

Title: Interleukin-1 Blockade in ST-segment Elevation Acute Myocardial Infarction: The Virginia Commonwealth University-Anakinra Remodeling Trial 3 (VCU-ART3)

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Interleukin-1 Blockade in ST-segment elevation acute myocardial infarction (STEMI)

A Randomized Placebo-controlled Double-blinded Study

VCU-ART3 study

STUDY PROTOCOL

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EDITS TO PRIOR VERSIONS

1) Changes to Version 08132014

- The personnel list has been updated.
- Section 5.2 – Description of biomarkers tested now updated.
- Section 6.2 – An additional exclusion criterion has been added, “Need for vaccination or desensitization that cannot be postponed for 14 days”.
- Section 8.3.1 – We provide a more detailed definition of “related” and “unrelated” to research in regards to adverse events.
- Appendix – Case report forms have been added.

2) Changes to Version 04062015

- The personnel list and study sites have been updated to reflect new site at Washington Hospital Center.
- Sections 5.2 and 7.6 – The timeframe for ordering the initial echocardiogram and biomarkers have been updated.
- Section 6.2 The inclusion criterion “planned or completed coronary angiogram for potential intervention” has been updated to reflect the 12 hours timeframe from symptoms, and enrollment within 12 hours from angiogram (max 24 hours from symptoms); “desensitization” has been clarified to “aspirin desensitization”
- Sections 7.7 and 7.8 – The description of biomarkers assessment has been updated. The name of the offsite laboratory has been updated to “True Health Diagnostics”.
- Section 7.8 – Procedures for follow-up beyond one year have been clarified. In-person clinical follow up ends at 12 months.
- Section 8.3 – The definition of Adverse Events (AEs) has been revised, and reporting plan clarified.
- Appendix C – Screening and enrollment form has been updated to reflect the changes in Section 6.2.

3) Changes to Version 11202015

- The personnel list has been updated
- Entry criteria have been updated to remove restrictions related to vaccinations

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Appendix A: DSMB Chapter for VCU-ART3

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Appendix C: Case Report Form and Data Collection Forms

1) PERSONNEL

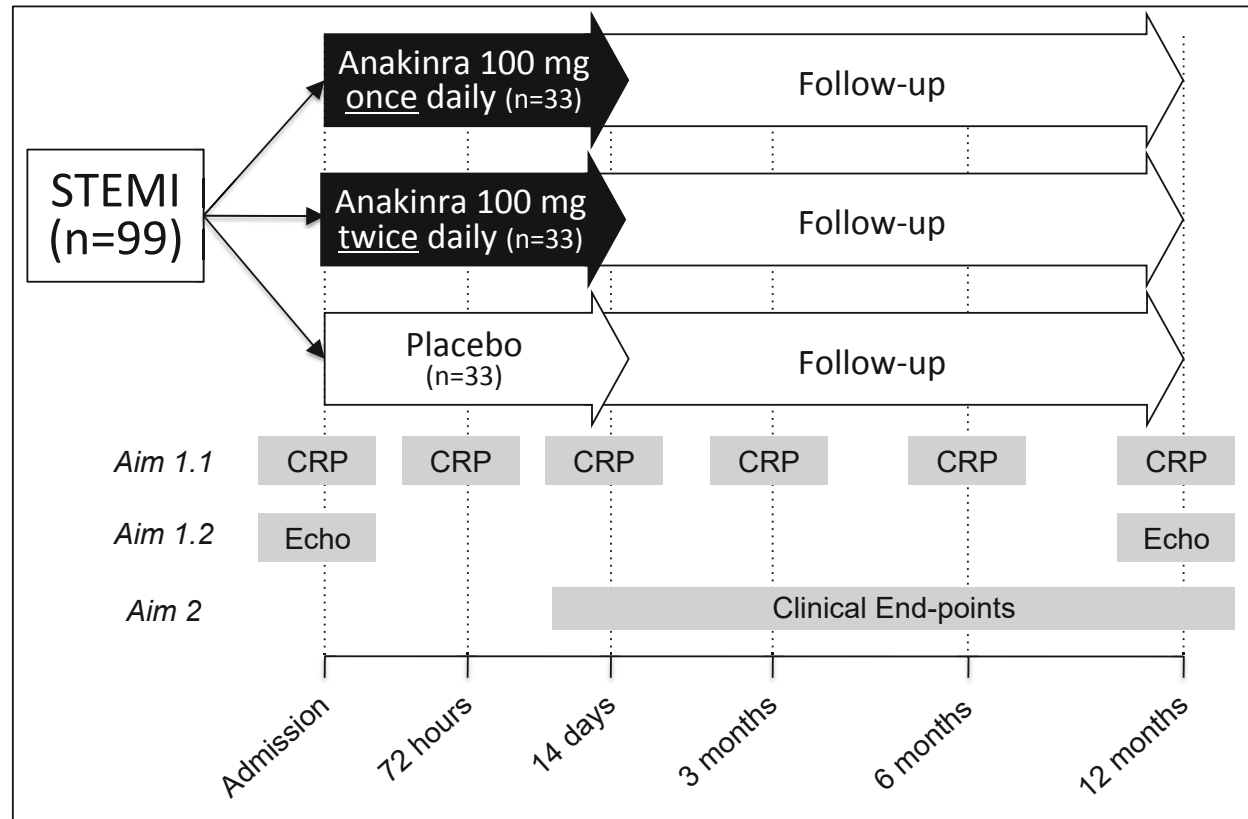
Name	Role	Institution/ Division
Antonio Abbate, MD/PhD	Co-Principal Investigator	VCU, Cardiology
Benjamin Van Tassell, PharmD	Co-Principal Investigator	VCU, School of Pharmacy
Darryn Appleton, MD	Investigator	Virginia Cardiovascular Specialists
Mary Ann Peberdy, MD	Investigator	VCU, Cardiology
Michael Lipinski, MD	Investigator	Washington Hospital Center, Cardiology
Ron Waksman, MD	Investigator	Washington Hospital Center, Cardiology
Salvatore Carbone, MS	Research Assistant	VCU, Cardiology
Robin Sculthorpe, PharmD	Investigational Pharmacy	VCU, Pharmacy
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Keyur Shah, MD	Event Adjudicating Committee	VCU, Cardiology
Elizabeth Miller, MD	Event Adjudicating Committee	VCU, General Medicine
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Gonzalo Bearman, MD	DMSB member	VCU, Infectious disease
Ion Jovin, MD	DSMB member	VCU, Cardiology / McGuire VA
Jeffrey Kushinka, MD	DSMB member	VCU, General Medicine
Christine DeWilde, RN	DSMB coordinator	VCU, Johnson Center
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Pierluigi Tricoci, MD	Consultant	Duke University
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Giuseppe Biondi-Zoccai, MD	Consultant	Sapienza University, Rome, Italy
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George Vetrovec, MD	Consultant	VCU, Cardiology
Juan Lu, PhD	Consultant	VCU, Biostatistics

Abbreviations: DSMB=Data Safety Monitoring Board

2) PROTOCOL SUMMARY

Title:	Interleukin-1 Blockade in ST-segment elevation acute myocardial infarction (STEMI)
Population:	99 patients with STEMI presenting within 12 hours of onset
Site(s):	Virginia Commonwealth University, Richmond, VA Virginia Cardiovascular Specialists, Richmond VA Washington Hospital Center, Washington DC
Study Duration:	36 months
Description:	Phase II clinical trial of Anakinra (standard and higher dose) for 14 days to quench the acute inflammatory response during STEMI and to prevent adverse cardiac remodeling and heart failure after STEMI
Objectives:	To determine the effects of IL-1 blockade with Anakinra (standard and higher dose) on the area-under-the-curve for C-reactive protein (as preferred inflammatory marker in STEMI, and a surrogate for IL-1 activity), the changes in left ventricular dimensions and function, and the clinical outcomes up to 1 year.
Study Design:	Multi-center, randomized, double-blinded, placebo-controlled clinical trial with allocation to Anakinra 100 mg daily, Anakinra 100 mg twice daily, or placebo for 14 days.
Estimated Time to Complete Enrollment:	24 months

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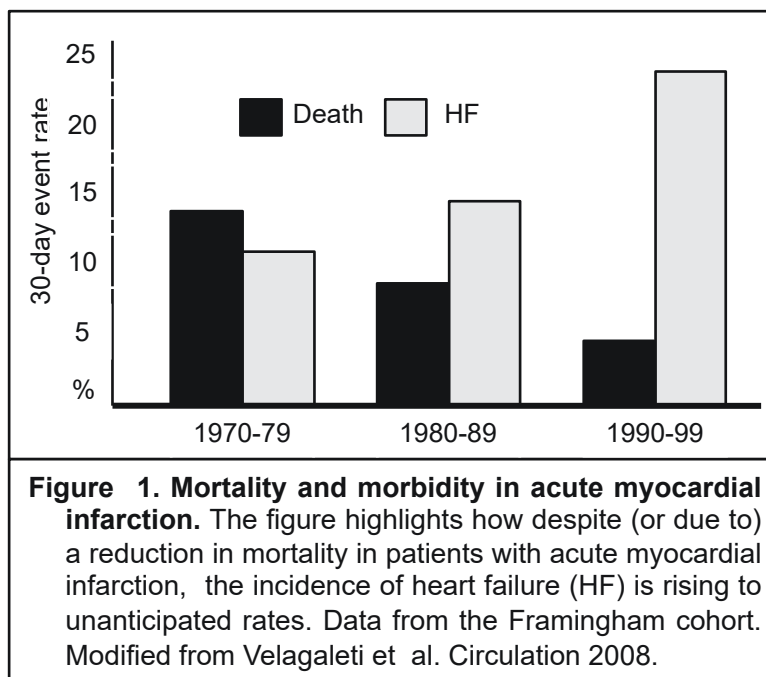
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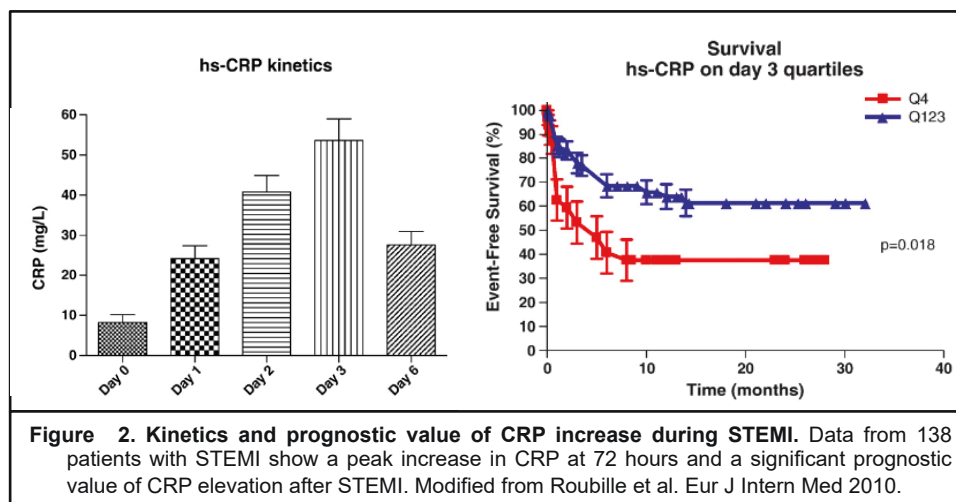
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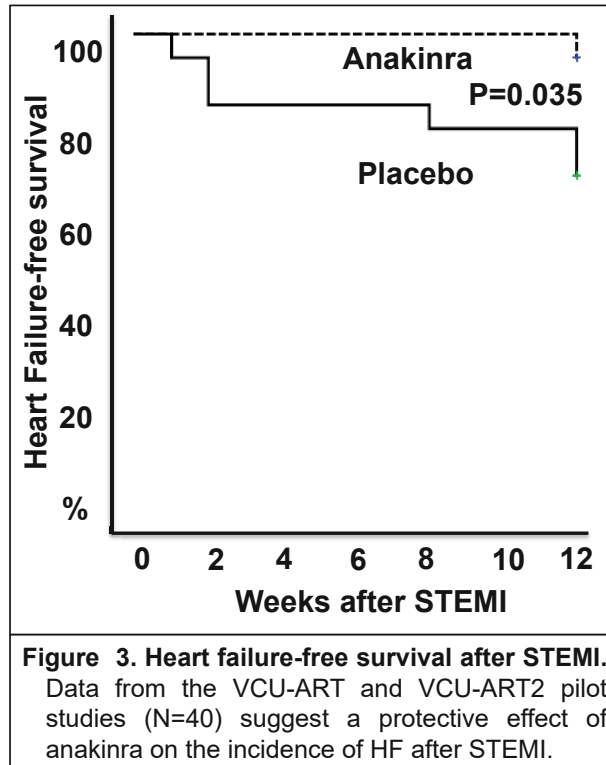
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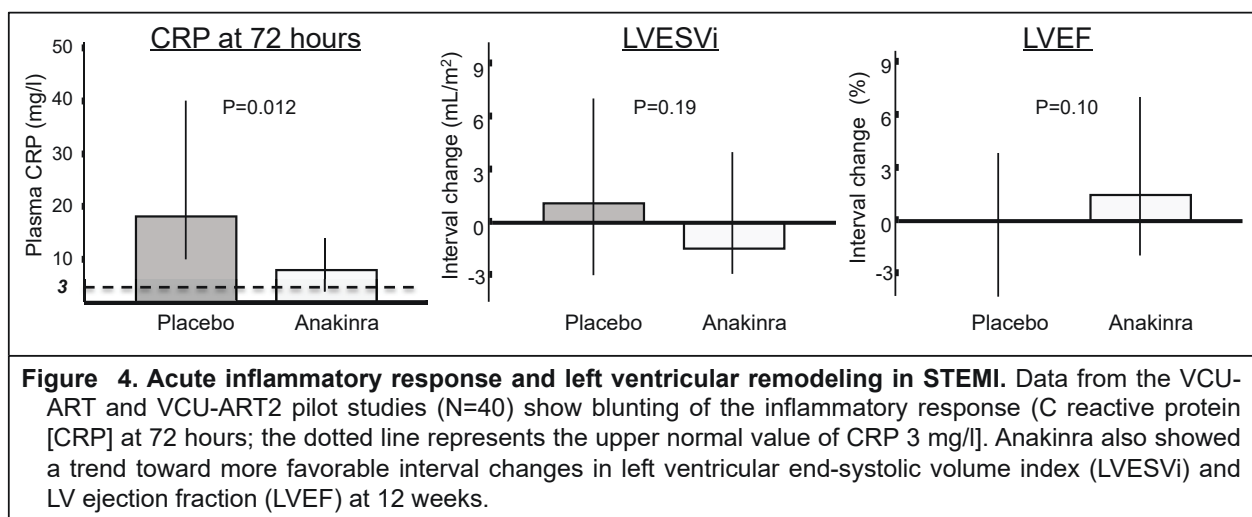
the membrane receptor, and 2 anti-IL-1 β antibody. All IL-1 blockers had similar effects limiting cardiac dilatation and dysfunction without impairing infarct healing.

Anakinra, recombinant human IL-1 receptor antagonist (Kineret™, Biovitrum, Sweden) is approved in USA and Europe for the treatment of rheumatoid arthritis⁷, and is also highly effective in the treatment of several inflammatory disease, and preliminary studies show benefits also in ischemic and hemorrhagic stroke and diabetes. The favorable safety profile of anakinra is witnessed by the hundreds of thousands of patients who have been treated in the past decades. Anakinra is associated with injection site reactions that are generally mild but occasionally severe. Also, anakinra is associated with an increased risk of infections (mainly upper respiratory infections) but it is not associated with an increased infection-related mortality showing that the infections occurring while on anakinra treatment are generally mild. Moreover, anakinra has been also tested in patients with severe sepsis and shock, and while it did not significantly reduce sepsis-related mortality, in a meta-analysis of all studies showed a favorable trend toward reduced mortality (-18%, P=0.08).

Based on the preliminary data in the animal AMI model and the established safety profile of anakinra, we have conducted 2 separate randomized double blinded pilot studies of anakinra vs placebo in patients with STEMI: the first was a pilot study in 10 patients, Virginia Commonwealth University Anakinra Remodeling Trial VCU-ART pilot study [*clinicaltrials.gov* NCT00789724],⁸ completed in 2010, followed by a second study in 30 patients, VCU-ART2 pilot study [*clinicaltrials.gov* NCT01175018].⁹ Both studies included patients with reperfused STEMI who were hemodynamically and clinically stable. The 40 patients were followed for 3 months and paired cardiac magnetic resonance analyses. Anakinra was used at a standard dose of 100 mg daily for 14 days. The primary purpose of these pilot studies was to establish safety and feasibility. Mortality and event rates were low in both groups likely reflecting a selection bias toward lower risk STEMI due to the fact that patients had to be stable enough to undergo cardiac MRI at 24 hours: median TIMI STEMI score was indeed 3 (interquartile range 1-4) and only 1 patient died (2.5%) within 3 months of STEMI. Overall anakinra showed an acceptable safety profile with only 2 patients (10%) experiencing adverse event requiring discontinuation of therapy (vs 2 [10%] in placebo, P=0.94). Injection site reactions were the most commonly encountered side effect occurring in 5 (25%) patients in the anakinra group and 2 (10%) in the placebo group. Nine adverse cardiac events (1 death, 2 recurrent MI, 6 new onset heart failure) occurred in 6 placebo patients, whereas 3 adverse cardiac events (2 recurrent MI and 1 new onset heart failure) occurred in 3 anakinra treated patients (P=0.25). Anakinra-treated patients were significantly less likely to experience new onset heart failure (1 patients, 5%) vs placebo-treated patients (6 patient, 30%, P=0.035, Figure 3).



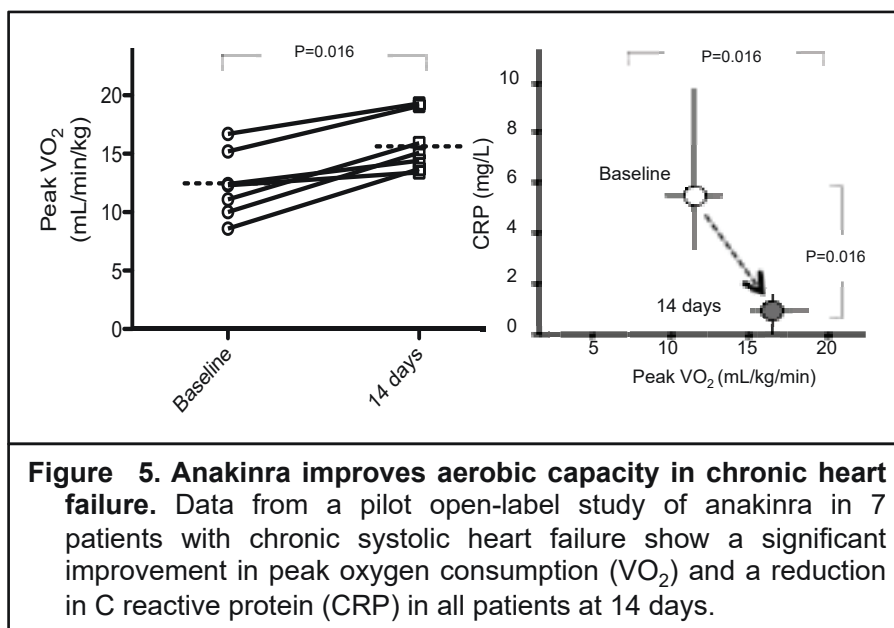
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does not have off-target effects, it does not promote fluid retention, hypertension, hyperglycemia or any other significant metabolic alterations. No direct effects of anakinra on hemodynamic parameters, cardiac function, platelet function or coagulation have been reported in volunteers. Therefore, IL-1 blockade is a much safer approach which is documented by the well established safety profile of anakinra.

IL-1 blockers are also substantially different from TNF- α blockers, which have shown disappointing results in the treatment of chronic heart failure. Indeed, although the 2 classes are occasionally considered interchangeable for the treatment of rheumatic diseases, they should not. It is true that elevated IL-1 β and TNF- α levels often coexist in acute and chronic illnesses and it is also true that TNF- α induces IL-1 β synthesis and release, yet the two cytokines have different dedicated signaling receptors and different signaling pathways. While IL-1 has a single signaling receptor (IL-1R1), TNF- α has 2 membrane receptors (type I and II) with different and opposing actions in the heart. The signaling downstream of the receptors is also different for TNF- α and IL-1 and the pathways are mostly not convergent. This explains the differences in efficacy, safety and tolerability of TNF- α and IL-1 blockers in different diseases. In example, patients with adult rheumatoid arthritis respond more favorably to TNF- α blockers whereas patients with juvenile forms respond more favorably to anakinra. The use of TNF- α blockers is associated with increased risk of reactivation of Mycobacterium tuberculosis infection whereas anakinra is not. Moreover, as a proof of the differences between the 2 cytokines, patients with TNF-related periodic fevers do not respond to IL-1 blockers and patients with cryopyrin-associated periodic syndromes (characterized by enhanced IL-1 activity) do not respond to TNF- α blockers. Therefore the fact that TNF- α blockers have failed to show a benefit in chronic heart failure does not predict whether IL-1 blockers will be effective in AMI, an entirely different clinical condition. In our pilot studies in patients with heart failure¹⁰, anakinra significantly reduced IL-6 and CRP levels but had no effects on TNF- α levels showing that IL-1 blockade does not provide a reduction in TNF- α . Furthermore, anakinra is not immunosuppressive, and actually it has been recently shown to prevent stroke-induced immunosuppression.

In summary, we know that IL-1 activity is enhanced in the heart following ischemia and infarction. Experimental animal studies show a central role of IL-1 in infarct healing and promotion of heart failure. Pilot clinical trials in patients with STEMI or heart failure also show a favorable safety profile and a favorable effect on outcomes. These data represent the basis for hypothesizing beneficial effects of IL-1 blockade in patients with STEMI who show signs of enhanced IL-1 activity and are at high risk for in-hospital and long-term mortality.

5) OBJECTIVES

The current research is designed to investigate the safety and efficacy of Anakinra (standard or higher dose) in patients with STEMI in a randomized double-blinded trial. We hypothesize that anakinra will quench the inflammatory response, improve cardiac remodeling, and reduce the incidence of heart failure.

5.1 Primary Endpoint

The primary endpoint of the study is the difference in the area-under-the-curve (AUC) for CRP between admission and day 14 between anakinra 100 mg daily and anakinra 100 mg twice daily compared with placebo.

Patients presenting with STEMI have an enhanced IL-1 response as witnessed by elevation in serum markers such as CRP.⁴ We anticipate that patients with STEMI will have increased CRP levels and its levels will predict adverse cardiovascular outcomes. We therefore hypothesize that anakinra (standard dose) will blunt the CRP increase during STEMI, as seen in the pilot studies, and that anakinra (high dose) will further reduce CRP compared with placebo and with anakinra (standard dose). The rationale for measuring AUC for CRP is that it integrates measurements across multiple time points to more accurately capture the acute inflammatory response and IL-1 activity, and is also an established prognostic marker in STEMI.

5.2 Secondary Exploratory Endpoints

Additional endpoints will include parameters measured at echocardiography, as well as biomarkers, and clinical outcomes.

Echocardiography: structural and functional echocardiographic parameters include left and right ventricular dimensions, mass, systolic and diastolic function. These will provide mechanistic insight as to whether the hypothesized changes in the acute inflammatory response will correlate with changes in cardiac dimensions or function. The echocardiogram will be ordered acutely (within 24 hours) and at 1-year follow up as clinically indicated.

Biomarkers: Blood will be collected at each time-point throughout the study (admission, 72 hours [or discharge whichever comes first], 2 weeks, 3, 6 and 12 months) and analyzed for complete blood cell count, metabolic markers (including lipids and lipoproteins, glycemic control and insulin resistance, liver and renal panel, sterols), inflammatory markers (i.e. high sensitivity CRP) and cardiac biomarkers (i.e. NT-proBNP and troponin I). The data will be collected and electronically stored for further analysis at the conclusion of the study. When feasible, results from clinically indicated studies will be used.

Clinical outcomes: Incidence of death (cardiac and non-cardiac), hospitalizations (for HF, for other cardiac causes not related to HF, or for non-cardiac reasons) will be recorded at each time-point throughout the study (discharge, 2 weeks, 3, 6 and 12 months) in every patient, and then once at the end of study, by review of chart and/or telephone interview. The investigators and clinicians caring for the patients will remain blinded to treatment allocation and to the CRP data. Adjudication of events will be performed by an *ad hoc* committee blinded to treatment allocation and to CRP data.

6) ENROLLMENT IN THE STUDY

6.1 Screening

Patients will be screened by the investigators at each site in an interval of time between arrival to the emergency room and 12 hours after completion of the coronary angiogram and angioplasty, with an emphasis toward earlier screening. Those patients who meet entry criteria will be approached by the investigators for enrollment. Potential subjects will be provided with an Informed Consent Form in accordance with the local Institutional Review Board. Enrolled subjects will then undergo complete screening for entry criteria (listed below). Where possible, investigators will rely on clinically available laboratory and imaging results; the remaining laboratory and imaging analyses will be ordered and billed to the study account. The timely treatment of patients with STEMI is facilitated by a system of telepaging that alerts the interventional team the need to activate the cardiac catheterization laboratory. The investigators involved in this research at each institute will also be alerted so to facilitate timely screening and enrollment of the subjects. A waiver to obtain authorization by the subjects to access personal health information during screening process will be obtained by the IRB at each center to allow for screening.

STEMI represents 1/3 of all AMI and approximately 10% of ED visits for chest pain. We estimate approximately 120 STEMI yearly at VCU, >150 STEMI yearly at the Washington Hospital Center, and >150 STEMI at the Virginia Cardiovascular Specialists-affiliated hospitals (Chippenham/Johnston Willis Medical Center and Henrico Doctors Hospitals) totaling more than 400 STEMI/year. We propose a conservative enrollment goal of 1 patient/week (total enrollment = 99 weeks). Should enrollment fall behind this goal, we will pursue recruitment at the nearby University of Virginia (Charlottesville, VA) and other community-based centers in Central or Northern Virginia.

6.2 Subject Inclusion and Exclusion Criteria

In order to be eligible for this study, patients must meet ALL the 3 Inclusion criteria and NONE of the Exclusion criteria.

INCLUSION CRITERIA:

- 1) Presentation to the hospital with acute STEMI defined as chest pain (or equivalent) with an onset within 12 hours and ECG evidence of ST segment elevation (>1 mm) in 2 or more anatomically contiguous leads that is new or presumably new
- 2) Coronary angiogram for potential intervention completed within 12 hours of symptom onset, and enrollment in the study within 12 hours of angiogram (max 24 hours from symptom onset)
- 3) Age>21 (NIH standard)

EXCLUSION CRITERIA:

- Inability to give informed consent
- Pregnancy or breastfeeding
- Preexisting congestive heart failure (AHA/ACC class C-D, New York Heart Association III-IV)
- Preexisting severe left ventricular dysfunction (EF<20%)
- Preexisting severe valvular heart disease
- Active infections (acute or chronic)
- Recent (<14 days) or active use of immunosuppressive drugs (including but not limited to high-dose corticosteroids [>1 mg/kg of prednisone equivalent], TNF- α blockers, cyclosporine) not including NSAIDs or corticosteroids used for IV dye allergy only)
- Chronic auto-immune or auto-inflammatory disease (including but not limited to rheumatoid arthritis, systemic lupus erythematosus)
- Known active malignancy of any type, or prior diagnosis in the past 10 years
- Anticipated need for cardiac surgery
- Active cancer (or prior diagnosis of cancer within the past 10 years)
- Neutropenia (absolute neutrophil count $<1,800/\text{mm}^3$ [or $<1,000/\text{mm}^3$ in African-American patients])
- Severe impairment in renal function (estimated glomerular filtration rate <30 ml/kg*min)
- Allergy to rubber or latex
- Allergy to products derived from Escherichia coli

7) STUDY DESIGN

We designed a multi-center, placebo-controlled, double-blinded randomized study of two different anakinra regimens (100 mg daily or 100 mg twice daily for 14 days). Patients will be enrolled and treated within 12 hours of coronary angiogram/angioplasty and within 24 hours of chest pain onset. A baseline echocardiogram will be ordered within the first 24 hours and repeated at 12 months, as clinically indicated. Biomarkers will be obtained at admission, 72 hours, 14 days, 3, 6 and 12 months.

7.1 Treatment with Anakinra

Anakinra and matching placebo syringes have already been provided by the manufacturer, Swedish Orphan Biovitrum (SOBI, Stockholm, Sweden) to the Investigational Pharmacy at the coordinating center at VCU, where the syringes are stored until ready to be administered to the patient. SOBI has also guaranteed a continuous supply of anakinra and placebo should the current supply expire prior to completion of the trial.

Patients will receive the first dose of anakinra 100 mg or placebo within 12 hours of coronary angiography/angioplasty. The drug will be administered by the nurse and the patients and will be instructed by one of the physicians or pharmacists in the team on how to store and self-administer the drug so they can continue at home twice daily for 14 days. The syringes will be labeled 1 through 28, the patient will be instructed to store them in the fridge and keep them at room temperature for few minutes prior to injection subcutaneously. Proper injection technique will be

taught. A sharp container sufficient to contain all 14 syringes will be given to the patient to dispose the syringes in, and to bring back at the 14-day visit.

One group of patients will receive anakinra 100 mg twice daily for 14 days, a second group will receive anakinra 100 mg alternated with placebo twice daily for 14 days so that anakinra will be given every 24 hours, the third group will receive placebo twice daily for 14 days. The patient will also be educated on expected side effects and need to inform the investigators about any foreseen and unforeseen events.

7.2 Allocation concealment

Anakinra or placebo (vehicle) dispensed in small syringes (1 ml) will be provided by the producer (Swedish Orphan Biovitrum) for subcutaneous injection twice daily. The syringes for anakinra or placebo will be undistinguishable, and labeled with consecutive numbers “1” through “28”. The randomization log will be prepared by a consultant outside the institutions involved in the enrollment (Giuseppe Biondi-Zoccai, MD, University La Sapienza, Rome, Italy) and sent electronically to the director of the Investigational Pharmacy at VCU (Robin Sculthorpe, PharmD). Access to randomization log will be restricted and allowed only on an emergency basis, or as indicated by the Data Safety and Monitoring Board, or at the end of the study including all data collection.

7.3 Patient Compliance with Study Intervention

One goal of the trial is to maximize adherence and retention throughout the study. Adherence will be addressed by count of unused syringes at the 14-day study visit.

7.4 Concomitant Medications

All concomitant medications will be recorded at each clinic visit. Administration of anakinra with medications that affect the immune system (i.e. immunosuppressant) or increase the risk of infection (i.e. cancer chemotherapy) is NOT permitted. If a patient requires treatment with such medications, he/she will not be eligible for inclusion in the study. If a patient already enrolled in the study requires such treatments, the investigational treatment (Anakinra or placebo) will need to be discontinued (see reason for discontinuation).

7.5 Standard Medical Management

Patients in the study will receive guideline-based medical treatments as indicated. Such treatments may include aspirin, P2Y12 inhibitors, β -adrenergic receptor blockers, angiotensin converting enzyme inhibitors or receptor blockers, aldosterone blockers, isosorbide dinitrate, hydralazine, digoxin, and statins.

7.6 Echocardiogram

The patient will undergo a transthoracic echocardiogram, ordered within the first 24 hours, and then again after 12 months, as clinically indicated, to measure left and right ventricular and atrial dimensions, left and right ventricular systolic function, transmitral flow Doppler spectra, mitral and

tricuspidal valve annulus tissue Doppler spectra, ejection time and stroke volume, inferior vena cava, aorta and pulmonary artery diameters and Doppler spectra, according to the recommendations of the American Society of Echocardiography.^[16-18] When feasible, results from clinically indicated studies will be used. All images and loops will be acquired in an electronic format and transferred to the VCU Pauley Heart Center for blinded centralized measurements at the end of the study.

7.7 Biomarkers assessment

Blood samples will be taken from a peripheral vein at admission, 72 hours, 14 days and 3, 6 and 12 months.

One EDTA-containing tube, one SST containing tube, one Serum Separator Clot Activator tube and one PPT tube will be used for analysis of plasma levels of biomarkers by the True Health Diagnostics LLC, Richmond, VA.

One sodium heparin tube will be used to analyze cytokines markers.

7.8 Study Schedule

	Inpatient: Admission	Inpatient: 72 hours	Outpatient Visit 1: 14 days	Outpatient Visit 2: 3 months	Outpatient Visit 3: 6 months	Outpatient Visit 4: 12 months
Screening *	X					
Consent	X					
Clinical assessment **	X	X	X	X	X	X
Investigational therapy	X	X	X			
Echocardiogram	X					X
CBC		X	X			
hs-CRP	X	X	X	X	X	X
Biomarkers	X	X	X	X	X	X

*_Pregnancy test will be performed, if indicated

**_Clinical assessment includes history and physical, medication reconciliation, and assessment of adverse events

When feasible, results from clinically indicated studies will be used.

Inpatient samples will be taken upon enrollment, at 72 hours (± 12 hours [or more if patient discharged before 60 hours]).

Samples will be centrifuged and then refrigerated, and shipped with cold packs within 24 hours to True Health Diagnostics LLC, Richmond, VA. The results will be sent to the PI at VCU and to each center by email or fax.

Outpatient visits will be scheduled at 14 days (± 2 days), 3 months (± 2 weeks), 6 months (± 2 weeks), and 12 months (± 2 weeks).

7.9 Cost coverage analysis

A cost coverage analysis will be conducted in each center prior to the initiation of the trial to determine what constitutes standard of care, which will be billed to the patient or the insurer, and what is considered 'research' which will be paid for with the study budget.

8) ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

Safety parameters will include data deriving from history and physical examination performed at each visit, laboratory data and results of functional and imaging tests. To enhance detection of adverse events between visits, all patients will be encouraged to contact the research team at any time with concerns or any perceived changes in their healthcare status.

Disease-related data (MI- and HF-related) will be assessed including changes in symptoms (or new symptoms), functional capacity, vital signs (including weight), renal function, or any significant changes in medications.

Data specific to the treatment will also be assessed. The patient will be asked about symptoms and examined for signs of infection. Considering that anakinra may mask signs of infection such as fever, a low threshold for further investigation will be advocated. A complete cell count will be measured at 72 hours and 14 days to exclude the unusual cases of anakinra-related neutropenia ($ANC < 1,000/mm^3$), for which suspension of active treatment will be encouraged until return to a value of $ANC > 1,800/mm^3$ (or $> 1,000/mm^3$ if patient is African-American).

Changes to treatment for side-effects or unanticipated problems will be performed without breaking the randomization code, unless deemed necessary for the treatment of the individual patient by the physician, in which case the physician will be made aware while the remainder of the team, especially the investigators performing and interpreting the tests, will be maintained blinded.

The risks of the tests performed have been described above. In order to reduce risk, the procedures will be performed by skilled practitioners in the standard clinical fashion.

Abnormal or incidental findings will be handled on a case by case basis as clinically indicated.

8.2 Data collection

The principal investigator at each site will be provided with a data collection sheets or case report forms on which data about the individual subject will be collected. The subjects will be identified as a consecutive number in each center (i.e. A01, A02, ...A08; B01, B02, ... B08; C01). The data collected on these forms will not contain any personal identifiable information. The forms will be transmitted to the coordinating center at VCU through either a secure HIPAA compliant fax line or email correspondence, or hand-delivered. A centralized database of deidentified data will be held at VCU.

8.3 Methods of Timing for Assessing, Recording, and Analyzing Safety Parameters

8.3.1 Adverse Events

All Adverse Effects (AEs) will be recorded on an AE form regardless of causality.

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product considered to causally related to the study treatment or research conduct. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient for medical care, or upon review by an investigator or study coordinator. An event that is considered by the investigator(s) to be expected and related to the natural history of the disease is NOT considered an AE.

All events considered AEs including local and systemic reactions not meeting the criteria for “serious adverse events” will be reported on the appropriate AE form. Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis, which would include a physician) and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the patient is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

All AEs must be graded for severity and relationship to study product.

Severity of Event: All AEs will be assessed by the clinician according to the following guidelines to quantify intensity:

- Mild: events require minimal or no treatment and do not interfere with the patient’s daily activities.

- Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning and may require systemic drug therapy or other treatment.
- Severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Life threatening: any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e. does not include a reaction that might have caused death had it occurred in a more severe form).

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Relationship to the intervention: All suspected AEs must have their relationship to study intervention assessed using the terms: associated or not associated. In a clinical trial, the study intervention must always be a suspect. To help assess, the following guidelines are used to assess causality:

- Definitely related: The event is temporally related to the administration of the study intervention and, in the opinion of the investigator, no other etiology explains the event.
- Probably related: The event is temporally related to the administration of the study intervention and represents, in the opinion of the investigator, the most plausible explanation of the event.
- Possibly related: The event is temporally related to the administration of the study intervention but, in the opinion of the investigator, it does not represent the most likely explanation of the event.
- Definitely Unrelated: The event is temporally independent of study intervention and/or the event appears, in the opinion of the investigator, to be explained by another etiology.

8.3.2 Serious Adverse Events

An SAE is any adverse event/experience occurring between baseline assessments and the patients final study visit that results in any of the following outcomes and is considered by the investigator(s) to be unexpected or not consistent with the natural history of the disease:

- Death
- Life threatening (subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All the unexpected SAE will be promptly (within 24 hours) reported to the local IRB and DSMB (see reporting procedures). The DSMB report to the investigators will be forwarded to the NHLBI Program Officer, including the discussion of the concerns, and the basis for any recommendations that the DSMB has made in response to the concerns (within 7 calendar days if fatal or life-threatening unexpected, suspected serious adverse reactions; or within 14 days for unanticipated problem that is not an SAE or within 15 calendar days for all non-fatal, non-life threatening unexpected, suspected serious adverse reactions, or within 30 days of receipt of the DSMB or IRB report for all other unanticipated problems or scheduled meetings).

8.4 Reporting Procedures

8.4.1 Serious Adverse Events

All unexpected SAEs that result in death or are otherwise reportable SAEs or AEs will be reported promptly to the Data Safety Monitoring Board (DSMB) within 1 business day of knowledge of the event.

AEs (serious or nonserious) that transpire secondary to an overdose must also be reported to the DSMB within 1 business day of knowledge of the event, using an AE form.

The SAE form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to the DSMB within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the DSMB of the event and completing the SAE form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report.

8.5 AE/SAE Data Collection

When an AE/SAE is suspected, it is the responsibility of the investigator(s) to review all documentation (e.g. hospital progress notes, laboratory and diagnostic reports) relative to the event. The investigator will then record all relevant information regarding a suspected AE/SAE on the AE form. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

8.6 The Data and Safety Monitoring Board (DSMB)

The DSMB is composed of members who are independent from the study operations, in compliance with the FDA guidance document (OMB control No. 0910-0581).

For this study, the DSMB is composed of a coordinator and 5 voting members, including a cardiologist from University of Florida in Jacksonville, Florida, a heart failure specialist, a general cardiologist, an infectious disease specialist, and a general internal medicine specialist. The DSMB will meet every 6 months or sooner in case of unanticipated serious adverse events. The DSMB coordinator will provide the board members with data regarding screening, enrollment, adverse events and withdrawals, and he/she will not participate in the voting. The board members

may request unblinding at any time. Upon request of the DSMB (following positive vote by 3 or more members), the coordinator will retrieve the randomization code for one or more individual patients (as needed). If necessary the DSMB will inform the investigators of the unblinding of the randomization code, if not necessary the investigators (and the patients) will be kept blinded. The DSMB may request an expert opinion by one or more non-members, however only the DSMB members will vote on any individual issue. The DSMB (following positive vote by 3 or more members) may request temporary or permanent halting of the study (see halting rules), or interruption of treatment of one or more patients. The minutes from each meeting will be distributed to the board members and to the IRB, and not to the investigators unless specifically requested by the DSMB. A brief conclusive statement addressing whether the study should continue as planned or not will be provided to the investigators and the IRB every 6 months. See Appendix – DSMB Chapter.

8.7 Regulatory Reporting

This study is conducted in accordance to the NIH Good Clinical Practice guidelines. An Investigational New Drug use (IND # 119067) from the Division of Cardiovascular & Renal Products, Center for Drug Evaluation & Research, Food & Drug Administration is held by Dr. Abbate. The study protocol, consent, and Data and Safety Monitoring Plan has been approved by the VCU IRB. The investigator will notify the Virginia Commonwealth University IRB Panel D, the *ad hoc* Data and Safety Monitoring Board, and the FDA of any severe unexpected adverse event. The investigators will provide the NHLBI staff with reports from the DSMB and the IRB in a timely fashion (within 7 calendar days if fatal or life-threatening unexpected, suspected serious adverse reactions; or within 15 calendar days for all non-fatal, non-life threatening unexpected, suspected serious adverse reactions, or within 30 days of receipt of the DSMB or IRB report for all other unanticipated problems or scheduled meetings).

8.8 Type and Duration of Follow-up of Subjects after Adverse Events

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, whichever occurs first. All AEs and SAEs documented at a previous visit/contact and designated as ongoing, will be reviewed at subsequent visits/contacts, where the designation may remain ongoing. The investigator will ensure that the follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. SAEs that are ongoing at the time of the subjects final study visit/contact will be documented as ongoing.

8.9 Halting Rules

The DSMB will monitor the progress of the present trial. No interim efficacy analyses are planned; however an interim analysis could be performed at any time to assess efficacy and futility, if requested by the 3 or more members of the DSMB. The DSMB will meet regularly to review safety data every 6 months (or sooner in case of unanticipated serious adverse events). All meetings and actions taken by the committee will be recorded along with the reasons for the actions. These documents will include any data summaries or analyses provided to the DSMB and will remain

confidential until the study is concluded. The DSMB may choose to stop enrollment on the basis of safety data observed. If safety concerns are found, further enrollment will not be allowed until issues are resolved. If no safety concerns are found, enrollment will continue until the target sample size is reached.

9) ADJUDICATION OF CLINICAL EVENTS

9.1 Event-adjudicating committee

The event-adjudicating committee is composed of a general cardiologist, a cardiologist with training in heart failure, and a general internal medicine specialist. The committee will meet at the end of the study and adjudicate all the events. The committee will be blinded to treatment allocation. In order to favor allocation concealment, the committee will also be blinded to C-reactive protein levels, which may be affected by treatment.

9.2 Definition of the events

The events adjudicated will include:

- Death;
- Cardiac death (in which a direct cause attributable to cardiac disease is present);
- Sudden cardiac death (in which cardiac death occurred out of the hospital and suddenly; or in the hospital due to ventricular arrhythmias unrelated to other concomitant cardiac conditions);
- Non-cardiac death (in which the event of death is considered not to be a direct consequence of cardiac disease);
- Incidence of heart failure during the index hospitalization (defined as dyspnea beginning or persisting >24 hours after admission and meeting both of the following criteria:
 - o physical signs of heart failure - including 2 or more of the following: edema, crackles/rales, jugular vein distention, hepatojugular reflex, tachypnea, rapid weight gain, S3 gallop, abdominal distension/ascites, radiologic evidence of worsening edema, pulmonary artery occlusive pressure (wedge) >18 mmHg or cardiac output <2.2 l/min-m²;
 - o need for additional/increased heart failure therapy - including one of the following: initiation or significant increase of oral diuretics, requirement of intravenous diuretics, inotropes or vasodilators, need for ultrafiltration due to decompensated heart failure;
- Re-hospitalization for any cause;
- Re-hospitalization for heart failure (meeting all criteria listed above for heart failure during index hospitalization)
- Incidence of heart failure (not hospitalized) defined as new or worsening dyspnea and meeting one of the two of the following criteria:
 - o physical signs of heart failure - including 2 or more of the following: edema, crackles/rales, jugular vein distention, hepatojugular reflex, tachypnea, rapid weight gain, S3 gallop, abdominal distension/ascites, radiologic evidence of worsening edema, pulmonary artery occlusive pressure (wedge) >18 mmHg or cardiac output <2.2 l/min-m²;

- need for additional/increased heart failure therapy - including one of the following: initiation or significant increase of oral diuretics, requirement of intravenous diuretics, inotropes or vasodilators, need for ultrafiltration due to decompensated heart failure;
- Acute myocardial infarction, as defined by the WHO consensus statement
- Unstable angina, or need for coronary revascularization
- Cardiac tachy- or brady-arrhythmias leading to a new hospitalization or to prolongation of hospital stay;
- Acute renal failure (defined as an increase in plasma creatinine levels of 50% or 0.5 mg/L);
- Acute respiratory failure (not due to heart failure);
- Sepsis or other serious infection requiring antibiotic therapy;
- Acute stroke.

The analysis will consider time to first event and time to each event. It will also consider event rates at 3, 6 and 12 months, in order to favor comparisons with other studies. The number of days free of hospitalization during the first 1, 3, 6 and 12 months will also be measured and compared between groups.

9.3 Implications of the findings of the event-adjudicating committee

The events will be adjudicated only after the completion of the study, and therefore the findings by the committee will have no implications on the conduct of the study.

10) DISCONTINUATION OF TREATMENT AND WITHDRAWAL

10.1 Reasons for Discontinuation of Treatment or Withdrawal from the Study

Patients may withdraw from the study at any time. The investigators can withdraw any patient at any time from the study if medically necessary. It will be extremely important to obtain complete follow-up data on each patient, except on those who withdraw consent to release such information. It will be documented whether or not each patient completed the study. If for any reason the study treatment or observations were discontinued, the reasons will be recorded and the IRB will be informed.

Reasons for discontinuation of anakinra (or placebo):

- 1) Neutropenia ($ANC < 1000/mm^3$)*;
- 2) Systemic infection (sepsis)*;
- 3) Surgery *;
- 4) Cancer;
- 5) Hypersensitivity reaction (rash, anaphylaxis);
- 6) Severe injection site reactions *;
- 7) Need for immunosuppressant therapy;
- 8) Stroke *.

* treatment may be restarted after condition resolved

10.2 Handling of Withdrawals

Loss to follow-up can occur due to patients' withdrawal or unreported death. Patients that have withdrawn from treatment will still be offered to complete all the functional assessments to analyze data in an intention-to-treat strategy. If patients are lost to follow up and their clinical condition cannot be established (alive vs dead, hospitalized vs not), they will be excluded from the initial analysis, and then reintroduced for sensitivity analysis considering all potential outcomes.

10.3 Termination of Study

The decision regarding continuation or termination of the study will be solely based on safety data. Interim analyses will be performed upon request by the DSMB. The co-PIs will meet every month (or sooner in case of unanticipated serious adverse events) to discuss enrollment, withdrawals, and adverse events. If protocol modifications are warranted, close consultation with the DSMB and the IRB will be required.

11) STATISTICAL CONSIDERATIONS

12.1 Study Hypothesis

We hypothesize that IL-1 blockade with anakinra will reduce the area-under-the-curve for CRP during the first 14 days with a greater reduction to be seen with high-dose anakinra, and that this will translate in more favorable cardiac remodeling and prevention of heart failure.

12.2 Sample Size Considerations

The sample size for this study is calculated according to the primary endpoint of difference in the AUC for CRP between anakinra (high dose) compared with anakinra (standard dose) and placebo. Given an expected average AUC for CRP of 350 ± 250 mg/l for placebo-treated STEMI patients (based on the pilot studies) and an average AUC for CRP of 175 ± 150 mg/l for anakinra (standard dose)(also based on the pilot studies), 33 patients per group would provide a 85% power (alpha 0.025 considering multiple groups) to detect a further 50% reduction in the anakinra (high dose)(estimated AUC for CRP of 88 ± 75 mg/l) vs anakinra (standard dose) and a >99% power (alpha 0.025) vs placebo. A conservative estimate of 20% loss to follow-up or withdrawal would retain >80% power for all analysis.

12.3 Statistical Analysis

For statistical analysis, all values will be reported as the median and interquartile range for potential deviation from Gaussian distribution. The differences between treatment groups will be computed using the Wilcoxon signed-rank test for continuous variables or Fisher's exact test for discrete variables. The differences in interval changes between the treatments will be compared using random-effect analysis of variance for repeated measures to analyze the effects of time and group allocation. Unadjusted p values will be reported throughout, with statistical significance set at the 2-tailed 0.025 level. The analyses will be completed using the Statistical Package for Social

Sciences, version 11.0.1, software (SPSS, Chicago, Illinois). Dr. Juan Lu, PhD, an expert in biostatistics and clinical trials will oversee all statistical analyses.

13) LITERATURE CITED

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DSMB CHARTER

Charter, Data and Safety Monitoring Board for

NHLBI 1R34HL121402-01

Interleukin-1 blockade in acute myocardial infarction:

Virginia Commonwealth University Anakinra Remodeling Trial -3
(VCU-ART3)

Updated on **August 13, 2014**

Executive Secretary: Christine DeWilde, RN – dewildec@vcu.edu

1 Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) for the study: **Interleukin-1 blockade in acute myocardial infarction: Virginia Commonwealth University Anakinra Remodeling Trial -3 (VCU-ART3)**

hereafter referred to as “VCU-ART3”.

The Charter is intended to be a living document. The DSMB may wish to review it at regular intervals to determine whether any changes in procedure are needed.

2 Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of **VCU-ART3**.

The DSMB is an independent group advisory to the Director, NHLBI, and is required to provide recommendations about starting, continuing, and stopping the study **VCU-ART3**. In addition, the DSMB is asked to make recommendations, as appropriate, to the investigators about:

- Participant safety
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Performance of individual centers and core labs (as needed)
- Notification of and referral for abnormal findings
- Efficacy of the intervention at study termination (no interim analyses planned)

3 Organization and Interactions

Communication with DSMB members will be primarily through the executive secretary. It is expected that study VCU-ART3 investigators will not communicate with DSMB members about the study directly, except when making presentations or responding to questions at DSMB meetings or during conference calls.

a. DSMB Members and NHLBI Program Staff

DSMB members and their expertise are listed in Appendix A. NHLBI Program Staff involved in the study. Consistent with NHLBI policy, the DSMB is assigned an Executive Secretary (ES) to provide an unbiased staff interface for the DSMB, especially during executive sessions. The ES is responsible for assuring the accuracy and timely transmission of the final recommendations and DSMB minutes.

b. Scheduling, Timing, and Organization of Meetings

DSMB meetings will be held at the Virginia Commonwealth University, Richmond, VA, unless otherwise specified. For DSMB members residing outside of Virginia, telephone participation will be allowed for all meetings. The purpose of the first meeting is to review and discuss this Charter, to provide an overview of study VCU-ART3 activities, to review and make recommendations about the protocol(s), and to determine the frequency of interim analyses and whether data will or will not be masked to identity of randomized groups. Enrollment in a study cannot begin until the DSMB's recommendation for approval has been accepted by the Director, NHLBI, and IRB approval has been obtained at each site.

Meetings are usually held approximately twice a year, every 6 months, with additional meetings or conference calls scheduled as needed. Once the DSMB has established its working routine, consideration can be given to replacing one meeting per year with a conference call, if the agenda permits. Meetings and conference calls will be scheduled by the DCC in collaboration with the NHLBI Program Office.

- For this DSMB, meetings will be held twice per year.
- The DSMB will monitor the progress of the present trial.
- No interim efficacy analyses are planned; however an interim analysis could be performed at any time to assess efficacy and futility, if requested by the 3 or more members of the DSMB.
- The DSMB may choose to stop enrollment on the basis of safety data observed. If safety concerns are found, further enrollment will not be allowed until issues are resolved. If no safety concerns are found, enrollment will continue until the target sample size is reached.

The agenda for DSMB meetings and calls may be drafted by the executive secretary. The secretary will finalize the agenda after consultation with the DSMB Chair. The agenda

and meeting materials should be distributed by the DCC 4 weeks before each meeting or call.

The ES will collect and document all potential conflicts of interest from each member of the DSMB related to the design, conduct, interpretation, and publication of the study. Before each meeting, when the agenda is sent out, the ES will ask all DSMB members to state whether they have developed any new conflicts of interest since last meeting. This review will be conducted in addition to the review for conflicts of interest conducted by the VCU IRB at the time of initial IRB approval. If a new conflict is reported, the Chair and staff will determine if the conflict limits the ability of the DSMB member to participate in the discussion. The DSMB also will review adverse event data, other safety data, quality and completeness of study data, and enrollment data at each meeting to ensure proper trial conduct.

It is expected that all DSMB members will attend every meeting or call. However, it is recognized that this may not always be possible. Quorum for voting is considered to be half the number of standing members plus one. The Board may wish to decide if particular expertise is needed within the quorum for the meeting to be valid. All standing Monitoring Board members are voting members. The Board may also wish to decide in advance whether *ad hoc* members can vote.

A quorum of this DSMB is considered to be 3 members

c. Discussion of Confidential Material

DSMB meetings and calls will be organized into open, closed, and executive sessions.

- During the **open sessions**, information will be presented to the DSMB by the study investigators and NHLBI staff as appropriate, with time for discussion.
- During the **closed sessions**, the DSMB, DCC, and NHLBI staff will discuss confidential data from the study VCU-ART3, including information on efficacy and safety by treatment arm, if available. The DSMB will decide whether to remain masked to the treatment assignments at each meeting. If the closed session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the closed session.

The DSMB may elect to hold an **executive session** in which only the DSMB members and NHLBI Executive Secretary are present in order to discuss study issues independently. Voting on recommendations will follow Roberts' Rules of Order (**Robert's Rules of Order Newly Revised (10th Edition) RONR** by Henry M. Robert III, William J. Evans (Editor), Daniel H. Honemann (Editor), Thomas J. Balch (Editor), Sarah Corbin Robert, Henry M. Robert III, General Henry M. Robert)

If the executive session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the executive session.

At the conclusion of the closed and executive sessions, the participants will be re-convened so that the DSMB Chair can provide a summary of the DSMB's recommendations. This provides an opportunity for study investigators, the DCC, and NHLBI to ask questions to clarify the recommendations. The meeting is then adjourned.

d. Reports of DSMB Deliberations

- **Formal minutes:** The NHLBI ES is responsible for the accuracy and transmission of the formal DSMB minutes for the Director, NHLBI, within 14 days of each meeting or call. These minutes prepared to summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting. Prior to submission to the Director, minutes will be reviewed by key NHLBI staff before being forwarded to the DSMB Chair for final review and approval. The DSMB Chair may sign the minutes or indicate approval electronically via email. Then, the minutes are sent to Office of the Director, NHLBI, for OD approval. Subsequently, recommendations of the Board are sent to the DCC and the primary study investigator(s); and included in the materials for the subsequent DSMB meeting to be approved by voice vote at that meeting. Once they have been voted and approved by the Board, they are considered Final.
- **Reports to IRBs:** Because this DSMB is convened to supervise a multi-center study, the NHLBI program office will prepare a memo documenting Board recommendations and submit it to primary study investigator(s) and DCC within 21 days of each meeting. Primary study investigator(s) or DCC will forward the memo to each participating research site. It is expected that all sites and the DCC will forward the memo to their IRB.
- If the DSMB does not identify any safety or other protocol-related concerns, within 30 days after a DSMB meeting, the NHLBI Program Office will prepare a Summary Report that will state that:
 - a review of outcome data, adverse events, and information relating to study performance (e.g., data timeliness, completeness, and quality) across all centers took place on a given date;
 - the observed frequency of adverse events did not exceed what was expected and indicated in the informed consent;
 - a review of recent literature relevant to the research took place and;
 - the DSMB recommended that the study continue without modification of the protocol or informed consent.

- If concerns are identified, the report to the clinical centers will outline the concerns, the DSMB's discussion of the concerns, and the basis for any recommendations that the DSMB has made in response to the concerns.
- The DSMB report to the investigators will be forwarded to the NHLBI Program Officer, including the discussion of the concerns, and the basis for any recommendations that the DSMB has made in response to the concerns (within 7 calendar days if fatal or life-threatening unexpected, suspected serious adverse reactions; or within 14 days for unanticipated problem that is not an SAE or within 15 calendar days for all non-fatal, non-life threatening unexpected, suspected serious adverse reactions, or within 30 days of receipt of the DSMB or IRB report for all other unanticipated problems or scheduled meetings).
- The report will be distributed by the **DCC** to each clinical center. It is the responsibility of each clinical center to forward this information to the local IRB.

e. Reports to the DSMB

For each meeting, the DCC, with input from NHLBI staff, will prepare summary reports and tables to facilitate the oversight role of the DSMB. The DSMB should discuss at the first or subsequent meetings what data they wish to review and how it should be presented.

f. Statistical Monitoring Guidelines

At the first meeting, review of the protocol will include review of the statistical analysis plan. The DSMB should discuss the adequacy of that plan. The final plan, whether part of a research protocol or separate document, will be maintained as an appendix to this charter. The DSMB should discuss the statistical monitoring procedures they propose to follow to guide their recommendations about termination or continuation of the trial (if applicable). These procedures could include guidelines for early termination for benefit, termination for futility, and termination for safety reasons (if applicable).

Appendix A: DSMB members**Dominick Angiolillo, MD, PhD DSMB Chair**

Dr. Angiolillo is an Associate Professor of Medicine in Cardiology at the University of Florida in Jacksonville. He is board certified in Cardiology and Interventional Cardiology, and serves as Medical Director for the Cardiovascular Research Program in the division of Cardiology.

<http://www.hscj.ufl.edu/directory/bio.aspx?id=1318>

Richard Cooke, MD DSMB Member

Dr. Cooke is an Associate Professor of Medicine in Cardiology at the Virginia Commonwealth University, and is the Chief of the Advanced Heart Failure Service in the VCU Pauley Heart Center. Dr. Cooke is board-certified in Internal Medicine, Cardiology, Heart Failure, and Interventional Cardiology. <http://www.pauleyheart.vcu.edu/staff/cooke.html>

Gonzalo Bearman, MD DSMB Member

Dr. Bearman is a Professor of Medicine and serves as Chief of the Division of Infectious Disease as well as Hospital Epidemiologist. Dr. Bearman is Board Certified in Internal Medicine, Infectious Diseases, and General Preventive Medicine and Public Health.

Ion Jovin, MD, PhD DSMB member

Dr. Jovin is an Associate Professor of Medicine in Cardiology, and serves as Director of the Cardiac Catheterization Laboratories at the Hunter McGuire Veterans Administration Medical Center in Richmond, VA. Dr. Jovin is board certified in Cardiology and Interventional Cardiology.

<http://www.pauleyheart.vcu.edu/staff/jovin.html>

Jeffrey Kushinka, MD DSMB member

Dr. Kushinka is an Associate Professor in the Division of General Internal Medicine, has served as Interim Chair for 2 years. He is also the clerkship director for 3rd Medical Students and an Associate Program Director for the Internal Medicine Residency Program. Dr. Kushinka is board certified in Internal Medicine.

Appendix B: MONITORING PLAN**Scope of the plan**

The monitoring plan has the goal to verify that the conduct of the study complies with the most updated version of the Research Protocol, and in compliance with the regulation of the Institutional Review Board, the Food and Drug Administration, and the guidance of dedicated Data and Safety Monitoring Board, and the National Institute of Health.

Responsible parties

Virginia Commonwealth University, research site: Antonio Abbate, MD

Washington Hospital Center, research site: Ron Waksman, MD

Virginia Cardiovascular Specialist, research site: Darryn Appleton, MD

Virginia Commonwealth University, investigational pharmacy: Robin Sculthorpe,
RPh

Coordinating Center Principal Investigator(s): Antonio Abbate, MD; Benjamin Van Tassell,
PharmD

FDA IND Principal Investigator: Antonio Abbate, MD, PhD

NIH Principal Investigator(s): Antonio Abbate, MD, PhD; Benjamin Van Tassell,
PharmD

The principal investigator (PI) at each local site, as indicated in the submission to the Institutional Review Board, is directly responsible for the conduct, oversight, and monitoring of study procedures at each site.

The local PI will supervise all study procedures, including the informed consent process, enrollment, withdrawal, and all decisions regarding study drug treatment.

The local PI will also be responsible for ensuring the accuracy of the data collected through verification with original source data.

Only de-identified data will be collected for the research record. However, the local PI will be able to obtain the original source documents if requested by a monitoring or inspecting

agency by linking the subject number with the identity of the subject, and retrieving the source document using document date, time and author, from the electronic medical record (or the existing paper record, if applicable).

All the shipments and handling of the investigational drug will be performed under the direct supervision of the Investigational Pharmacy Director at the Virginia Commonwealth University, who will be responsible for documentation of received and dispensed drug, storage, handling and preparation for patient use. The randomization log is also kept in the Investigational Pharmacy and is used for patient allocation. The randomization code will be kept secret and released only to the PI upon written request. The local PI may request breaking the randomization code if deemed necessary for patient care, see Protocol for details.

The handling and dispensing of the investigational drug at each individual site will occur under the direct supervision of the local PI, also listed as FDA IND investigator on the 1572 Form.

Communication between the study investigators and the FDA will occur through the IND principal investigator, or, if not available, through one of the IND investigators. Investigators other than those listed on the 1572 Form will have no role in handling or dispensing the investigational drug, nor will have any role in decision making in this regard.

The local investigators and coordinators will respond directly to the local PI. The coordinating center PI at the Virginia Commonwealth University will be responsible for oversight of individual local PIs.

The local PI is responsible for communication with the coordinating center. Such communication will occur either by phone (direct and protected line [804-828-0513]), by secure fax (804-828-6765) or by secure email (antonio.abbate@vcuhealth.org OR bvantassell@vcu.edu).

The local PI is responsible for completing the data collection sheet and also for providing a de-identified copy of the source documents (while maintaining ability to access and provide de-identified data if necessary) in a timely manner.

The local PI is responsible for complying with the regulations set for reporting of adverse events or non-compliance with the research procedure to the local Institutional Review Board and at the same time to Coordinating Center PI.

The Coordinating Center PI will be responsible of informing all local PIs, and also for complying with the regulations set for reporting of adverse events to the Data and Safety Monitoring Board, the FDA, and the NIH.

Appendix C: Case Report Forms

- Screening and Enrollment form (1 page)
- Enrollment check list (1 page)
- Enrollment Log (1 page)
- Individual Patient Cover Sheets (3 pages)
- Individual Visit Assessment Form (4 pages)
- Adverse Event reporting form (1 page)

VCU-ART3 Screening and enrollment form

Subject number: VCU-ART3 _____ Initials _____ Date _____

INCLUSION CRITERIA: *(All 3 criteria need to be met)*

- ☐ Presentation to the hospital with acute ST-segment elevation myocardial infarction (STEMI) defined as chest pain (or equivalent) with an onset within 12 hours and ECG evidence of ST segment elevation (>1 mm) in 2 or more anatomically contiguous leads (new or presumably new)
- ☐ Coronary angiogram for potential intervention completed within 12 hours of symptom onset, and enrollment in the study within 12 hours of angiogram (max 24 hours from symptom onset)
- ☐ Age>21 (NIH standard)

EXCLUSION CRITERIA (check only if applicable → *patient excluded*):

- Inability to give informed consent
- Pregnancy or breastfeeding
- Preexisting congestive heart failure (AHA/ACC class C-D, New York Heart Association III-IV)
- Preexisting severe left ventricular dysfunction (LVEF<20%)
- Preexisting severe valvular heart disease
- Active infections (acute or chronic)
- Recent (<14 days) or active use of immunosuppressive drugs (including but not limited to high-dose corticosteroids [>1 mg/kg of prednisone equivalent], TNF-alpha blockers, cyclosporine) not including NSAIDs or corticosteroids used for IV dye allergy only)
- Chronic auto-immune or auto-inflammatory disease (including but not limited to rheumatoid arthritis, systemic lupus erythematosus)
- Known active malignancy of any type, or prior diagnosis in the past 10 years
- Anticipated need for cardiac surgery
- Neutropenia (absolute neutrophil count<1,800/mm³ [or <1,000/mm³ in African-American patients])
- Severe impairment in renal function (estimated glomerular filtration rate <30 ml/kg*min)
- Recent or planned use of vaccination with live attenuated viruses OR planned aspirin desensitization during current admission
- Allergy to rubber or latex
- Allergy to products derived from Escherichia coli

Inclusion and exclusion criteria verified by _____ on _____ (date)

- ☐ Patient given a copy of the informed consent and sufficient time to read and have questions, answered.
- ☐ The original signed copy is stored for research, a signed copy is given to the patient, and an additional copy is placed in the chart.

The consenting process is completed by _____ on _____ (date)

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VCU-ART3**Enrollment Check List****VCU-ART3 Subject Number _____ Initials _____ Site _____ Date _____**

- ☐ Check Inclusion/Exclusion criteria and sign the "Screening and Enrollment Form"
- ☐ Review Informed Consent Form with Patient and complete all signatures (patient and person who conducted informed consent discussion)
- ☐ Give patient a copy of the signed consent form and Research Team contact card
- ☐ Give a copy of the consent to secretary to be placed in the patient's chart
- ☐ Order Investigational Drug on Cerner
- ☐ Call Investigational Pharmacy (or ICU Pharmacy if overtime)
- ☐ Review the "Nurse Protocol" with the Nurse
- ☐ Fill VCU Lab Sheet Form completing parts highlighted in yellow
- ☐ Have nurse to collect blood sample and apply Label from "Labs Sheet Form"
- ☐ Send sample to send to VCU Central Lab (tube station #160)
- ☐ Witness nurse administer investigational drug
- ☐ Complete Data Collection Form (Initial Assessment: STEMI presentation, etc...)
- ☐ Complete Vital Signs Form

Enrollment Check List verified by (Initials) _____ on _____ (date)

VCU-ART3 - ENROLLMENT LOG -- Site _____

ENROLLED (Initials/Date)

1		
2		
3		
4		
5		
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24		
25		

EXCLUDED (reason oly)

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E4	
E5	
E6	
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E11	
E12	
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E21	
E22	
E23	
E24	
E25	

HM20000024 – Interleukin-1 blockade in acute myocardial infarction

Participant Study ID:			
Hospital Admission Date: __/__/____ Hospital Discharged Date: __/__/____ Length of Stay in the Hospital: _____			
Questions: - Was the patient in the ICU? NO / YES If YES, how long? _____ - Was the patient re-admitted between baseline and 14-day FU? NO / YES - Was the patient re-admitted between 14-day FU and 12-week FU? NO / YES - Was the patient re-admitted between 12-week FU and 24-week FU? NO / YES - Was the patient re-admitted between 24-week FU and 52-week FU? NO / YES		Drug Dispensed to Participant Date: __/__/____ # of syringes dispensed: _____ Date for 14-day follow-up: __/__/____ Drug Returned by Participant at 14-day FU Date: __/__/____ # of syringes returned: _____	
Eligibility Confirmed on __/__/____ Signed/Performed by: _____		If Re-Consented: Date ICF signed: __/__/____ Withdrew Consent: Date: __/__/____ Reason? _____	
Informed Consent: Version __/__/____ IRB approval __/__/____; signed on __/__/____		Notes:	
Randomization: __/__/____		Notes:	
Study Time Point	Study Procedure	Completed	Notes
Baseline (Day 1) __/__/____	Note in CIS re: Clinical Trial/ICF Process		
	Blood Draw (baseline – HDL or VCU)		
	Concomitant Rx		
	Baseline History		
	Drug Ordered		
	Drug Dose #1 administered		
	Echocardiogram (ordered)		
	Drug Dose #2 administered		
Day 2 (24 hrs) __/__/____	AE review		
	Drug Dose #1 administered		
	Drug Dose #2 administered		
	Other:		
Day 3 (48 hrs) __/__/____	AE review		
	Drug Dose #1 administered		
	Drug Dose #2 administered		
	Other:		

HM20000024 – Interleukin-1 blockade in acute myocardial infarction

Day 4 (72 hrs) _/_/_	72 hrs Labs (HDL)		
	AE review		
	Drug Dose #1 administered		
	Drug Dose #2 administered		
	Other:		
Day 5 _/_/_	AE review		
	Drug Dose #1 administered		
	Drug Dose #2 administered		
	Other:		
Day 6 _/_/_	AE review		
	Drug Dose #1 administered		
	Drug Dose #2 administered		
	Other:		
Day 7 _/_/_	AE review		
	Drug Dose #1 administered		
	Drug Dose #2 administered		
	Other:		
Day 8 _/_/_	AE review		
	Drug Dose #1 administered		
	Drug Dose #2 administered		
	Other:		
Day 9 _/_/_	AE review		
	Drug Dose #1 administered		
	Drug Dose #2 administered		
	Other:		
Day 10 _/_/_	AE review		
	Drug Dose #1 administered		
	Drug Dose #2 administered		
	Other:		
Day 11 _/_/_	AE review		
	Drug Dose #1 administered		
	Drug Dose #2 administered		
	Other:		
Day 12 _/_/_	AE review		
	Drug Dose #1 administered		
	Drug Dose #2 administered		
	Other:		
Day 13 _/_/_	AE review		
	Drug Dose #1 administered		
	Drug Dose #2 administered		
	Other:		
Day 14 _/_/_	Blood Draw (14-day HDL)		
	AE review		
	Investigational Drug Reconciliation		
	Concomitant Rx		
	Other:		

HM20000024 – Interleukin-1 blockade in acute myocardial infarction

12-week FU _/_/_	Blood Draw (12-week HDL)		
	Concomitant Rx		
	AE review		
	Other:		
24-week FU _/_/_	Blood Draw (24-week HDL)		
	Concomitant Rx		
	AE review		
	12-month Echocardiogram ordered		
	Other:		
52-week FU _/_/_	Blood Draw (52-week HDL)		
	Concomitant Rx		
	AE review		
	1-year Echocardiogram		
	Other:		
Additional Notes: - SAEs Reported? - Deviations?			

VCU-ART3 Subject # _____ Initials _____ Clinical Site: VCU / VCS / WHC

Initial Assessment: STEMI presentation

Date _____, time of symptom onset _____, ED arrival _____, PCI time _____

ECG - ST segment elevation (circle all that apply): V1 V2 V3 V4 V5 V6 I II III aVF aVL

Clinical conditions: (check all that apply)

- ☐ hypotension/shock; ☐ pulmonary edema; ☐ ventricular arrhythmias
☐ persistent pain; ☐ altered mental status

Procedural data: check all that apply)

- ☐ thrombectomy; ☐ stent implantation, check ☐ if at least 1 is drug-eluting stent
☐ bivalirudin; ☐ abciximab/epitfibatide; ☐ aspirin; ☐ clopidogrel; ☐ prasugrel; ☐ ticagrelor

Past Medical History: (check all that apply)

- ☐ Prior MI; ☐ Prior PCI; ☐ Prior CABG; ☐ Heart Failure; ☐ Prior CVA; ☐ Hypertension
☐ Diabetes; ☐ Hyperlipidemia; ☐ Current Tobacco user; ☐ Peripheral Vasc Disease
☐ Chronic Kidney Disease; ☐ Chronic Obstructive Lung Disease; ☐ Afib; ☐ DVT/PE

Notes _____

STUDY ITEMS: (check all completed)

- ☐ Consenting; ☐ Initial Labs (local/central lab) on ____/____/____ at ____:____ AM/PM
☐ Investigational drug first dose administered on ____/____/____ at ____:____ AM/PM
☐ Medication Reconciliation; ☐ Echocardiogram ordered (possibly <24 hrs)
 Body weight: ____kg/____lb Height: ____m/____ft BMI: ____kg/m²
 Blood Pressure: ____/____ mmHg HR: ____min
☐ 72 h Labs (±12 hours) (local/central lab) on ____/____/____ at ____:____ AM/PM

Hospital outcomes (check all that apply)

- ☐ hypotension/shock, check ☐ if requiring inotropes, pressors or mechanical support
☐ pulmonary edema, check ☐ if requiring mechanical ventilation
☐ ventricular arrhythmias, check ☐ if sustained, requiring cardioversion
☐ acute renal failure, check ☐ if requiring renal replacement therapy
☐ re-infarction; ☐ repeat emergent PCI; ☐ staged PCI

Duration of hospitalization: _____ days.

Notes _____

DISCHARGE PLANNING: (check all completed)

- ☐ Dispensing of investigational drug (____syringes) by _____ (date _____, time ____)
☐ Patient education on drug handling, storage, and self-administration (by _____)
☐ Outpatient Hospital Follow up (11-17 days) scheduled on _____ (location ____)
☐ Discussed with patient how to contact research team 24/7 at 804-828-0513

version 04062015

VCU-ART3 Subject # _____ Initials _____ Clinical Site: VCU / VCS / WHC

Follow up visit #1: 14 day (11-17 days)

Date of STEMI _____, Date of F/U visit _____

Clinical conditions: (check all that apply)

- ☐ recurrent angina/myocardial infarction, check ☐ if leading to re-hospitalization
☐ heart failure symptoms, _____ NYHA class (I→IV), check ☐ if re-hospitalization
☐ re-hospitalization for other cause (complete dedicated sheet)
☐ death, check ☐ if presumed cardiac death, check ☐ if sudden death

Notes _____

Past Medical History: (changes vs prior – new diagnoses)☐ _____; ☐ _____; ☐ _____; ☐ _____

Notes _____

STUDY ITEMS: (check all completed)

- ☐ Assessment of compliance with investigational drug performed by _____
 (used syringes _____; returned syringes _____)
☐ Send-out Labs (HDL); ☐ Medication reconciliation;
☐ Scheduling F/U visit for _____, location _____
 Body weight: _____ kg/_____ lb Height: _____ m/_____ ft BMI: _____ kg/m²
 Blood Pressure: _____/_____ mmHg HR: _____ min

Follow up visit # 2: 3 months (10-14 weeks)

Date of STEMI _____, Date of F/U visit _____

Clinical conditions: (check all that apply)

- ☐ recurrent angina/myocardial infarction, check ☐ if leading to re-hospitalization
☐ heart failure symptoms, _____ NYHA class (I→IV), check ☐ if re-hospitalization
☐ re-hospitalization for other cause (complete dedicated sheet)
☐ death, check ☐ if presumed cardiac death, check ☐ if sudden death

Notes _____

Past Medical History: (changes vs prior – new diagnoses)☐ _____; ☐ _____; ☐ _____; ☐ _____

Notes _____

STUDY ITEMS: (check all completed)

- ☐ Send-out Labs (HDL); ☐ Medication reconciliation;
☐ Scheduling F/U visit for _____, location _____
 Body weight: _____ kg/_____ lb Height: _____ m/_____ ft BMI: _____ kg/m²
 Blood Pressure: _____/_____ mmHg HR: _____ min

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VCU-ART3 Subject # _____ Initials _____ Clinical Site: VCU / VCS / WHC

Follow up visit #3: 6 months (22-26 weeks)

Date of STEMI _____, Date of F/U visit _____

Clinical conditions: (check all that apply)

- ☐ recurrent angina/myocardial infarction, check ☐ if leading to re-hospitalization
☐ heart failure symptoms, _____ NYHA class (I→IV), check ☐ if re-hospitalization
☐ re-hospitalization for other cause (complete dedicated sheet)
☐ death, check ☐ if presumed cardiac death, check ☐ if sudden death

Notes _____

Past Medical History: (changes vs prior – new diagnoses)☐ _____; ☐ _____; ☐ _____; ☐ _____

Notes _____

STUDY ITEMS: (check all completed)

- ☐ Send-out Labs (HDL); ☐ Medication reconciliation;
☐ Repeat echocardiogram to be scheduled for 12 month visit
☐ Follow up visit for _____, location _____

Body weight: _____ kg/_____ lb Height: _____ m/_____ ft BMI: _____ kg/m²

Blood Pressure: _____/_____ mmHg HR: _____ min

Follow up visit #4: 12 months (11-13 months)

Date of STEMI _____, Date of F/U visit _____

Clinical conditions: (check all that apply)

- ☐ recurrent angina/myocardial infarction, check ☐ if leading to re-hospitalization
☐ heart failure symptoms, _____ NYHA class (I→IV), check ☐ if re-hospitalization
☐ re-hospitalization for other cause (complete dedicated sheet)
☐ death, check ☐ if presumed cardiac death, check ☐ if sudden death

Notes _____

Past Medical History: (changes vs prior – new diagnoses)☐ _____; ☐ _____; ☐ _____; ☐ _____

Notes _____

STUDY ITEMS: (check all completed)

- ☐ Send-out Labs (HDL); ☐ Medication reconciliation;
☐ Repeat echocardiogram;
☐ Scheduling F/U visit with clinical provider

Body weight: _____ kg/_____ lb Height: _____ m/_____ ft BMI: _____ kg/m²

Blood Pressure: _____/_____ mmHg HR: _____ min

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VCU-ART3 Subject # _____ Initials _____ Clinical Site: VCU / VCS / WHC

Follow up visit: Extra-visit

Date of STEMI _____, Date of F/U visit _____

Clinical conditions: (check all that apply)

- ☐ recurrent angina/myocardial infarction, check ☐ if leading to re-hospitalization
☐ heart failure symptoms, _____ NYHA class (I→IV), check ☐ if re-hospitalization
☐ re-hospitalization for other cause (complete dedicated sheet)
☐ death, check ☐ if presumed cardiac death, check ☐ if sudden death

Notes _____

Past Medical History: (changes vs prior – new diagnoses)☐ _____; ☐ _____; ☐ _____; ☐ _____

Notes _____

STUDY ITEMS: (check all completed)

- ☐ Send-out Labs (HDL); ☐ Medication reconciliation;
☐ Repeat echocardiogram to be scheduled for 12 month visit
☐ Follow up visit for _____, location _____

Body weight: _____ kg/ _____ lb Height: _____ m/ _____ ft BMI: _____ kg/m²

Blood Pressure: _____/ _____ mmHg HR: _____ min

VCU-ART3 study

Version April 6, 2015

VCU-ART3 Study EVENT FORM**VCU-ART3 Subject _____ Initials _____**Hospitalization, date _____Death, date _____

- | | |
|--|---|
| <input type="checkbox"/> Acute Decompensated Heart Failure as primary diagnosis (see Protocol) | <input type="checkbox"/> Out of hospital and sudden |
| <input type="checkbox"/> Acute Coronary Syndrome as primary diagnosis | <input type="checkbox"/> In-hospital, associated with ventricular arrhythmia not secondary to other cardiac disease |
| <input type="checkbox"/> Arrhythmia as primary diagnosis | <input type="checkbox"/> In-hospital, associated with acute cardiac issue |
| <input type="checkbox"/> Acute Renal Failure | <input type="checkbox"/> In-hospital, associated with acute non cardiac issue (Specify _____) |
| <input type="checkbox"/> Acute Respiratory Failure (not due to heart failure) | <input type="checkbox"/> Other (Specify _____) |
| <input type="checkbox"/> Sepsis, or Severe Infection | <input type="checkbox"/> Unknown |
| <input type="checkbox"/> TIA/Stroke | |
| <input type="checkbox"/> Other (Specify _____) | |

Other events date _____
 (not leading to hospitalization)

- ☐ Injection site reaction
☐ Rash ☐ Fever
☐ Infection (requiring antibiotic tx ☐)
☐ Nausea/Vomiting/Diarrhea
☐ Others: (Specify _____)

Interruption of Treatment,
date _____

- ☐ Mandated by protocol
☐ Decision made by patient

ADVERSE EVENT: YES ☐ NO ☐**ANTICIPATED ☐ , NOT ANTICIPATED ☐**

SEVERITY:
MILD ☐ ; MODERATE ☐ ; SERIOUS ☐

RELATED TO RESEARCH:
UNRELATED ☐ ; POSSIBLY ☐ ;
PROBABLY ☐ ; DEFINITELY ☐

**IF SERIOUS, UNANTICIPATED, and RELATED TO RESEARCH →
 REPORT IMMEDIATELY TO THE PRINCIPAL INVESTIGATOR(s)**

Completed By, Name_____
Signature_____
DateAttach de-identified Notes from chart or notes (check ☐ if not available)_____
Principal Investigator(s)_____
Signature_____
DatePrompt report to the IRB/DSMB needed ☐ completed ☐ by _____ on _____

VCU-ART3 EchocardiDoppler Analysis

Date _____ Subject number: _____ Initials _____

Instructions:

- *This study is performed during the admission (as early as possible) and at 12 month follow up as part of standard clinical care. The patient and Insurance may be billed for.*
- *Images to be acquired on a digital format and then transferred to VCU for central lab measurements.*
- *The study requires a Limited EchocardiDoppler analysis – if a more complete exam is deemed necessary, then proceed with full study.*
- *Measurements for research-purposes do not need to be performed on-line, neither need to be done at off-line at the individual center, they will be performed single batch at the end of the clinical trial at VCU central lab.*

Obtain apical 4-chamber view:

- **Record 2 dimension imaging to measure LVEDV and LVESV**
○ LVEDV ____ / LVESV ____
- **Record Color-Doppler of Mitral Inflow and Regurgitation**
○ Quantify regurgitation _____
- **Record Color-Doppler of Left Ventricular Outflow tract**
- **Record transmitral Doppler flow spectra** E ____ / DT ____ / A ____ HR ____
- **Record lateral wall Mitral Annular tissue Doppler spectra**
E'lat ____ / A'lat ____ / S'lat ____
- **Record septum Mitral Annular tissue Doppler spectra**
E'sept ____ / A'sept ____ / S'sept ____
- **Record Tricuspidal Annulus tissue Doppler spectra** S'lat ____
- **Record TAPSE (M-mode)** Excursion ____

Obtain apical 2-chamber view:

- **Record 2 dimension imaging to measure LVEDV and LVESV**
○ LVEDV ____ / LVESV ____

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