Government of South Australia
SA Health

Clinical Trial Protocol

Title

The use of N-acetylcysteine(NAC) and Ramipril to improve clinical outcomes in Tako-Tsubo Cardiomyopathy (TTC): A multi-centre randomised placebo trial

Version 1: 11/11/15

Amendment 1: 14/12/15.

(1) Removed MR spectroscopy from flow chart
(2) Removed patients who are unable to consent
(3) Included mechanism for identifying extreme response to SF-36 and notifying the general practitioner

Amendment 2: 16/03/2016

(1) Dr Devan Mahadevan added as a Principal Investigator

Amendment 3: 10/May/2017

(1) Additional analysis for heart failure biomarkers and future research.
(2) Addition to subject follow up schedule.
(3) Amendment to unblinding procedure.
(4) Sample location, storage and security.

1. Investigators

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2. Classification/ Purpose of Study

2.1 Type of research

Multicentre randomised placebo controlled clinical trial within South Australia.

Participating sites include tertiary-referral university teaching hospitals with on-site cardiac catheterisation laboratories and primary PCI facilities. The participating centres and principal investigators are: The Queen Elizabeth Hospital (Prof J Horowitz and Dr A Sverdlov), Lyell McEwin Hospital (Dr Devan Mahadevan) and the Royal Adelaide Hospital (A/Prof M Worthley).

2.2 Purpose of Study

Stress cardiomyopathy (Tako-Tsubo Cardiomyopathy; TTC) was once thought to be a relatively rare form of transient regional cardiac dysfunction, occurring largely in ageing women. Given the apparently benign course of this condition, little attention has been directed until recently to its cause, or to appropriate treatment. However, it is now apparent that TTC is neither rare nor benign and accounts for about 10% of "heart attacks" in women. Our studies have led to expedited diagnosis, and have delineated a number of aspects of the natural history of TTC. Specifically, attacks, presenting usually as episodes of chest pain and/or dyspnoea, engender major problems both early and late:

A. Early: TTC actually represents a form of catecholamine-triggered myocardial inflammation (of varying severity), which may engender lethal arrhythmias. However the main cause of death post hospital admission is development of severe hypotension, which causes death in 2 – 3% of cases.

B. Late: Recovery is slow, due to persistent inflammation and energetic impairment within myocardium, and is associated with prolonged impairment of quality of life. There is also a substantial risk of recurrence.

Furthermore, we have data from post-mortem studies and from a rat model of TTC developed in our laboratory that myocardial inflammation is associated with increased nitrosative stress.

We therefore hypothesise that measures to reduce nitrosative stress will result in both diminution of severity of attacks and accelerated recovery.

3. Background

Tako-Tsubo Cardiomyopathy (TTC), also known as apical ballooning syndrome, stress cardiomyopathy, and "broken heart syndrome" represents a major cause of cardiovascular morbidity and mortality, especially among ageing women.(1, 2) TTC was first recognised clinically by Japanese investigators a little over 20 years ago, and was initially thought to be a relatively rare disorder with a benign prognosis.(3)

It has now emerged that TTC is neither rare nor benign. Indeed, TTC is frequently precipitated by physical or emotional stress, especially but not exclusively in women aged >50 years. We have recently demonstrated that:-
(a) TTC accounts for approximately 10% of cases initially diagnosed as S-T elevation myocardial infarction (STEMI) in women.(4)
(b) Only a about 40% of cases of TTC present as "STEMI": in the majority of cases, myocardial damage is limited, as may be ECG changes.(5)
(c) TTC often complicates other severe illnesses, with associated substantial mortality rates.(6)

The diagnosis of TTC, previously made entirely by exclusion of relevant fixed coronary artery disease(7) has been expedited by greater awareness of the epidemiology of the condition, the characteristic "multi-regional" ECG changes, marked elevation of NT-pro-BNP levels, and extensive myocardial oedema on cardiac MRI imaging (without associated infarction)(5, 8). Hypokinesis usually predominantly affects the apex of the left ventricle (LV), but in approximately 30% of cases there may be more marked mid-ventricular changes:- early ventriculography or echocardiography therefore also assists diagnosis.(9) Clinically, little information is available about the first few hours after onset of TTC, because the diagnosis is rarely made for at least 4 hours. However, the majority of patients present with ischaemia-like chest pain.
Hypotension and shock are frequently early complications: the mechanism(s) responsible for haemodynamic impairment are probably combinations of impaired left ventricular contractility, together with inadequate tachycardic response and in some cases (BNP-mediated) vasodilatation.(10) Mitral regurgitation and left ventricular outflow tract obstruction are occasionally contributory factors.(11) Although life-threatening tachyarrhythmias and thrombo-embolism also represent occasional causes of early death in TTC, the majority of in hospital mortality is due to shock.(6) There is currently no consensus as to the optimal treatment regimen for this early phase of the illness, either for the purpose of improving haemodynamics in order to prevent shock, or in order to limit myocardial injury.

However, we have recently reported a meta-analysis of mortality rates post TTC:- it is clear that development of shock is the main basis for the 2-6% in-hospital mortality rates,

and that administration of catecholamine (for example in the treatment of hypotension), if anything, increases this mortality (6).

The clinical course of TTC after the first 24 hours is usually one of rapid symptomatic improvement. Chest pain usually diminishes, and a number of studies have shown rapid improvement in left ventricular regional wall motion over a period of approximately 7 days (12). On the other hand, it has recently emerged that complete recovery is usually delayed for at least 3 months, with evidence of persistent LV systolic dysfunction associated with ongoing symptoms of lassitude, exertional dyspnoea and sometimes chest pain; approximately 50% of patients remain symptomatic 1 year post acute attacks.(13) Recurrent acute attacks of TTC occur in 2-3% of patients per annum (14, 15). Thus it is clear that TTC exerts a substantial impact on health care status of ageing women, engendering associated health care costs which can be estimated at greater than $20 million per annum in the Australian population. Furthermore, TTC is still substantially under-diagnosed, particularly when it complicates co-existent acute illnesses (for example cerebral haemorrhage or acute respiratory illness). It remains uncertain how frequently this problem ("secondary TTC") occurs, but it may account for many peri-operative "infarcts" and probably adds to the mortality rates associated with the precipitating co-mortality. (6)

The lack of established therapeutic options for limitation of cardiac dysfunction in TTC is paralleled by considerable uncertainty as regards the pathogenesis of the disorder. However, it is clear that release (or administration) of catecholamines initiates many attacks.(16, 17) Apart from the frequent association of attacks of TTC with antecedent severe emotional stress, elevated plasma catecholamine levels have frequently been documented in TTC patients, and in our previous studies severity of attacks correlated directly with plasma normetanephrine levels.(5, 8) Furthermore, administration of catecholamines, or of drugs which elevate catecholamine levels, has been shown to trigger attacks of TTC. In animal models, administration of high doses of catecholamines induces TTC-like changes.(18) European investigators have recently presented data from studies in rats suggesting that stimulation of myocardial β2-adrenoceptors may initiate a regional cardiodepressant effect.(19, 20) This may explain the finding that (predominantly) β1adrenoceptor antagonists appear to have little impact on the clinical course of the disease.(11)

However TTC is not merely a state of transient negative inotropy: it is an intense chemical pancarditis. This can be demonstrated most easily by MRI imaging: myocardial oedema is intense, not only at the LV apex, but throughout the LV, and resolves slowly, being persistent at 3 months after acute attacks.(8) We have now shown that persistent myocardial inflammation in TTC is also associated with:-

(1) Elevation of plasma BNP and NT-proBNP levels for at least 3 months.(5)

(2) Impairment of myocardial energetics, as measured by 31P-MRS, for at least 4 months.(21)

(3) Impaired quality of life for at least 3 months.(22)

(4) Impaired left ventricular global longitudinal strain for at least 3 months.(22)

We have also recently demonstrated that TTC is associated with increased circulatory nitric oxide (NO) signalling(23) and intramyocardial evidence of increased nitrosative and oxidative stress(24,25). Specifically, patients with TTC exhibited marked increases in platelet responsiveness to NO relative to age-matched female controls, while in patients dying of shock precipitated by TTC there was increased myocardial content of 3-nitrotyrosine (3-NT), a product and marker of ONOO- effect (nitrosative stress). Furthermore, as well as nitrating tissue proteins, ONOO- also induces DNA damage and activates the DNA-repairing enzyme poly(ADPribose)polymerase-1 [PARP-1], generating poly(ADP)ribose [PAR] and inducing ATP depletion. PAR concentrations in myocardium also tended to be elevated(24) in myocardium from TTC patients. On the other hand, plasma concentrations of 3-NT were not elevated 24 hours post onset of TTC(26) in most cases.

We have also developed a model of TTC utilizing intraperitoneal injection of single doses of isoproterenol into female Sprague-Dawley rats. In this model, impairment of apical strain 24 hours post isoproterenol injection was associated with intramyocardial accumulation of 3-NT relative to levels of expression in control rats, consistent with presence of nitrosative stress in this model.(25) The basis for this nitrosative stress may be excessive activation of NO synthases (NOS), which are coupled to myocardial β2-and β3-adrenoceptors. The resultant generation of ONOO- leads to protein nitration and activation of PARP-1, leading to ATP depletion, myocardial contractile impairment and increased rates of apoptosis. In this model, we also noted increased myocardial content

of thioredoxin-interacting protein (TXNIP),(25) which is activated by regional hypoxia or localized shear stress distortions, and which in turn may "amplify" inflammatory activation.

Currently, in clinically based studies, we wish to test the hypotheses that agents that limit nitrosative stress might:-

(i) Reduce the severity of inflammation and associated energetic impairment in TTC (assuming early initiation) and

(ii) (ii) Accelerate recovery from TTC

We will utilize intravenously infused N-acetylcysteine (NAC) to limit early ONOO- generation. NAC is a potent scavenger of H2O2 and HOCI, and inhibits activation of NAD(P)H oxidase, a major source of O2- and thus ONOO- (27). For chronic studies, the ACE inhibitor ramipril will be utilized. ACE inhibitors have been shown to inhibit both nitrosative stress(28) and TXNIP expression.(29) Furthermore meta-analysis of available data indicates that ACE inhibitor therapy appears to reduce risk of recurrence of TTC.(15) A large registry study has also found an association between ACE inhibitors and improved survival.(30)

4. Participants

Inclusion Criteria

i) Acute episodes of TTC

ii) Provisional diagnosis of TTC will be based on:-

(a) Symptoms of chest pain and/or dyspnoea

(b) Elevation of NT-proBNP levels

(c) Demonstration of regional wall motion abnormality within LV consistent with TTC via ventriculography or echocardiography. Echocardiography will be performed on all patients, irrespective of whether or not they undergo initial cardiac catheterisation, within 48 hours of admission. Data will be archived for later blinded analysis.

iii) Definitive diagnosis of TTC will require demonstration of myocardial oedema on cardiac MRI, and exclusion of myocardial infarction by cardiac MRI or exclusion of relevant coronary artery disease by angiography. The difference in diagnostic

criteria reflects the fact that exclusion of myocardial infarction (usually by coronary angiography) may not be performed on admission in all presumptive NAC patients in the absence of ST-segment elevation electrocardiogram.

Exclusion Criteria

i) For NAC component:

(a) Delay beyond 24 hours post onset of symptoms before making presumptive diagnosis:- in all cases NAC infusion must begin within 24 hours of onset of symptoms.

(b) Simultaneous administration of long-acting nitrates or intravenous glyceryl trinitrate (GTN). If the patient had been commenced on intravenous GTN on presentation, this should be immediately ceased. Patients can be invited to participate in the trial upon cessation of intravenous GTN.

(c) Previous adverse reaction to NAC.

(d) Patients with any contraindications to Cardiac MRI.

ii) For Ramipril component

(a) Previous adverse reaction to ACE inhibitors.

(b) Current therapy with ACE inhibitor or angiotensin receptor blocker.

(c) Severe renal functional impairment: calculated creatinine clearance <30mL/min.

Patients with severe renal function impairment (calculated creatinine clearance <30mL/min) will be excluded from Gadolinium administration during MRI imaging due to its association with nephrogenic systemic sclerosis in this population.

Patients who are unable to provide informed consent will be excluded from the study.

Criteria for withdrawal

(a) The study will be of 3 months' duration: patients may withdraw at any time for any reason.

(b) Adverse reaction to trial medication.

(c) Patient will be withdrawn from the study if ongoing investigations suggest an alternative diagnosis to TTC.

5. Study Design

i) General structure

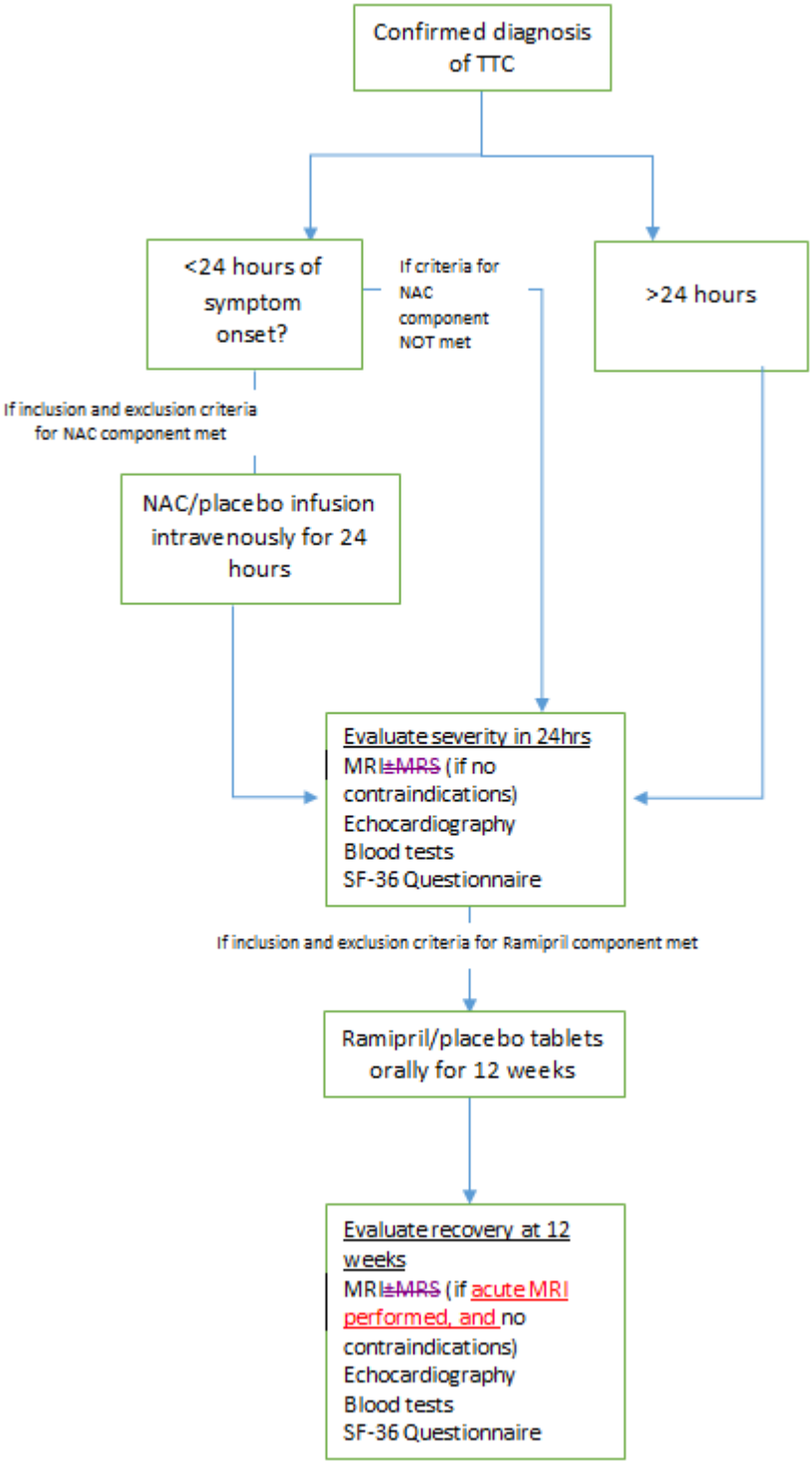
(a) The study will be approved by the institutional Ethics of Human Research Committee and will be registered with Australia New Zealand Clinical Trials Registry.

(b) Informed consent will be obtained in writing prior to study entry.

(c) Patients enrolled in the study will receive additional pharmacotherapy at the discretion of the treating physician. In general, patients will not receive catecholamines, tricyclic antidepressants or serotonin/noradrenaline reuptake inhibitors because of their potential to aggravate TTC. They will not be commenced on nitrate therapy due to its potential to cause significant hypotension. In general patients will be treated with unfractionated or low molecular weight heparin for at least 24 hours because of the risk of mural LV thrombosis during the acute stages of TTC. Patients may also be treated with β-adrenoceptor antagonists at the discretion of the treating physician, although available human data do not provide support for such therapy.(15)

(d) Patients will be evaluated in the Coronary Care Unit for at least the first 24 hours of admission.

Figure 1: Flowchart for NAC and Ramipril in TTC



ii) NAC Component:

Patients entering this component of the protocol will be evaluated closely as regards changes in haemodynamic status over the first 24 hours of treatment.

(a) Time of onset of symptoms and time of initiation of NAC infusion will be noted.

(b) 10g of NAC (50mL NAC) or identical placebo (50mL 0.9% sodium chloride) will be added to 450mL 5% Dextrose, thereby achieving a total volume of 500mL. The infusion will commence at 20mL/hour for 25 hours, ie completing the infusion of 500mL. This is similar to the protocol previously utilized in acute coronary syndromes.(31)

(c) Blood will be withdrawn at entry and after 24 hours for determination of:-

(i) Markers of myocardial necrosis: troponin T and creatine kinase

(ii) Inflammatory markers: NT-proBNP and hsCRP.

(iii) Plasma normetanephrine and metanephrine concentrations.

(iii) Plasma concentrations of 3NT.

(iv) Heart failure biomarkers: Galectin-3, Follistatin-like-3,Syndecan-1, Follistatin, Activin-A, VEGF-A165b, VEGF-A and Secrete Frizzled protein 5 (Sfrp5) and other markers that may become scientifically important to this study question and future studies.

(d) All episodes of hypotension will be documented fully, as will the need for specific treatment of such episodes.

(e) Cardiac MRI imaging will be performed within 24 hours of the end of the NAC infusion in order to quantitate regional wall motion and extent of myocardial oedema. This will be the basis for the primary end-point of the NAC component.

iii) <u>Ramipril component:</u>

Patients entering this component of the protocol will be evaluated largely as regards extent of recovery over 3 months following the onset of TTC.

(a) Treatment with ramipril or identical placebo will be initiated within 24 hours of cessation of NAC infusion.

(b) Baseline investigations for the ramipril component will be identical to those performed at the conclusion of the NAC component.

(c) Ramipril or placebo medication will be given as an initial dose of 5 mg per day, and increased after 2 weeks to 10 mg/day, at which time, patients will be followed up by study investigators to deem suitability and safety for an increasing dose ie if not hypotensive. A further supply of Ramipril or placebo will then be

provided to each patient. All medication will be administered at night to minimize risk of symptomatic hypotension.

(d) Patients will be reviewed clinically 2 and 12 weeks after starting ramipril.

(e) After 12 weeks, the following investigations will be performed:-

(i) Cardiac MRI imaging, to quantitate residual extent of myocardial oedema

(ii) Transthoracic echocardiography. Data obtained will include LV ejection fraction, cardiac dimensions, calculated RV systolic pressure and GLS. Data will be archived for blinded analysis.

(iii) Quality of life evaluation, using SF36.

(iv)Residual inflammatory activation, utilizing hsCRP and NT-proBNP.

(f) All participating subjects will be followed up indefinitely with a yearly phone call.

(iv) Confidentiality:

Data from all participants will be de-identified. A code will be generated for each participant at the time of enrolment and this will correspond to the order of which they were enrolled.

(v) Randomisation Procedure:

Treatment arms will be pre-determined by a computer-generated algorithm with randomisation blocks of 10 and balanced for each participating institution. Randomised treatment allocations will be prepared as numbered treatment boxes containing the study drug. The study boxes will be held in the Coronary Care Unit of each of the participating hospitals. When the decision to randomise the patient has been made, the drug pack to be used will be the next available study drug pack on the list. The drug pack number allocated to the patient will be assigned to the patient. Study drug box and contents (used or unused) must be kept. Patient Kit Boxes must not be opened until the randomisation process is completed and a randomisation/study number is allocated.

(vi) Study Medication: Study medication will be provided to each site in patient study medication kit boxes. Each Patient Kit Box will have a label on the outside describing the contents and the kit randomisation number, and will contain:

NAC Component – 5 x 10mL ampoules of NAC, or 5 x 10mL of 0.9% sodium chloride.

OR*,*

Ramipril Component – 14 tablets of 5mg Ramipril, or 14 tablets of placebo drug identical in presentation of Ramipril tablets.

a) Receipt of Supplies. The Clinical Trial Pharmacist at each site will, upon receipt of supplies, conduct an inventory and complete a supplies receipt.

b) Storage. The trial medication will be stored in a secure area, free of environmental extremes with access restricted to study personnel but will be made easily accessible to Coronary Care Unit study personnel in order to facilitate rapid initiation of therapy.

c) Compliance. Timing and mode of administration of study drug may not be changed. If the infusion/bolus is temporarily stopped due to adverse events, line infiltration or pump failure it should be restarted as soon as possible and the events documented in the CRF and patient record.

d) Accountability. Once a Patient Study Medication Kit Box has been allocated to a patient it may not be re allocated to another patient under any circumstances. If the patient is randomised and then withdraws from the study before study drug is administered, prepared study drug must be discarded and the events clearly documented on the CRF and in the patient record. Drug accountability is the responsibility of the site and accurate records must be kept at the site.

e) Blinding and unblinding.

This is a double-blind study. Intravenous N-Acetylcysteine, and a placebo-equivalent infusion will be indistinguishable in physical appearance and labelled as “Study Drug – Placebo/N-Acetylcysteine”. To facilitate the blinding process, the infusion should be made up by an on duty ward nurse that will not be responsible for immediate patient care. For instance, at the QEH, a N1B nurse will be responsible for making up the infusion for the patient in N1A.

Oral Ramipril tablets and placebo tablets will also be indistinguishable in appearance, and be labelled as “Study Drug – Placebo/Ramipril”. The

treatment each patient will receive will not be disclosed to the Investigator, study personnel, patients or study personnel.

The Co-ordinating Trial Pharmacist at The Queen Elizabeth Hospital will have access to the study treatment allocation but will only disclose this to the Members of the DSMB and in the event of an emergency.

Unblinding is strongly discouraged unless it is considered necessary by the treating physician in the interest of the patient's safety. If unblinding is necessary, it must only be undertaken for the patient in question. Study unblinding can be readily undertaken by opening the unblinding envelope located in the site file at each participating site. Following unblinding, the Investigator must notify The Queen Elizabeth Hospital Cardiology Unit immediately and the circumstances under which the blind was broken must be recorded in the patient record.

6. End points and Analysis of Results

All results will be analysed according to intention to treat.

(a) NAC component

The primary objective of this component of the protocol will be to determine whether administration of NAC reduces the severity of evolving episodes of TTC, with resultant amelioration of haemodynamic impact. Therefore the primary end-point will be LV oedema score (T2 signal intensity [summated] T2-WSI) on MRI performed immediately post NAC. Secondary end-points will be 3NT level, NT-proBNP, hsCRP, metanephrine and normetanephrine levels after NAC, and extent of recovery at 3 months (see Ramipril component).

(b) Ramipril component

The primary objective of this component will be to determine whether ramipril improves the extent of recovery of LV systolic function 3 months post onset of TTC by measuring differences in GLS

Furthermore, a key secondary objective will be to determine whether ramipril improves quality of life (as measured by SF36) and whether this putative benefit is correlated with extent of recovery of LV function. Effects on inflammatory markers will also be utilized as secondary end-points.

7. Power calculations

(a) NAC component

Utilizing mean data on T2-WSI values from our previous analyses of early changes in TTC, mean values of approximately 0.7 ± 0.15 units. For n = 70 patients, the study will therefore have approximately 80% power to detect a reduction by 30% mean values with NAC ($p < 0.05$).

(b) Ramipril component

Power calculations for the ramipril component have been made for 3 important measurements:-

i. GLS: Our recent echocardiographic data in TTC patients revealed mean GLS values at 3 months' recovery of approximately – 18 ± 3%. With n = 80, the study has approximately 80% power to detect >2% improvement in the active treatment group, and >90% power to detect a 3% improvement at $p< 0.05$.

8. Timelines

We intend to start this clinical trial by 04/01/2015. We intend to complete this clinical trial in 27 months following initiation, with all data available for analysis at 30 months.

9. Outcomes and Significance

TTC has been a seriously under-diagnosed disorder, usually confused with acute myocardial infarction. Now that it is possible to establish the diagnosis of TTC rapidly in most patients, it is appropriate to consider the therapeutic implications of this disorder. Potentially important complications of TTC include the early development of shock (a

major cause of mortality), slow symptomatic recovery due to ongoing inflammation and energetic impairment, and the substantial risk of recurrence. Overall, TTC imposes a considerable burden on the community via associated health care costs.

The planned study will provide clinical data as to the practicality of its therapeutic amelioration of TTC, either by:
(1) Decreasing severity of attacks (NAC component), or
(2) Accelerating recovery (ramipril component)

To date, no clinical trials have been undertaken in TTC, and the only animal experiments so far reported have involved the use of β-adrenoceptor antagonists (a treatment which has proved ineffective clinically). The prerequisite for therapeutic options to be trialled in a disorder is that the consequences of the disorder are substantial and that adequate numbers of patients are available to test the hypothesis properly. It has gradually emerged that TTC is far from rare (with our current rate of new diagnoses approximating to 80 cases per annum) and that most patients experience ongoing lassitude and exertional dyspnoea for at least 3 months. Hence therapeutic intervention to accelerate recovery is clearly justified, as indeed is the use of agents to limit the extent of initial myocardial injury.

10. Informed Consent, Data Security and Confidential Issues

(a) Patients' primary treating clinician, after obtaining verbal consent from patients, will notify study investigators of their presentation. Full explanation regarding the study will be undertaken by the research investigators/study coordinator prior to study enrolment to ensure participants have made an informed decision. A participant information sheet will be provided to each patient as well for that purpose. Study will commence once patients sign the informed consent form.
Participants are allowed to withdraw consent and participation from the study at any point in time at no compromise to patients' health or relationships with the health system.

(b) Electronic data will be stored on secured departmental servers, and will be password protected and only accessible to study investigators. Hard copies of data will be

stored securely within the Research Department of the Cardiology Unit at the Queen Elizabeth Hospital.

(c) All blood samples collected during the study will be de-identified and stored in a secured place in a -80degree freezer at the Basil Hetzel Institute. Blood will be stored for a period of 15 years. Genetic analysis of blood is excluded.

(d) Upon patient recruitment, identifiers will be removed and replaced with a code. This code is the number of the drug pack that was randomised to the patient on recruitment. Subsequent researchers handling the data will only do so using that code. A document will be generated at the time of de-identification, so that it is possible to link the code to the original identifier if required. This document will be secured in a database electronically on departmental servers, and will be password protected and again only accessible to study investigators.
No identifying data will be used in publications or presentations.

11. Ethical Considerations and Hazards

(a) The difficulty with obtaining informed consent in acutely ill patients has been identified. We will reaffirm consent when the patient is clinically stable and give them an opportunity to ask questions/withdraw from the study if they so wish.

(b) The patient will require additional investigations. These investigations are necessary to help us determine the effectiveness of the proposed therapy.

- A total of approximately 100mL of additional blood will be taken and stored over the course of the entire study and may be associated with minimal discomfort or bruising. The risk of infection is remote. Where possible, blood will be drawn at the same time as other routine bloods to avoid additional discomfort.
- Patients who are claustrophobic may find MRI unpleasant and stressful, short term anxiolytics may be used to counteract this at the discretion of participants' treating Cardiologist: under extreme circumstances the MRI procedure may be terminated.

(c) Participants may be exposed to N-acetylcysteine and/or Ramipril during this study. Both are generally well-tolerated, but potential side effects from these therapies are: (please see attached Product Information for more details)

a. NAC component

Injecting site reaction, nausea, vomiting, and very rarely anaphylactoid reaction (bronchospasm, angioedema, dyspnoea, hypotension, tachycardia, urticarial)

b. Ramipril component

Hypotension (dizziness, headache, nausea, palpitations), vomiting, cough, hyperkalaemia and renal function impairment, and very rarely angioedema or a hypersensitivity reaction (angioedema, bronchospasm, dyspnoea, rash)

(d) In the event that the study investigators identified from a participant an extreme response on SF-36 questionnaire (i.e. SF-36 score <5) that require further management and investigation, the investigators will notify their general practitioners via phone. If not contactable, the investigators will strongly advice each participant to seek help from their general practitioner, or if it is a matter of emergency, to present to the Emergency Department.

12. Monitoring and Data Quality Assurance

(a) Case Reports Forms and Source documents

Representatives of The Queen Elizabeth Hospital Cardiology Units will conduct monitoring visits within 2 weeks of randomisation of the first 2 patients. Monitoring visits will then occur every 1-2 months depending on recruitment rates. The Investigator will allow The Queen Elizabeth Hospital, The Royal Adelaide Hospital or Lyell McEwin Health Service Cardiology Unit's representative to have access to relevant medical records, inventory records of study drug and any additional relevant records. The Queen Elizabeth Hospital Cardiology Units will generate a summary report to the site after each monitoring visit.

(b) Maintaining Quality of Data and Integrity of Study

The Queen Elizabeth Hospital Cardiology Unit will undertake the following to ensure accuracy, completeness and reliability of the data collected:

Site initiation and training

Regular monitoring visits and prompt reporting of any areas of concern to the site.

Access to 24-hour clinical support for the site

Ongoing communication to the site

Prompt response to clinical questions/problems from the site

Prompt resolution to data queries issued to the site.

13. Responsibilities of Study Personnel

13.1 Investigator

The Investigator will ensure that:

13.1.1 Study Personnel

(a) All staff conducting the study are qualified and appropriate.

(b) All staff involved with the study are fully instructed on the study procedures and are given access to the study protocol and other study relevant information.

(c) A list of names, responsibilities and signatures of all study personnel will be located in the study file.

(d) Curriculum Vitae of all personnel involved in the study will also be present.

(e) Ensure that all persons associated with the study have access to safety updates or other relevant information as the study progresses.

13.1.2 Human Research Ethics Committee (HREC)

(a) This Protocol, Patient Information Sheet and Consent Form and all other relevant materials are submitted to the Ethics of Human Research Committee and approval obtained prior to commencing the study.

(b) The chairperson of the HREC will sign a letter of approval of this Protocol and related study material.

(c) The study will not be initiated until this letter as well as approval from the Research Governance Office has been forwarded to The Queen Elizabeth Hospital Cardiology Unit and The Queen Elizabeth Hospital Cardiology Unit has given permission for the site to commence enrolment.

(d) The HREC will receive an annual report on the study progress.

(e) All safety report or SAE's are forwarded to HREC.

(f) A final Study Report is submitted to the HREC at the completion of the study.

13.1.3. Study Participants

(a) Written, informed consent is to be obtained from each subject prior to entering the study.

(b) Patients will receive a full explanation of the nature and purposes of the study from the Investigator or Co-investigator. It will be understood that the study is for research purposes only and may not provide any therapeutic benefit to the individual. The patient will also understand that he/she is free to withdraw from the study at any time without prejudice and that his/her identity will remain confidential.

(c) The Patient Information Sheet and Consent form will conform to the recommendations listed in the ICH Guidelines for Good Clinical Practice.

(d) The Principal Investigator or Co–Investigators will obtain the written informed consent (as approved by the HREC) of each subject prior to participation in the study. Consent will be obtained before any study related procedures are

instituted and in accordance with the current revision of the Declaration of Helsinki. Informed Consent statements will be dated and signed by the Principal Investigator/Co-Investigators and the patient.

(e) A full copy of the approved Patient Information Sheet will be given to the patient. Signed copies of the consent form will be given to the patient as well as filed with their case notes.

(f) With the consent of the patient, a letter stating the nature of the trial, treatments, expected benefits or adverse drug events and concomitant drugs to avoid will be sent to the subject's general practitioner or primary care physician and treating cardiologist.

13.1.4. Records and Data

(a) Collect, record, report and correct data in a timely and proper manner.

(b) Maintain source and other study records during and after the study.

(c) CRF's are complete and accurate on completion of the study.

(d) All data associated with the study is stored safely for at least 15 years.

13.1.5. Documents to be retained by the Site

The following documents will be kept in a secure place for at least 15 years from the end of the study:

(a) A signed copy of the protocol and any amendments

(b) Correspondence with the Human Research Ethics Committee

(c) Drug accountability forms and dispensing logs

(d) Relevant laboratory normal ranges

(e) The subject consent forms

(f) Case Report Forms

(g) Source data

(h) A signed copy of the Final Study Report

13.1.6. General

(a) The study is conducted in accordance with this protocol and the Guidelines for Good Clinical Research Practice in Australia or the ICH Guidelines.

(b) Notify The Queen Elizabeth Hospital Cardiology Unit by fax in a timely fashion of clinical events that are serious.

(c) The study medication is used only in accordance with the protocol and only in subjects included in the study.

(d) Suitable arrangements are made for patients to make contact with him in the event of an emergency.

(e) Notify patients involved in the study of any information that may affect their willingness to enrol or continue in the study.

13.2 Study Co-Coordinator

The study coordinator will oversee the progress of the study and ensure that it is conducted in accordance with the study protocol.

13.3 Project Manager

The Project Manager will ensure that the study is being conducted in accordance with good clinical practice guidelines at all sites.

13.4 Hospital Pharmacist

It is the pharmacists' responsibility to receive and store the study medication in a secure place under appropriate conditions within each participating study centre. The responsible study pharmacist will be responsible for dispensing all study medications according to the protocol.

13.5 The Queen Elizabeth Hospital Cardiology Unit

Before clinical trial supplies are released and the study begins, the following documents will be present for each participating site

(a) The signed protocol and any amendments

(b) The signed letter of the Institutional Ethics Committee approval and letter of constitution and copies of any other correspondence relevant to the study

(c) Up-to-date curriculum vitae for the Principal Investigator and other personnel involved in the study.

(d) TGA approval letter

(e) Correspondence from Insurance Services pertaining to Indemnity for the study.

14. Study Funding

This study is an initiative of The Queen Elizabeth Hospital Cardiology Unit.

15. Protocol Controls

15.1 Adherence to Protocol

By signing the Investigator Signature Page of this protocol, the Investigator confirms in writing that he/she has read, understands and will comply with the requirements of the study protocol and will conduct the study in accordance with the ICH, TGA and NHMRC guidelines for conducting clinical studies.

15.2 Protocol Amendments and Deviations

Protocol modifications that impact on subject safety or the validity of the study will be approved by the HREC. The Investigator will not deviate from the protocol without prior approval from The Queen Elizabeth Hospital Cardiology Unit and the HREC. In the event of an emergency, the Investigator may implement any medical or surgical procedure as considered necessary for the wellbeing of the patient. However all such deviations must be promptly reported The Queen Elizabeth Hospital Cardiology Unit and the HREC.

15.3 Disclosure

The contents of this protocol and results obtained from the study remain the property of The Queen Elizabeth Hospital, Cardiology Unit and will be regarded as confidential. Results obtained from the study will not be disclosed in whole or in part to others without the written consent of The Queen Elizabeth Hospital Cardiology Unit.

16. Declaration

Chief Investigator

I confirm that this document is an accurate and complete account of the intended research, that I have read it thoroughly, and it has my approval and commitment. I will ensure that any changes to the protocol or any serious adverse reactions and the final results of the study are notified to the Human Research Ethics Committee as soon as possible.

The research will be conducted in accordance with the NHMRC National Statement on Ethical Conduct in Research Involving Humans (2007) and the principles of the Declaration of Helsinki and its Amendments

I confirm that I am familiar with these principles.

Signed: .....

Name: PROF JOHN D HOROWITZ

Date: .....

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