Warfarin and Thrombolysis: What are the risks?

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Objectives

- Discuss atrial fibrillation and stroke
- Discuss warfarin treatment for AFib
- Discuss risk associated with combining Warfarin and tPA treatments
- NOACs
- Point of Care Testing

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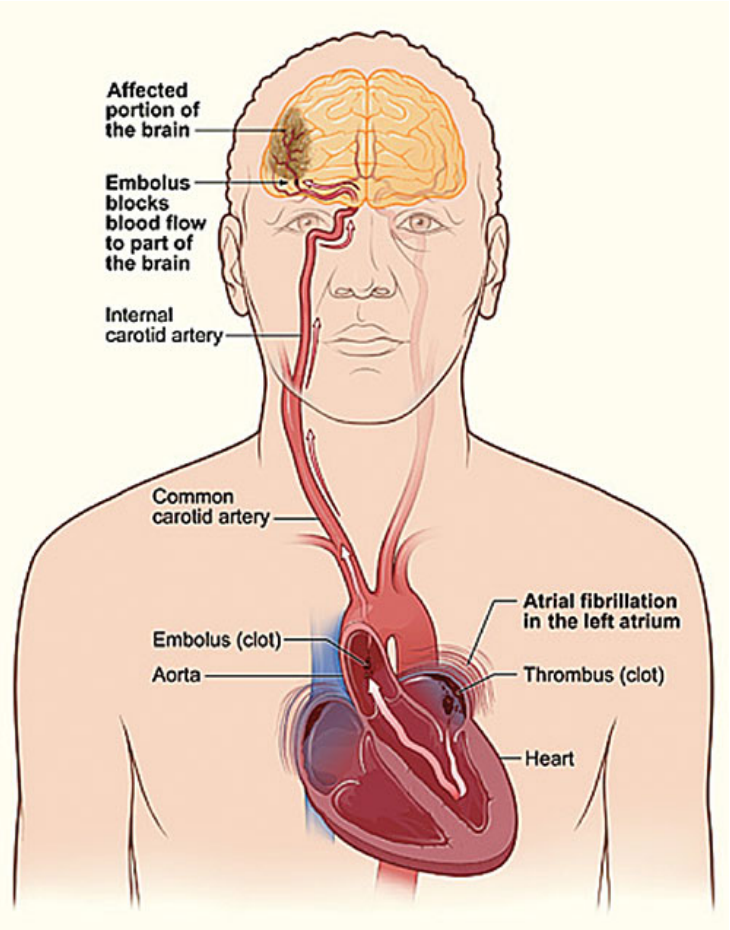
BACKGROUND: AFIB, WARFARIN, INR

Background – AFib and Stroke

- Atrial fibrillation (AFib) is an irregular heart beat which causes the atria to have less efficient contractions
- This can cause blood to pool in the atria leading to blood clots in the atria
- If a piece of clot breaks away and travel up the carotid artery it could cause an ischemic stroke



https://www.nlm.nih.gov/medlineplus/magazine/issues/winter15/images/afibpersonlarge.jpg

Background – AFib and Stroke

- Overall prevalence of AFib in the population ~1%
- Prevalence increases with age
  - 4% in individuals 60+
  - 9% in individuals 80+
- Despite anticoagulation therapy 1 – 4% of AFib patients may experience an ischemic stroke
- AFib is estimated to cause ~15% of ischemic strokes

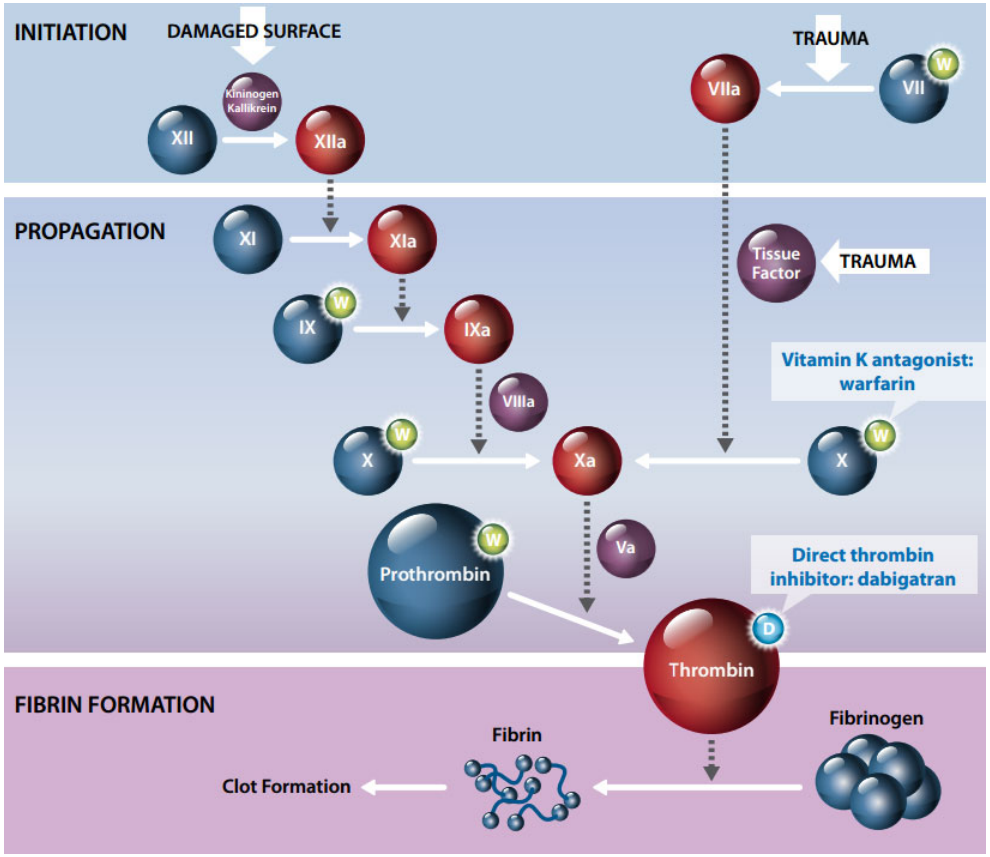
Background – AFib Treatments

- To mitigate this stroke risk AFib patients are often treated with anticoagulants
  - This can include warfarin, dabigatran, heparin, aspirin, etc.

- Patients could be taking anticoagulants for a number of other reasons as well
  - DVT/PE
  - Mechanical heart valve
  - Anti-phospholipid syndrome

Background – What is Warfarin?

- Warfarin is a Vitamin K antagonist which can be taken orally
- It disrupts the clotting cascade at several steps to prevent thrombus formation



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Background – Issues with Warfarin

- Numerous interactions with food and drugs
  - Foods containing vitamin K (dark leafy green veggies) can counter act warfarin effects and decrease INR
  - Certain medication interactions can cause increased INRs
- Requires individualized dosing for every patient and routine coagulation monitoring
  - Time and labour intensive
- If below target levels the patient is at an increased risk of clotting
  - Commonly dosed to target an INR of 2 – 3
- However, its effects can be easily reversed with medication

Background - INR

- International Normalized Ratio
- Begin with a prothrombin time test which measures how long in seconds it takes for your blood to clot
- The INR is the standardization of this result
  - Adjusted for clotting reagent used
- Normal INR is 1
  - The higher your INR the longer it takes for your blood to clot
- Most patients taking an anticoagulant have a target INR of 2 – 3

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WARFARIN USE AMONG STROKE PATIENTS

Current Warfarin Prescription Trends

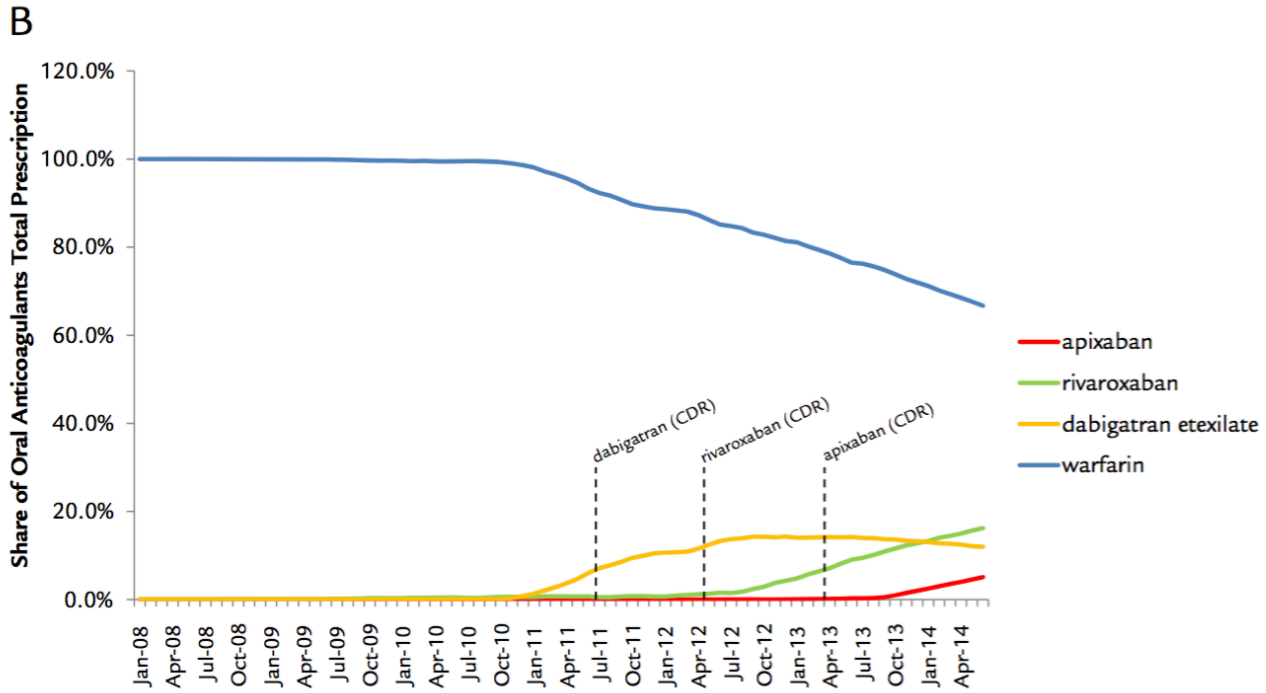

Figure 2. Total annual prescription volumes (A) and total monthly prescription shares (B) of oral anticoagulant (OAC) agents. Dates of Common Drug Review recommendations of each of the non–vitamin K antagonist OACs (NOACs) for stroke prevention in patients with atrial fibrillation are shown. Data on warfarin have not been adjusted to account for the fact that the approved indications for the NOACs represent only 70% of all OAC prescriptions. Source: IMS Brogan Canadian Compuscript.

Weitz et al. Trends in Prescribing Oral Anticoagulants in Canada, 2008-2014. *Clin Ther*. 2015;37(11):2506–2514.e4.

How Many Stroke Patients are on Warfarin?

Risks of Intracranial Hemorrhage Among Patients With Acute Ischemic Stroke Receiving Warfarin and Treated With Intravenous Tissue Plasminogen Activator

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Li Liang, PhD
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Context Intravenous tissue plasminogen activator (tPA) is known to improve outcomes in ischemic stroke; however, patients receiving long-term chronic warfarin therapy may face an increased risk for intracranial hemorrhage when treated with tPA. Although current guidelines endorse administering intravenous tPA to warfarin-treated patients if their international normalized ratio (INR) is 1.7 or lower, there are few data on safety of intravenous tPA in warfarin-treated patients in clinical practice.

Objectives To determine the risk of symptomatic intracranial hemorrhage (sICH) among patients with ischemic stroke treated with intravenous tPA who were receiving warfarin vs those who were not and to determine this risk as a function of INR.

Design, Setting, and Patients Observational study, using data from the American Heart Association Get With The Guidelines–Stroke Registry, of 23 437 patients with ischemic stroke and with INR of 1.7 or lower, treated with intravenous tPA in 1203 registry hospitals from April 2009 through June 2011.

Main Outcome Measure Symptomatic intracranial hemorrhage. Secondary end points include life-threatening/serious systemic hemorrhage, any tPA complications, and in-hospital mortality.

INTRAVENOUS TISSUE PLASMINOGEN activator (tPA) is currently the only effective treatment to improve outcomes for acute ischemic stroke[1,2]; however, treatment with

Get With The Guidelines (US data): 7.7% of stroke patients who were given tPA were on Warfarin

How Many Stroke Patients are on Warfarin?

Safety of Intravenous Thrombolysis for Ischemic Stroke in Patients Treated with Warfarin

Michael V. Mazya, MD,[1] Kennedy R. Lees, MD, FRCP,[2] Romesh Markus, MD, FRACP,[3] Risto O. Roine, MD, PhD,[4] Raymond C. S. Seet, MD, MRCP,[5] Nils Wahlgren, MD, PhD,[1] and Niaz Ahmed, MD, PhD,[1] for the Safe Implementation of Thrombolysis in Stroke Investigators

Objective: Controversy surrounds the safety of intravenous (IV) tissue plasminogen activator (tPA) in ischemic stroke patients treated with warfarin. The European tPA license precludes its use in anticoagulated patients altogether. American guidelines accept IV tPA use with an international normalized ratio (INR) $\leq$ 1.7. The influence of warfarin on symptomatic intracerebral hemorrhage (SICH), arterial recanalization, and long-term functional outcome in stroke thrombolysis remains unclear.

Methods: We analyzed data from 45,074 patients treated with IV tPA enrolled in the Safe Implementation of Thrombolysis in Stroke (SITS) International Stroke Thrombolysis Register. A total of 768 patients had baseline warfarin treatment with INR $\leq$ 1.7. Outcome measures were SICH, arterial recanalization, mortality, and functional independence at 3 months.

Results: Patients on warfarin with INR $\leq$ 1.7 were older, had more comorbidities, and had more severe strokes compared to patients without warfarin. There were no significant differences between patients with and without warfarin in SICH rates (adjusted odds ratio [aOR] = 1.23, 95% confidence interval [CI] = 0.72–2.11 per SITS-MOST; aOR = 1.26, 95% CI = 0.82–1.70 per European Cooperative Acute Stroke Study II) after adjustment for age, stroke severity, and comorbidities. Neither did warfarin independently influence mortality (aOR = 1.05, 95% CI = 0.83–1.35) or functional independence at 3 months (aOR = 1.01, 95% CI = 0.81–1.24). Arterial recanalization by computed tomography/magnetic resonance angiography trended higher in warfarin patients (62% [37 of 59] vs 55% [776/1,475], p = 0.066). Recanalization approximated by disappearance at 22 to 36 hours of a baseline hyperdense middle cerebral artery sign was increased (63% [124 of 196] vs 55% [3,901 of 7,099], p = 0.022).

Interpretation: Warfarin treatment with INR $\leq$ 1.7 did not increase the risk for SICH or death, and had no impact on long-term functional outcome in patients treated with IV tPA for acute ischemic stroke.

ANN NEUROL 2013;74:266–274

SITS (European Data): 2.5% of stroke patients who were given tPA were on Warfarin

How Many Stroke Patients are on Warfarin?

- Canadian Data? The Canadian Stroke Network Registry only captures patients discharged on Warfarin (not pre stroke Warfarin use)
- In Calgary…from the HASTE project (June 2012 thru June 2015
  - 350 patients treated with tPA
  - 39 of these were on Warfarin pre stroke (11%)

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DOES WARFARIN AND TPA MIX?

Warfarin and tPA – Animal Studies

- Moderate increase in sICH rates when combining tPA and warfarin treatments
  - However, in these studies animal INRs were between 4 – 8 (or sometimes not reported at all)

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Warfarin and tPA – Human Studies

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Main Outcome Measure Symptomatic intracranial hemorrhage points include life-threatening/serious systemic hemorrhage, any tP and in-hospital mortality.

If the patient's INR is ≤ 1.7 there is <u>no increased risk</u> of sICH, ICH, mortality, or poor hospital discharge outcome

ORIGINAL ARTICLE

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WARFARIN, INR, AND STROKES

Why Do Warfarin Treated Patients Have Strokes?

- Warfarin has relatively high rates of non-compliance
  - Discontinuation rates have varied from 10% to 33%
- It is possible that the “warfarin treated” patients we see with low INRs are actually non-compliant

High INR and Stroke

- But what about the one's with high INR?
- Logically patients with high INRs shouldn't be clotting
- Mechanisms of action:
  1. **The patient was non compliant in the preceding weeks**
  2. Patients with lupus can have inaccurate INR readings
  3. In cancer patients clots can form even with therapeutic INRs

Why 1.7?

- According to AHA/ASA guidelines INRs > 1.7 are thought to be attributable to medications and not other causes
  - Liver failure
  - Sepsis
  - Non medication coagulopathy

Warfarin and tPA – High INRs

- What if the patient's INR is > 1.7?
  - No trials looking at patients with elevated INRs receiving tPA
- 115 cases of Warfarin treated patients with INR > 1.7 given tPA have been reported
  - Of these only 1 developed a sICH
- 138 cases of non-warfarin induced high INR patients being treated with tPA have also been reported
  - No difference in outcome as compared to patients with lower INRs
- In HASTE (Calgary) 3 of 39 warfarin/tPA treated patients had INR > 1.7
  - None of these patients experienced tPA related complications. Their mRS scores ranged from 1 – 4
- Trial evidence is needed, but the risk here is likely low too.

How Many Warfarin Treated Stroke Patients Have High INRs?

- In the GWTG Registry (US data) < 10% of Warfarin patients had INR > 1.7
- In the SITS Registry (European data) 30% of Warfarin patients had INR > 1.7
- In HASTE (Calgary) 8% of Warfarin patients had INR > 1.7

- So, 8 – 30% of Warfarin treated patients potentially have elevated INR > 1.7

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NOACS

Novel Oral Anticoagulants (NOACs)

- NOACs target individual clotting proteins
  - Ex. dabigatran, rivaroxaban, apixaban, edoxaban
- Do not require extensive monitoring or individualized dosing
- Dabigatran and apixaban are more effective than warfarin at reducing stroke risk in AFib
- Have reduced risk of serious bleeding complications compared to warfarin
  - However few reversal agents exist for NOACs
  - Recently idarucizumab was proven a safe and effective reversal agent for dabigatran

What about NOACs and tPA?

- Animal studies have shown no increased sICH risk when combining tPA with NOACs
- Fewer studies in this area as NOAC use is not as common as warfarin
- However, one pilot study found no difference in sICH rates among NOAC and non-anticoagulated patients
- This was echoed in recent preliminary findings from a GWTG substudy

What About NOACs and tPA?

- INR is calibrated for vitamin-K antagonists
  - Not useful for patients taking NOACs
- PT also cannot be used for dabigatran as it is a thrombin inhibitor
- Can use aPTT to assess anticoagulation in patients taking NOACs

What About NOACs and tPA?

AHA/ASA Scientific Statement

Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

Platelets and Coagulation Studies: Recommendations

1. **The safety and efficacy of intravenous alteplase for acute stroke patients with platelets <100 000/mm^3, INR >1.7, aPTT >40 seconds, or PT >15 seconds are unknown, and intravenous alteplase is not recommended (*Class III; Level of Evidence C*).**

According to AHA/ASA guidelines aPTT > 40 is a contraindication to tPA therapy

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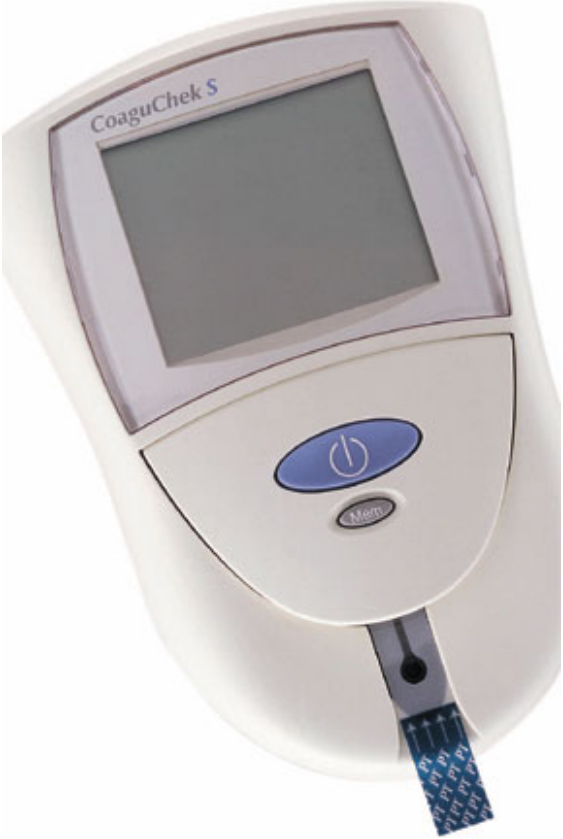
POINT OF CARE TESTING

Point of Care Testing (POCT)

- POCT can be done at the bedside via finger poke
- Several studies have compared POCT INR to lab INR results
  - Margin of error ranging from 0.2 – 0.7 depending on study
  - The POCT INR was usually an **overestimate** of the lab INR



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Point of Care Testing?

AHA/ASA Scientific Statement

Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke

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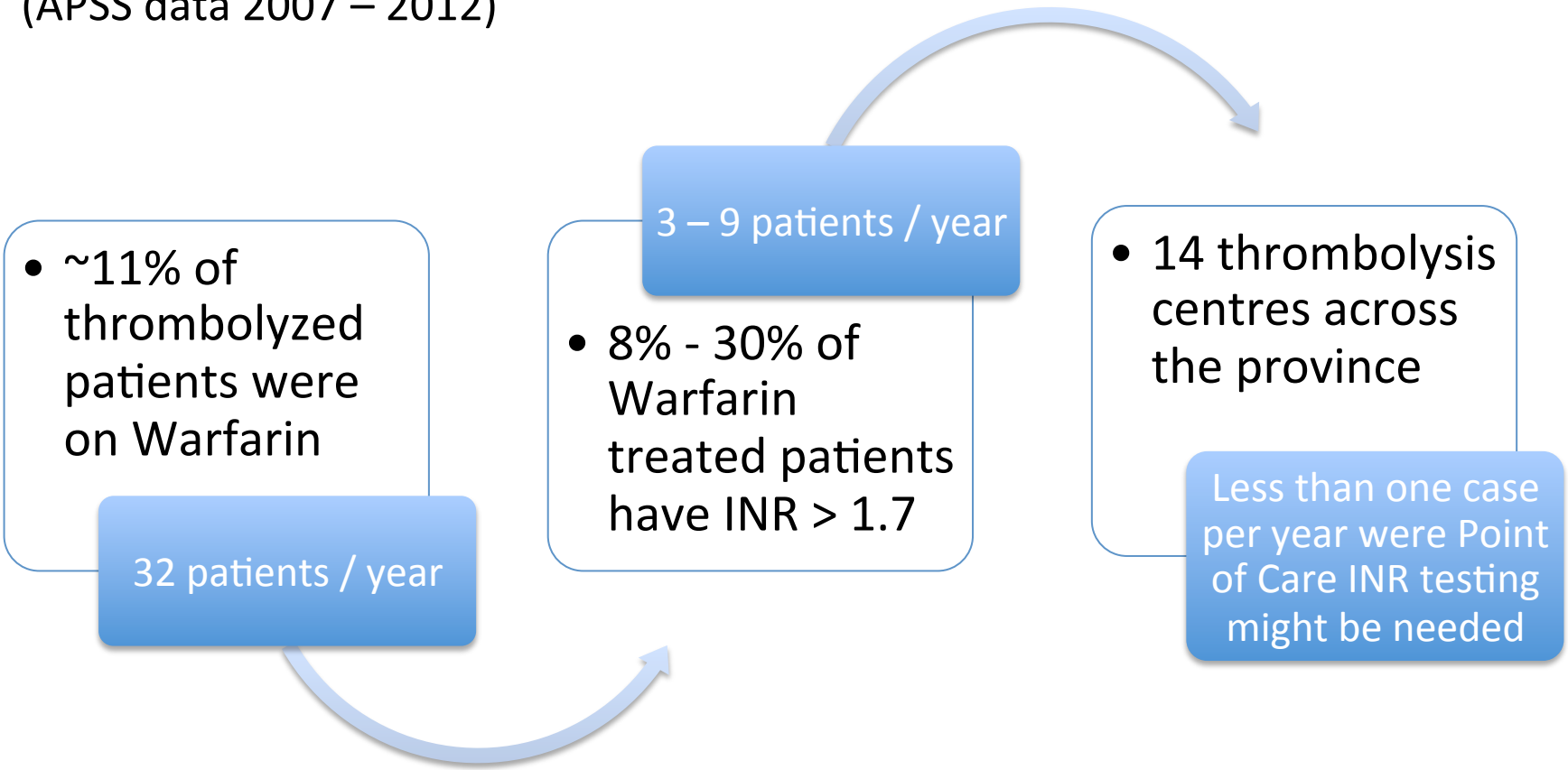
2. **Given the extremely low risk of unsuspected abnormal platelet counts or coagulation studies in a population, it is reasonable that urgent intravenous alteplase treatment not be delayed while waiting for hematologic or coagulation testing if there is no reason to suspect an abnormal test (*Class IIa; Level of Evidence B*).**

If there is no reason to suspect abnormal INR treatment should not be delayed for testing

Point of Care INR Testing?

Approximately 285 stroke patients are given tPA each year **across the province** (APSS data 2007 – 2012)



Summary

- AFib is attributable to 15% of ischemic stroke
- AFib is often treated with Warfarin
  - Warfarin works well, it only fails in 1 – 4% of patients (generally due to non-compliance)
- Between 2 – 11% of tPA eligible patients may be on warfarin (GWTG, SITS, HASTE)
- If INR is low (≤1.7) there is **no increased risk** for poor outcomes when giving tPA

Summary

- INR is low (≤1.7) in warfarin treated stroke patients most of the time (GWTG, SITS, HASTE)
- Case reports of patients with high INR receiving tPA have not shown negative outcomes
  - Further study here is needed

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