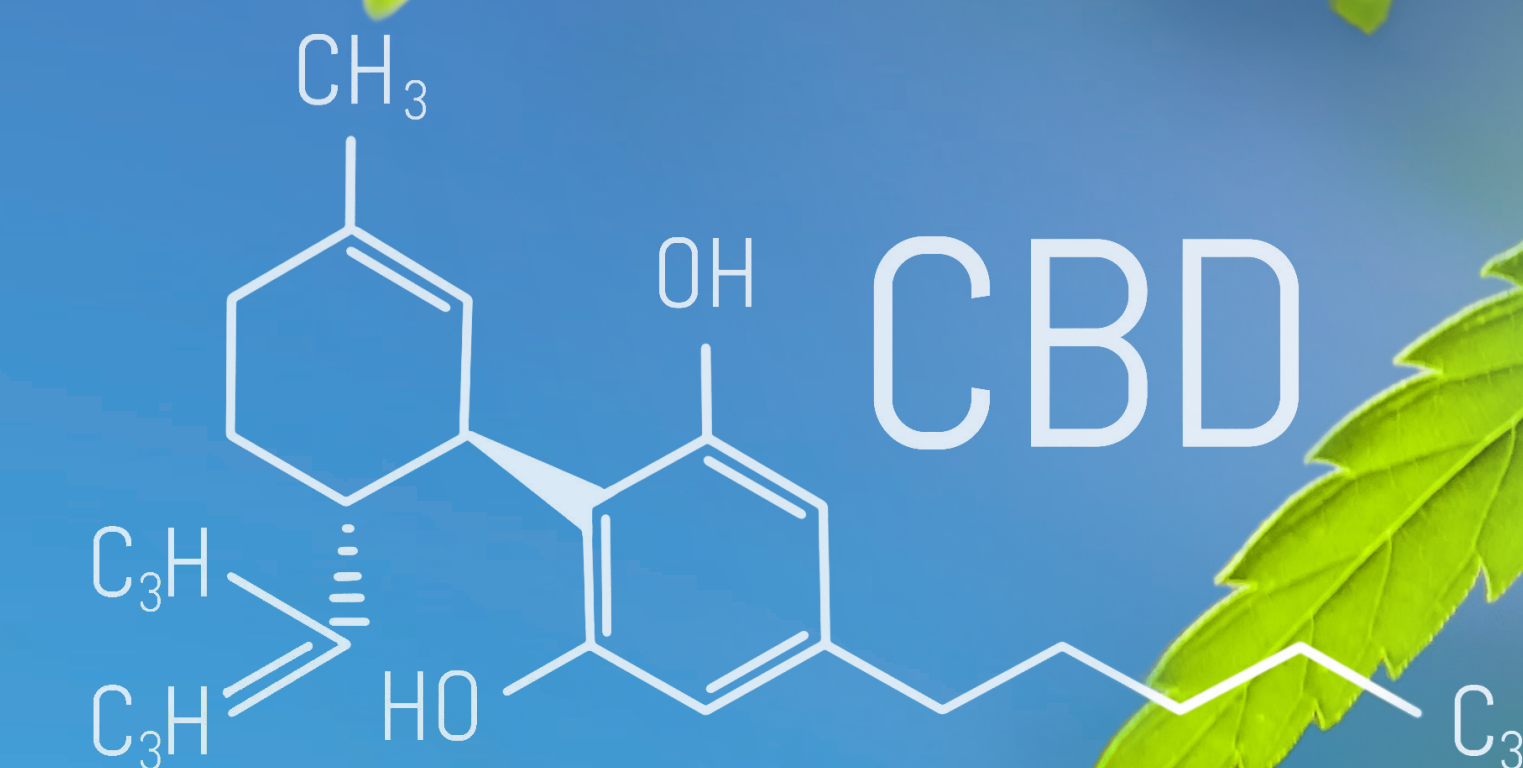


Cannabidiol (CBD) and CYP2C19

Loss of clopidogrel effectiveness through the use of cannabidiol?

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Background:

The Canadian Stroke Best Practice Guidelines recommend the use of clopidogrel:

“In very high risk TIA patients or minor stroke of non cardioembolic origin, a combination of clopidogrel and acetylsalicylic acid should be given for a duration of 21 to 30 days followed by antiplatelet monotherapy (such as acetylsalicylic acid or clopidogrel alone [Evidence Level A]”

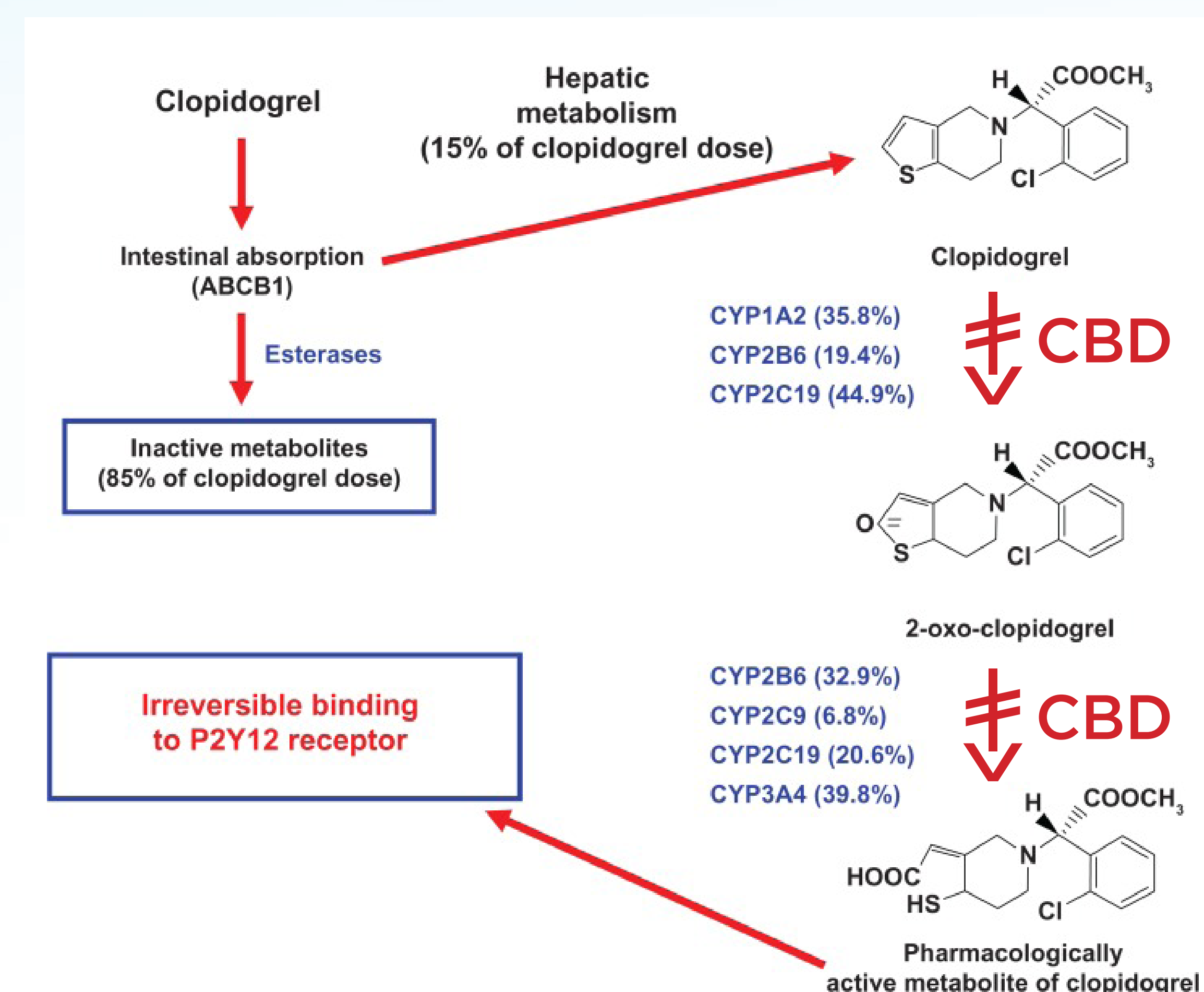
Clopidogrel, a prodrug, requires activation through the cytochrome P450 enzyme system, primarily via CYP 2C19. Failure to convert to the active metabolite renders this medication ineffective at platelet inhibition, leaving the patient unprotected from its intended use. Drugs which inhibit the activity of CYP 2C19 have the potential to interact with clopidogrel. One such drug that is known to inhibit CYP 2C19 is cannabidiol (CBD).

CBD is one of 400 chemicals found in the Cannabis species and is highly marketed, on its own or in various combinations with Δ9-tetrahydrocannabinol (Δ9-THC).¹ Marijuana is currently the most used illicit substance in the world.² In October 2018, it was legalized in Canada.

Objectives:

Create awareness of this potential drug interaction which would have clinically significant impact on patient outcomes and influence the Canadian Best Practice Guidelines.

Results:



Determinants to optimize response to clopidogrel in acute coronary syndrome. Giusti B et al. Pharmacogenomics and Personalized Medicine. 3(1): 33-50 (2010)

CBD is known to be a potent enzyme inhibitor of CYP 2C19, as well as 3A4, both responsible for clopidogrel activation.^{5,6}

References:

- 1) Cannabis, a complex plant: different compounds and different effects on individuals. Atakan Z. Ther Adv Psychopharmacol. 2(6): 241-254 (2012)
- 2) Marijuana Use and Cardiovascular Disease. Franz CA et al. Cardiology in Review. 24(4): 158-162 (2016)
- 3) Determinants to optimize response to clopidogrel in acute coronary syndrome. Giusti B et al. Pharmacogenomics and Personalized Medicine. 3(1): 33-50 (2010)
- 4) Image from cannatechtoday.com
- 5) Cannabidiol is a Potent Inhibitor of the Catalytic Activity of Cytochrome P450 2C19. Jiang R et al. Drug Metabolism and Pharmacokinetic. 28(4): 332-338 (2013)
- 6) Potent inhibition of human cytochrome P450 3A isoforms by cannabidiol: role of phenolic hydroxyl groups in the resorcinol moiety. Yamaori S et al. Life Sciences. 88(15-16): 730-736 (2011)
- 7) Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton pump inhibitor: an analysis of 2 randomised trials. O'Donoghue ML et al. Lancet. 374:989-997 (2009)
- 8) No consistent evidence of differential cardiovascular risk amongst proton-pump inhibitors when used with clopidogrel: meta-analysis. Kwok CS et al. International Journal of Cardiology. 167:965-974 (2013)

Discussion:

The challenge is to prove the interaction between CBD and clopidogrel is significant to our patients. Future studies will need to examine the interaction both in vitro and in vivo.

In vitro, platelet reactivity testing can be done. However, in vivo testing may not translate into increased MACCE (major adverse cardiovascular and cerebrovascular endpoints). As an example, despite the observed attenuation of the in vitro antiplatelet effects of clopidogrel in patients also treated with a proton pump inhibitor (PPI) such as omeprazole, it was shown that use of a PPI is not associated with an increased risk of adverse clinical outcomes.^{7,8}

This interaction will have important clinical implications beyond the world of stroke. Clopidogrel is a staple within cardiovascular medicine with use in settings post-percutaneous intervention (PCI), post myocardial infarction and in peripheral artery disease.

Conclusions:

- Ask patients if they use any form of cannabis as part of a complete medication history.
- It is reasonable to recommend against the use of recreational cannabis.
- It should be suggested for patient not to consume medicinal cannabis while taking clopidogrel and alternatives of therapy should be considered.
- If eliminating cannabis is not an option, consider selecting an alternate anti-thrombotic strategy.



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Thunder Bay Regional Health Sciences Centre



Geo-mapping Technology to Inform Timely Access to Stroke Care for patient in Rural areas of Northwestern Ontario

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Background:

In Northwestern Ontario (NWO), a land mass of half a million square kilometers with a population of approximately 230,000. Acute stroke care is provided by one tertiary level hospital and four Telestroke hospitals. (Figure 1 – Map of Stroke services).

Direct transportation protocols facilitate the transport of suspected stroke to the closest acute care hospital capable of providing required services.

Transportation decisions are based on protocols, human judgment and experience. Geomapping Technology and Artificial Intelligence (AI) can be used to inform timely access to stroke care. The proposed intelligent system helps informing the right decision based on geographic information, weather information, patient transport information, and resources available at the nearest hospital/telestroke site.

Objectives:

- Understanding how an application may assist clinicians referring or accepting patients across emergency systems for access to stroke diagnosis and treatment opportunities.

Methods:

- We use Google maps, machine learning techniques and graph theory to build intelligent decision-support algorithms for timely access to acute stroke care.
- Historical data from Ornge (air) and land ambulance services are used to perform a quantitative analysis of the nature of transportation decisions made in the past and historical reality.
- To compare “what happened with what could happen”, we will use existing patient data to simulate patient care pathways. The simulations can be used to identify where improvements could be made and resources better utilized.
- Business logic includes 6 case scenarios as follows:
 1. From anywhere to EVT site. May need to travel to Thunder Bay site or other site (London, Hamilton, Winnipeg, etc.).
 2. From Telestroke Site to EVT site. May need to travel to Thunder Bay or other site (London, Hamilton, Winnipeg, etc.).
 3. Patient at any clinic with Regional Critical Care Response. Must get to CT scan.
 4. Remote Location without Regional Critical Care Response nor Telestroke. Must get to CT scan.
 5. Walk-in at any hospital (Figure 2: Flowchart of Business Logic).
 6. All other sites. Ornge transportation required.

Case Vignette:

- Case Vignette: Patient drove to Hospital in Red Lake. Red Lake Margaret Cochenour Memorial Hospital activated Northwest EMS to land transfer (Northwestern Ontario Acute Stroke Bypass and Transfer Agreement) to Dryden Regional Health Centre (Telestroke Site). Patient received tPA treatment—patient was flown to Thunder Bay Regional Health Sciences Centre (Regional Stroke Centre) via air ambulance by ORNGE, for EVT treatment (Figure 3: Geomap of Case Vignette Scenario: Remote Bypass and ORNGE flight).

Figure 1: Current Map of Stroke Services in Northwestern Ontario

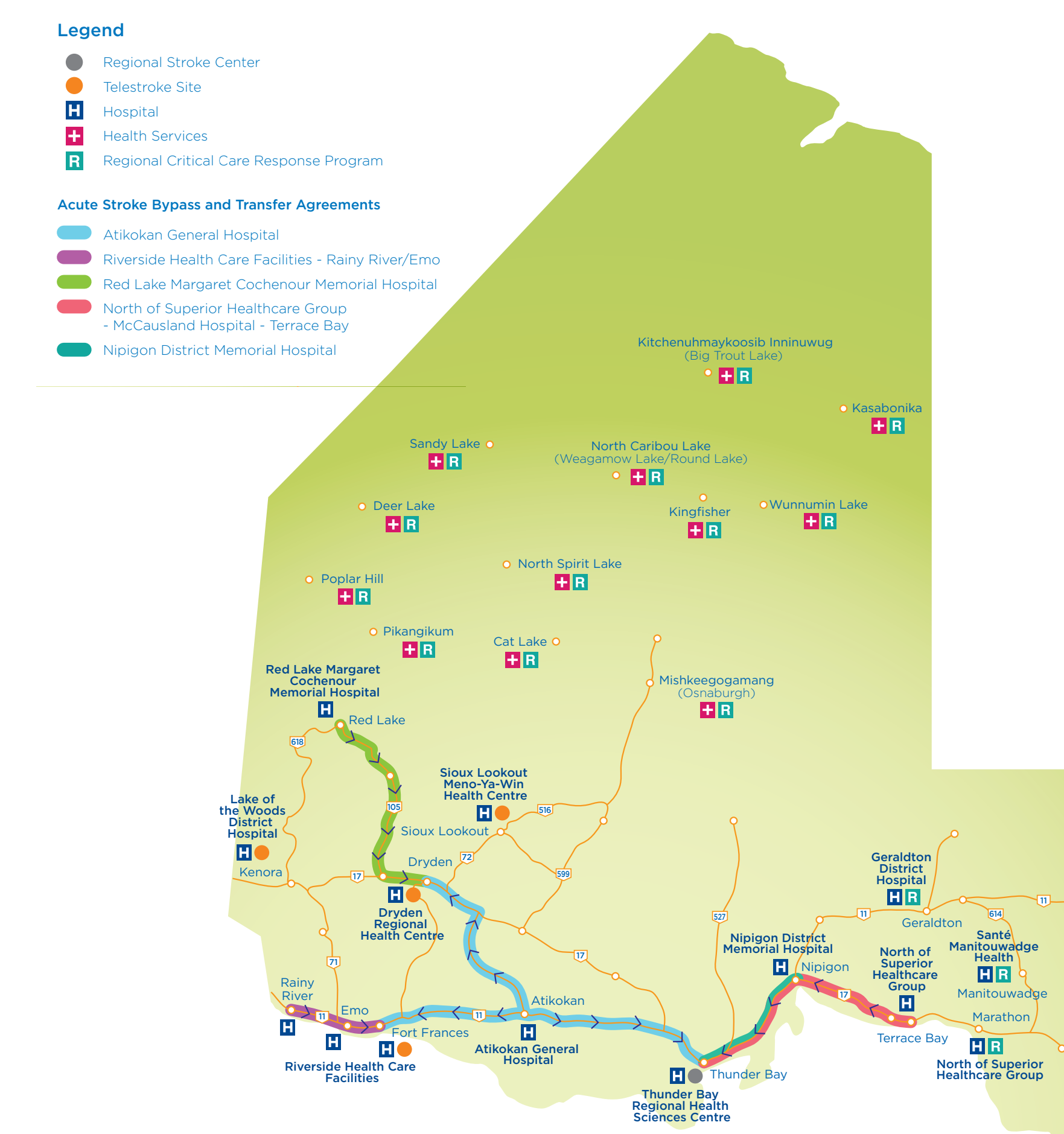


Figure 2: Flowchart of Business Logic

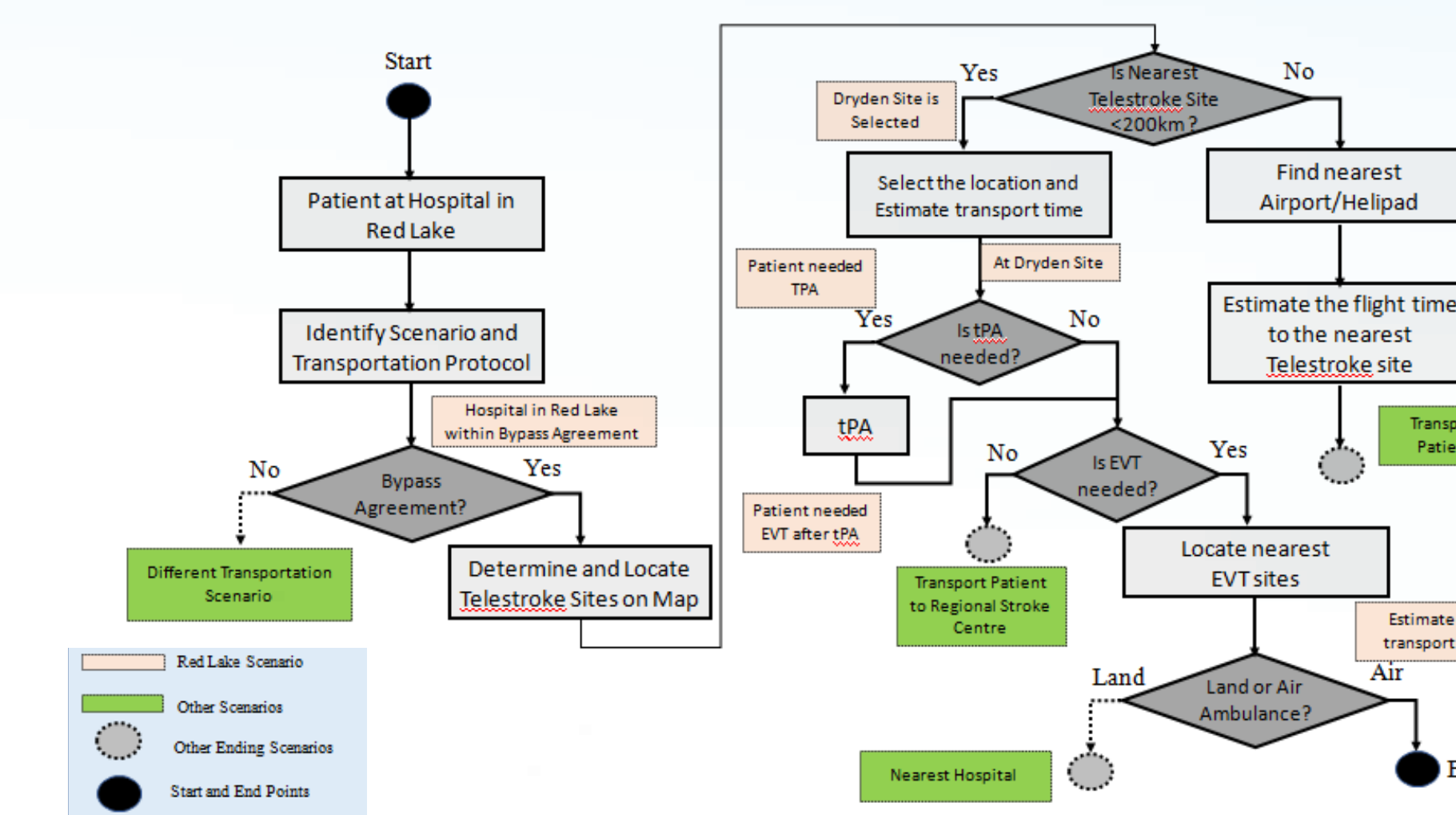
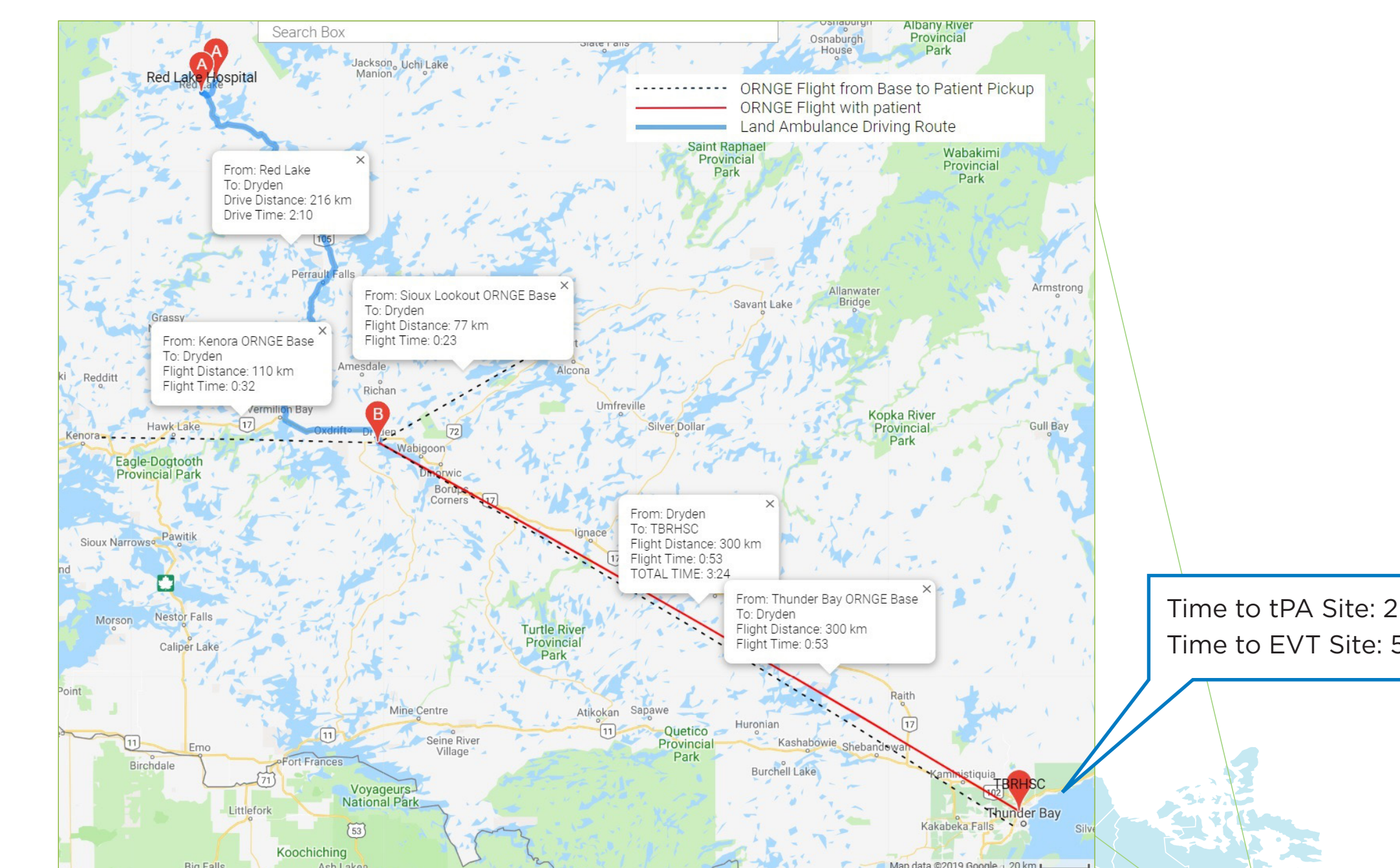


Figure 3: Geomap of Case Vignette Scenario, Remote Bypass and ORNGE flight



This case vignette demonstrates time for a land ambulance transfer time from Red Lake to Dryden of 2h 10m*. Then the patient would utilize air ambulance from Dryden to Thunder Bay 3h 24m**.

Estimated time from patient presentation to tPA centre is 2h 10m. Estimated time from patient presentation to EVT centre is 5h 34m.

*Time estimates do not include door in door out, 'DIDO' at Dryden site. **Air ambulance resources need to depart to Dryden from a base in Sioux Lookout, Kenora or Thunder Bay. Historical data indicates resources from Sioux Lookout base present best option for shortest transport time for patient care. Total time to care includes departure from a Sioux Lookout, transfer of patient care, and travel to final care destination.

Results:

- Historical data, current and potential patient care pathways will be utilized.
- This will be used to inform decision makers in reviewing current policies for stroke care access in NWO.

Conclusions:

- We are developing an innovative geo-mapping system that provides support for evidence-based decision making to facilitate the transfer of patients to the appropriate level of care.



WHY 911? Optimizing Stroke Care in Northwestern Ontario

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Background:

- Heart and Stroke, Ontario FAST 2018 polling results show the public dials 911 when a person suddenly experienced the signs of stroke. The results demonstrate a decline in recognition and understanding of the signs of stroke from 2015 to 2018.
- The Ontario Stroke Report Card for North West Local Integrated Health Network 2013-2018 states 50.8% of stroke and TIA patients arrive at the ED by ambulance despite the provincial benchmark being 65.9%. NWO is the lowest performer provincially for this indicator over the last 5 years.
- We needed to understand WHY our patients do not call 911.

Objective:

- To determine if Northwestern Ontario residents know the signs of stroke and how to access stroke care.
- To understand why people call 911 and choose not to call 911 during stroke symptom onset.
- To support and guide public awareness initiatives, EMS training and stroke patients and family education.

Methods

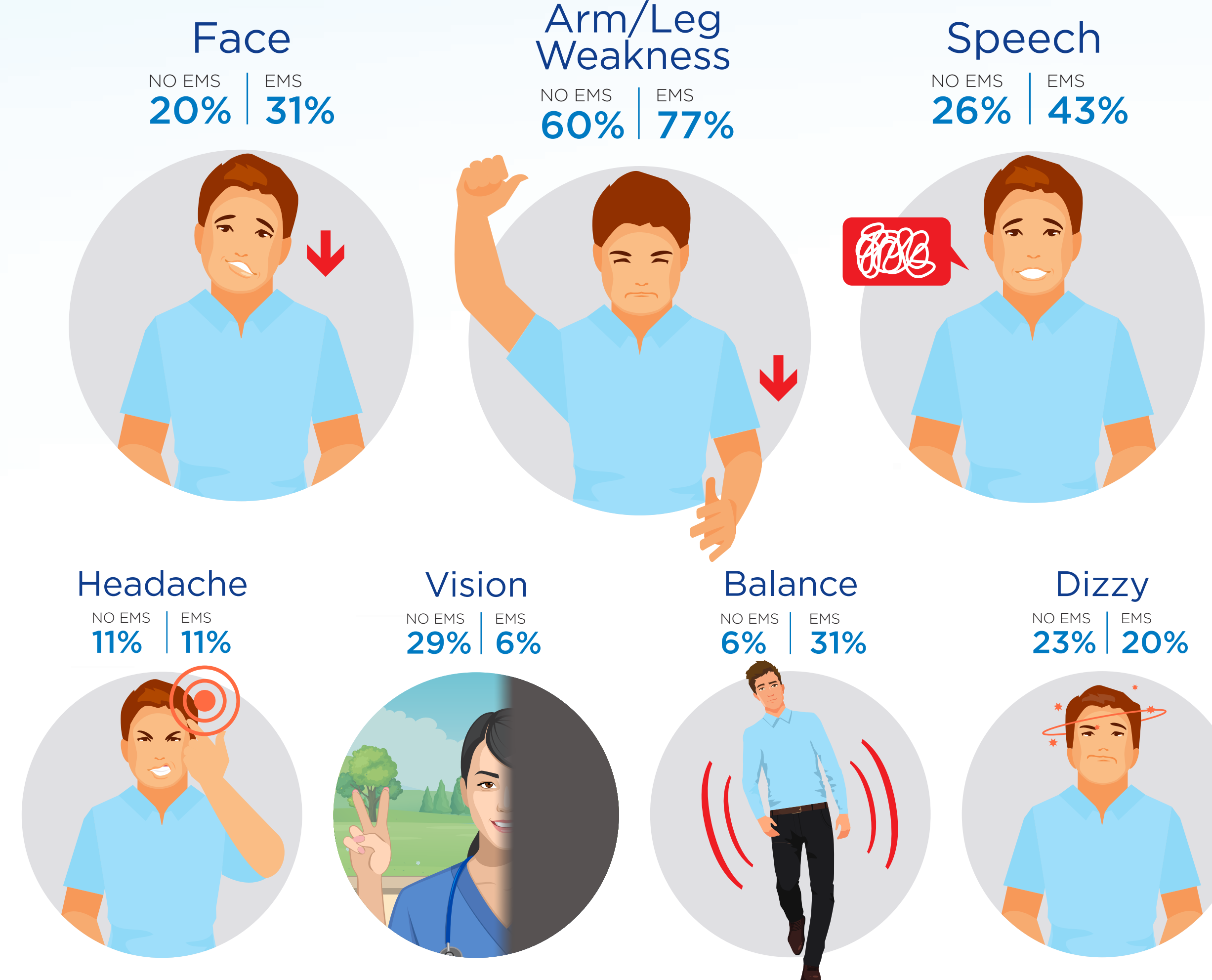
- August to December 2018, patients and families were interviewed to understand why they did or did not call 911.
- The questionnaire followed the same format and answers were open-ended to record individual experiences.

Figure 1

Characteristics of Patients Interviewed Sept 7 to Dec 6 - 2018 70 cases	
Interview	
Patient only	69%
Family only	4%
Both Pt and Family	27%
Gender	
Male	56%
Female	44%
Home Location	
City of Thunder Bay	54%
Regional	46%
Average Age of Pt	
65 yrs	
Average Age of Pt with Arrival Method	
EMS	69 yrs
No EMS	60 yrs
Arrival Method	
EMS	50%
Self Transport	50%
EMS Arrival Method with Gender	
Male	54%
Female	46%
No EMS Arrival Method with Gender	
Male	54%
Female	46%
No EMS Activation to Arrival Method	
Spouse	26%
Children / Friend	51%
Self	20%
Taxi	3%
Stroke checklist delivered	100%

Figure 2

Signs vs Arrival Method

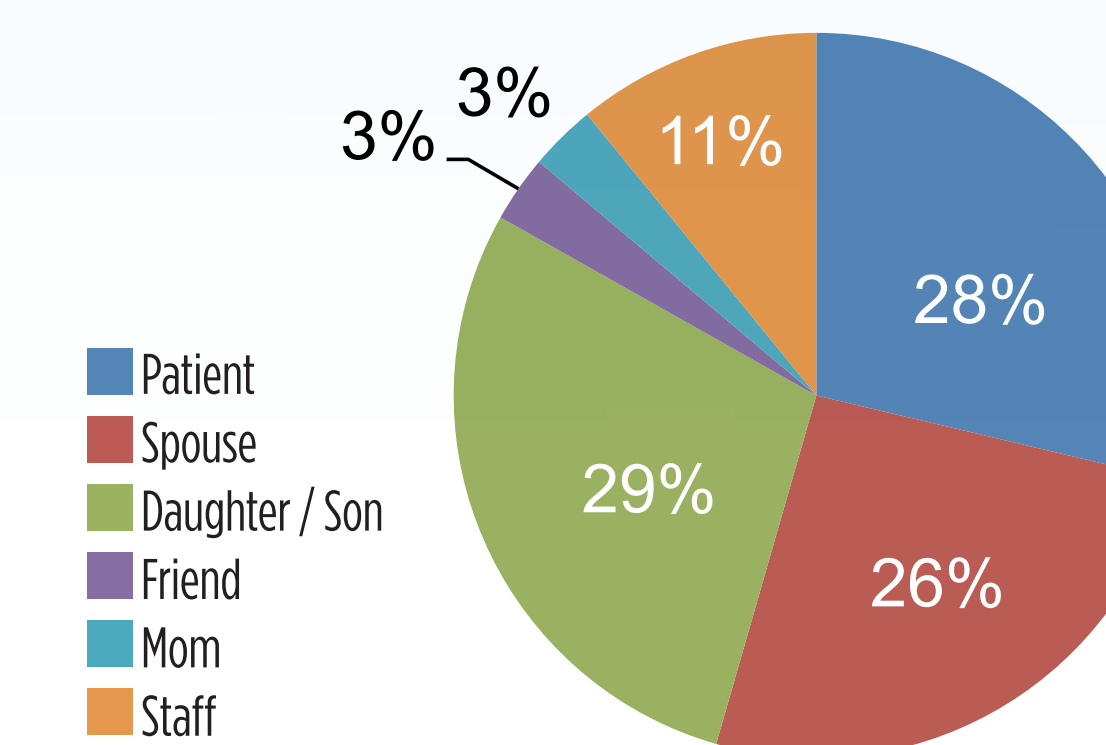


Results:

- 70 patients' interviewed.
- 50% patients activated EMS with 50% patients self transporting to ED.
- Patients did not call 911 because they didn't know it was a stroke, didn't think it was an emergency or had other symptoms.
- Those who called 911 knew the signs, saw it advertised, or had history of stroke.
- Bystanders recognized the signs and called 911 for the patients in both scenarios.

Figure 3

Patients who arrived via EMS:
Who called 911?



Patient who arrived via EMS
How did you know to call 911?

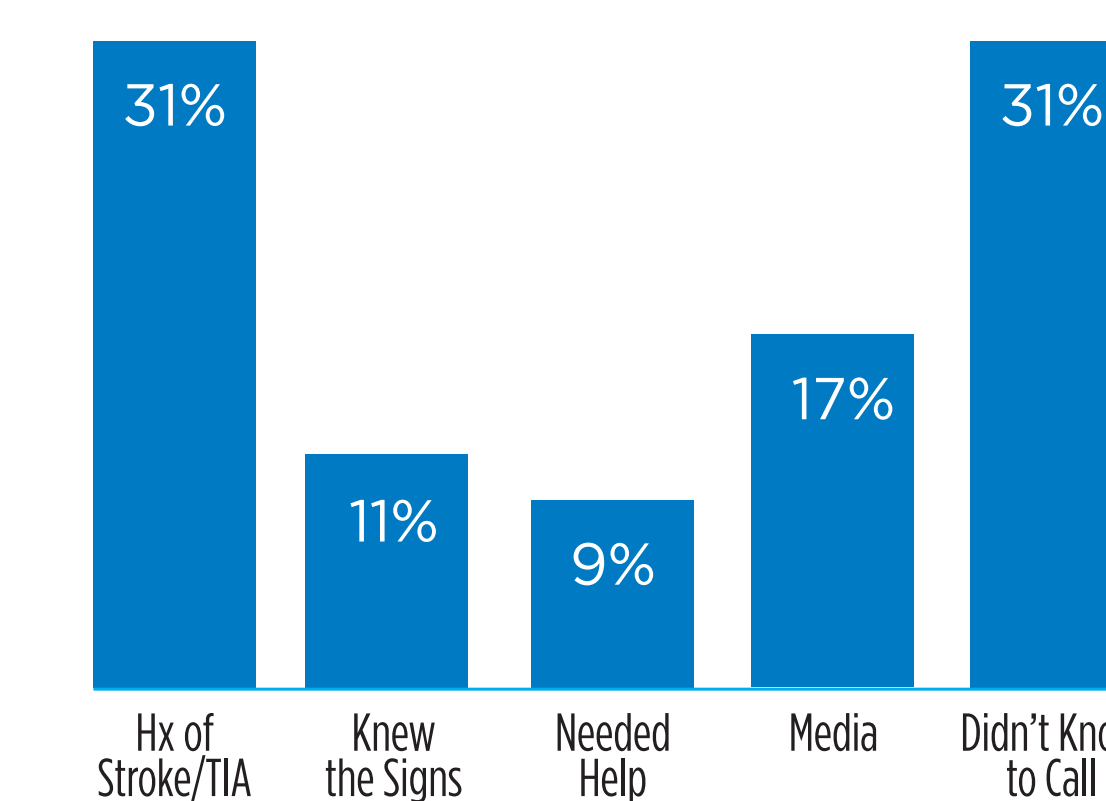


Figure 4

Patient who arrived NOT with EMS Did you consider calling 911? Rationale	35/70 (50%) patients called 911
No, never considered calling 911 due to: Total: 91% NO	
Didn't know it was a stroke	29%
Wasn't an emergency	26%
Cost	9%
Driving already / live close / live far / go with family & friends	37%
Yes, but did not due to: Total: 9% YES	
Cost	6%
Took taxi: Less expensive and wanted spouse to come	3%

Conclusions

- Engaging patients determined whether existing public awareness initiatives and education at discharge are meeting the needs of the patients.
- The goal is 10% increase on the Ontario Stroke Report Card to increase the number of people accessing 911.
- Why 911 project will guide: Public Awareness Initiatives, EMS and First Responder Training, Stroke Patients and Families Education.

Public Awareness Initiatives:

determine our target audiences, content and delivery of public education.

- FAST campaign in Physician offices and public spaces including churches.
- BE FAST to include the Balance and Vision in education.
- Educate bystanders about their important roll.
- Focus on treatment times in education, importance of call 911, why FAST Decals, what can paramedics do to help.
- Emphasis the critical first hour in stroke care.
- Use video production to utilize in education. Display at health fairs / presentations, TVs in hospital, Physicians' offices.

EMS and First Responder Training:

continue to provide education in stroke care for this stakeholder group.

- Work with EMS to assist in the message of FAST.
- BE FAST: use data and research to make an addition to training and education.
- Emphasis the critical first hour in stroke care: work with the paramedics through education.
- Use video production for EMS training.
- Increase training and education through EMS LMS.

Stroke Patients and Families Education:

upon discharge the importance of accessing 911 for stroke care.

- Review the importance of calling 911.
- Provide stroke checklist.
- Educate about treatment times and not delaying access to care.
- Develop a discharge video for patients and families.
- Regional Patients: Explain first responders' role and specific EMS and access to care.