Left Atrial imaging prior to Cardioversion: Leveraging computed tomography to rule Out Thrombus. (LA CLOT) – A Pilot Study of Hospitalized and Emergency Department Patients

Principal Investigator: Dr. Benjamin Chow
Co-investigators: Dr. Emel Celiker guler, Dr. Andrew Crean, Dr. Carole Dennie, Dr. Gary Small, Dr. Guy Hebert, Dr. Mehrdad Golian, Dr. Ian Stiell

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia with an estimated 12 million individuals afflicted in European Union, 5.9 million in the USA and 350,000 in Canada are affected.[1, 2] The prevalence of AF is increasing and is projected to rise in the EU to 17.9 by 2050 and 10 million people in the USA by 2060.[2-4] AF and its associated complications are a growing economical burden on the healthcare system and this burden on healthcare will continue to rise.[5]

Atrial Fibrillation Guidelines

Canadian AF guidelines updated recommendations in November 2018 regarding electrical/pharmcologic cardioversion.[6] Prior to this update, previous guideline recommendations have been:[7]

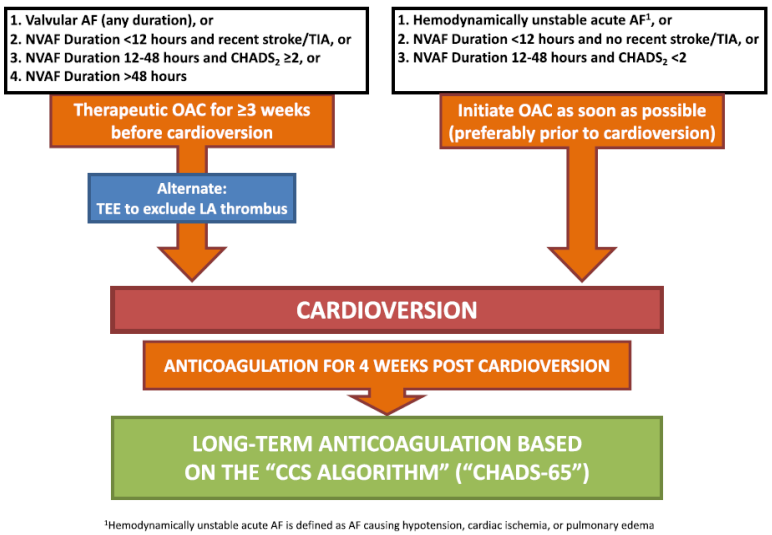
Non-anticoagulated AF/atrial flutter patients (without indication for emergent cardioversion) requiring rhythm control:

1) May proceed to cardioversion if non-valvular AF onset was <48hours,
2) If AF/atrial flutter onset is unknown or >48 hours
    a. Anticoagulate and consider cardioversion after 3 weeks
    b. Admit to hospital for transesophageal echocardiography (TEE) prior to cardioversion
    c. Refer for outpatient TEE prior to cardioversion

Transesophageal Echocardiography Prior to Cardioversion

TEE is considered the reference standard to rule-out left atrial (LA) and left atrial appendage (LAA) thrombus prior to cardioversion. Several studies have examined the accuracy of TEE for detecting LAA thrombus. Compared to autopsy and intraoperative findings, TEE has a mean sensitivity of 100% and mean specificity of 99%.[8] Klein et al. showed that TEE could be used prior to cardioversion to exclude LA thrombus with no significant increase in adverse embolic events.[9]

The new Canadian guidelines have made new recommendations (Figure) that may have downstream ramifications on resources.[6] They have suggested that "pharmacological or electrical cardioversion of symptomatic AF or atrial flutter without at least 3 weeks of previous therapeutic anticoagulation be reserved for patients with":
1) "non-valvular AF who present with a clear AF onset within 12 hours in the absence of recent stroke or transient ischemic attack (within 6 months)", and
2) "non-valvular AF and a CHADS2 score < 2 who present after 12 hours but within 48 hours of AF onset", and
3) "as an alternative to at least



3 weeks of therapeutic anticoagulation before cardioversion, TEE may be used to exclude cardiac thrombus".

As such, these recommendations will likely reduce the frequency of immediate cardioversions (in the emergency department), increase referrals for inpatient and outpatient TEEs, and increase hospital admissions. We propose a randomized control trial that will assess the utility of cardiac CT to improve patient access and timely care. The results of this study could have worldwide impact by improving patient quality of life and timely access to cardioversion.

Imaging to Rule Out LA Thrombus

Currently, TEE is considered the reference standard technique for the detection of intracardiac thrombus. Although the gold standard, a TEE-guided therapy is still associated with an embolic rate of 0.8%.[9] TEE does have limitations which include: need for NPO x 6-8 hours, patient discomfort, potential complications asscoiated with the procedure (infection, aspiration, perforation, bleeding, etc) or with sedation.[10]

Contrast enhanced ECG-gated cardiac CT (CCT) is a sensitive, noninvasive alternative method used to exclude of left atrial and LAA thrombus. CCT provides high spatial and good temporal resolution and its ability to detect thrombus has been evaluated.[11-15] CCT, compared to TEE, for the exclusion of thrombus in the LAA had a sensitivity and specificity of 100% and 99.3%, respectively (Table 1).[16] A high sensitivity is needed to minimize risk of embolus, and if a thrombus is detected on CT, a confirmatory TEE may be performed or patients may receive anticoagulation. Some argue that the potential benefits of CT and its lower associated procedural risk, the risk:benefit ratio would still favour CT.

This research is novel because it will be the first to demonstrate in a RCT, that CT can be used as an alternative to TEE. More importantly, demonstrating that CT is cost-effective would be extremely attractive to all stakeholders given the growing financial burden of healthcare.

Hypothesis

- Primary Hypothesis: Compared to TEE, CCTA will:
    1. Reduce time to cardioversion for in-patients
- Secondary Hypotheses: Compared to TEE, CCTA will:
    1. Reduce length of hospital or emergency room stay,
    2. Improve patient quality of life (QoL),
    3. Not increase adverse events (arterial embolism, procedural complications, bleeding),
    4. Have superior cost-effectiveness.

Study Objective

Overarching objective: To evaluate CCT as an alternative to TEE to expedite cardioversion, improve patient care and reduce hospital admissions for AF and atrial flutter.

- Primary Objective: To determine if CCT can reduce time to cardioversion for in-patients
- Secondary Objectives:
    - To determine if CCT can reduce length of stay (in-patient hospitalization and emergency department)
    - To determine if CCT improves patient QoL
    - To determine if CCT is associated with fewer or more adverse events
    - To determine the specificity of CCT (in patients with filling defects and subsequent TEE)

Outcomes Measures

1. Time to cardioversion (Time from referral for imaging)
2. Hospital admission rate
3. Length of hospital stay (in-patient and emergency department stay)

4. QoL before cardioversion, at hospital discharge and at 30 days
5. Adverse events (embolic (arterial) event, procedural complication, major bleed (need definition))
    a. Embolic arterial event
    b. Procedural complication
    c. All bleeding
    d. Major bleeding
6. Operating characteristics (specificity, PPV) of CCT (subanalysis of patients receiving TEE after CCT)

Study Design

This randomized controlled trial will randomize patients undergoing cardioversion for AF or atrial flutter before 3 weeks of anticoagulation. This pilot (Vanguard) study will aim to demonstrate feasibility of enrolment and assist with final sample size calculation.

Inclusion Criteria

- Patients admitted to hospital or seen in the ED who require LA imaging prior to cardioversion
- Age ≥18 years old
- Able and willing to comply with the study procedures

Exclusion Criteria

- Indication for acute cardioversion (e.g. hemodynamic instability, acute coronary syndrome (ACS), or pulmonary edema)
- Unwillingness or inability to provide informed consent
- Contraindication to Cardiac CT
    - Severe renal insufficiency(GFR< 45ml/min)
    - Allergy to intravenous contrast agents
    - Contraindications to radiation exposure (for example, pregnancy)
    - Inability to perform 20-second breath-hold
- Contraindication to TEE
    - Unrepaired tracheoesophageal fistula
    - Esophageal obstruction or stricture
    - Perforated hollow viscus
    - Poor airway control
    - Severe respiratory depression
    - Uncooperative, unsedated patient

Methods

Recruitment

Patients who meet the inclusion/exclusion criteria will be randomized to either the interventional arm (CCT) or standard of care (SOC) arm (TEE). Prior to randomization, written informed consent will be obtained from each patient. Patients will undergo imaging as per clinical routine and reports will be issued immediately.

TEE protocol

TEE will be performed as per clinical routine using multiple standard tomographic planes to rule-out LA/LAA thrombus. Echocardiographic analysis will include: LAA-emptying velocity, and grading the severity of LAA spontaneous ECHO. The severity of the SEC will be graded on a 4 point scale with 1 = minor homogeneous contrast enhancement, 2 = significant homogeneous contrast

enhancement, 3 = significant, dense, and inhomogeneous, slow-moving contrast, and 4 = dense slow-moving contrast.

Cardiac CT protocol

As per local protocol, a non-contrast enhanced prospective ECG-triggered image acquisition will be acquired. This will be followed by a contrast-enhanced prospective ECG-triggered will be acquired using a tri-phasic contrast protocols. Delayed CT images will be acquired 60 seconds after the initial contrast-enhanced CT scan.Cardiac CT image interpretation will be performed as per clinical routine. The LA and LAA will be assess for filling defects and characterized based upon attenuation values. If LA/LAA thrombus cannot be excluded, filling defects will be assessed on the delay images. Increases in attenuation would be consistent with pseudo-thrombus from 'slow flow' and 'incomplete opacification'. Areas where attenuation does not change significantly (persistent filling defect) will be diagnosed as thrombus. It will be recommended that patients with thrombus will undergo TEE.

Prevention of Bias

Enrolled patients will be processed through the usual clinical routine for patient booking and investigators will not influence timing of booking.

Duration of Follow-up

Patients will be followed for 30 days after cardioversion using electronic charts and telephone follow-up for QoL measures.

Sample Size Calculation

This pilot (Vanguard) study will aim to demonstrate feasibility of enrolment and assist with final sample size calculation.

Statistic Methods

Statistical analyses will be performed using SAS and/or SPSS. Statistical significance will be defined as $p<0.05$. Continuous variables will be presented as means and standard deviations, and categorical variables will be presented as frequencies with percentages. To compare variables, the Wilcoxon rank sum or T-test will be used to compare continuous variables and Fisher's exact test for categorical variables. Costs will be calculated using Ontario Case Costing Initiative and the Ontario Schedule of Physician Fees and Benefits.

Randomization

Randomization will occur at time of referral for TEE and be performed using a random generator. Patients will be stratified according hospital location (CICU versus ward versus emergency department) and according to mode of cardioversion (electrical versus pharmacologic) and patient sex.

Ethical Considerations

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it affords greater protection to the patient. It is the responsibility of the investigator, or a person designated by the investigator to obtain signed informed consent from each patient prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The investigator or designee will also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. If new safety information results in

significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary.

The protocol, informed consent and any accompanying material provided to the patient will be submitted by the investigator to the Ottawa Health Science Network Research Ethics Board (OHSN-REB) as appropriate. An approval letter or certificate (specifying the protocol number and title) from the OHSN-REB must be obtained before study initiation by the investigator specifying the date on which the committee met and granted the approval. This applies whenever subsequent amendments/modifications are made to the protocol. Any modifications made to the protocol, informed consent or material provided to the patient after receipt of the REB approval must also be submitted by the investigator in accordance with local procedures and regulatory requirements.

Conflict of Interest

The investigators have no conflicts of interest to disclose.

Direct Access to Source Data/Documents

The Investigator and the study centre will accept responsibility of monitoring and auditing as well as inspections by the Ottawa Health Science Network Research Ethics Board and the University of Ottawa Heart Institute. They will also provide all study-related records, as well as source documents to these instances when they are requested to. The confidentiality of the participant's identity shall be well protected and consistent with local and national regulations when the source documents are subject to direct access.

Data Handling and Record Keeping

The Investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: [1] Investigator's Study File and [2] patient clinical source documents. The Investigator's Study File will contain the protocol/amendments, CRF/DCS and schedule of assessments, Independent Ethics Committee/Institutional Review Board approval with correspondence, sample informed consent, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc.

Patient clinical source documents will include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, special assessment reports, signed informed consent forms. All personal health information collected will be kept confidential unless release is required by law. For audit purposes only, the Ottawa Health Science Network Research Ethics Board and the University of Ottawa Heart Institute may review the patients' medical records under the supervision of Dr. Benjamin Chow and his staff. The Master list containing the patients' personal health information will be kept separate from the patient screening and enrollment logs. The Master List which links the patient with the independent study number will only be accessible by Dr. Benjamin Chow and his staff. The master link and study files will be stored separately and securely.

All paper records will be stored in a locked filing cabinet and /or office. All electronic records, including the Master List, will be stored on a secure internal hospital server and password protected, again only accessible by Dr. Benjamin Chow and his staff. No identifiable information will be stored on any mobile devices (laptops, USB keys, CDS, DVDs, etc). The Investigator must keep source documents as described above on file for 10 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, according to local regulations.

Publication Policy

In accordance with standard editorial and ethical practice, the results of this study will be published or presented at congresses or scientific meetings. Patients will not be identifiable in any publications or presentations.

References

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV and Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370-5.
2. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB and Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119-25.
3. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, Witteman JC, Stricker BH and Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J*. 2013;34:2746-51.
4. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH, Jr., Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M and Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129:837-47.
5. Patel NJ, Deshmukh A, Pant S, Singh V, Patel N, Arora S, Shah N, Chothani A, Savani GT, Mehta K, Parikh V, Rathod A, Badheka AO, Lafferty J, Kowalski M, Mehta JL, Mitrani RD, Viles-Gonzalez JF and Paydak H. Contemporary trends of hospitalization for atrial fibrillation in the United States, 2000 through 2010: implications for healthcare planning. *Circulation*. 2014;129:2371-9.
6. Andrade JG, Verma A, Mitchell LB, Parkash R, Leblanc K, Atzema C, Healey JS, Bell A, Cairns J, Connolly S, Cox J, Dorian P, Gladstone D, McMurtry MS, Nair GM, Pilote L, Sarrazin JF, Sharma M, Skanes A, Talajic M, Tsang T, Verma S, Wyse DG, Nattel S, Macle L and Committee CCSAFG. 2018 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. *Can J Cardiol*. 2018;34:1371-1392.
7. Macle L, Cairns J, Leblanc K, Tsang T, Skanes A, Cox J, Healey J, Bell A, Pilote L, Andrade J, Mitchell L, Atzema C, Gladstone D, Sharma M, Verma S, Connolly S, Dorian P, Parkash R, Talajic M, Nattel S, Verma A and Committee. CAFG. 2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. *Can J Cardiol*. 2016;32:1170-1185.
8. Hahn RT, Abraham T, Adams MS, Bruce CJ, Glas KE, Lang RM, Reeves ST, Shanewise JS, Siu SC, Stewart W and Picard MH. Guidelines for performing a comprehensive transesophageal echocardiographic examination: recommendations from the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. *J Am Soc Echocardiogr*. 2013;26:921-64.
9. Klein AL, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, Davidoff R, Erbel R, Halperin JL, Orsinelli DA, Porter TR, Stoddard MF and Assessment of Cardioversion Using Transesophageal Echocardiography I. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med*. 2001;344:1411-20.
10. Mathur SK and Singh P. Transoesophageal echocardiography related complications. *Indian J Anaesth*. 2009;53:567-74.
11. Mosleh W, Sheikh A, Said Z, Ahmed MA, Gadde S, Shah T, Wilson MF, Beck H, Kim C and Sharma UC. The use of cardiac-CT alone to exclude left atrial thrombus before atrial fibrillation ablation: Efficiency, safety, and cost analysis. *Pacing Clin Electrophysiol*. 2018.
12. Hur J, Kim YJ, Lee HJ, Nam JE, Hong YJ, Kim HY, Lee JW and Choi BW. Cardioembolic stroke: dual-energy cardiac CT for differentiation of left atrial appendage thrombus and circulatory stasis. *Radiology*. 2012;263:688-95.
13. Martinez MW, Kirsch J, Williamson EE, Syed IS, Feng D, Ommen S, Packer DL and Brady PA. Utility of nongated multidetector computed tomography for detection of left atrial thrombus in patients undergoing catheter ablation of atrial fibrillation. *JACC Cardiovasc Imaging*. 2009;2:69-76.
14. Kim YY, Klein AL, Halliburton SS, Popovic ZB, Kuzmiak SA, Sola S, Garcia MJ, Schoenhagen P, Natale A and Desai MY. Left atrial appendage filling defects identified by

multidetector computed tomography in patients undergoing radiofrequency pulmonary vein antral isolation: a comparison with transesophageal echocardiography. *Am Heart J*. 2007;154:1199-205.
15. Shapiro MD, Neilan TG, Jassal DS, Samy B, Nasir K, Hoffmann U, Sarwar A, Butler J, Brady TJ and Cury RC. Multidetector computed tomography for the detection of left atrial appendage thrombus: a comparative study with transesophageal echocardiography. *J Comput Assist Tomogr*. 2007;31:905-9.
16. Hur J, Pak HN, Kim YJ, Lee HJ, Chang HJ, Hong YJ and Choi BW. Dual-enhancement cardiac computed tomography for assessing left atrial thrombus and pulmonary veins before radiofrequency catheter ablation for atrial fibrillation. *Am J Cardiol*. 2013;112:238-44.
17. Kim SC, Chun EJ, Choi SI, Lee SJ, Chang HJ, Han MK, Bae HJ and Park JH. Differentiation between spontaneous echocardiographic contrast and left atrial appendage thrombus in patients with suspected embolic stroke using two-phase multidetector computed tomography. *Am J Cardiol*. 2010;106:1174-81.
18. Jaber WA, White RD, Kuzmiak SA, Boyle JM, Natale A, Apperson-Hansen C, Thomas JD and Asher CR. Comparison of ability to identify left atrial thrombus by three-dimensional tomography versus transesophageal echocardiography in patients with atrial fibrillation. *Am J Cardiol*. 2004;93:486-9.
19. Hur J, Kim YJ, Lee HJ, Ha JW, Heo JH, Choi EY, Shim CY, Kim TH, Nam JE, Choe KO and Choi BW. Left atrial appendage thrombi in stroke patients: detection with two-phase cardiac CT angiography versus transesophageal echocardiography. *Radiology*. 2009;251:683-90.
20. Sawit ST, Garcia-Alvarez A, Suri B, Gaztanaga J, Fernandez-Friera L, Mirelis JG, D'Anca M, Fuster V, Sanz J and Garcia MJ. Usefulness of cardiac computed tomographic delayed contrast enhancement of the left atrial appendage before pulmonary vein ablation. *Am J Cardiol*. 2012;109:677-84.
21. Lazoura O, Ismail TF, Pavitt C, Lindsay A, Sriharan M, Rubens M, Padley S, Duncan A, Wong T and Nicol E. A low-dose, dual-phase cardiovascular CT protocol to assess left atrial appendage anatomy and exclude thrombus prior to left atrial intervention. *Int J Cardiovasc Imaging*. 2016;32:347-54.

Table 1. Sensitivity and Specificity of CCTA with Delayed Imaging for the Detection of LA thrombus (compared to TEE).

Reference	Delayed Images	Sensitivity	Specificity
Kim (17)	+	100%	98%
Jaber (18)	+	100%	100%
Hur (19)	+	100%	98%
Hur (12)	+	100%	100%
Sawit (20)	+	100%	100%
Lazoura (21)	+	100%	100%
Mean		**100%**	**99.3%**

Table 2. Cost of CT and TEE in Canada and US.

	Canada	USA (National Payment Amount)	
CT	$	$581.76	
TEE	$	$505.81	