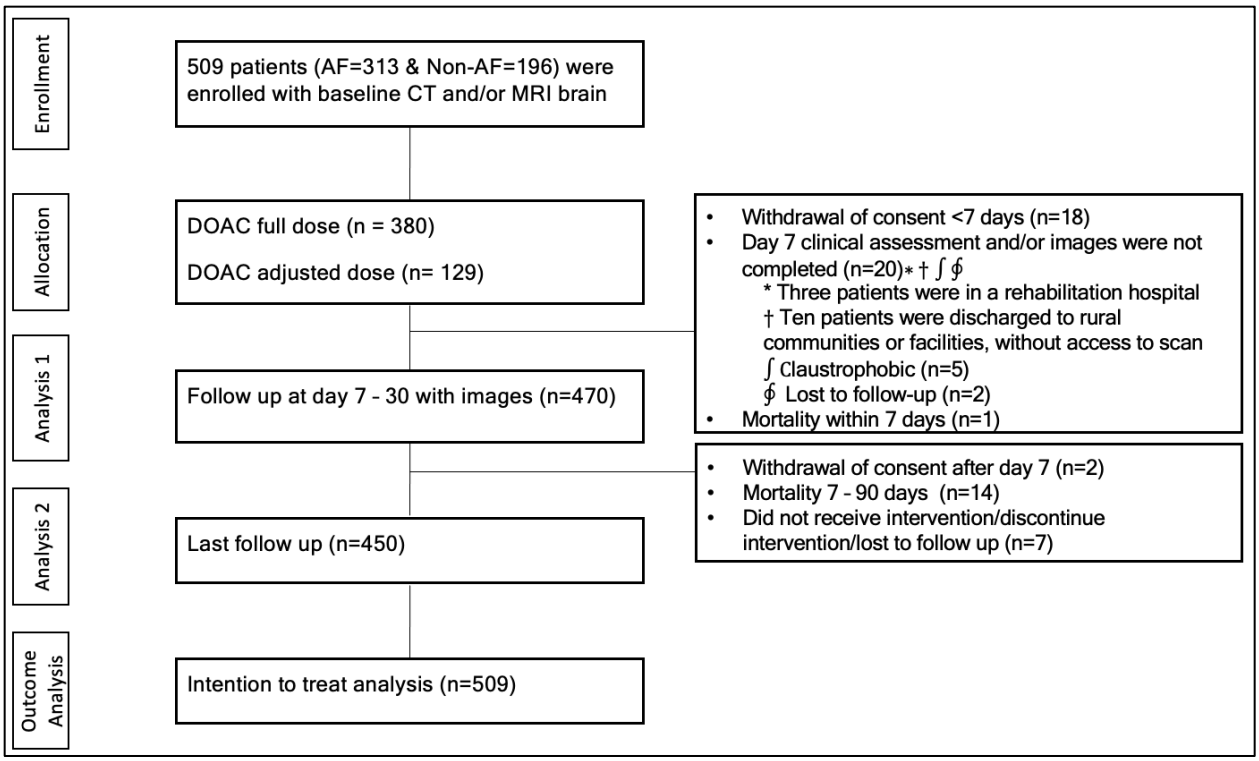

Figure 6.1. Consort diagram of enrollment, allocation, follow-up, and outcomes. Day 7 follow-up included clinical and imaging assessment, while last follow up included clinical assessment.

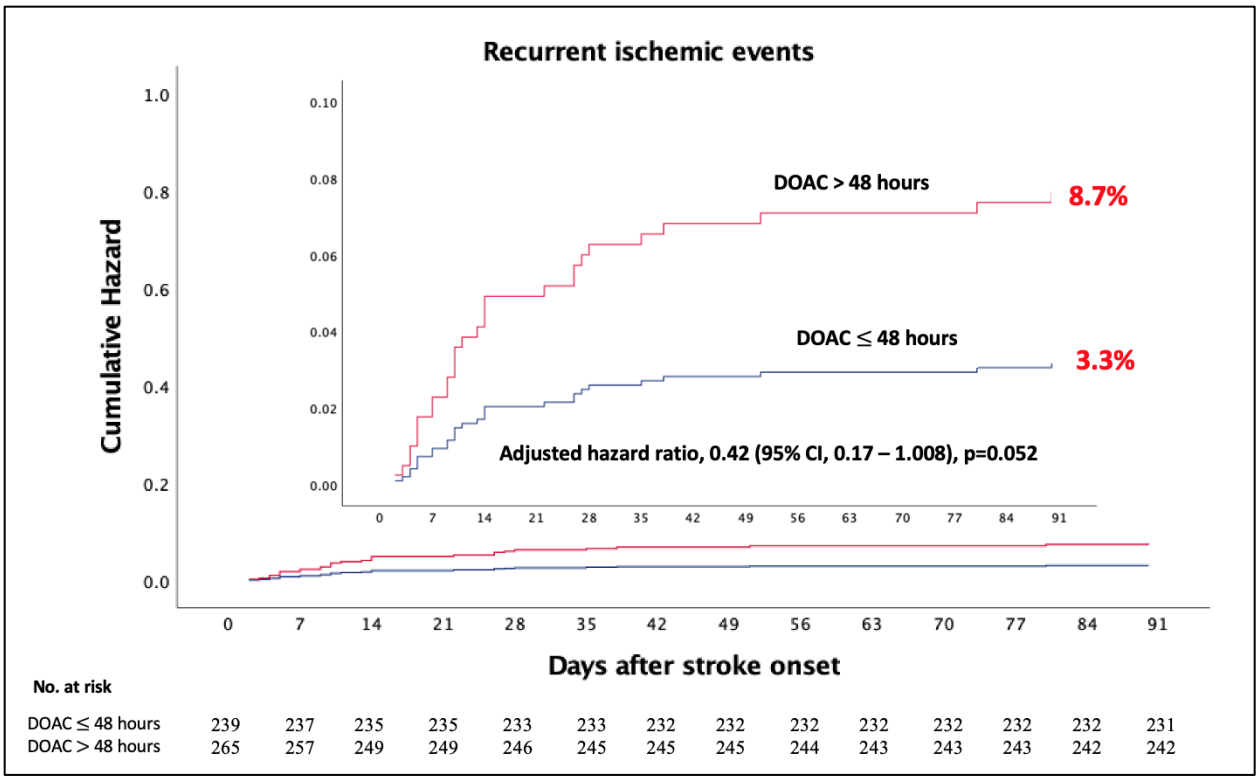

Figure 6.2. Cumulative hazard of recurrent ischemic events in patients initiated on a DOAC ≤ 48 hours vs. > 48 hours after adjusting for age, stroke severity, and infarct volume. Note that 101 patients in the Canadian Pradaxa Acute Stroke Safety trial were followed for 30 days only.

DOAC, direct oral anticoagulants

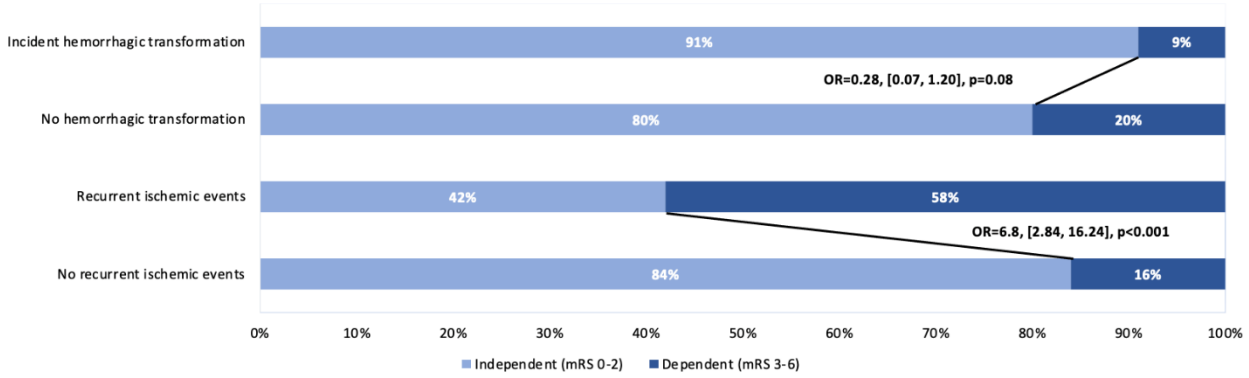

Figure 6.3. Day 90 functional outcomes in patients with/without incident hemorrhagic transformation (HT) and patients with/without recurrent ischemic events. The presence of incident HT did not affect functional outcome, but recurrent ischemic events were associated with a decreased likelihood of good functional outcomes.

mRS, modified Rankin Scale; OR, odds ratio

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Chapter 7

Interim analysis for a randomized controlled trial of early anticoagulation with edoxaban after ischemic stroke in patients with atrial fibrillation

Running title: Lixiana Acute Stroke Evaluation Registry (LASER)

7.1 Abstract

Background: The optimal timing of anticoagulation after stroke in patients with atrial fibrillation (AF) is unknown. We aimed to demonstrate the safety of edoxaban initiation within five days of AF related stroke and to determine predictors of hemorrhagic transformation (HT).

Methods and design: LASER (Lixiana Acute Stroke Evaluation Registry**)** is a randomized controlled trial of patients with AF randomized 2:1 within five days of symptom onset to early (≤5 days, n=100) or delayed (6-14 days, n=50) edoxaban initiation. An interim analysis for 68 patients was conducted. Baseline and follow-up CT scans were assessed for HT and graded using Heidelberg Bleeding Classification (HBC). The primary endpoint was incident HT rates, which were assessed as Objective Performance Criteria.

Results: A total of 68 patients, mean age 76.85 ± 9.7 years, were randomized to early or delayed edoxaban initiation. The median (interquartile range) time from index event onset to edoxaban initiation was 5 (3-6) days. Baseline National Institutes of Health Stroke Scale (NIHSS) was 5 (2-10). Incident radiographic HT occurred in 9 patients, 5 of whom were in the early arm and 4 in the delayed arm (Odds ratio, 1.79 (95% confidence interval 0.41 – 7.75), p = 0.46). No symptomatic HT occurred in both arms. Baseline NIHSS predicted incident HT (OR, 1.19 (95%

CI, 1.04–1.37); p=0.014). Recurrent ischemic events occurred in 3/45 (6.6%) of early-assigned and 2/23 (8.7%) of delayed-assigned patients (OR, 1.33 (95% CI, 0.21 – 8.60), p = 1.0). All the clinical and functional outcomes were similar in the early and delayed groups at day 7 and day 90.

Discussion: In an interim analysis of RCT, early edoxaban initiation within 5 days after AF - related ischemic stroke was not associated with an increased risk HT.

7.2 Introduction

The optimal timing of anticoagulation after ischemic stroke is an area of clinical equipoise. It is clearly established that patients with atrial fibrillation (AF) who develop ischemic stroke are at high risk for recurrence and require long-term anticoagulation. Previous studies have reported that starting older anticoagulants within 48 hours after acute ischemic stroke is associated with a reduction in the rate of recurrent ischemic events, but that is offset by an increased risk of hemorrhagic transformation (HT).[1-3] More recently, four direct oral anticoagulation (DOACs) have shown a lower risk of intracranial hemorrhagic complications compared to older anticoagulants, and they are now the standard of care for long-term stroke prevention in non-valvular AF.[4-7] In the pivotal phase III DOAC randomized controlled trial (RCT), patients were not eligible for randomization as early as 7 days and up to 30 days after ischemic stroke. Current stroke guidelines are inconsistent regarding the timing of DOAC initiation.[8-10] The Canadian Stroke Best Practice guidelines recommend timing of anticoagulation based on clinical severity and infarct size, as seen on CT scan, but neither are well defined.[10] This guideline statement is based on expert opinion originally included in the European Heart Rhythm Association recommendations, but neither are based on randomized evidence.[8]

Edoxaban is one of the DOACs approved for the prevention of ischemic stroke in patients with AF.[7] Patients within 30 days of ischemic stroke were excluded from the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation - Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial. As with other DOACs, there are no randomized data related to the use of edoxaban early after ischemic stroke. Previous open label studies of DOAC use in acute stroke have demonstrated that the rate of symptomatic HT is likely

to be nil. Although clinical severity and infarct volume appear to increase HT risk [11-14], the association is highly inconsistent.

We have previously demonstrated the rate of asymptomatic HT in serial imaging studies to be as lower as 3% in CT-based studies [13, 14] and up to 13% in MRI based studies.[15] Although asymptomatic HT is of questionable clinical significance, it does share a common pathophysiological pathway with larger symptomatic HT.[16, 17] This may therefore make it a useful objective evaluation criterion when assessing the effect of early versus delayed DOAC initiation. However, there are no data related to the difference in asymptomatic HT rates in patients randomized to early versus late DOAC initiation. Our aim was to determine the event rates in these two groups with reasonable precision. We therefore completed an interim analysis for RCT of patients with AF randomized 2:1 within five days of symptom onset to early (≤5 days, n=45) or delayed (6-14 days, n=23) edoxaban initiation. Serial imaging using Computed Tomography (CT) was utilized to determine the rate of radiographic HT. Additionally, we assessed the rate of recurrent ischemic stroke, but recognized this is a hypothesis generating only due to the small trial sample size.

7.3 Methods

7.3.1 Study design

LASER is a randomized controlled, parallel-group, two-arm, assessor-blinded trial with an associated registry (clinicaltrials.gov NCT03494530). The trial protocol has been previously published.[18] Patients with previously known or newly diagnosed AF-related ischemic stroke were randomized 2:1 to early (≤5 days) or delayed (6-14 days) edoxaban initiation. Ischemic stroke was defined as evidence of acute focal cerebral infarction confirmed on CT/MRI and/or focal hypoperfusion/vessel occlusion on multimodal CT, or by sudden focal and objective

neurological deficits (i.e. NIHSS ≥ 1) of presumed ischemic origin persisting > 24 hours. Informed consent was obtained from the patient or substitute decision maker in all cases prior to enrolment. The research protocol was approved by our local Human Research Ethics Board.

7.3.2 Patient Population

Sixty-Eight patients from a Comprehensive Canadian Stroke Center were enrolled. Eligible patients were randomized within five days of symptom onset after baseline CT.

7.3.3 Randomization

Eligible patients were randomized 2:1 following open label simple randomization procedure to early (≤5 days) or delayed (6-14 days) edoxaban initiation via a centralized web-based randomization process, Research Electronic Data Capture (REDCap, Vanderbilt university).[19, 20] After randomization to early or delayed arms, the decision to time the edoxaban initiation within the specific arm was at the treating physician's discretion.

7.3.4 Treatment

Randomized patients were treated with edoxaban 60 mg once daily. The edoxaban dose was reduced to 30 mg once daily if any of the following characteristics are present at the time of randomization or during the study: estimated creatinine clearance (CrCl) of 30 to 50 ml per minute using Cockcroft-Gault Equation or body weight ≤ 60 kg. Prior to edoxaban initiation, all patients were treated as per the clinical standard of care using antiplatelet(s) and anticoagulation for deep venous thrombosis (DVT) prophylaxis. Any antithrombotic therapy prior to randomization was recorded.

7.3.5 Clinical assessment

All randomized patients were followed for 90 days after edoxaban initiation. A National Institute of Health Stroke Scale (NIHSS) score was assessed at baseline, 7 and 90 days after edoxaban initiation. Functional outcome was assessed with a modified Rankin Scale (mRS) score at baseline, 7 and 90 days after edoxaban initiation. Montreal Cognitive Assessment (MoCA) was performed at baseline, and day 90 after edoxaban initiation. Functional outcomes at 90 days were dichotomized as favourable (mRS score 0-2) and unfavourable (mRS score 3-6). Quality of life was assessed with the EuroQol-5 Dimension (EQ-5D) and Visual Analog Scale (VAS) at day 90.

7.3.6 Standardized image acquisition and central analysis

In addition to diagnostic imaging, all patients have a baseline CT prior to randomization and follow up CT 7±2 days after edoxaban initiation. Therefore, all patients have a minimum of two scans (diagnostic and pre-randomization). In the event of clinical deterioration, CT scans were repeated. In patients treated with thrombolysis and/or endovascular thrombectomy, a 24-hour post-treatment CT was used as the baseline study prior to randomization.

Anonymized dicom CT data were analyzed centrally. Any HT, as well as other intracranial hemorrhage, seen at baseline and day 7 were graded using the Heidelberg Bleeding Classification (HBC).[21] Incident radiographic HT seen on follow-up CT scan was defined as new or progressive HT. Progressive HT was defined as any increase in the severity grade between the baseline and follow-up scan.

7.3.7 Study outcomes

The primary study endpoint was the rate of incident (new or progressive) radiological HT. The secondary endpoint was the rate of symptomatic HT, defined as intracerebral

hemorrhage within and beyond infarcted brain tissue with PH >1/3 the volume of the ischemic infarct (Class 2 in HBC) associated with clinical deterioration (worsening of NIHSS score by ≥ 4 points) within 30 days of treatment initiation.[21, 22] Other secondary endpoints were recurrent ischemic stroke within 90 days of randomization, recurrent sub-clinical infarcts on follow up CT at 7±2 days post edoxaban initiation, systemic hemorrhagic complication rate within 90 days of randomization, NIHSS at day 7 and 90, mRS score at day 7 and 90, favourable mRS at day 90, and mortality within 90 days, quality of life at 90 days assessed by (EQ-5D) and Visual Analog Scale (VAS).

7.3.8 Sample size estimates

A sample size of 150 patients, randomized 2:1 (≤5 days:6-14 days) was planned to detect an asymptomatic hemorrhage rate of 3% (95% CI 0.6-8.5%) in the early treatment arm (n=100) and 4% (95% CI 0.5-13.7%) in the late treatment arm (n=50). This was planned to have confidence interval width of a maximum of 13.7%, allowing enough precision to demonstrate the safety of early treatment. The rationale for adopting a 2:1 randomization approach was to increase the precision around the estimate of safety in the early treatment arm, without substantively losing power.

7.3.9 Statistical analysis

The primary analysis was intention-to-treat, irrespective of edoxaban compliance. The primary endpoint of incident HT rates (Odds ratio (OR) and 95% Confidence Intervals (CI)) in the early vs delayed groups was calculated. Crude rates were planned to be adjusted only if there are baseline imbalances in stroke severity (NIHSS), infarct volume or HT. Univariate logistic regression analyses were used to assess potential relationships between CT and clinical factors including age, clinical severity (NIHSS score), history of diabetes/glucose level,

hypertension/blood pressure and HT risk. The five-digit health state in EQ-5D, was calculated using the Canadian preference weights, as described previously.[23] All statistical analyses were performed using the Statistical Package for Social Sciences version 23.0.0 (IBM SPSS Statistics Inc, 2015, Armonk, NY, USA).

7.4 Results

7.4.1 Baseline Characteristics

Between September 2018 and May 2021, a total of 68 patients (39% female) were randomly assigned to early (≤5 days, n=45) or delayed (6-14 days, n=23) edoxaban initiation (Figure 7.1). Of the 68 patients randomized to both arms, two patients crossed from delayed to early arm and one patient crossed from early to delayed arm. Those patients were included in the efficacy analysis as intention-to-treat, and in the safety analysis as per-protocol. One patient withdrew consent prior to the follow up CT scan at day 7. Six patients withdrew consent after the day 7 assessment. Three patients died prior to the follow up CT scan at day 7 and three patients after the day 7 assessment. All the mortalities were related to medical complications. At day 7, CT scan was not obtained in eleven patients randomized to early arm and six patients in the delayed arm (Figure 7.1).

Participants had a mean age of 76.85 ± 9.7 and 27 (39%) were women. The median (interquartile range) time from index event onset to edoxaban initiation was 5 (3-6) days. The lower dose of edoxaban (30 mg daily) was used in 13/68 (19.1%) patients and the remainder received 60 mg daily. Of the 68 patients randomized to both arms, 46 patients (67.6%) have been previously diagnosed with AF. Median baseline NIHSS was 5 (2-10). Asymptomatic (clinically undetected) HT, graded as HBC 1A (scattered small petechiae with no mass effect) was present in 12 patients at baseline, 5 of whom were in the early arm and 7 in the delayed arm.

Asymptomatic HT, HBC 1B (confluent petechiae with no mass effect) was present in 8 patients at baseline, all of them were in the early arm. Lastly, asymptomatic HBC 3C (subarachnoid hemorrhage) was present in 2 patients at baseline, both of them were in the early arm. Baseline demographic and clinical characteristics were similar in both groups (Table 7.1).

7.4.2 Primary and Secondary End Points

Incident radiographic HT occurred in 9 patients, 5 of whom were in the early arm (3 HBC 1A, 1 HBC 1B & 1 HBC 1C) and 4 in the delayed arm (3 HBC 1A &1 HBC 1B) (OR, 1.79 (95% CI 0.41 – 7.75), p = 0.46; Table 7.2). Symptomatic HT occurred in no participants in either arm (OR N/A). Asymptomatic HBC 1C occurred in one patient in the early arm (p=1.0). New ICH outside the infarcted brain tissue or intracranial-extracerebral hemorrhage (HBC 3A-D) occurred in no patients in either arm (OR N/A).

7.4.3 Recurrent Ischemic Events

Recurrent ischemic events occurred within 90 days in 5 patients (7.3%). Of these 5 patients, 3 were enrolled into early arm and 2 in delayed arm (OR, 1.33 (95% CI, 0.21 – 8.60), p = 1.0; Table 7.2). Three patients suffered pulmonary embolism. In 2/5 (40%) patients with recurrent ischemic event, edoxaban dose was 30 mg daily. Predictors for recurrent ischemic events were not identified.

7.4.4 Systemic Hemorrhagic Complications

Severe gastrointestinal bleeding occurred in one patient in the delayed arm (p=0.34; Table 7.2). No other serious adverse events were reported within the study period.

7.4.5 Clinical Outcomes

At day 7 and day 90, the NIHSS, mRS scores, MoCA, quality of life and mortality were similar in the early and delayed groups (Table 7.2). All 9 patients with incident radiographic HT had unfavourable functional outcome (mRS 3-6) at 90 days. The presence of Incident HT was significantly associated with functional outcome ($p<0.0001$). Of the 5 patients with recurrent ischemic events, 4 had unfavourable functional outcomes (OR=6.01, [0.64, 57.61], p=0.155). In the Cox Proportional Hazards Regression Analysis, there was no significant difference in the risk of recurrent ischemic events and mortality in the early and delayed groups after adjusting for age, sex, and NIHSS (HR, 2.94 (95% CI, 0.55 – 15.70), p=0.21; Figure 7.2).

7.4.6 Predictors of Incident Radiographic Hemorrhagic Transformation

Incident radiographic HT occurred in 9 patients (13.2%; Figure 7.3) with a median NIHSS of 10 (7–16). The only predictor of incident radiographic HT was NIHSS (OR, 1.19 [95% CI, 1.04–1.37]; p=0.014). Neither early nor delayed arm predicted HT. As univariate analyses revealed only one potential predictor of HT with $P<0.10$ (NIHSS), multivariate regression was not performed.

7.5 Discussion

In this interim analysis of RCT, incident HT was seen in 13.2% of patients, none of whom were symptomatic. Even in cases where HT was present at baseline (32.4%) prior to anticoagulation, edoxaban initiation did not result in symptomatic HT. Initiation of edoxaban within 5 days (early arm) of ischemic stroke onset was not associated with an increased risk of incident radiographic HT compared to 6-14 days (delayed arm), 14.7% vs. 23.5%, respectively. Conversely, early recurrent ischemic events occurred in 7.3% of patients, all of whom were symptomatic. Of all the recurrent ischemic events, 80% occurred in the first 10 days, suggesting

the risk of ischemic events is highest early after the index event. In contrast to HT, which was clinically silent, recurrent ischemic events were always clinically evident. While there was no identified predictor for recurrent ischemic events, NIHSS was the only predictor for the incident radiographic HT. Symptomatic HT after anticoagulation is an infrequent event, which makes it difficult to predict and also complicates studies aimed at risk stratification of patients with AF-related stroke. These data might be useful for a safety/efficacy study sample size power calculation. Documentation of asymptomatic HT requires serial pre and post-treatment imaging, but the latter is highly variable in clinical practice and studies to date.

In our pilot safety studies with rivaroxaban, dabigatran and apixaban we observed low rates of symptomatic HT when these DOACs were initiated within 14 days of symptom onset.[13-15] While encouraging with respect to the safety of early DOAC initiation, these studies are far from definitive. Several trials are being conducted for the safety and efficacy of early versus delayed anticoagulation after ischemic stroke in patients with AF.[24-26] Patients in these trials are randomized to DOAC initiation as early as 24 hours and up to 5 days after onset, or delayed initiation 6-14 days. The primary endpoint in these trials is the composite of recurrent ischemic stroke and symptomatic HT. Patients' allocation to the treatment arms in most of these trials is determined by stroke severity and/or size.

This interim analysis has a few limitations. The small sample size (68 out of the planned sample size, 150 participants) in addition to the fact that the trial is not powered to detect differences in clinical outcomes, including symptomatic HT and recurrent infarction makes it impossible to confirm or reject the safety of early (≤5 days) edoxaban initiation.

7.6 Conclusions

In an interim analysis of RCT, early edoxaban initiation after ischemic stroke was not associated with an increased risk of incident radiographic HT. No symptomatic HT occurred in both arms over the study period. Baseline NIHSS predicted incident radiographic HT. Our results suggest that the risk of recurrent ischemic events and mortality in the early and delayed groups after adjusting for age, sex, and NIHSS was similar.

7.7 Study organization and funding

This study is funded by a grant from the Alberta Innovates Technologies Futures and the University Hospital Foundation in partnership with Servier Canada (the Servier Alberta Innovation Health Fund (SAIHF)). LASER is also supported by infrastructure provided by the Quality Improvement & Clinical Research (QUICR) CRIO grant. Dr. Butcher holds a New South Wales Health Senior Cardiovascular Scientist award. Dr. Jickling has salary and grant support from HSFC and CIHR.

7.8 Acknowledgments

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Table 7.1. Baseline Patient Characteristics

	Overall (n= 68)	**Early arm (n= 45)**	**Delayed arm (n= 23)**
Mean ± SD, Age	76.85 ± 9.7	77.36 ± 9.2	75.87 ± 10.8
Female (%)	27 (39%)	17 (37.8%)	10 (43.5%)
Edoxaban 60 mg (%)	55 (80.9%)	36 (80%)	19 (82.6)
Median (IQR), Time from index event onset to edoxaban initiation (days)	5 (3-6)	4 (3-5)	6 (6-6)
Prior history of AF (%)	46 (67.6%)	32 (71.1%)	14 (60.9%)
Prior stroke (%)	16 (23.5%)	12 (26.7%)	4 (17.4%)
Intracerebral hemorrhage (%)	0 (0%)	0 (0%)	0 (0%)
Hypertension (%)	50 (73.5%)	30 (66.7%)	20 (87%)
Diabetes mellitus (%)	21 (30.9%)	10 (22.2%)	11 (47.8%)
Dyslipidemia (%)	36 (52.9%)	25 (55.6%)	11 (47.8%)
Smoking history (%)	11 (16.2%)	10 (22.2%)	1 (4.3%)
Mean ± SD, Baseline SBP	142 ± 17	141.4 ± 16.26	143.57 ± 18.44
Mean ± SD, Baseline DBP	80.5 ± 18	80 ± 16.66	81.52 ± 21.35
Mean ± SD, Baseline glucose level	7.65 ± 2.68	7.1 ± 2	8.7 ± 3.5
Median (IQR), Baseline NIHSS	5 (2-10)	6 (2-12)	4 (1-8)
Median (IQR), Baseline pre-mRS	0 (0-0)	0 (0-1)	0 (0-0)
Median (IQR), Baseline MoCA	19 (12.5 – 22)	19 (13.75 – 21.5)	14 (11 – 23.5)
Baseline HT	22 (32.4%)	15 (33.3%)	7 (30.4%)
HBC 1A	12 (54.5%)	5 (33.3%)	7 (100%)
HBC 1B	8 (36.4%)	8 (53.3%)	0 (0%)
HBC 1C	0 (0%)	0 (0%)	0 (0%)
HBC 2	0 (0%)	0 (0%)	0 (0%)
HBC 3A	0 (0%)	0 (0%)	0 (0%)
HBC 3B	0 (0%)	0 (0%)	0 (0%)
HBC 3C	2 (9.1%)	2 (13.3%)	0 (0%)
HBC 3D	0 (0%)	0 (0%)	0 (0%)

SD, standard deviation; IQR, interquartile range; AF, atrial fibrillation; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institute of Health Stroke Scale; mRS, Modified Rankin Scale; MoCA, Montreal Cognitive Assessment; HT, hemorrhagic transformation; HBC, Heidelberg Bleeding Classification

Table 7.2. Primary and secondary outcomes

	Early arm (n= 45)	Delayed arm (n= 23)	Odds ratio (95% CI)	p value
Primary outcome				
Incident radiological HT	5/34	4/17	1.79 (0.41 – 7.75)	0.46
Secondary outcomes				
Symptomatic HT (HBC 2)	0/46	0/22	N/A	N/A
New parenchymal hemorrhage (HBC 1C or asymptomatic HBC 2)	1/34	0/17	N/A	1.00
New ICH outside the infarcted brain tissue or intracranial-extracerebral hemorrhage (HBC 3A-D)	0/34	0/17	N/A	N/A
Systemic hemorrhagic complication(s)	0/46	1/22	N/A	0.34
Recurrent ischemic event(s)	3/45	2/23	1.33 (0.21 – 8.60)	1.00
Median (IQR) day 7 mRS	3 (1.25 – 4)	2 (1 – 3)	N/A	0.20
Median (IQR) day 7 NIHSS	2.5 (0 – 9.25)	0 (0 – 3)	N/A	0.44
Median (IQR) day 90 mRS	2 (1 – 4)	1 (0 – 3)	N/A	0.23
Median (IQR) day 90 NIHSS	2 (0.25 – 6)	2 (0 – 13.5)	N/A	1.00
Median (IQR) day 90 MoCA	24 (17 – 27)	22 (21 – 22)	N/A	0.49
Median (IQR) day 90 EQ-5D index score	0.82 (0.66 – 1.00)	0.83 (0.60 – 1.0)	N/A	0.67
Median (IQR) day 90 EQ-5D VAS score	74 (60 – 80)	75 (60 – 83.75)	N/A	0.65
Favourable functional outcome (mRS 0-2)	23/45	16/23	0.46 (0.16 – 1.32)	0.20
Mortality	6/45	0/23	N/A	0.09

CI, confidence interval; HT, hemorrhagic transformation; HBC, Heidelberg Bleeding Classification; N/A, not applicable; ICH, intracerebral hemorrhage; mRS, Modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; MoCA, Montreal Cognitive Assessment; EQ-5D, The EuroQol five-dimensional; VAS, visual analog scale

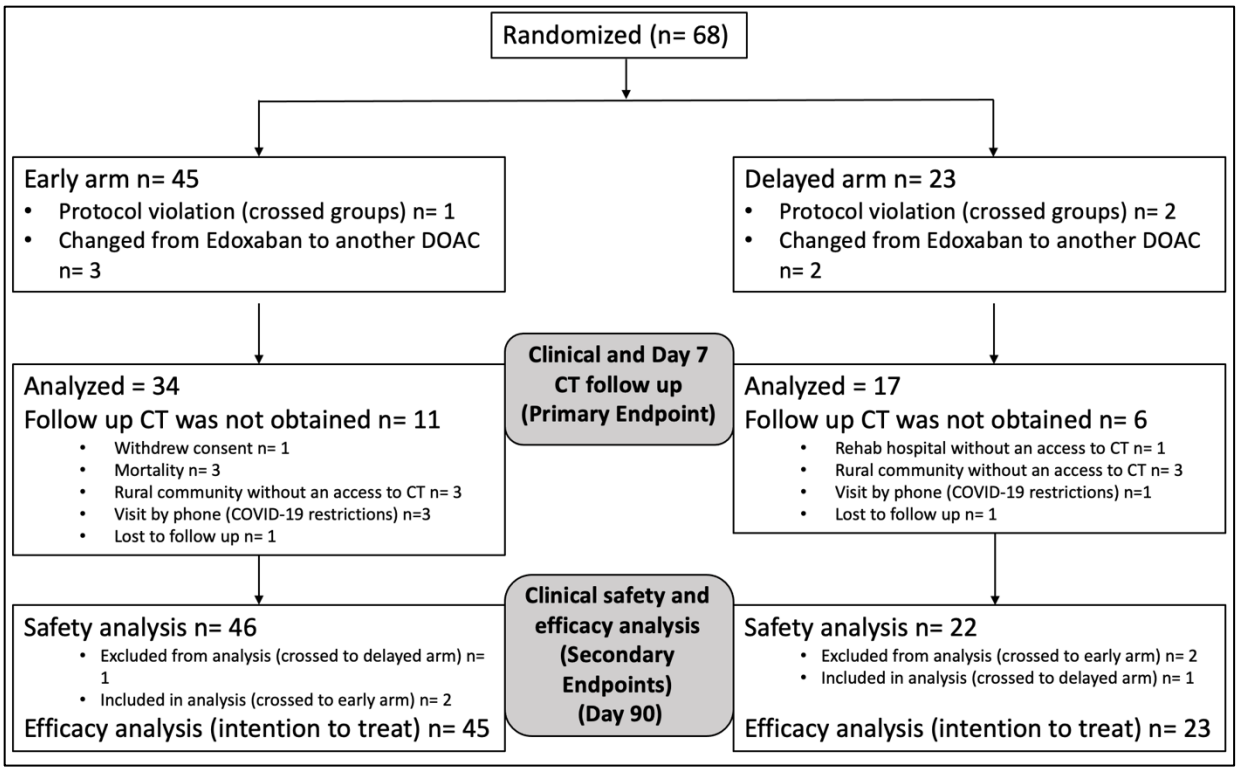

Figure 7.1. Consort diagram of enrollment, allocation, follow-up, and outcomes.

Day 7 follow-up included clinical and imaging assessment, while last follow up included clinical assessment.

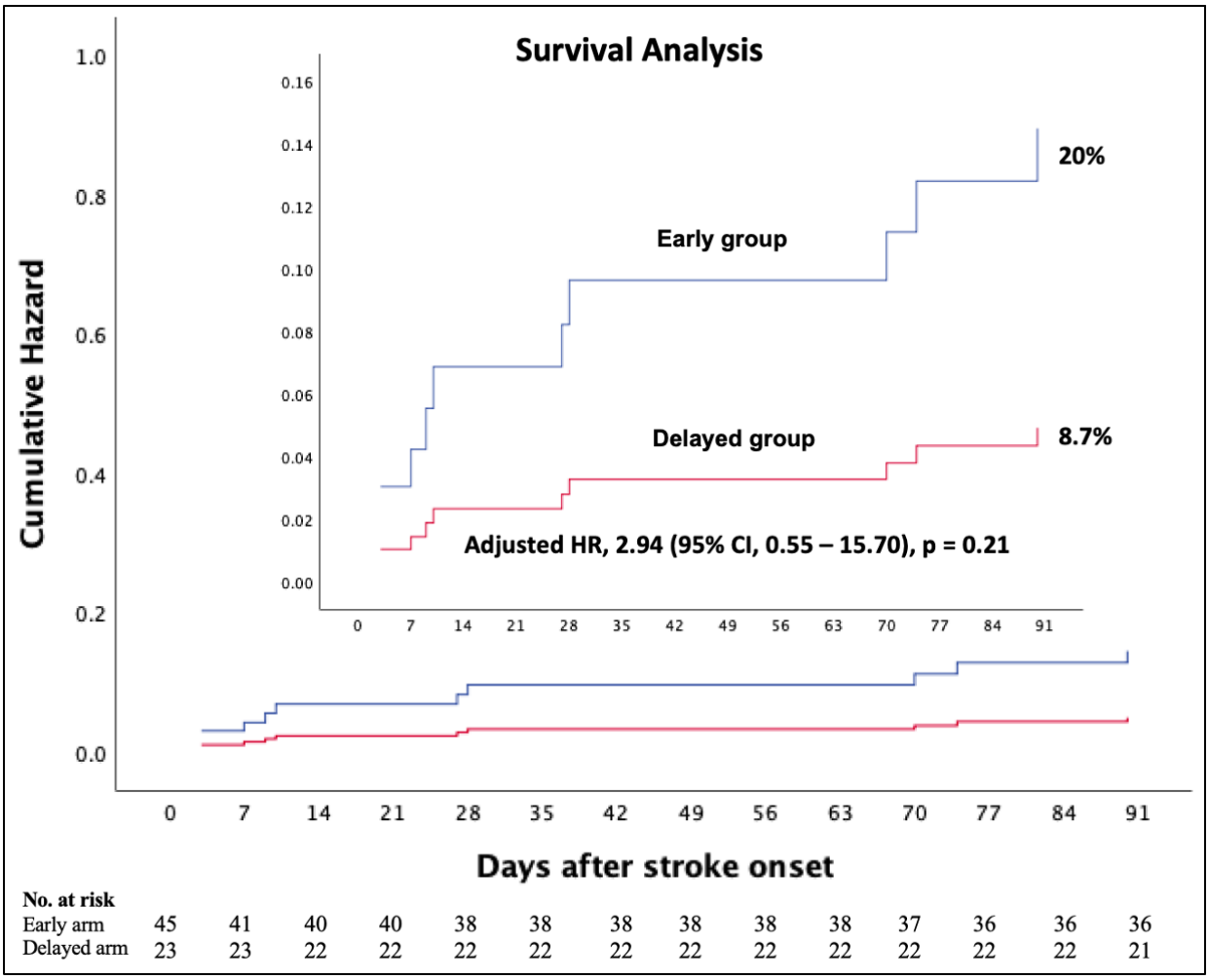

Figure 7.2. Cumulative hazard of recurrent ischemic events and mortality in patients randomized to early vs. delayed arm after adjusting for age, sex, and NIHSS.

HR, Hazard Ratio; CI, confidence interval

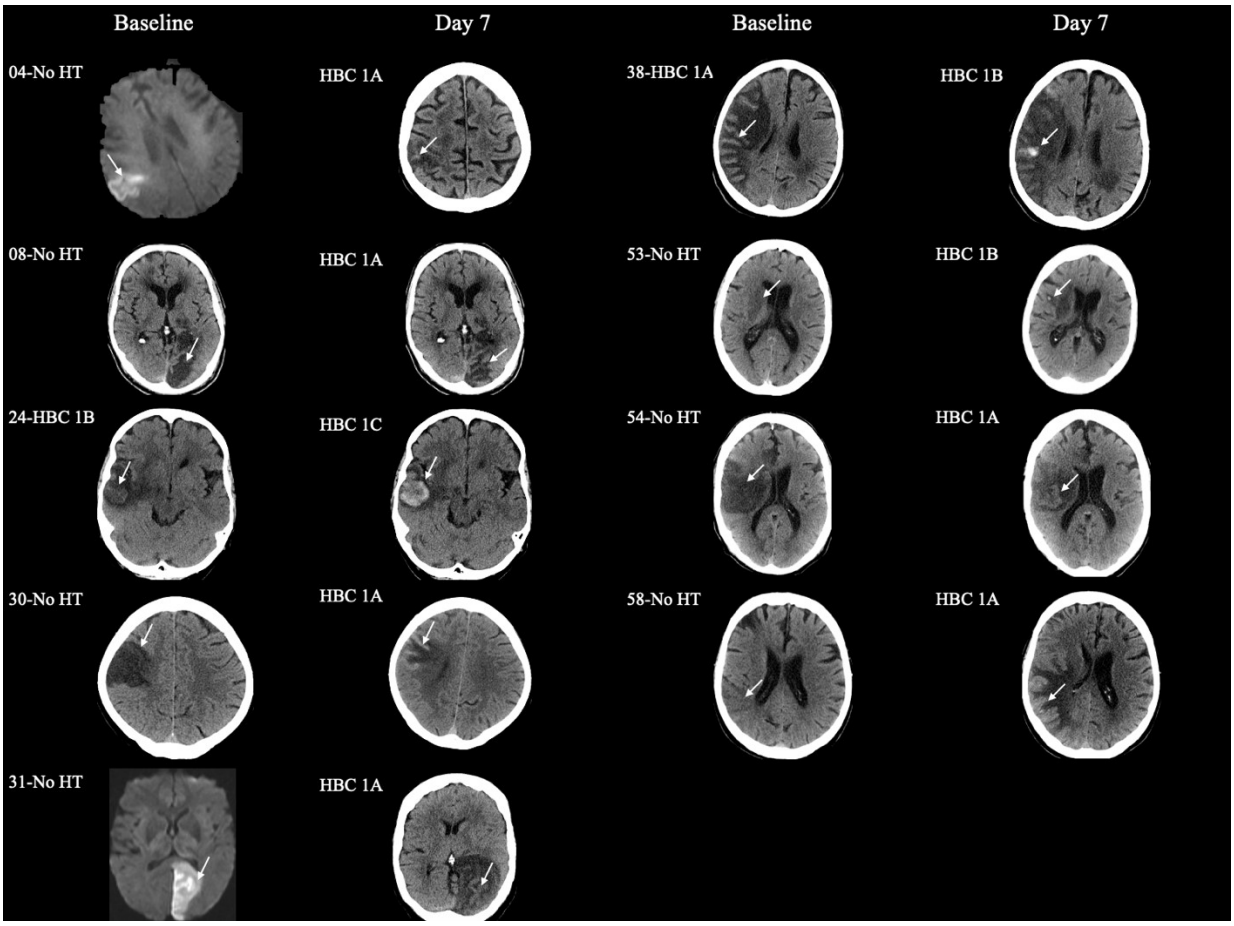

Figure 7.3. All cases of hemorrhagic transformation (HT) seen in the follow-up scan in this interim analysis were incident (asymptomatic).

HBC 1A was defined as scattered small petechiae, no mass effect, HBC 1B as confluent petechiae, no mass effect, and HBC IC as Hematoma within infarcted tissue, occupying <30%, no substantive mass effect.

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Chapter 8

Discussion and future directions

8.1 Summary and interpretation of the results

Research presented in this dissertation has provided a comprehensive assessment of the clinical conundrum in deciding the time to initiate DOAC after acute ischemic stroke in patients with AF. A multi-step approach of research questions and study designs have been developed to overcome this common and unresolved clinical challenge. We first designed clinical- and imaging- based prospective studies of patients with AF treated with DOAC within 14 days of TIA or ischemic stroke.[1, 2] This study design has provided us with the opportunity to understand the natural history of AF-related ischemic stroke and risk of HT and recurrent ischemic events. Additionally, it allowed us to examine the effects of HT subtypes and recurrent ischemic events on clinical and functional outcomes. Further, it gave us the chance to assess each HT grade independently and evaluate the risk of progression to a higher grade. Finally, it led us to study different clinical and radiological predictors of HT and recurrent ischemic stroke. The rich data that were generated from the first two studies moved us to the next step, which was designing and developing an RCT with an associated registry to demonstrate the safety of using DOAC within five days of acute ischemic stroke and establish more predictors of HT and recurrent ischemic stroke.[3] This study is underway at University of Alberta Hospital and almost half of the planned sample size has been collected and analyzed, as discussed in chapter 7. We then completed an international electronic survey to assess the current global practice on this topic. Shedding light on the international practice variability would call attention to this clinical dilemma and inform designs of subsequent clinical trials in this field. Lastly, we completed a

pooled analysis for individual patient data from four prospective studies and two RCT of DOAC initiation within 14 days of ischemic stroke to enhance the statistical power and the ability to study the natural history, assess predictors, and compare outcomes.

By conducting these series of studies using clinical and serial imaging data at baseline and following DOAC initiation, we demonstrated the rate of incident HT to be as low as 3-6% in CT-based studies and up to 13% in MRI-based studies, none of whom were symptomatic. Additionally, initiating DOAC as early as 48 hours after ischemic stroke onset did not seem to increase the risk of incident radiographic HT when adjusted for age, NIHSS, and infarct volume. Even in cases with baseline HT prior to anticoagulation, DOAC did not result in symptomatic HT. Contrarily, early recurrent ischemic events were more common, all of whom were symptomatic. Most of the recurrent ischemic events occurred in the first 14 days, suggesting the risk of ischemic events is highest early after the index event. In contrast to HT, which was detected incidentally on follow-up imaging and was not observed to independently influence the functional outcomes, recurrent ischemic events were always clinically evident and associated with poor functional outcomes. In the pooled data from all the studies, infarct volume was a predictor of both baseline and incident radiographic HT. This would suggest that incident radiographic HT could potentially represent the natural history in the evolution of the infarct.

Our results suggest that symptomatic HT rates will likely to be low in randomized trials of DOAC initiation post AF-related stroke. Conversely, recurrent ischemic stroke will potentially be the clinical outcomes of interest in the RCTs. However, HT remains a critical complication to consider as even a slight increase in frequency may outweigh any benefits of early anticoagulation. Although incident radiographic HT in our studies was asymptomatic and only detected incidentally on follow-up imaging, it likely shares a common mechanism and

pathophysiological pathway with more severe symptomatic HT.[4, 5] This observation is one of the strengths of our design as incident radiographic HT can be a useful objective evaluation criterion when assessing the impact of early versus delayed DOAC initiation. Documentation of incident radiographic HT requires systematic pre- and post-treatment imaging, but the latter has been highly variable in studies to date. Serial and systematic collection of HT rates constitute Objective Performance Criteria, which may be important surrogate markers even in larger trials, where the expected absolute number of symptomatic HT cases is likely to remain low. The data presented in this dissertation might be useful for designing and calculating sample size requirements for future safety/efficacy trials of early versus delayed DOAC initiation.

Research presented in this dissertation has some limitations which include the lack of a comparator group in most studies, relatively small sample size, and including both CT and MRI data. Indeed, the effect of current practice patterns is clearly demonstrated in the fact that initiating DOAC is delayed in patients with larger infarcts compared to small or no visible infarcts. Mild to moderate stroke severity patients are over-represented in our studies, making it impossible to confirm or reject the safety of early DOAC initiation in patients with larger infarcts.

8.2 Current practice

Anticoagulation using DOACs has been shown to be as effective as older anticoagulants in preventing recurrent ischemic stroke in patients with AF and also has a lower risk of intracranial hemorrhagic complications.[6-10]. However, the timing of DOAC initiation after acute ischemic stroke in these patients remains unclear. As discussed, current guidelines are inconsistent and variable among different organizations and countries.[11-17] Randomized trials are required to confirm or reject the safety and efficacy of early DOAC initiation. Where

feasible, every effort should be made to recruit patients with AF-related ischemic stroke in RCTs. Where recruitment in ongoing RCTs is not possible, Figure 8.1 provides a suggested schematic approach for clinicians on what to do in the current clinical practice setting. This schematic approach does no replace clinical judgement where clinicians need to weigh benefits and potential risks of early DOAC initiation in individual patients.

This practice of delaying DOAC administration due to concerns that patients with large infarcts are more prone to symptomatic HT appears reasonable at present. The absolute risk of HT, however, and the optimal timing in individual patients remains unknown. A follow-up neuroimaging scan before initiating DOAC is often used in clinical practice to assess infarct progression or hematoma expansion but whether these factors should guide decision, and how, remain unknown. Serial and systematic collection of HT rates constitute objective criteria which may be important surrogate markers even in larger trials, where the expected absolute number of symptomatic HT cases is likely to remain low.

8.3 Future directions

The optimal timing of DOAC after AF-related ischemic stroke will remain a common clinical equipoise until randomized trials of early versus delayed DOAC are completed.[3, 18-20] Ongoing trials include LASER (Lixiana Acute Stroke Evaluation Registry, NCT03494530), TIMING (Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation: a Prospective Multicenter Registry-based Non-inferiority Randomized Controlled Clinical Trial, NCT02961348), ELAN (Early Versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients With Atrial fibrillation, NCT03148457), START (Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation, NCT03021928) trials, and OPTIMAS (OPtimal TIming of Anticoagulation After

Acute Ischemic Stroke, NCT03759938). These trials have been reviewed recently [20] and an updated summary is provided in Table 8.1.

Patients in the above-named trials are randomized to a DOAC, initiated as early as 48 hours and up to 5 days after onset, or delayed to 6-14 days. The primary endpoint in these trials is the composite of recurrent ischemic stroke and symptomatic HT. While using a composite endpoint will increase the number of events and statistical power, the contrasting outcomes could potentially dilute the net treatment effect (i.e. early initiation might potentially reduce recurrent stroke but increase symptomatic HT, and vice versa) and lead to a neutral primary outcome result.

The observed current practice of delaying DOAC initiation in patients with larger infarcts is relevant to the ongoing RCTs, where randomization is either stratified by infarct volume/size [18](ELAN, NCT03148457) and/or includes arms with relatively broad initiation time windows of several days, extending up to 14 days after symptom onset.[3, 19](OPTIMAS, NCT03759938) This form of stratification by infarct volume or by having broad initiation time windows where the decision to time the treatment at the treating physician's discretion, even in the context of randomization, may play a role in introducing a bias. It may also limit the understanding of whether the timing of DOAC initiation should be adjusted based on infarct size and/or clinical severity of the index event to reduce the risk of HT. While these trials are expected to advance the field, the broad randomization windows, the contrast effect of used composite outcomes, and lack of systematic imaging post treatment in most of the trials may leave some clinical equipoise and also facilitate continuation of current practice patterns based on expert opinion.

8.4 Conclusions

Currently available data suggest that early DOAC initiation after AF-related stroke is safe and perhaps even efficacious. However, this needs to be confirmed by ongoing randomized trials of early versus delayed DOAC initiation.

Table 8.1. Summary of ongoing randomized trials assessing the safety and efficacy of early versus delayed DOAC initiation after AF-related ischemic stroke

	LASER [3]	ELAN	OPTIMAS	TIMING [19]	START [18]
NCT number	NCT03494530	NCT03148457	NCT03759938	NCT02961348	NCT03021928
Intervention arm (early)	≤ 5 days after ischemic stroke	≤ 48 h after minor and moderate stroke or at day 6 + 1 day after major stroke	≤ 4 days after ischemic stroke	≤ 4 days after ischemic stroke	**Adaptive trial design:** Time to treatment delay of 3, 6, 10, or 14 days after mild/moderate ischemic stroke. 6, 10, 14, or 21 days after severe ischemic stroke
Control arm (delayed)	Between day 6 and 14 after ischemic stroke	Minor stroke after day 3 + 1 day, moderate stroke after day 6 + 1 day and major stroke after day 12 + 2 day	Between day 7 and 14 after ischemic stroke	Between day 5 and 10 after ischemic stroke	
Follow-up period	90 days	30 days (secondary outcomes at 90 days)	90 days	90 days	30 days (secondary outcomes at 30 and 90 days)
Including patients with HT	Yes	Yes	Yes	Yes	Yes
Using systematic imaging	Yes	No	No	No	No
Primary outcome	Incident radiographic HT	Composite of major bleeding, recurrent ischemic stroke, systemic embolism and/or vascular death	Composite of recurrent symptomatic ischaemic stroke, symptomatic intracranial haemorrhage and systemic embolism	Composite of recurrent ischemic stroke, symptomatic intracerebral hemorrhage, or all-cause mortality	Composite of recurrent ischemic stroke, systemic embolism, and major bleeding
Including biomarkers	Ability of leukocyte RNA to predict HT is included as a secondary outcome	----------	----------	Cardiovascular biomarkers (Troponin, NT-proBNP, and GDF-15)	----------
Sample size	150	2000	3478	3000	1500
Estimated end of study	December 2022	October 2021	September 2022	Not updated	August 2021
Treatment	Edoxaban	Any of the DOACs	Any of the DOACs	Any of the DOACs	Any of the DOACs

NCT, The National Clinical Trial number; h, hours; HT, hemorrhagic transformation; DOAC, direct oral anticoagulant; NT-proBNP, N-terminal pro b-type natriuretic peptide; GDF-15, Growth/differentiation factor-15

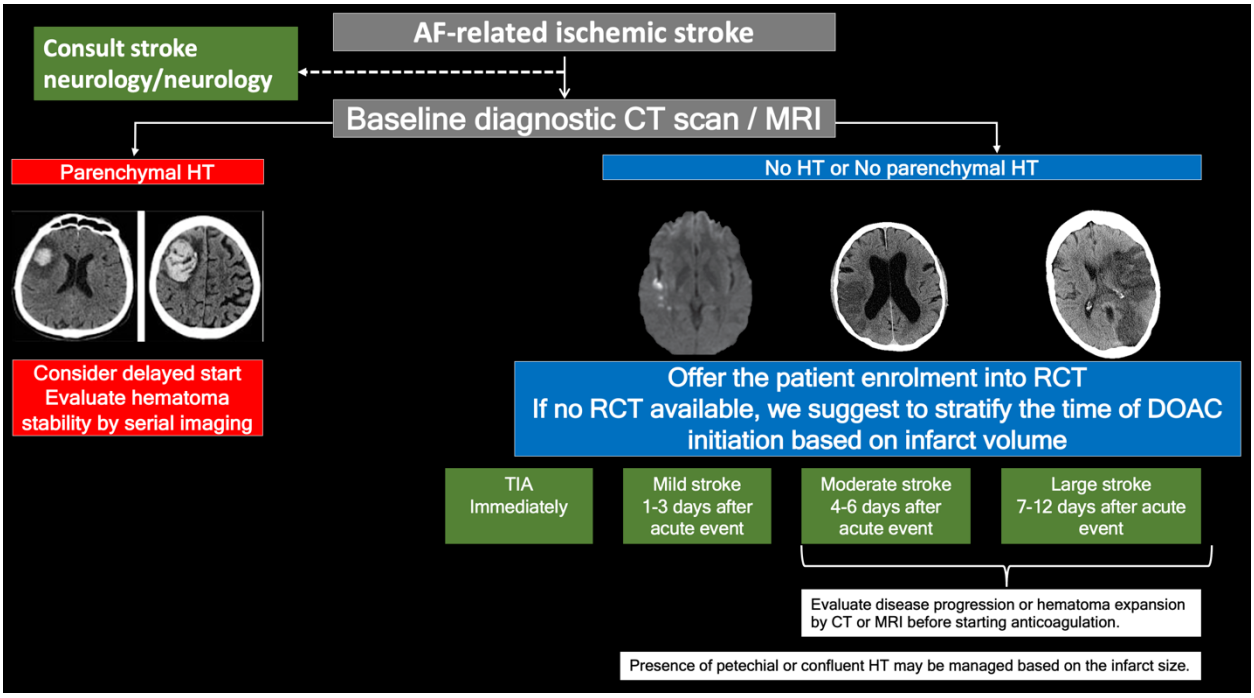

Figure 8.1. A suggested schematic approach for the timing of DOAC initiation after AF-related ischemic stroke in the meantime while RCTs are being completed.

AF, atrial fibrillation; HT, hemorrhagic transformation; RCT, randomized clinical trial; DOAC, direct oral anticoagulant; TIA, transient ischemic attack; CT, computed tomography; MRI, magnetic resonance imaging

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