CONFIDENTIAL

PROTOCOL TITLE

Canadian Pradax Acute Stroke/TIA Safety Study (CPASS)

Protocol No: CSC2012-01
Version: 2.3
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Sponsor: Dr. Ken Butcher

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AMENDMENTS:

1.	2.	3.	4.

Coordinating Investigator Agreement:

I have read this protocol and agree to abide by all provisions set forth within. I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice.

Professor Ken Butcher
Division of Neurology
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Signature: _____

Date: _____

Synopsis

Study Title:	**Canadian Pradaxa Acute Stroke Safety Study (CPASS)**
Protocol Number:	CSC2012-01
Development Phase:	Phase IV Registry
Indication:	Minor Stroke (NIHSS Score ≤ 3) and Transient Ischemic Attack Patients with a known history of or demonstrated atrial fibrillation (paroxysmal or persistent), who can be treated with dabigatran following stroke.
Study Drugs: (Including test, comparator, dosage form, dosing regimen and route)	Dabigatran Etexilate Dose: 150 mg PO BID OR 110 mg PO BID (dose determined by patient age and renal function) Route: PO Comparator : None (open label, single arm trial)
No. Subjects:	500
No. Centres:	15 centres within Canada
Study Duration:	2 years. Patients will participate in the trial for 1 month.
Objectives of the Study:	The primary aim of the CPASS registry is to demonstrate the safety of early anticoagulation with dabigatran following cardioembolic stroke. Safety will be established by demonstrating low rates of hemorrhage in this setting.
Study Endpoints: (Primary and Secondary)	*Primary Outcome* Symptomatic Hemorrhagic Transformation Rate (PH2) associated with clinical deterioration, defined as worsening of NIHSS score of 4 or more points within 30 days of initiating dabigatran therapy. *Secondary Outcomes* Any parenchymal haemorrhage (PH1 or PH2) on follow-up CT scan at 7±2 days post-enrolment Symptomatic hemorrhagic transformation rate (defined as above) in patients treated with warfarin prior to the index stroke/TIA.

Recurrent TIA/Ischemic Stroke within 30 days of enrolment

Systemic hemorrhagic complication rate within 30 days of enrolment

Study Design: Multicentre, prospective, open-label, single arm phase IV study.

Eligibility Criteria (Inclusion and Exclusion)

Inclusion criteria

1. All patients will be ≥ 18 years of age.
2. Minor ischemic stroke, defined as NIHSS score ≤ 3. Transient Ischemic Attack (TIA), defined as acute focal neurological deficits, with complete resolution of symptoms within 24 h of onset. In cases where onset time cannot be established, it will be considered to be the time when the patient was last known to be well.
3. Atrial Fibrillation (AF, paroxysmal or persistent). AF must be confirmed with ECG/Holter monitor, or by history All patients prescribed dabigatran according to the Canadian product label by the treating physician following their stroke/TIA. The decision to treat with dabigatran and the timing of the first dose will be determined by the attending physician, independent of the registry. All patients will have a CT scan or MRI, with findings consistent with an ischemic etiology of symptoms.
4. Ability to obtain informed consent obtained from patient or legally authorized representative.

Exclusion criteria

1. Acute or chronic renal failure, defined as eGFR <30 ml/min (Cockcroft Gault formula).
2. Known hypersensitivity to dabigatran or any other contraindication to dabigatran therapy, as per Canadian label information.
3. Prior treatment with dabigatran or any other novel oral anticoagulant (including all Factor Xa antagonists). Treatment with warfarin prior to the stroke/TIA is acceptable, but enrolment cannot begin until the INR is ≤1.5.
4. Prior symptomatic ischemic stroke (TIA is not an exclusion criterion)
5. Any significant ongoing systemic bleeding risk, i.e.

active GI/GU bleeding or recent major surgery.

6. Clinically significant recent past history or clinical presentation of ICH, subarachnoid haemorrhage (SAH), arterio-venous (AV) malformation, aneurysm, or cerebral neoplasm. At the discretion of each Investigator.
7. Hereditary or acquired hemorrhagic diathesis.
8. Anticipated inability to comply with follow up.
9. Any condition that, in the judgment of the investigator could impose hazards to the patient if study therapy is initiated or affect the participation of the patient in the study.

Study Procedures: This is a phase IV registry study. No additional procedures are included in the study. Standard clinical data will be collected. This will include a physical examination and NIHSS score assessment at baseline.
In addition, all neuro-imaging will be collected. Standard imaging includes a non-contrast CT brain at baseline and 7±2 days post-treatment.
Repeat NIHSS score assessment at the time of the 7 day CT scan.
Repeat clinical and NIHSS score assessment 30 days post-enrolment will also be collected when performed as part of standard care.

Safety Parameters/analysis: An independent DSMB will be sent blinded outcome data, including all cases with symptomatic or asymptomatic parenchymal haemorrhage. The DSMB will review adverse events after every 100 patients recruited.

Imaging Parameters/Analysis All imaging data collected as part of standard care will be sent to the core imaging lab for analysis.

Image Analysis. Dicom CT data will be transferred to the Stroke Imaging Laboratory at the University of Alberta for post-processing and analysis. All image assessments will be performed using the Quantomo software package (Cybertrial Inc, Calgary, AB).

All cases of hemorrhagic transformation seen on day 7 scans will be graded using the ECASS (European Cooperative Acute Stroke Study) hemorrhage classification scheme:[1]

1. PH2 - parenchymal hemorrhage as a blood clot in more than 30% of the infarcted area with substantial space-

occupying effect.
2. PH1 - parenchymal hemorrhage as blood clots in 30% or less of the infarcted area with some slight space-occupying effect.
3. HT2 - hemorrhagic transformation 2 - confluent petechiae within the infarcted area but no space-occupying effect.
4. HT1 - hemorrhagic transformation 1 – small petechiae along the margins of the infarct.
5. R - remote ICH, i.e. not topographically related to the infarct (most often in the contralateral hemisphere).

A symptomatic ICH will be defined as PH2, associated with an NIHSS deterioration of ≥4 points.

Laboratory Parameters/Analysis: Standard bloodwork, including aPTT, INR and TT (when ordered) within 20 days will be collected. No additional bloodwork will be collected for the study.

Sample Size Determination: There are currently insufficient data upon which to base a sample size. The expected rate of hemorrhagic transformation has never been accurately or prospectively documented in this population. The sample size of 500 patients is expected to be sufficient to demonstrate the frequency of hemorrhagic transformation within this population.

Statistical Analyses: The primary outcome will be occurrence of PH2 at 30 days. Secondary outcomes will be ischemic stroke, any intracerebral hemorrhage, MI and death. In addition we will compare the rate of hemorrhagic transformation in patients started on dabigatran within 7 days of stroke/TIA versus those started >7 days after symptom onset.

Descriptive statistics will be used to describe all outcomes (see protocol section 7.1).

Canadian Pradaxa Acute Stroke/TIA Safety Study (CPASS)

Canadian Stroke Consortium

Protocol Version 2.3

November 14, 2013

1. Introduction

1.1 Medical Background

A transient ischemic attack (TIA) has traditionally been defined as a focal neurologic deficit lasting less than 24 hours, but alternative definitions based on tissue injury have been more recently proposed.[2] This clinical definition has been based on the assumption that TIAs are associated with complete resolution of brain ischemia occurring rapidly enough to cause only transient symptoms and no permanent brain injury, i.e. stroke. A recently completed MRI research study at the University of Alberta indicates that TIA and minor stroke actually represent a continuum of symptoms secondary to brain ischemia.[3] There is also substantial evidence that the period shortly after a TIA or minor stroke is one of elevated recurrent stroke risk; as high as 17% at 3 months.[4, 5] We have previously reported that MRI markers of new infarction are actually present within 7 days of the index event in 18% of patients.[3] TIA and minor stroke can therefore be seen as a sentinel warning for impending major stroke, which offers a potential window for therapeutic intervention. Given the large number of patients who suffer a TIA/minor stroke, it is important to identify and target those patients at highest risk for early recurrence.

Treatment of Minor Stroke/TIA: In addition to urgent and rapid investigation of stroke mechanism after TIA/minor stroke, a logical approach to prevent early recurrence is aggressive hyperacute antithrombotic therapy. This treatment strategy is aimed at preventing both recurrent thromboembolism and propagation of existing thrombi. In acute coronary syndrome patients, antithrombotic therapy consists of both anticoagulants (low molecular weight heparin) and combination antiplatelet agents (ASA+high dose clopidogrel, or more recently prasugrel/ticagrelor). In TIA/stroke, the choice of antithrombotic agent varies with the mechanism of cerebral ischemia. The initial therapy in most patients consists of antiplatelet therapy, generally ASA. Combination antiplatelet therapy is sometimes used empirically following TIA/minor stroke, although this may not be an ideal approach either. A previous trial in 392 patients demonstrated a trend towards reduction of recurrent events by day 90 when patients were treated with a combination of ASA and clopidogrel for 90 days (Absolute Risk Reduction = 3.3% [95% CI -1.9, 9.4]), but this was also complicated by excess hemorrhagic events.[6] In unselected ischemic stroke patients (treated irrespective of the presence or absence of atrial fibrillation), the benefits of traditional anticoagulants, particularly heparin, have been consistently offset by an increased incidence of intracranial hemorrhagic complications.[7] The risk benefit ratio appears to be similar in patients with and without atrial fibrillation, although there are significant knowledge and evidence gaps with respect to the timing of anticoagulation in patients with cardioembolic stroke.

Timing of Anticoagulation after Cardioembolic TIA/Stroke:

It is clearly established that patients with atrial fibrillation who have suffered a stroke/TIA are at high risk for recurrence and require long-term anticoagulation. What is unknown is the optimal timing of anticoagulation after an ischemic stroke has occurred. Following cardioembolic stroke, atrial fibrillation patients are at risk for early recurrent thrombo-embolism. Estimates of the rate of recurrent stroke in this setting vary widely. Previous studies have indicated new ischemic strokes occur at rates anywhere from 3% to 20% within two weeks of the index event.[8-11] This is the primary rationale for early anticoagulation after cardioembolic stroke. There is some evidence that early anticoagulation is associated with improved outcomes after ischemic stroke.[12] Indeed, it has been shown that early heparin use does reduce recurrent ischemic stroke risk by 2.1%, but this is offset by a 1.7% increase in the rate of HT.[13] Studies of low molecular weight and unfractionated heparin use in acute stroke have generally indicated these agents are associated with moderately increased risk of HT.[9-11, 14] There are currently no data indicating the frequency of HT associated with early warfarin treatment, without heparin bridging.

Based on the above evidence, current best practice guidelines recommend against urgent anticoagulation in patients with moderate to severe ischemic stroke, however, due to the elevated risk of hemorrhagic transformation (HT) immediately after stroke.[15] A specific time point at which to begin anticoagulation is not recommended in guideline statements.[15] This clinical equipoise has resulted in significant variation in practice patterns. Currently, most CSC physicians base the timing of anticoagulation on clinical severity and infarct size, as seen on CT scan. Most physicians will defer anticoagulation anywhere from 5 to 14 days after ischemic stroke when infarct volume is extensive. In patients with small infarct volumes, assessed with CT or MRI, however, anticoagulation is often begun within 24-72 hours of stroke onset, and in some cases immediately after clinical assessment and CT scan.

The oral direct thrombin inhibitor dabigatran has recently been approved for the primary and secondary prevention of ischemic stroke in patients with atrial fibrillation. Uptake of dabigatran within the Canadian stroke community has been rapid. It has several advantages, relative to warfarin. These include superior protection from cardioembolic stroke, lower rates of intracranial hemorrhage, fixed doses and an absence of coagulation monitoring requirements.[16] Recent discussions amongst Canadian Stroke Consortium (CSC) members have led to the identification of three major outstanding issues related to dabigatran use in patients with cerebrovascular disease:

1. Timing of dabigatran initiation after ischemic stroke/transient ischemic attack (TIA)
2. Safety of thrombolytic agents after ischemic stroke in patients taking dabigatran
3. Optimal management of intracranial hemorrhage in patients taking dabigatran

From both the population health and stroke physician perspectives, the most important clinical problem is the first of these issues. Approximately 20% of acute stroke/TIA is secondary to atrial fibrillation, which is diagnosed at the time of the stroke in the majority of cases. In addition, many patients with known atrial fibrillation are not treated until after an ischemic stroke.[17] The timing of dabigatran initiation after ischemic stroke/TIA is therefore an everyday problem that must be addressed on stroke units across the country.

Dabigatran and Ischemic Stroke:

Due to the uncertain safety of anticoagulation immediately after stroke, patients with recent stroke (< 2 weeks from symptom onset) have been excluded from clinical trials of newer anticoagulants. Dabigatran is unique in that unlike other antithrombotic drugs studied in cerebrovascular disease, it appears to be associated with a much lower risk of intracranial hemorrhagic complications, and a reduction in ischemic stroke.[16] It is probable that dabigatran can be used safely in patients with acute and subacute ischemic stroke. *We therefore expect that dabigatran will be associated with low rates of HT when administered acutely following cardioembolic stroke.* Patients will therefore be protected from early recurrent stroke, without the concomitant increased risk of hemorrhagic complications associated with other anticoagulants.

Treatment Opportunities:

The primary benefit of early anticoagulation is a reduction in early recurrent embolic events and therefore improved outcomes. Dabigatran offers the possibility of rapid therapeutic anticoagulation in this setting, a significant benefit over the days to weeks required to achieve a therapeutic INR with warfarin. The complexities associated with initiating warfarin therapy result in a significant treatment gap. Data from the Registry of the Canadian Stroke Network indicate that nearly 50% of patients with cardioembolic stroke are not anticoagulated one year after their index event.[17] Early treatment initiation is expected to result in improved rates of anticoagulation following stroke and greater adherence to therapy. The acute stroke period, when patients are cared for in stroke units, by specialized physicians

represents an opportunity to optimize therapy, including lifelong anticoagulation. If it can be demonstrated that dabigatran can be safely administered early after stroke, as warfarin is used currently, it may ultimately result in higher rates of long-term anticoagulation and consequently a reduction in stroke rates. The current wording in the product monograph stipulating a delay in initiation of dabigatran will result in continued use of warfarin in patients for whom Dabigatran would have greater safety and efficacy.

Given the equipoise and variable practice patterns amongst CSC physicians, the safety of dabigatran after stroke can be effectively addressed using a prospective single arm study design. We have sufficient variability and ischemic stroke patient volume nation-wide to ensure a broad based sample with respect to stroke severity and timing of dabigatran initiation. We have therefore designed a registry of dabigatran treatment following ischemic stroke/TIA. A unique feature of the CPASS registry is the central collection and reading of all imaging data. This will provide invaluable information related to both the nature and predictors of any HT associated with early dabigatran use. The CSC has successfully conducted a phase IV registry of this nature, including central image reading and analysis, in the past (Canadian Alteplase for Acute Stroke Effectiveness Study).[18]

1.2 Drug Profile

Proprietary name: Dabigatran etexilate (INN). The pro-drug dabigatran etexilate is used in its salt form dabigatran etexilate mesilate (BIBR 1048 MS).

Chirality: Dabigatran etexilate mesilate has no chiral centres and therefore does not form enantiomers. Geometric isomers (tautomers) are possible.

Physical Appearance: Yellow-white to yellow powder. The crystals have a rod-like habit.

Melting Point: 180 ± 3 °C (DSC: 10 K min-1 heating rate)

Dissociation Constants: pKa1 = 4.0 ± 0.1, pKa2 = 6.7 ± 0.1

Apparent Partition Coefficient: The partition coefficient of the neutral form (free base) is log P = 3.8

Hygroscopicity: Non-hygroscopic

pH-Solubility Profile: Solubility is strongly pH dependent with increased solubility at acidic pH. The solubility in water is 1.8 mg/mL

2. Canadian Pradax Acute Stroke/TIA Safety Study (CPASS) Rationale and Objectives

2.1 Rationale

Ideally, anticoagulation should be started as soon as possible following a stroke/TIA in patients with new or previously diagnosed atrial fibrillation. This prevents early recurrent events and also ensures long-term secondary prevention strategies are implemented at the point of maximum medical contact, which is always at the time of the acute event. The rate of hemorrhagic complications associated with older anticoagulants has never been well characterized, but is recognized as a genuine risk that must be considered and generally delays anticoagulation. As described above, intracranial hemorrhagic complication rates in dabigatran-treated patients are markedly lower than those associated with older anticoagulants. Thus, dabigatran is hypothesized to be an ideal drug for early anticoagulation after acute stroke/TIA.

Although aggressive antithrombotic therapy has been shown to reduce the number of new ischemic events following stroke/TIA, this has always been offset by an increase in the risk of hemorrhagic complications. Dabigatran appears to be much safer with respect to intracranial bleeding and therefore offers a unique treatment opportunity in these high-risk patients. A registry will provide critical reassurance to stroke clinicians concerned about precipitating hemorrhagic transformation. If it can be

demonstrated to be safe, early treatment with dabigatran can be recommended, which may lead to lower rates of cardioembolic stroke recurrence. In addition, this will facilitate optimal treatment of patients who require long-term anticoagulation after ischemic stroke.

2.2 Study Objectives

1. Demonstrate the safety of early dabigatran initiation after minor stroke/TIA in patients with atrial fibrillation.
2. Determine the frequency of asymptomatic hemorrhagic transformation after 7 days of dabigatran treatment following stroke/TIA
3. Determine the effect of asymptomatic hemorrhagic transformation on functional and neurological outcome at 30 days.

2.3 Risk-Benefit Assessment

The risk of recurrent stroke after TIA/minor stroke in AF patients is estimated to range from 3-20%. It is expected that early anticoagulation will reduce the rate of re-emoblization by at least 85%. The risk of symptomatic hemorrhagic transformation in patients administered heparin within one week is 1.7%. Intracranial hemorrhagic complication rates in RE-LY were 1/3 that of warfarin. We hypothesize that a similar pattern of increased safety with respect to intracranial hemorrhagic complications will be seen in the acute setting. Thus, symptomatic hemorrhagic transformation rates of 0.6% are expected, which is comparable to the rate seen in patients treated with antiplatelet agents alone. The major expected benefit of this study is early anticoagulation, resulting in fewer cases of prolonged delays to the initiation of appropriate secondary prevention therapy.

3. Canadian Pradax Acute Stroke/TIA Safety Study (CPASS) Design

3.1 Study Aim and Design: The primary aim of the CPASS registry is to demonstrate the safety of early anticoagulation with dabigatran following cardioembolic stroke. CPASS is a prospective open label single arm observational study. Safety will be established by demonstrating low rates of hemorrhage in this setting.

3.1.1 Administrative Structure: CPASS is a Canadian Stroke Consortium led study. The study coordinating centre is at the University of Alberta. Case report forms and data monitoring will be completed electronically, using an online EDC system. All imaging data will be read centrally at the Stroke Imaging Laboratory at the University of Alberta.

3.2 Study Design Considerations: A randomized controlled design was considered (dabigatran versus warfarin). This is considered impractical for a number of reasons. Novel oral anticoagulants are recommended as first line agents for stroke prevention in AF patients by the Canadian Cardiovascular Society.[19] These agents are associated with improved safety with respect to bleeding complications. This makes randomization of a patient to warfarin who would otherwise be prescribed dabigatran somewhat ethically dubious. In addition, a randomized design would necessitate a very large study, which would not be completed in a reasonable period of time. A registry design allows us to address the question of safety in a systematic fashion. A safety threshold has been defined for any anticoagulant use early after stroke, based on the rates of warfarin-associated intracranial hemorrhage, which have been reported to be 0.5 to 2.5 per 100 patient years.[20-24] The registry design therefore permits determination of whether or not dabigatran is within this threshold. Finally, the systematic collection of clinical and imaging data will allow us to determine any risk factors for hemorrhagic transformation associated with early anticoagulation.

3.3 Selection of Population. A log of all patients included in the study (consent obtained) will be maintained at the trial coordinating centre, irrespective of whether they are treated or not. Only patients actually treated with dabigatran will be followed in the registry. Basic patient demographics, ethnicity, stroke severity (NIHSS), medications, including previous warfarin use, previous stroke/TIA, other co-

morbidities, particularly hypertension, diabetes, hypercholesterolemia and ischemic heart disease, CHADS-Vasc, HAS-BLED, history of gastrointestinal or other hemorrhage will all be recorded (**Appendix 1**).

3.3.1 Patients. Male and female patients with acute TIA or ischemic stroke will be recruited from the Emergency Departments and stroke units at CSC investigator sites. All patients will have documented evidence of atrial fibrillation (permanent or paroxysmal). Informed consent will be obtained from patients or surrogate decision makers prior to enrolment in all cases.

3.3.2 Inclusion Criteria. All patients will be 18 years or older. Eligible patients will have ischemic stroke (NIHSS score ≤ 3) or TIA (complete resolution of focal neurological deficits within 24 hours) and atrial fibrillation (paroxysmal or persistent). The decision to treat with dabigatran and the timing of the first dose will be determined by the attending physician, independent of the registry. In cases where stroke onset time cannot be established, it will be considered to be the time when the patient was last known to be well. All patients will have a CT scan or MRI, with findings consistent with an ischemic etiology of symptoms. Patients taking warfarin *prior to* the stroke/TIA will be eligible, but INR must be ≤1.5 prior to initiation of dabigatran.

3.3.3 Exclusion Criteria. Patients in whom dabigatran is contraindicated according to the Canadian product monograph will not be eligible. , i.e. severe renal failure or significant ongoing bleeding risk, will not be eligible. These specific contraindications in the Canadian product monograph at the time are:

- Severe renal impairment (CrCl < 30mL/min)
- Hemorrhagic manifestations, bleeding diathesis, or patients with spontaneous or pharmacological impairment of hemostasis
- Lesions at risk of clinically significant bleeding, e.g. extensive cerebral infarction (hemorrhagic or ischemic) within the last 6 months, active peptic ulcer disease with recent bleeding
- Concomitant treatment with strong P-glycoprotein (P-gp) inhibitors, i.e. oral ketoconazole
- Known hypersensitivity to dabigatran or dabigatran etexilate or to any ingredient in the formulation or component of the container
- Concomitant treatment of dabigatran etexilate with any other anticoagulant, including unfractionated heparin (UFH), except at doses used to maintain a patent central venous or arterial catheter, low molecular heparins (LMWH), such as enoxaparin and dalteparin, heparin derivatives, such as fondaparinux, anti-thrombin agents, such as bivalirudin, and oral anticoagulants, such as warfarin, rivaroxaban, apixaban, except under circumstances of switching therapy to or from dabigatran
- Presence of prosthetic heart valve(s) requiring anticoagulation due to valvular status itself

Patients with a history of symptomatic ischemic stroke prior to the index event will not be eligible. All patients taking dabigatran or any other novel oral anticoagulant (including all Factor Xa antagonists) prior to the stroke will be ineligible. Individuals on warfarin at the time of the incident event are eligible, provided the INR is ≤1.5 prior to initiation of dabigatran.

4.0 Treatments

4.1 Prescribed Study Treatments. Patients in whom dabigatran is initiated within 14 days of TIA/stroke symptom onset will be included in the registry. The timing of initiation of therapy within that 14 day window will be determined by the treating physician. The factors related to physician choice of initiation time (relative to symptom onset) will be recorded (**appendix 5**).

4.1.1 Identity of test products and comparators. NA.

4.1.2 Treatment Group Assignment. NA.

4.1.3 Selection of Dose. Patients will be treated either at a dose of 110 mg BID or 150 mg BID. The dose will be determined by treating physician. The physician rationale for the dose selected will be recorded in all cases (**appendix 6**).

5. Variables and Assessment.

5.1.1 Effectiveness. This is a registry of the safety of early anticoagulation (see 5.2). A measure of the effect of early anticoagulation will be assessed; the rate of new ischemic stroke/TIA occurrence within the 30-day study period will be recorded. It is recognized that the event rate will be low and the study is neither designed, nor powered to demonstrate a decrease in early ischemic stroke rates.

5.1.2 Primary Outcome (Safety). The primary study outcome measure is the symptomatic hemorrhagic transformation rate (PH2 associated with clinical deterioration, defined as worsening of NIHSS score of 4 or more points, within 30 days of initiating dabigatran therapy).

5.1.2 Secondary Outcomes.

The rate of any objective hemorrhagic transformation on the day 7 post-dabigatran initiation non-contrast CT scan.

The rate of secondary hemorrhagic transformation in patients taking warfarin prior to the stroke/TIA.

The rate of hemorrhagic transformation in patients started on dabigatran within 7 days of stroke/TIA versus those started >7 days after symptom onset. Recurrent TIA/Ischemic Stroke within 30 days of dabigatran initiation.

Systemic hemorrhagic complication rate within 30 days of dabigatran initiation.

The rate of hemorrhagic transformation in patients started on dabigatran within 7 days of stroke/TIA versus those started >7 days after symptom onset.

5.2 Assessment of Adverse Events.

5.2.1 Definitions of Adverse Events.

Adverse Event. An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious Adverse Event. A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability/incapacity, requires or prolongs patient hospitalization, is a congenital anomaly/birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Intensity of Adverse Event. The intensity of the AE should be judged based on the following:

1. Mild: the adverse event is temporary and easily tolerated by the subject;
2. Moderate: the adverse event causes the subject discomfort and interrupts the subject's normal activities.

3. Severe: the adverse event causes considerable interference with the subject's normal activities and may be incapacitating or life threatening including hospitalization or prolongation of hospitalization.

Causal Relationship of Adverse Event. Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant disease and relevant history. Assessment of causal relationship should be recorded in the case report forms.

Yes: There is a reasonable causal relationship between the product administered and the AE.
No: There is no reasonable causal relationship between the product administered and the AE.
Worsening of the underlying disease or other pre-existing conditions will be recorded as an (S)AE in the CRF.

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in CRF, if they are judged clinically relevant by the investigator.

5.2.2 Adverse Event Reporting. Investigators will report AEs using standardized event, resolution and association codes. The SAE reporting period includes the entire study duration (1 month) and an additional three days. All acute coronary syndromes (ACS) will be reported.

The Principal Investigator shall forward all (1) SAEs and non-serious AEs relevant to the reported SAE and (2) non-serious AEs which are assessed as related to the study drug by fax (1-888-723-0333) to the BI Safety Contact Point (Dr. Ralph Ferguson).

For forwarding SAEs, any non-serious AE relevant to the reported SAE, and all related non-serious AEs, the Principal Investigator shall use the study specific non-interventional study AE report form.

All reports concerning SAEs and any non-serious AEs relevant to the reported SAE, and any related non-serious AEs shall be forwarded to the BI Safety Contact Point immediately (within twenty four hours or next business day whichever is shorter).

The Principal Investigator shall be responsible to follow up on all information regarding a reported Drug Exposure during Pregnancy. Principal Investigator shall ensure that any SAE / related AE during and after pregnancy will be reported to the BI Safety Contact Point on the study specific non-interventional study AE report form and the timeline described above.

The AE reporting process is further described in the Safety Data Exchange Agreement.

5.2.3 Assessment of safety laboratory parameters.

Imaging Data Collection. No additional imaging will be required for study participants. Only standard clinical data will be collected. Acute baseline CT scans will be collected. Dicom files will be transferred to a central imaging database. All patients will have a follow-up non-contrast CT scan 7±2 days after enrolment, in order to assess for early asymptomatic hemorrhagic transformation. In the event of any clinical deterioration, a repeat CT scan will be performed immediately. In addition, any supplemental brain imaging completed within the first 30 days after enrolment will be collected.

Image Analysis. Dicom CT data will be transferred to the Stroke Imaging Laboratory at the University of Alberta for post-processing and analysis. All image assessments will be performed using software developed specifically for CT brain image analysis (Quantomo software package, Cybertrial Inc, Calgary, AB). The extent of any objective acute and chronic ischemic changes on all CT scans will be

assessed using Alberta Stroke Program Early CT Scores (ASPECTS).[25] It is expected baseline scans will not have evidence of acute ischemic changes, but this will be verified centrally. The extent of periventricular leukoariosis will also be measured using planimetric techniques and an intensity threshold algorithm included in the Quantomo softare package.

All cases of hemorrhagic transformation seen on post-dabigatran treatment scans will be graded using the ECASS (European Cooperative Acute Stroke Study) hemorrhage classification scheme:[1]

6. PH2 - parenchymal hemorrhage as a blood clot in more than 30% of the infarcted area with substantial space-occupying effect.
7. PH1 - parenchymal hemorrhage as blood clots in 30% or less of the infarcted area with some slight space-occupying effect.
8. HT2 - hemorrhagic transformation 2 - confluent petechiae within the infarcted area but no space-occupying effect.
9. HT1 - hemorrhagic transformation 1 – small petechiae along the margins of the infarct.
10. R - remote ICH, i.e. not topographically related to the infarct (most often in the contralateral hemisphere).

A symptomatic ICH will be defined as PH2, associated with an NIHSS deterioration of ≥4 points.

6. Investigational Plan

6.1 Visit Schedule / Clinical Data Collection. No additional procedures or assessments will be mandated for study participants. Standard clinical assessments and data will be collected. This will include baseline National Institutes of Health Stroke Scale NIHSS, Glasgow Coma Scale (GCS) and vital signs, which will be recorded in a case report form. Stroke risk factors, past medical history and medications, baseline complete blood count, coagulation profile and renal function tests will also be recorded. CHADS2 and CHADSVaSC scores will also be recorded. Clinical endpoints will be ischemic stroke or intracranial hemorrhage within 30 days of anticoagulant initiation. All cerebral ischemic and intracranial hemorrhagic endpoints will be centrally adjudicated from anonymized clinical records, with the intracranial hemorrhages classified as described above. A data collection form will be filled out for each subject at 30 days post-enrolment indicating clinical status and occurrence of outcome events.

6.2 Details of Study Procedures

6.2.1 Screening and run-in procedures. NA.

6.2.2 Treatment Period. Patients will be treated long-term with dabigatran if deemed appropriate by the attending physician and the patient is in agreement. The study outcome event period is 30 days from drug initiation. The SAE reporting period is an additional 7 days.

The time from symptom onset to dabigatran initiation will be recorded in the CRF. In all cases, dabigatran will be prescribed by a stroke neurologist participating in the registry. The location of the patient at the time of dabigatran initiation will be recorded (inpatient/outpatient/Emergency Department).

6.2.3. End of Trial and follow-up. The registry data collection period will be complete after 30 days.

7. Statistical Methods and Sample Size

7.1 Statistical Analysis and Sample Size Considerations: The registry will include 500 patients. This sample size is considered adequate to ensure inclusion of a significant number of patients treated at a range of time points within the post-stroke period. The primary analysis will be done on an Intention

To Treat basis. We will also complete a sensitivity analysis on individuals who discontinued dabigatran treatment and/or switched to other antithrombotic agents. Based on the inclusion/exclusion criteria, there will not be any individuals taking dabigatran concomitantly with other antithrombotic drugs.

The primary and secondary outcomes will be defined with descriptive statistics. The rate of PH2 (and all other forms of hemorrhagic transformation) will be defined as a ratio (%) of the total number of patients enrolled in the study (ITT analysis).

The primary stratification variable is warfarin use prior to the TIA/minor stroke. The secondary strata are 1. Dabigatran dose (150 mg BID versus 110 mg BID) and 2. Time to initiation of therapy (0-2 days, 3-7 days and > 7 days). All results including baseline patient characteristics will be stratified by use of warfarin prior to the event and by the dabigatran dose after the event as described in **appendices 2-4**.

Limitations. There are recognized limitations to this study. The eligibility criteria are consistent with a low risk population, and the results of this study will not be generalizable to other, higher risk stroke/TIA populations. Even in the population of TIA and minor stroke patients, the time between symptom onset and treatment initiation may vary with the severity of the clinical presentation. Although it is not our intention, clinicians may be more likely to initiate therapy earlier in patients with complete resolution of all neurological deficits. Only dabigatran treated patients will be included in this registry. Unintended selection bias may also arise from survival bias over the time from incident stroke/TIA to time of dabigatran treatment and start of follow-up. Finally this is a small (500) single arm study with a relatively short (30 day) follow-up period. This short time period will permit assessment of the most important safety variable (hemorrhagic transformation rates). It will also minimize loss to follow-up. Although functional outcome is generally assessed at 90 days, this pilot study is too small to adequately assess that endpoint.

7.2 Hypotheses Statements:

Not applicable. The study is hypothesis generating only.

7.3 Interim Analyses. No interim analyses are planned.

8. Informed Consent, Data Protection, Study Records

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.
The investigator should inform Boehringer-Ingelheim immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

The rights of the investigator and of Boehringer-Ingelheim with regard to publication of the results of the study are described in the investigator-initiated study contract. As a general rule, no study results should be published prior to finalization of the study report.

8.1 Source Documents. Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator site. Data reported in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, pending on the trial; also current medical records must be available.

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Appendix 1: Baseline patient characterists to be collected in case report form.

Variable	Stratification (if applicable	
Sex	M	F
Age	>80	<80
Prior TIA	Y	N
Prior Stroke	Y	N
Carotid Stenosis	Y	N
Carotid Endarterectomy	Y	N
Carotid Stent	Y	N
Prior STEMI	Y	N
Prior NSTEMI	Y	N
CABG	Y	N
Coronary Stent	Y	N
Chronic Renail Failure	eGFR <60 >50 ml/min	eGFR >30 <50 ml/min
Diabetes	Y	N
HbA1c	>7%	<7%
Hypertension	Y	N
Systolic BP at recruitment	>140 mmHg	<140 mmHg
Diastolic BP at recruitment	>90 mmHg	<90 mmHg
CHF history	Y	N
Dementia history	Y	N
Medications	List	
Current Smoker		
Ex-smoker		
CHADS2 (0-6)		
CHADS-VASc (0-6)		
HAS-BLED (0-6)		
Alcohol/drug abuse	Y	N
History of PE/DVT	Y	N
Impaired liver function	Y	N
Prior intracranial hemorrhage	Y	N
Prior GI/GU hemorrhage	Y	N
Prior other hemorrhage	Y	N
Prior cerebral aneurysm	Y	N
peripheral artery disease (PAD), aortic plaque	Y	N
time since first AF diagnosis	Y	N
Previous cardioversion	Y	N
Ethnicity		
Heart rate		
Weight/height/BMI		

Appendix 2: Patient characteristics stratified by prior stroke treatment and dabigatran dose post TIA/stroke.

	Treatment prior to TIA/stroke				
	VKA naive		VKA		
	Dabigatran dose post TIA/stroke				
Baseline	110 mg	150 mg	110 mg	150 mg	P value (VKA niaive vs. VKA)
Age, Sex					
Prior TIA					
Indext event					
TIA/stroke					
Treatment					
Lysis, surgery					
Dabigatran treatment initiation after TIA/stroke					
0-2 days					
0					
1					
2					
3-7 days					

Appendix 3: Patient characteristics stratified by time of treatment intitiation after TIA/stroke.

	Dabigatran treatment initiation after TIA/stroke		
	0-2 days	3-7 days	>7 days
Prior untreated			
110 mg dabi (post TIA/stroke)			
150 mg Dabi (post TIA/stroke)			
Prior VKA			
110 mg dabi (post TIA/stroke)			
150 mg Dabi (post TIA/stroke)			
Baseline charateristic			
Age, sex, … prior TIA/stroke			
Index event			
TIA/stroke			
Treatment			
Lysis, surgery			

Appendix 4: Outcome events stratified by prior TIA/stroke treatment and dabigatran dose post TIA/stroke.

	Treatment prior TIA/stroke				
	VKA niaive		VKA		
	Dabigatran dose post TIA/stroke				
	110 mg	150 mg	110 mg	150 mg	
Symptomatic HT					
0-2 days after DE Initiation					
3-7 days after DE Initiation					
>7 days after DE Initiation					
Asymptomatic HT					
0-2 days after DE Initiation					
3-7 days after DE Initiation					
>7 days after DE Initiation					
Recurrent Stroke/TIA					
0-2 days after DE Initiation					
3-7 days after DE Initiation					
>7 days after DE Initiation					

Appendix 5: Factors in physicians's decision when to initiate post TIA/stroke treatment.

	Most important	Important	Less important	Not important
Baseline characteristic				
Age, sex, prior TIA/stroke, CrCl				
Index event				
TIA				
stroke				
Stroke Severity (NIHSS)				
Infarct Size (CT/MRI)				
Thrombolysis				
Previous Surgery				
Other medications (list drug(s) factored in decision)				
Co-morbidiities (list those factored in decision)				
Others				

Appendix 6: Factors in physicians' choice of dabigatran dose.

	Most important	Important	Less important	Not important
Baseline characteristics				
Age, sex, prior TIA/stroke. CrCl/eGFR				
Index event				
TIA				
stroke				
Treatment				
Lysis, surgery				
Others				