Apixaban Versus Warfarin in Patients With Left Ventricular Thrombus: A Prospective Randomized Outcome Blinded Study on the Size Reduction or Resolution of Left Ventricular Thrombus

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STUDY PROTOCOL

Title

Apixaban versus warfarin in left ventricular thrombus: A prospective randomized outcome blinded study on the size reduction or resolution of left ventricular thrombus.

Introduction

Left Ventricular Thrombus (LVT) is a blood clot in the left ventricle (LV) of the heart. It is a well-recognized complication of acute myocardial infarction (AMI) and congestive heart failure (CHF) due to severely impaired LV systolic function. Previously, the incidence of LVT was reported to be as high as 30%-40% in patients with an anterior AMI. For patients with a non-anterior AMI, the risk of LVT was lower (<5%) (Asinger *et al.*, 1981). Although controversial, in the contemporary era of routine early revascularization and more aggressive anticoagulation, the incidence of LVT complicating an anterior AMI is likely reduced and is currently estimated at 5% to 15% (Kalra *et al.*, 2000; Greaves *et al.*, 1997; Nayak *et al.*, 2004). In patients with dilated cardiomyopathy and CHF, the reported frequency of LVT varies from 10%-30%, depending on the series (Ciaccheri *et al.*, 1989; Gottdiener *et al.*, 1983). Hence in certain parts of the world where there was delay to revascularization due to logistical and financial reasons the rate of incidence is presumably higher. Then the choice of anticoagulation is vital for lower risk of bleeding and complications in patients with multiple co-morbidities.

The pathophysiologic mechanisms for LV thrombus formation is the so-called "Virchow's triad" that commonly exists in patients after AMI or in those with dilated cardiomyopathy and congestive heart failure. The triad consists of stasis of blood, endothelial injury or dysfunction and hypercoagulable state. In general, LVT can occur within 24 hour but commonly within the first 1-2 weeks after an AMI (Nayak *et al.*, 2004; Visser *et al.*, 1983). Late occurrence of LVT is usually associated with adverse chamber remodelling, dilatation, reduced global function, and aneurysm formation. Factors associated with a higher risk of developing LVT have been well-studied, particularly in the post-MI setting. There are few high risk echocardiographic features for development of LVT such as large infarct size and extent, anterior more common than inferior, severe global and regional LV systolic dysfunction with presence of congestive heart failure, elevated LV end systolic volume with LV dilatation, spontaneous echo contrast, abnormal flow pattern within LV, apical rotating flow and vortex ring formation (Van Dantzig *et al.*, 1995; Neskovic *et al.*, 1998).

The main complication of LVT remains systemic embolization, particularly in cerebral circulation. In a meta-analysis of studies performed in patients after anterior MI, the estimated odds ratio (OR) for increased risk of emboli in the presence of echocardiographically demonstrated LVT (11 studies, 856 patients) was 5.45 (95% confidence interval (CI), 3.02 –9.83) (Vaitkus *et al.*, 1993). The clinical features have not been found to be predictive of risk but the following echocardiographic characteristics of LVT are associated with a higher risk of embolization when the thrombus is mobile, protruding with presence of central echolucency (Haugland *et al.*, 1984; Visser *et al.*, 1985).

LVT remains an important complication in patients with ischemic heart disease after anterior AMI and in those with dilated cardiomyopathy and systolic heart failure. The diagnosis of LVT remains important, since anticoagulation will reduce the risk of systemic embolization and stroke. Despite advances in other imaging modalities, namely the cardiac computerized tomography (CT) and magnetic resonance imaging (MRI), echocardiography still remains the most important tool for diagnosis and risk stratification in patients predisposed to developing LVT. Largely due to cost and availability of the echocardiography. The transthoracic echocardiography (TTE) remains the most common imaging modality to use. When images are technically adequate coupled with competent operator, TTE has a sensitivity of 90%-95% and a specificity of 85%-90% for detection of LVT in studies where the presence of thrombi was confirmed at surgery or autopsy (Visser *et al.*, 1983; Cacciapuoti *et al.*, 1986).

The 2004 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Management of Patients with ST-elevation (STE) MI, (Antman *et al.*, 2004) recommended the use of oral anticoagulation, targeted to an international normalized ratio (INR) of 2.0-3.0, for at least 3 months (Class I, Level of Evidence B) and perhaps, indefinitely in patients without an increased risk of bleeding (Class I, Level of Evidence C) in post-STEMI patients with documented LVT (Antman *et al.*, 2004). This recommendation is based primarily on observational studies demonstrating that patients with LVT treated with heparin and warfarin had better outcomes and fewer cerebral emboli. In a meta-analysis of published studies in patients with LVT post-MI,(Vaitkus *et al.*, 1993) the odds ratio (OR) of anticoagulation versus no anticoagulation in preventing embolization (7 studies, 270 patients) was 0.14 (95% CI, 0.04 - 0.52). Additional therapeutic interventions, such as thrombolysis or surgery, are rarely needed. In clinical practice,

echocardiographic imaging is routinely used to follow patients being treated for LVT. Repeated imaging of the left ventricle after 3 months of therapy may allow discontinuation of anticoagulation earlier than 6 months, if evidence of thrombus is no longer present, particularly if there is recovery of apical wall motion (Steg PG *et al.*, 2012).

Based on ESC guidelines for STEMI 2012, anticoagulation should be considered in patients with extensive anterior infract leading to large anterior wall motion abnormalities involving apical segments. Especially, if they are at low risk of bleeding, to prevent the development of thrombi. For patients with confirmed mural thrombi, the consensus is that they require oral anticoagulant therapy with vitamin K antagonists for up to 6 months (Steg PG *et al.*, 2012). However, this has not been revisited in the era of stenting and double antiplatelet. Combining oral anticoagulation and double antiplatelet into a triple therapy increases bleeding risks. The optimal duration of such triple antithrombotic therapy is unknown and should take into account the relative risks of bleeding and stent thrombosis. Repeated imaging of the left ventricle after 3 months of therapy may allow discontinuation of anticoagulation earlier than 6 months, if evidence of thrombus is no longer present, particularly if there is recovery of apical wall motion (Steg PG *et al.*, 2012).

Rationale

Recently, novel oral anticoagulants (NOACs) have emerged as alternative to VKA for thromboembolism in patients with non-valvular atrial fibrillation. The indication of NOACs was then expanded to cover the treatment of DVT and pulmonary embolism following non-inferiority trials with VKA (Buller HR *et al.*, 2012; Agnelli *et al.*, 2013). However, the effect of NOACs on

left ventricular thrombus has not yet been studied in a prospective randomized trial. Only recently one study looked at left atrial thrombus. "XTRA" a study on the usage of rivaroxaban in patients with non valvular atrial fibrillation with left atrial appendage thrombus has been initiated in 2013 in Europe. This was an open label single group interventional phase III trial and the result is still pending (Lip GY *et al.*, 2015).

In the Malaysian population, due to the lower rate of primary angioplasty, we are seeing more ischeamic induced left ventricular failure and hence higher prevalence of left ventricular thrombus (LVT) as opposed to Western population. We believe similar scenario might be happening in other developing countries as well as poorer nations. Hence the treatment was always with VKA – warfarin coupled with IV heparin in the beginning and resulting in longer stay in the hospital in order to achieve the targeted INR. The emergence of NOACs is an ideal alternative with lesser bleeding rate and no monitoring needed leading to shorter length of hospital stay. Available literatures consisting of case reports have shown favourable outcomes with the use of NOACs in left ventricle thrombus especially apixaban (Tohru *et al.*, 2013; Mano *et al.*, 2014; Atakan *et al.*, 2015; Nakasuka *et al.*, 2014). The use of apixaban in LVT will be beneficial for patients who are most of the time at increased risk of bleeding due to the concurrent use of antiplatelet, elderly age and presence of renal and/or liver impairment. The study will add another indication for NOACs specifically apixaban.

The purpose of the study is to assess the size reduction and resolution of LVT. This study will give a preliminary data for further studies in the future. Specifically on the usage of the novel oral anticoagulant apixaban on LVT patients in order to prevent catastrophic morbidity and mortality from cardiac thromboembolic event.

Objectives

To compare the novel oral anticoagulant apixaban with the standard therapy of warfarin on the size reduction or resolution of left ventricular thrombus over 3 months.

Research hypothesis

The resolution of LVT in patients with apixaban was equal or better compared to warfarin based on LVT size reduction in cm^2 or total resolution over 3 months

Methodology and Material

Definition of LV thrombus patients

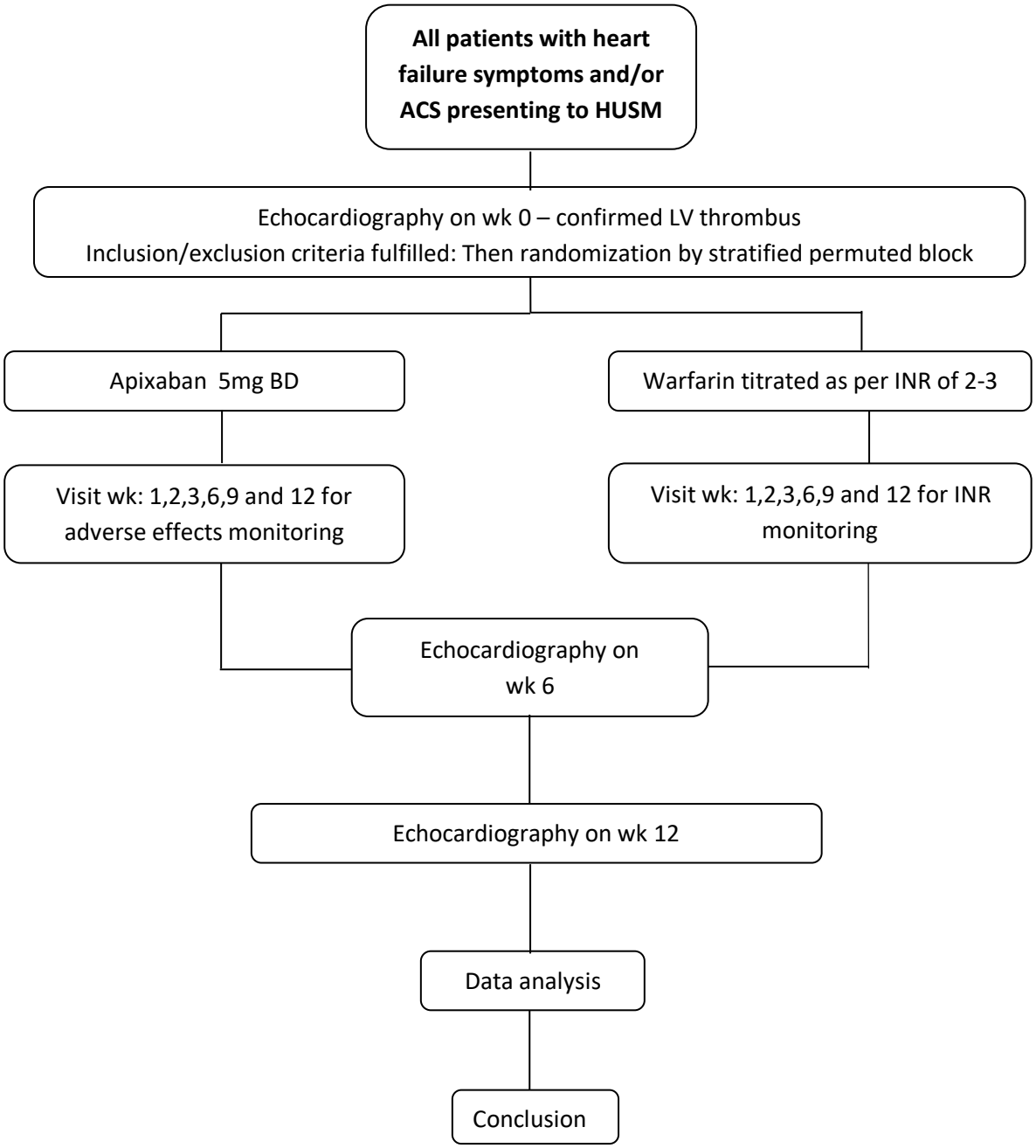
Patients with symptoms of heart failure or recently acquired acute coronary syndrome (ACS) who developed LV thrombus and highly visible spontaneous echo contrast (grade 4) confirmed on 2-D echocardiography by two operators.

Study Design

This is a two arms open label interventional and prospective randomized controlled outcome blinded endpoint (PROBE) study

Study flow chart

Figure 1



Study Period

October 2016 to October 2018

Reference and study population

Reference population are all patients with left ventricular thrombus with history of left ventricular failure from any causes and with/without prior stroke event.

Study populations are patient who presented to the study centres with acute coronary syndrome (ACS) and/or heart failure with or without prior stroke. They will have 2D echocardiography from October 2016 till October 2018.

Sampling Method

- LVT patients fulfilling the inclusion and exclusion criteria were selected by convenience sampling
- And treatment allocation will be decided by randomized stratified permuated block sampling using computer software: block stratified randomization windows version 6.0. The computer program used to generate these sheets makes block stratified assignments with user selected block size. The pseudorandom number generator is a linear congruential algorithm of Park and Miller with Bays-Durham shuffling. It has a period of over 2 billion. (Reference: Press WH *et al.* Numerical Recipes in C. Cambridge University Press, 1992, p 280.)
- Strata decided are age 55 years old above and presence of diabetes mellitus.

Inclusion Criteria

1. Age 18 – 80 years old
1. Presence of LV thrombus or spontaneous echo contrast (SEC) grade 3 or 4 (Patel VG 1996), with regional wall motion abnormalities
2. HASBLED score less than 3
3. No episodes of major bleeding in the past 6 months

   a) Major bleeding defined as

   - episodes of bleeding with significant drop in haemoglobin(Hb)level of at least 2gm/dL - Includes upper and lower gastrointestinal bleed
   - The need for blood transfusion (pack cell) of at least 2 unit
   - Recent surgery with bleeding complications and lost of Hb as in (i) or (ii)
   - Any intracranial bleeds with neurological deficits

Exclusion Criteria

1. Patient with unstable arrhythmias and/or recurrent cardiogenic shock
2. Patient with large ischemic stroke on recruitment-defined as involving >1/3 of cerebral hemisphere or deemed to have high chance of haemorrhagic transformation
3. Patient with permanent pacemaker
4. Patient who is post valve replacement therapy
5. Patient who is pregnant.
6. Patient with advanced kidney disease at stage V and not on dialysis (CrCl <15 mL/min)
7. Patient with advanced liver disease with coagulopathy
8. Patient with organized and old left ventricular thrombus

Study sites

- This study will require multiple centres across Malaysia subjected to the relevant ethical committee approval.
- The confirmed centres for now are :
  1. The Echocardiography Unit Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian, Kelantan.

     - prevalence of LVT in USM is approximately 70 a year or 5 to 6 patients a month. (source: patients registration books, echocardiography unit, HUSM)
  2. National Heart Institute (IJN), Kuala Lumpur.

     - prevalence of LVT in IJN is approximately 5 to 10 patients a month. (source: Datuk Dr Ahmad Khairuddin B Mohamed Yusof, senior consultant cardiologist specialized in cardiac imaging, IJN)
- Term of references will contain points as below.
  1. Data ownership belong to USM.
  2. Recruitment of patients is by competitive sampling. i.e. if USM had reached the targeted sample size, then other center will cease their recruitment and vice versa.
  3. Safety of the patients is the responsibility of each principle investigator and subjected to local ethical approval guidelines.
  4. Main author for publication will be from USM.
  5. Each principal investigator will be the co-author.
  6. Each center need to obtain their own source of fundings, in the absence of major grant.
  7. No insurance will be provided for the duration of the study.

8. Investigators will not be paid for the duration of the study and involvement will be voluntary with no honorarium payment.

Study methodology

- Patients who are diagnosed with left ventricular thrombus (LVT) by echocardiography will be selected and screen for inclusion and exclusion criteria (convenience sampling).
- Screening will be done by the principal investigator/ co-investigators who must be physician and not involved in doing echocardiography.
- Blood investigations for screening will be carried on, which include full blood count, liver and renal function test as well as coagulation profile.
- Informed consent will be obtained preferably in the cardiology clinic/ day care after all screening results available.
- Once consented, the patient would be randomized using stratified permuted block randomization for the treatment arm into two (2) groups.
- The first group will be given the study drug which is apixaban at 2.5mg BD from day one onwards until wk 12. The dose of 2.5mg BD is chosen for wider safety profile as well as suitable for patients with the following characteristics: age $\geq$ 80 years, weight $\leq$ 60kg or serum creatinine $\geq$ 133 micromol/L.
- While the second group will receive the standard therapy which consisted of heparin infusion overlapping with warfarin with the targeted INR of 2-3.
- Patients will be discharged failure symptoms improved.

- In the presence of recent ACS and patients not yet undergone angioplasty, only a single antiplatelet will be used concurrently.
- If patient had to go for early/emergency percutaneous coronary intervention with a coronary stent then the choice of stent will have to take consideration of the higher risk of bleeding on triple therapy.
- Once a coronary stent inserted then patient will put on triple therapy (apixaban/ warfarin + dual anti platlet). There's a recent study comparing bleeding risk between warfarin and NOAC in triple anticoagulant therapy, of which, the bleeding risks were significantly lower in NOAC with triple therapy compared to those of warfarin triple therapy. (Deepak *et al.*, 2016)
- **The study will be assisted by 2 nurses with one will help in randomization, nursing support and documentation. While another nurse is a trained echo technician who will do serial echocardiography for the patients.**
- The echocardiography nurse will be doing the first echo scan at the designated weeks in a allocated room (room A)
- The second echo will be done by a cardiologist at another allocated room (room B) on the same day with the first scan.
- Both the second nurse(echo technician) and the cardiologist will not have access to the medical folder and the treatment strategy. They are only required to fill in the given echocardiography report form. See Patient Data Collection Form (3) and (4).
- This blinding process will be monitored by the first study nurse while making all effort not to reveal any information to the echocardiography operators.
- Only previous echocardiography report will be available for the operator reference if requested.

- The completed echocardiography data entry forms will be kept separately from other forms for outcome blinding purpose.
- The study visits are scheduled at week 0,1,2,3,6,9 and (not more than 15 weeks). Week 0, 6 and 12 are for echocardiography and INR review while the rest are for outpatient visit which include INR monitoring and screening for any adverse events.
- Patient Data Collection Form (1) is for the first visit while form number (2) is for subsequent visits.
- Screening for adverse events include blood investigations for hemoglobin level, renal and liver function for both groups.
- The INR would be monitored nine times including week 0 and week 1,2,3,6,9 and 12.
- Achieved INR with TTR of more than 60% (Connolly S *et al.*, 2008) is considered adequate anticoagulation in the warfarin group. In total 3 echocardiography will be done to each patient and LV thrombus size is charted in cm^2.
- The spontaneous echo contrast (SEC) would be quantify based on the score of 0-4 as reported by Patel VG 1996:-

0 = None

1 = Faint but definite contrast, more linear than curving in

2 = Spontaneous contrast of intermediate intensity between

3 = Easily observed spontaneous contrast, swirling in nature

4 = Dense, rope-like spirals with a slow moving pattern with motion pattern within the LV grades 1 and 3 but not heavily dense or slow moving in the LV.

- The LV thrombus size in cm^2 for percentage of reduction or total resolution during the first 3 months confirmed by echocardiography are the primary endpoints.
- When there is no contraindication, the apixaban/warfarin will be continued after total resolution of LVT till the next visit with echocardiography. This is to make sure the resolution is maintained on 2 echocardiography (6 weeks apart).
- The investigators will not have access to the echocardiography data except when it is time to stop the oral anticoagulation following 6 weeks of total resolution.
- Echocardiography report will be unblinded when major events such as stroke, major bleeding, new onset acute coronary syndrome with or without left ventricular failure or any other events that are life threatening.
- After 3 months (up to 15 weeks) has elapsed then each patient will undergo the last echocardiography. The result will have three possibilities:

1. Total resolution persisted
2. Residual smaller thrombus
3. Organized thrombus
   - Note: No universal definition available apart from experts' opinions. It is described as fixed or flatter thrombus with area of calcifications, homogenous echogenicity with no area of echolucency and high acoustic impedance on the outer layer (Delewi R *et al.*, 2012; Haugland *et al.*, 1984; Ports TA *et al.*, 1978)
   - A successful treatment defined as complete resolution or organized clot achieved at any time before 15 weeks without any thrombotic events.

- A failure of treatment is defined as less than 50% reduction over the same period or any thrombotic events regardless of the left ventricular size.
- In the case of residual smaller thrombus all anticoagulant will be switched on warfarin as per local protocol after week 15. The decision for longer term anticoagulation after study ended will depend on the primary managing team based on available clinical and echocardiography findings.
- Demographic and clinical data such as past medical history and echocardiography findings etc. will be obtained by the folder review. While body weight, blood pressure etc. would be documented as per visit.
- After 15 weeks has elapsed, follow up will be done by clinic follow up every 2 months till the end of study duration of 24 months.
- Any major cardiovascular events including bleeding, stroke and death from any cause will be recorded and analyzed.
- Bleeding attributed to the effect of the anticoagulation is considered as the safety endpoint.
- After an episode of major bleeding, an OGDS or CT scan brain depending on the site of bleeding will be done after 4-6 weeks time for reassessment.
- The decision to continue warfarin/apixaban after 6 weeks will be based on the risk of stroke from residual thrombus against the risk of future bleeding. The next dose of warfarin/apixaban will be reduced to lowest possible therapeutic dose and INR of 1.7- 2.2 (Chung J *et al.* 2015) (29) when the managing physician decided to restart the anticoagulant.
- All adverse events will be documented and serious adverse events (SAE) will be communicated to the related ethical committee within 24 hour. The echocardiography findings will be unblinded and patient will be withdrew from the study in the event of SAE.

- Any patients who withdraw their consent or has to be terminated early for any reasons, will be put on warfarin if they're on the study drug and follow up as per local guidelines.

Procedures and visits schedule

Visit week	0	1	2	3	6	9	12
Procedures							
Informed consent	/						
Full clinical review	/			/		/	
ECHO	/				/		/
A/E review		/	/	/	/	/	/
ECG	/						
INR/APTT	/	/*	/*	/*	/*	/*	/*
FBC	/	/	/	/	/	/	/
RFT	/		/		/		/
LFT	/		/		/		/

Note: * For patients on warfarin only.

Sample size calculation

- Based on the best number for a study- the minimum number per group is 12 “the rule of 12” Belle and Julious (Griffiths HR *et al.*, 2014).
- David Schoenfeld (David Schoenfeld *et al.*, 1980) in his paper suggested that in most cases of studies, 25 subjects would be sufficient for a meaningful difference between the groups.
- After considering the resources available and time constraint imposed. A total of 100 patients were decided (50 in each group) to prove our hypothesis

Statistical Analysis

- Statistical calculation will be based on intention to treat analysis. Sample size calculation as mentioned previously. The full analysis set will include patients who have received at least 1 dose of medication or had 1 or more post randomization, follow-up evaluation.
- For primary and secondary outcomes, descriptive statistics and 95% confidence intervals will be used to summarize the differences between groups.
- All data will be entered in SPSS version 24. The descriptive statistics of variables is presented as mean (SD) for continuous variables and frequency (%) for categorical variables.
- The comparison of LV thrombus size (cm^2) between warfarin and apixaban groups is based on the 2 variables (categorical and repeated numerical data) and would be analysed using the model statistical analysis of general linear model with repeated measures ANCOVA.
- Model assumptions for the Repeated Measures ANCOVA analysis are then checked for normality, homogeneity of variances and compound symmetry to check correlation across all measurements. Histogram and box and whisker plot will be used for testing the normality of the residuals from the repeated measurement of LVT area (cm^2) and normality reported.

Overall linearity assumptions are fulfilled when the scatter plot of the predicted values for the LVT area (cm^2) are charted against the residual for the LVT area (cm^2). Homogeneity testing is performed using Levene's test, and the equal variances assumption is met *(P* > 0.05). Box test is applied to test covariance. Compound symmetry then checked for all of the measurements using Mauchly's test of sphericity. The *P* value of <0.05 indicates that assumption of compound symmetry is not met. In that case, analysis will continue with multivariate test or univariate test with Epsilon correction. When the time and LVT area interaction is significant (*P* < 0.05) then further analysis will produce adjusted means with confidence interval. Analysis will be continued with adjusted confidence interval using the Bonferroni adjustment method.

- Differences exhibiting *P* values below 0.05 were considered significant

Ethical consideration

The risks and safety precautions

a) The study will require patients to take the standard anti-coagulant drug for atrial fibrillation and DVT/pulmonary embolus (apixaban) for an experimental benefit in left ventricular thrombus as opposed to the warfarin which is the standard treatment. The control group will be on warfarin.

b) The risk of inadequate anticoagulant is thromboembolic stroke while the side effect will be bleeding.

c) Enrolled patients will receive all necessary ACS and anti-failure medications on top of the study drug or warfarin.

d) In-patients are expected to be the main participants in this study. However in the event of an out patient coming in for an echocardiography who turned to be positive for LVT then he/she will be admitted for further management. Once informed consent obtained, he/she will be randomized on the choice of treatment arm. In this study no placebo is given.

e) Full blood count and coagulation profile will be taken on each patient on every visit to monitor hemoglobin levels and exclude occult bleeding.

f) Renal and liver function test will also be taken on every visit. Any derangement more than 30% from baseline for renal function and 1.5x ULN of the liver enzymes or billirubin will be reported as adverse event.

g) In the event of bleeding, patients and family members will be reminded to come to the emergency department as soon as possible and to skip the next dose of warfarin/apixaban. Warfarin induced major bleeding has a clear set of international guidelines on reversal of INR. The apixaban bleeding occurs at a lower rate and tend to be lesser in severity. However in the event of apixaban induced major bleeding then partial reversal of prothrombin time prolongation has been seen after administration of prothrombin complex concentrates (PCCs) in healthy volunteers. The use of other procoagulant reversal agents like activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (rFVIIa) may be utilized when available but has not been evaluated. Minor bleeding will be managed by close observation and supportive care after stopping the medication.

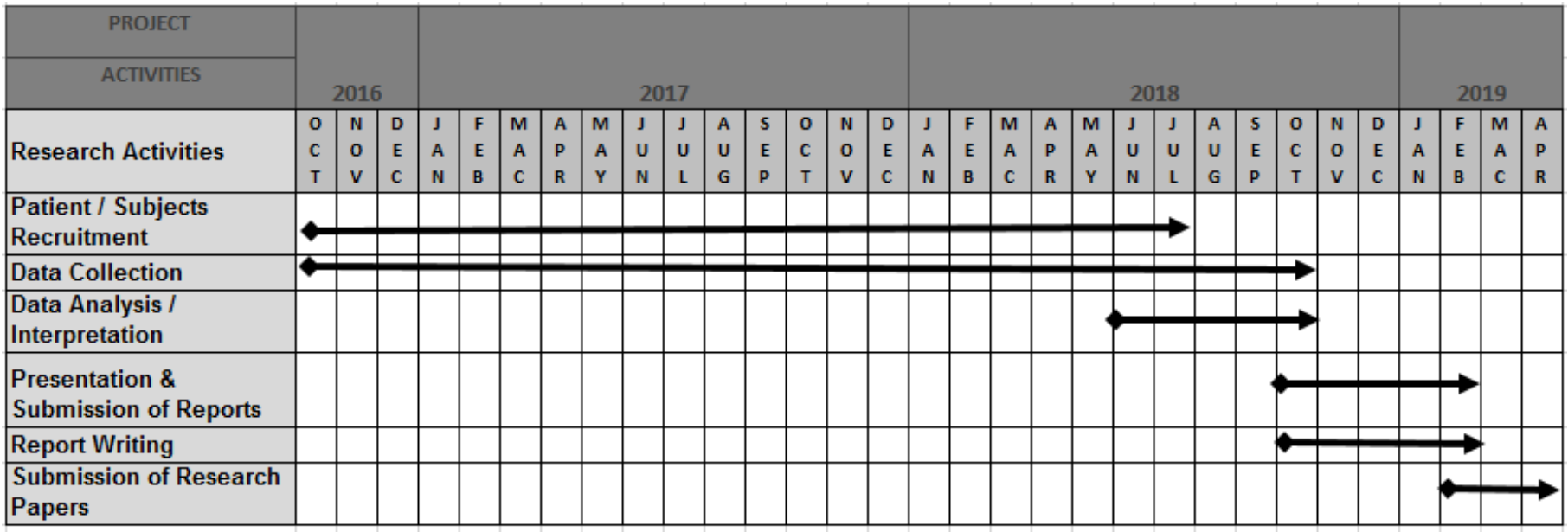
h) Patients can walk in to the clinical trial unit or echocardiography unit on any suspected adverse events. The list of phone numbers of all investigators and study nurses will be made available to all patients.

i) CT scan brain will be done immediately on the discovery of new neurological deficits or in the likely event of stroke

The benefits from this study

a) This study would be the first in the world utilizing novel anticoagulant agent in left ventricular thrombus
b) The use of apixaban in LVT will benefit patients greatly if its efficacy and lesser rate of bleeding proven against warfarin. Patients would benefit on the convenience and safety of apixaban over warfarin.
c) On the contrary, a negative findings will guide the physician worldwide that not all anticoagulants is suitable for intracardiac thrombus and unnecessary risks will be avoided on many patients.
d) The demographics and local data on LVT will be made available from this study that would be beneficial for further knowledge in LVT management and risk assessment.

Gantt Chart of Research Activities: Apixaban versus warfarin in left ventricular thrombus: A prospective randomized outcome blinded study using two dimensional transthoracic echocardiography by two operators



Milestones

1. Patient recruitement: October 2016 ‣ July 2018
2. Data collection: October 2016 ‣ October 2018
3. Data analysis: June 2018 ‣ October 2018
4. Presentation & submission of reports: October 2018 ‣ February 2019
5. Report writing: October 2018 ‣ February 2019
6. Submission of research papers: February 2019 ‣ April 2019

Patient information and consent form

Patient Information Sheet

TOPIC : Apixaban versus warfarin in left ventricular thrombus: A prospective randomized outcome blinded study on the size of left ventricular thrombus between apixaban and warfarin

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1. Introduction

You are invited to take part voluntarily in the study as above. For your information, left ventricular thrombus is a condition whereby there is a blood clot in one of the heart chamber. In this case the heart chamber involved is known as the left ventricle. When a patient developed diseases that weakened the force of the heart muscle contraction then the blood will be pumped out at lower energy resulting in slower blood out-flow from the left ventricle. Hence the blood stay in the left ventricle at longer time with slower flow predisposing to clot formation. The most common disease that cause left ventricular thrombus is ischaemic heart disease due to coronary artery obstruction. The reduced or sudden interruption of blood supply will lead to damaged or death to the heart muscle. Other diseases are dilated cardiomyopathy whereby the heart chambers become enlarged to the extent the muscle was stretched and loss its contractility. This disease can be due to multiple causes such as valvular heart disease, stress induced, alcoholism, viral infection and hereditary. The thrombus or blood clot inside the heart will cause stroke if it dislodged from the heart muscle in the left ventricle and travel to the brain. In patients who just had a heart attack or heart failure symptoms, echocardiography will be done as early as possible to look for left ventricular thrombus or clot so that treatment with anticoagulants can be given urgently.

2. Purpose of Study

Current treatment for left ventricular thrombus is anti-coagulant or blood thinning agent known as warfarin. Recently at least three novel oral anticoagulant agents were introduced in the treatment of atrial fibrillation(irregular heart beats that predispose to stroke) and the later indication is for the treatment of pulmonary embolism and

deep vein thrombosis (DVT). They make the blood thin like warfarin by acting at different sites in the coagulation pathway. The drugs will require no blood taking for INR monitoring (the measure of blood thinning level;it is compulsory when patients on warfarin), hence less visit and more convenience to patients. Latest studies also showed lesser rate of bleeding as compared to warfarin and hence relatively safer. One of these novel oral anticoagulant is apixaban. This study will compare apixaban with warfarin in terms of efficacy in reduction or resolution of left ventricle thrombus size as well as prevention of stroke and the side effect of bleeding.

3. Qualification to Participate

Before agreeing to participate in this study, please understand this information sheet carefully. Only adult patients (>18 y.o) with confirmed left ventricular thrombus by echocardiography will be included in the study. Then you will be assessed based on bleeding risk including any recent episodes of major bleeding in the last 6 months prior to this. If you are found to have very high bleeding risk then you will be excluded from this study.

If you have had a recent coronary angioplasty with coronary stents inserted coupled with high bleeding risk then you are not eligible for this study. Futhermore, you are exluded if you just had a heart attack with unstable blood pressure and heart rhythym, recent large stroke, underlying advance kidney disease stage V or advance liver disease with tendency to bleed. Lastly, if you have had pacemaker inserted or prosthetic valve(s) inserted then you are also not eligible to participate.

Information regarding this study will be given to you or your legal representative over telephone and written consent will be taken.

4. Study procedures

Once the doctors discovered that you have blood clot in your heart by echocardiography you will be counseled on the need of urgent treatment in the hospital. You will be given either one of the treatment; warfarin or apixaban by random allocation. Once the drug is started you will be required to stay in the hospital until INR (2-3) is achieved if you are on warfarin but in case of you are put on apixaban then your length of stay in the hospital is according to the doctors that are treating you for the heart attack or failure. At the time of discharge you will be given a timetable on the return appointments for titrating warfarin dose as to maintain INR level of 2-3 and repeat echocardiography. There are 8 visits (week 1, 2, 3, 6, 9, 12, 18, 24) in total in which week 6, 12 and 24 are for repeat echocardiography. You will have blood investigations taken on each visit for INR monitoring if you are on warfarin. On the hand, if you are on apixaban, the return visits are for screening of bleeding (hemoglobin level) as well as to check on kidney and liver function for any contraindications to the treatment.

The size of left ventricular thrombus will be measured on every echocardiography visit. In case of the total resolution of the thrombus happened on any of the visit, your drug will be continued until the next echocardiography appointment (another 6 weeks). Maximum weeks on the drug will be 26 weeks. The duration of the study is 24 months whereby after 24-26 weeks has elapsed, you will be followed up every 2 months for general well being assessment. In a rare case of persistent mobile/soft thrombus after 26 weeks then you will be put on your current drug until the end of the study as long as no contraindications to it. Other medications for your current medical problems will be prescribed as usual for this study. Your medical records will be evaluated and information will be analyzed.

5. Possible risks

The risk of stroke with the use of apixaban in the left ventricular thrombus is unknown hence the need for this study. However based the data from atrial fibrillation (irregular heart beat that predispose to stroke) studies, apixaban has reduced the risk of stroke equal to therapeutic dose of warfarin. Patients on apixaban has lower risk of bleeding with the exception of the risk of gastrointestinal bleeding was reported slightly higher with apixaban in one study. This study will not provide you with an insurance cover. You will be however, closely monitored in this study as to lower the risk of stroke and bleeding. On every appointments you will be assessed by the doctors involved in this study for any medical problems and signs of bleeding from the gastrointestinal tract. Due to the close monitoring, blood investigations will be done on every visit and you will feel uncomfortable during blood taking procedure. Your immediate family members must be informed regarding your bleeding tendency. Hence, they must inform the doctors once any suspicious bleeding occurs.

6. Reporting Health Experiences

If you have any injury, bad effect, or any other unusual health experience during this study, make sure that you immediately tell the nurse or Dr. W. Yus Haniff W. Isa [MMA Registration No.40454] at 097673985 ext. 6592 or 0199228373, or Dr Niny Hwong [No. MMC: 51933] at 09-7673000/ 012-8592892. You can call at anytime, day or night, to report such health experiences. In the event of true or suspicious bleeding, you must stop the study drug/ warfarin and come to the cardiology clinic/ day care immediately during office hour if able, othewise, family members must bring you to the nearest hospital as soon as possible.

7. Participation in the study

Your participation is voluntary. You may refuse to disclose any information or refuse to take part in this study without any penalty or loss of any benefits to which you are entitled for. The doctors will continue to look after your well being irrespective of your choice with regard to this study including if you withdraw your consent to participate later on. There will be no monetary rewards/ honorarium for participating in this

study. However all necessary requirements for procedures and transportation during the study duration will be provided.

8. Possible benefits

The possible benefits of this study are:-

- All the cost of the study drugs will be borned by the researchers.
- If additional investigations are required under the study, then researchers will assist in whatever way possible.
- You may be informed of all the clinical findings and investigations throughout this study
- The result of this study will hopefully benefit the future patients at large especially those with heart failure and left ventricular thrombus.

9. Enquiries

If you have any further questions about this study, please contact Dr W. Yus Haniff, MMC no: 40454, (09-7673987) or Dr Niny Hwong, MMC no: 51933 (09-7673000), Medical Department, Hospital Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan.

If you have any questions regarding the Ethical Approval, please contact;

En. Mohd Bazlan Hafidz Mukrim
Setiausaha Jawatankuasa Etika Penyelidikan (Manusia) USM
Pusat Inisiatif Penyelidikan -Sains Klinikal & Kesihatan
USM Kampus Kesihatan.
No. Tel: 09-767 2354 / 09-767 2362
Email : bazlan@usm.my/jepem@usm.my

10. Confidentiality

Any information acquired during this study whether medically related or not, is confidential and would not be made public unless required by law. Data obtained from the study does not identify you individually. However data from the study may be used in future for other medically or scientifically related reasons.

Thank You

Attachement S

Patient Consent Form (Signature Page)

Research Title : **Apixaban versus warfarin in left ventricular thrombus: A prospective randomized outcome blinded study on the size reduction or resolution of left ventricular thrombus**

Researcher's Name : **Dr W. Yus Haniff W. Isa**

Co – Researchers : Dr Niny Hwong Perng Ling / Dr Ng Seng Loong/ Datuk Dr. Ahmad Khairuddin B Mohamed Yusof/ Prof. Dato Zurkurnai Yusof/ Prof. Syed Hatim Noor@Nyi Nyi Naing/ Prof. Gregory Y.H. Lip.

To become a part this study, you or your legal representative must sign this page

By signing this page, I am confirming the following:

i. I have read all of the information in this Patient Information and Consent Form including any information regarding the risk in this study and I have had time to think about it.
ii. All of my questions have been answered to my satisfaction.
iii. I voluntarily agree to be part of this research study, to follow the study procedures, and to provide necessary information to the doctor, nurses, or other staff members, as requested.
iv. I may freely choose to stop being a part of this study at anytime.
v. I have received a copy of this Patient Information and Consent Form to keep for myself.

Patient Name (Print or type)	**Patient Initials** and Patient Number
Patient I.C Number **(new)**	**Patient I.C** No. **(old)**
Signature of patient or Legal Representative	**Date** (ddMMyy) (add time of day if appropriate)
Name & Signature of Individual Conductiong Informed Consent Discussion (Print or Type)	**Date** (ddMMyy)
Name & Signature of witness	**Date** (ddMMyy)

Notes: All subject/patient who involved in this study will not be covered by insurance

Patient Data Collection Form (1)-Visit 0

Note: Circle or tick all applicable box and sections. Write down all important details.

Folder RN :	**Subject No:**	**0 0 0**

For investigator use:	Sex:	M = 1	F= 2

DOB:	Age (yr):	**<34**	1	**35-44**	2	**45-54**	3	**55-64**	4	**65-74**	5	**75>**	6

Malay	1	Chinese	2	Indian	3	Siamese	4	Others	5	

Address :

Telephone No:	Occupation :

Clinical Data:

Medical Problems:	DM	1	HPT	2	IHD	3	CRHD	4	AF	5
	CKD	6	HPL	7	Other Cardiomyopathy - Specify			8		

Date of LVT diagnosis/Date of 1st follow up:	Day		Month		Year	

LVT cause:	IHD/CAD	1	Cardiomyopathy	2	Other:specify	3

Symptoms prior to 1st ECHO	No symptoms = 0	With symptoms = 1

SOB	1	Chest pain	2	Weakness/stroke	3	Giddiness	4	lethargy	5
Palpitation			6						

History of bleeding	Y=1 N=0	Major bleeding-state site	Minor bleeding-state site

HASBLED SCORE:

Circle that aply. Then total the score. Maximum is 8.

HPT (SBP>160mmHg)	1	Labile INRs Or <60% TTR	1
Abnormal renal function Creatinine > 200 mmol/L	1	Elderly > 65 years old	
Abnormal Liver function Bilirubin >2xULN, AST/ALT/ALP >3xULN	1	Drugs predispose to bleeding (antiplatelet, NSAIDs, etc.)	1
Stroke/TIA	1	Alcohol usage	1
Bleeding History/Anaemia	1		
Total score			

Patient Data Collection Form (2a)- NOT FOR ECHOCARDIOGRAPHER

Note: Circle or tick all applicable box and sections. Write down all important details.

Folder RN :							**Subject No:**	**0**	**0**	**0**	
Visit No:			Date:								
Hospital admission (0 =N, 1 = Y) Date:			Define the cause								
Stroke (0=N , 1 = Y)			If Yes		Ischaemic = 0		haemorrhagic = 1				
Bleeding ep. 1	No bruising No bleeding	0	Bruising	1	Minor bleeding	2	Major bleeding	3			
Bleeding ep. 2	No bruising No bleeding	0	Bruising	1	Minor bleeding	2	Major bleeding	3			
Current Symptoms	0=No	1=Yes									
SOB	1	Chest pain	2	Weakness /stroke	3	Giddiness	4	lethargy	5	lethargy	6
Palpitation	6										
NYHA score		CCS score – if applicable			EHRA score – if applicable						
Warfarin (0=N, 1=Y) Dos ____mg OD		INR-Achieved? (0=N, 1=Y)		INR on this visit :							

Current Medications: (Circle that apply and write dosage od/bd)

B-blocker (0=N, 1=Y)	Carvedilol (1)	Metoprolol (2)	Bisoprolol (3)	Propanolol (4)	_____mg OD/BD
Digoxin (N = 0 , Y = 1)	Amiodarone (N=0 , Y = 1)				_____mg OD/BD/TDS
CCB (0=N, 1=Y)	Diltiazem (1)	Verapamil (2)			_____mg OD/BD/TDS
ACE (0=N, 1=Y)	Ramipril (1)	Enalapril (2)	Perindopril (3)	Captopril (4)	_____mg OD/BD/TDS
ARB (0=N,1=Y)	Valsartan (1)	Irbesartan (2)	Losartan (3)	Telmisartan (4)	_____mg OD

Patient Data Collection Form (2b)- NOT FOR ECHOCARDIOGRAPHER

Diuretic (0=N, 1=Y)	Frusemide (1)	Chlorothiazide (1)	HCTZ (3)	_____mg OD/BD/TDS
	Spironolactone (4)			
Antidiabetic	Gliclazide	Metformin	Short acting insulin	long acting insulin
Antidiabetic (fill in if applicable)				
Statin (0=N, 1=Y)	Atorvastatin (1)	Simvastatin (2)	Pravastatin (3)	_____mg OD
	Rosuvastatin (4)			
Anti Platlet (0=N, 1=Y)	Aspirin (1)	Clopidogrel (2)	Ticagrelor (3)	_____mg OD
Others (0=N, 1=Y)	Isordil (1)	Vastarel (2)	Ivabradine (3)	_____mg OD/BD/TDS
Others-Specify				

Physical Examination

BP (mmHg):	Pulse :	Pulse oximeter on R/A:			Weight (kg): Height(cm):	
JVP raised (Y/N)	Lung Clear	Crepitation level (R/L/Both)			LZ	MZ	UZ
CVS : Gallop (Y/N)		Abdomen :				
PR done (Y/N)		Malaena (Y/N)				
Lower limbs oedema	Y	N	Level of edema:	ankle	knee	sacral
Neurological examination						
Upper limbs normal (Y/N)	If N specify	Tone	Power	Reflex	Coordination	Sensation
Lower limbs normal (Y/N)		Tone	Power	Reflex	Coordination	Sensation
If this is follow up of previous findings, please state whether it is improved, similar or worsening						
Name of physician						
Signature and stamp						

Patient Data Collection Form (3) - TTE

Folder RN :	**Subject No:**	**0**	**0**	**0**		
Visit week :						
Echo no :						

2D- TRANSTHORACIC ECHO – FIRST OPERATOR

LVIDd (cm)		LVIDs (cm)	CO(L/min)=
EF (simpson method)		SV(cc) = [LVOT(cm)]^2 x 0.785=	
LV aneurysm	(0=N, 1=Y)	LVOT Pg(mmHg)=	
RMWA	(0=N, 1=Y)	TEI index= AVCO-LVET/LVET=	
Area of hypokinetic			
Pericardial effusion	(0=N, 1=Y)	measurement	
A0: PA			
MR (0=N, 1=Y)	TR (0=N, 1=Y) Max PG:	AR (0=N, 1=Y) P1/2=	AS (0=N, 1=Y) Mean PG:

SEC (0=N, 1=Y)	SEC score	0	1	2	3	4

Comments:			
LV Thrombus present	(0=N, 1=Y)	Size in cm^2	
Type of Thrombus	Mural/sesile	Protruding	pedunculated
Mobile	(0=N, 1=Y)		
Organized? (0=N, 1=Y)	Note: It is described as fixed or flatter thrombus with area of calcifications, homogenous echogenicity with no area of echolucency and high acoustic impedance on the outer layer (Delewi R 2012; Haugland JM 1984; Ports TA 1978)		
Final impression:			
Name of operator:			
Signature:		Official stamp:	

Folder RN : No:	**Subject**	**0**	**0**	**0**		

Visit week :

Echo no :

2D- TRANSTHORACIC ECHO – SECOND OPERATOR

LVIDd (cm)		LVIDs (cm)	CO(L/min)=
EF (simpson method)		SV(cc) = [LVOT(cm)]^2 x 0.785=	
LV aneurysm	(0=N, 1=Y)	LVOT Pg(mmHg)=	
RMWA	(0=N, 1=Y)	TEI index= AVCO-LVET/LVET=	
Area of hypokinetic			
Pericardial effusion	(0=N, 1=Y)	measurement	
A0: PA			
MR (0=N, 1=Y)	TR (0=N, 1=Y) Max PG:	AR (0=N, 1=Y) P1/2=	AS (0=N, 1=Y) Mean PG:

SEC (0=N, 1=Y)	SEC score	0	1	2	3	4

Comments:			
LV Thrombus present	(0=N, 1=Y)	Size in cm^2	
Type of Thrombus	Mural/sesile	Protruding	pedunculated
Mobile	(0=N, 1=Y)		
Organized? (0=N, 1=	Note: It is described as fixed or flatter thrombus with area of calcifications, homogenous echogenicity with no area of echolucency and high acoustic impedance on the outer layer (Delewi R 2012; Haugland JM 1984; Ports TA 1978)		
Final impression:			
Name of operator:			
Signature:		Official stamp:	