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‘This is the peer reviewed version of the following article: Lambrakis, K., French, J. K., Scott, I. A., Briffa, T., Brieger, D., Farkouh, M. E., ... Chew, D. P. (2019). The appropriateness of coronary investigation in myocardial injury and type 2 myocardial infarction (ACT-2): A randomized trial design. *American Heart Journal*, 208, 11–20. <https://doi.org/10.1016/j.ahj.2018.09.016>

which has been published in final form at

<https://doi.org/10.1016/j.ahj.2018.09.016>

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Accepted Manuscript

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PII: S0002-8703(18)30293-X
DOI: <https://doi.org/10.1016/j.ahj.2018.09.016>
Reference: YMhj 5787
To appear in: *American Heart Journal*
Received date: 17 August 2018
Accepted date: 30 September 2018

Please cite this article as: Kristina Lambrakis, John K. French, Ian A. Scott, Tom Briffa, David Brieger, Michael E. Farkouh, Harvey White, Anthony (Ming-Yu) Chuang, Kathryn Tiver, Stephen Quinn, Billingsley Kaambwa, Matthew Horsfall, Erin Morton, Derek P Chew , The appropriateness of coronary investigation in myocardial injury and Type 2 myocardial infarction (ACT-2): A randomized trial design. *Ymhj* (2018), <https://doi.org/10.1016/j.ahj.2018.09.016>

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The appropriateness of coronary investigation in myocardial injury and Type 2 myocardial infarction (ACT-2): A randomized trial design

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Running Title: Design of ACT-2

Word Count: Total (including abstract, text, tables, legends, references): 6365

References: 23

Key Words: Troponin, Type 2 Myocardial Infarction, Coronary Investigation, Clinical Trial

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Abstract

Background: Elevated troponin level findings among patients presenting with suspected acute coronary syndrome (ACS) or another inter-current illness undeniably identifies patients at increased risk of mortality. Whilst enhancing our capacity to discriminate risk, the use of high-sensitivity troponin assays frequently identifies patients with myocardial injury (i.e. troponin rise without acute signs of myocardial ischaemia) or type 2 myocardial infarction (T2MI, oxygen supply-demand imbalance). This leads to the clinically challenging task of distinguishing type 1 myocardial infarction (T1MI, coronary plaque rupture), from myocardial injury and T2MI in the context of concurrent acute illness. Diagnostic discernment in this context is crucial as MI classification has implications for further investigation and care. Early invasive management is of well-established benefit among patients with T1MI. However, the appropriateness of this investigation in the heterogeneous context of T2MI, where there is high competing mortality risk remains unknown. Whilst coronary angiography in T2MI is advocated by some, there is insufficient evidence in existing literature to support this opinion as highlighted by current national guidelines.

Objective: To evaluate the clinical and economic impact of early invasive management with coronary angiography in T2MI in terms of all-cause mortality and cost effectiveness.

Design: This prospective, pragmatic, multi-centre, randomised trial among patients with suspected supply demand ischaemia leading to troponin elevation, (n=1800, T2MI [1500], chronic myocardial injury [300]) compares the impact of invasive angiography (or CT angiography as per local preference) within 5 days of randomization versus conservative management (with or without functional testing at clinician discretion) on all-cause

mortality by 2 years. Randomized treatment allocation will be stratified by baseline estimated risk of mortality using the APACHE III risk score. Cost-effectiveness will be evaluated by follow-up on clinical events, quality of life and resource utilization over 24 months.

Summary: Ascertaining the most appropriate first line investigative strategy for these commonly encountered high risk T2MI patients in a randomized comparative study will be pivotal in informing evidence-based guidelines that lead to better patient and health-care outcomes.

Introduction

Complexity in the interpretation of cardiac myonecrosis, largely troponin, has led to the development of Universal Definitions of Myocardial Infarction (MI) conceptually classifies MI subgroups. (1) Diagnostic discrimination of these conceptual subgroups has implications for further management. The advancement of high-sensitivity troponin assays, whilst enhancing our capacity to risk stratify patients, is however increasingly making subgroup differentiation a clinically challenging task. Type 1 MI (T1MI), defined as a spontaneous MI due to coronary plaque rupture, has a strong evidence-base for the use of early invasive management (angiography \pm revascularization) thus its use in this context is highly recommended and has become common practice. The management of type 2 MI (T2MI), defined as an MI resulting from myocardial nutrient demand and blood supply imbalance due to physiological or pathological stressors, and myocardial injury, rudimentally defined as elevated troponins without clinical signs of acute myocardial ischaemia, remains haphazard as a consequence of insufficient guiding evidence. (2-4) T2MI is associated with worse clinical outcomes and a much greater mortality rate than T1MI, even when accounting for precipitating illness and a degree of myocardial injury (figure 1) (5-7).

Currently, practical differentiation of T2MI versus T1MI almost always relies on investigative coronary angiography to exclude or identify culprit coronary lesions (diagnosing T1MI) yet the appropriateness of coronary angiography among the T2MI patient population, where there is high concurrent competing risk of mortality from inter-current illness and increased bleeding risk, remains uncertain and evidence validating the benefits of subsequent coronary interventions is lacking. (7,8) As such, management of T2MI remains highly variable, guideline recommendations are limited, and clinical equipoise persists. (9)

To date, few studies formally integrating risk assessment into the strategy of coronary investigation have been undertaken. A randomised trial of routine early angiography versus conservative management that carefully evaluates baseline patient risks and competing risks is critical to the development of robust recommendations for these commonly encountered high morbidity and mortality patients.

Methods

Objectives and Hypotheses

The primary objective of the study is to evaluate the impact of an early anatomic investigation of the coronary arteries on 24-month all-cause survival among T2MI patients within a pragmatic multi-centre randomised clinical trial. Secondary objectives are to examine the ECG, echocardiographic and biomarker characteristics, and patient competing risk profile associated with benefit from early coronary investigation with respect to late mortality. A third objective is to define the incremental cost-effectiveness of applying early coronary investigation versus conservative management in T2MI.

The primary hypothesis of this study is that knowledge of the coronary anatomy in T2MI leads to the use of therapies that result in an improvement in survival at 24 months. The secondary hypothesis is that the survival benefit associated with early anatomic investigation is determined by the degree to which cardiac risk is reduced relative to competing risks.

Study Design

This prospective open-labeled parallel clustered RCT with blinded endpoint assessment (PROBE) study is designed to couple objective competing-risk assessment in all eligible patients with the randomized allocation to anatomic coronary investigation or an conservative management. Patients (n=1800) will be randomised to either routine angiography (with further testing and coronary revascularization at clinician discretion) within 5 days versus conservative management (with functional testing at clinician discretion) (figure 2).

Given this population's high comorbidity burden and competing cardiac and non-cardiac risks, the primary endpoint will be all-cause mortality (i.e. survival). Additionally, in order to focus on patients with a greater likelihood of supply-demand ischaemia, enrolment of patients with chronic myocardial injury (pattern 2: See "Standardized risk assessment and troponin pattern") will be capped at n=300 and outcomes will be exploratory in this subpopulation. Clinical events will be determined during 24-month follow-up. All enrolled patients will have their baseline Global Registries for Acute Cardiac Events (GRACE) risk score and Acute Physiology, Age and Chronic Health Evaluation (APACHE) III scores

evaluated. (10,11) Block randomization will be undertaken within strata, based on troponin pattern, predicted risk of in-hospital mortality (APACHE III) and enrolling hospital. Aside from the allocated management strategy and associated timelines, all other subsequent management including secondary prevention therapies will be left to clinician discretion. The utility of clinical, echocardiographic and biomarkers in identifying patients with T2MI who may benefit from routine invasive management remains undefined thus uncertain, hence these sub-analyses will remain observational and exploratory. (Reg. No. ACTRN12618000378224p).

Funding source and Authorship

This research is supported by funding from the National Health and Medical Research Council of Australia (APP1146512). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Standardized Risk Assessment and Troponin Pattern

Table 1 describes the patient eligibility criteria. The study will enrol in-hospital patients with at least one elevated (“rule-in”) troponin result (i.e. Troponin T (Roche Elecsys): $>52\text{ng/L}$ and Troponin I (Abbott Architect, Dimension Vista, Beckman Access): ≥ 5 times the assay-specific upper limit of normal) using the local laboratory standards, presenting with an defined intercurrent illness. These values have been selected to ensure a clinical population with heightened risk of recurrent cardiac events. Furthermore, the kinetics of the troponin rise will be examined using the following patterns:

1) Troponin Pattern 1 (Acute Myocardial Injury): A rise and/or fall in troponin from at least 2 samples defined as:

- a) Hs-Troponin T: A rise and/or fall in the absolute troponin level of ≥ 2.5 ng/L/hour (i.e. a change of ≥ 15 ng/L in 6 hours) between any troponin results before randomization OR a relative change in troponin $\geq 20\%$ between earlier and later samples (i.e. $100 * (\text{hs-TnT}[\text{later}] - \text{hs-TnT}[\text{earlier}]) / \text{hs-TnT}[\text{earlier}] \geq 20\%$) documented on any troponin results before randomization. (12,13)

Hs-Troponin I: An absolute elevation of ≥ 10 times the upper limit of normal specific for that assay using gender-specific cut-points (i.e. Abbott Architect : ≥ 160 ng/L for females and ≥ 260 ng/L for males); OR change in troponin $\geq 20\%$ between earlier and later samples (i.e. $100 * (\text{hs-TnI}[\text{later}] - \text{hs-TnI}[\text{earlier}]) / \text{hs-TnI}[\text{earlier}] \geq 20\%$) documented on any troponin results before randomization. (14)

2) Troponin Pattern 2 (Chronic Myocardial Injury): A stable elevation in the troponin requires at least 2 samples and defined as:

- a) Hs-Troponin T: A rise and/or fall in the absolute troponin level of < 2.5 ng/L/hour (i.e. a changed of < 15 ng/L in 6 hours) between all available troponin results prior to randomization; AND, a relative change in troponin $< 20\%$ between earlier and later samples (i.e. $100 * (\text{hs-Tn}[\text{later}] - \text{hs-Tn}[\text{earlier}]) / \text{hs-Tn}[\text{earlier}] < 20\%$) between all available troponin results prior to randomization with at least 2 troponin samples taken at least 3 hours apart.
- b) Hs-Troponin I: An absolute elevation of < 10 times the upper limit of normal specific for that assay using gender specific cut-points (i.e. Abbott Architect :

<160ng/L for females and <260ng/L for males); AND a relative change in troponin <20% between earlier and later samples (i.e. $100 * (\text{hs-TnI}[\text{later}] - \text{hs-TnI}[\text{earlier}]) / \text{hs-TnI}[\text{earlier}] < 20\%$) any troponin results before randomization with at least 2 troponin samples taken at least 3 hours apart.

All participants will have clinical symptomatology, ECGs, and all available cardiac imaging assessed to determine the presence of coronary ischaemia. This information will permit the adjudication of the enrolling diagnosis as either type 2 MI or acute myocardial injury according to the 4th Universal Definition of Myocardial Infarction.

Recognizing the potential impact of the varying underlying hazards for mortality across different primary illnesses (i.e. competing risks), each patient's specific APACHE III prognostic score for in-hospital mortality will be calculated for use in discriminating low, intermediate and high baseline risk patients. A standard risk assessment pro forma will be used to provide detailed baseline risk stratification. This will include clinical components of the APACHE III, GRACE and Thrombolysis in Myocardial Infarction (TIMI) risk score, as well as documentation of left ventricular (LV) function, preexisting chronic conditions, and pre-morbid functional capacity using a 7 point frailty index assessing ability to perform daily activities. (10,11,15,16) Haematological and biochemical assessment will include haemoglobin, white cell count (WCC), creatinine, albumin, C-reactive protein (CRP) and BNP/NT-proBNP.

Randomized management strategies

Based on baseline risk, patient randomization will occur in blocks of size 4 within predicted strata of <10%, 10-20% and >20% in-hospital mortality risk, thus enabling exploratory analysis of an interaction between the efficacy of angiography and the patient's baseline risk. Furthermore, to ensure balance between troponin pattern and local hospital preferences for invasive coronary angiogram (ICA) versus CT coronary angiogram (CTCA) anatomic investigation, patients will be block randomized by site and troponin pattern at the time of enrolment.

Consenting patients will be randomized to either:

- 1) Routine Coronary Investigation undertaken within 5 days of randomization: If invasive coronary angiography is selected as per local practice, radial or femoral access will be permitted. Revascularisation will be at the discretion of the treating team. Angiography undertaken outside the 5-day window will be considered a protocol violation, but these patients will be retained in the analysis. CTCA is an acceptable alternative to invasive angiography and may be the preferred modality in the enrolling institution. If undertaken as first line test, CTCA must be undertaken within the same time windows. (Subsequent progression to invasive angiography will be by physician discretion).
- 2) Conservative management: Functional testing may be undertaken within the 14 day post randomization period as per local clinical decision. Functional testing may be either with ECG, stress echocardiography, nuclear perfusion scanning, or stress MRI. CTCA, while not invasive, is not considered functional testing.

Management crossover between conservative/functional testing and invasive angiography

To minimize unwarranted crossover from conservative management to invasive investigation, the following criteria will be used to guide clinical decision-making regarding the use of angiographic investigation:

- 1) Ongoing symptoms of angina (Canadian Cardiovascular Society (CCS) classification II-IV); or,
- 2) The development of non-sustained or sustained ventricular tachycardia;
- 3) Development of heart failure (New York Heart Association (NYHA) II-IV); or,
- 4) Evidence of inducible ischaemia on functional testing where there is >10% of the myocardium deemed to be at risk. Patients with abnormal or equivocal functional ECG testing should subsequently undergo functional testing with additional cardiac imaging.

Data Collection and Outcome Measures

The primary outcome will be all cause mortality (survival) up to 24 months. Major secondary clinical outcomes assessed at 30 days, 12 months and 24 months are defined in table 2.

All patients will be followed to assess the frequency of diagnostic procedure(s)/service(s) at initial presentation and during follow-up (e.g. stress testing, echocardiography, invasive investigation and revascularization), inpatient costs/total length of stay (LOS), outpatient health care attendance(s) (i.e. general practitioner and specialist attendances), readmission(s), as well as the use of guideline-recommended pharmacotherapies where

indicated. At 30 days, 12 months and 24 months, patients will be contacted by telephone and assessed for vital status, rehospitalisation and quality of life (EuroQoL 5 dimensions 5 levels (EQ-5D-5L)). (17) In hospital costs will be sourced from hospital billing systems, while outpatient costs will be determined through the national Medical Benefits Schedule and Prescribing Benefits Schedule (i.e. Australia's nationalized health funding system)

Ethical Considerations and Study Governance

All patients will be asked to provide written informed consent. Primary approval has been granted by the local Clinical Human Research Ethics Committee. The Steering Committee, consisting of cardiologists, general physicians and implementation experts, will provide oversight to the study. A Clinical Event Adjudication Committee, independent of the study management team, will be providing blinded evaluation (events de-identified for treatment arm, hospital and patient details) of the primary and secondary endpoints. The study employs a Data Safety Monitoring Board (DSMB) to ensure patient safety, leveraging the existing administrative data infrastructure to facilitate event adjudication. This is an investigator-initiated study funded by the National Health and Medical Research Council of Australia (APP1146512).

Sample Size Determination

All sample size calculations assume a Type I and II error rates of 5% and 20%, respectively. Given the substantial all-cause mortality rate among these patients, design assumptions have been expressly chosen to detect a clinically relevant improvement in survival with the anatomic investigative strategy. Informing the design is the observed all-

cause mortality rate of 41% by 12 months (from SA Hospitals 2009-2011). A baseline survival rate of 70% by 2-year has been assumed and this study is designed to detect an absolute increase in survival of 7% by 2 years with the anatomic investigation strategy (i.e. a relative increase in survival within the coronary investigation arm of 10% [Hazard ratio: 0.73]) in the patients with T2MI [troponin pattern 1] which translates to a number needed to treat (NNT) of 14. Consequently, accounting for lost to follow-up rate of 3%, the study will enrol 1500 patients. The effect of early coronary investigation among patients with pattern 2 (n=300) is exploratory.

Methods of Statistical Analyses

The primary analysis population will be intention-to-treat including all patients randomised to the study and reported according to CONSORT guidelines. Missing data will be imputed using multiple imputations, redrawing 20 samples. Sensitivity analyses will also be conducted per-protocol (i.e. primary comparison included only those patients receiving their randomized allocation).

The primary analysis will compare the survival time (freedom from the primary endpoint of all-cause mortality) between the routine coronary anatomical and conservative/functional testing arms using log-rank testing within the population randomised within the Troponin Pattern 1 criteria (i.e. Troponin pattern 1 intention-to-treat (ITT) population [target N=1500]). Major secondary analyses will evaluate the study arms with respect to survival time free from the primary endpoint: within the entire population (I.e. Troponin patterns 1 and 2 ITT population [target N=1800]); the Troponin pattern 2 ITT population; and the

interaction between the enrolling troponin pattern and the study arms. These analyses will also be undertaken evaluating the endpoint of two-year freedom from mortality and recurrent cardiovascular events by survival analysis using shared frailty models to account for correlated event rates within hospitals. An exploratory subgroup analysis based on initial coronary investigation (i.e. CTCA versus ICA) will also be undertaken.

An economic evaluation comparing mean outcomes and incremental costs of invasive angiography to those for conservative management will be conducted. This evaluation will take the form of a cost-utility analysis with the primary outcome expressed as incremental costs per quality adjusted life year (QALY) gained over 24 months. To calculate QALYs, patient level measures of utility derived from the EQ-5D 5L instrument will be integrated with survival curves using the quality-adjusted survival analysis (QASA) method. (18)

Incremental costs associated with both trial arms will be estimated using patient data obtained from the Medical Benefits Scheme (MBS), Pharmaceutical Benefits Scheme (PBS) and Australian Refined Diagnosis Related Group (AR-DRG) cost weights.

Bootstrapped mean costs and outcomes between the intervention and control groups will be compared, and incremental cost effectiveness ratios (ICERs) presented with confidence intervals. Uncertainty in the economic evaluation results will be taken account of through appropriate one-way and multi-way sensitivity analyses.

Discussion

To optimally evaluate the unbiased impact of routine assessment of coronary anatomy on clinical care and outcomes in T2MI, a prospective randomised comparison is required as

observational designs with inadequate correction of selection bias often have a strong impact on outcomes. Prospective randomization and blinded event adjudication provides the most practical and least biased estimate and strategy effect. The endpoint of all-cause mortality has been chosen as it is considered most patient-relevant when weighing both cardiac and non-cardiac risks. Standardized evaluation of the pre-test probability of non-coronary risk through the APACHE III score will inform the clinical translation of these results within the routine care of patients with greatly varied risk. Independent and blinded adjudication of the admission (index) diagnosis and clinical events will provide a robust evaluation of the clinical relevance of routine coronary investigation for myocardial injury and type 2 MI.

Previous research demonstrates that mortality among patients with T2MI often occurs early following the index event, akin to T1MI, but with a constant and elevated recurrent MI risk over time in contrast to decreasing rates of recurrent MI within weeks to months after the index event in T1MI. This pattern would be consistent with a “non-plaque rupture” mechanism. (5) Data from the SWEDEHEART registry (n=20,138) corroborates the substantial increase in mortality within this population. Compared with T1MI, T2MI was also associated with much lower rates of ICA (35.9% vs. 77.3%, $p<0.001$), anti-platelet therapy and secondary prevention pharmacologies, and a crude increased hazard for mortality (HR:1.86 [95% C.I. 1.66 to 2.08]) by 12 months. (6) Importantly, after adjusting for baseline differences in clinical characteristics and in-hospital management, there was no longer any difference in 12-month all-cause mortality (HR: 1.03 [95% C.I. 0.86 to 1.23]) between T2MI and T1MI. This observation suggests the potential value of applying established CAD management, specifically ICA/CTCA, in the high-risk/high competing

risk T2MI population. The value of routine invasive management among patients with competing non-cardiac risks however remains unclear. Figure 3 describes the interaction between the patient risk profile and diagnostic clarity (with implications for the provision of evidence based therapies) across the spectrum of possible manifestations of coronary artery disease.

Within this paradigm, patients presenting with myocardial injury and T2MI represent the “last unexplored area” in discovering the impact of a first-line coronary anatomic investigative strategy. Whether competing risks from non-cardiac conditions obscure the benefits of invasive management, and at what level of competing risk this occurs, remains a commonplace clinical dilemma. All available evidence demonstrates that patients with acute myocardial injury and type 2 MI experience a very high rate of all-cause mortality, in part related to associated non-coronary competing risks. The outcome and effect size used in the planning of this study have been selected to reflect patient relevant improvements in median survival of greater than 1 year with coronary anatomic investigation. Arguments for the routine use of angiography include: 1. Clarification of diagnosis through identification of unrecognized T1MI (plaque rupture) versus fixed coronary obstructions versus no coronary obstruction and; 2. Documentation of coronary pathology as a focus for revascularization and pharmacological therapy which have provided benefits in other acute presentations of coronary artery disease. (3,19) Arguments against the early anatomical investigation include: 1. The comorbidities of these patients are too great and aggressive intervention could be regarded as futile; 2. The risk of bleeding may be pronounced with the addition of heparin, aspirin and P2Y₁₂ inhibitors. 3. The time-course benefits of coronary interventions among patients with inter-current illnesses are unknown, hence any

benefit afforded by improved diagnostic precision may be overwhelmed by the impact of non-coronary competing risks. Better quantification of cardiac risk, competing risk and their interaction with the possible benefits of anatomical investigation requires more robust evidence to inform guideline recommendations and clinical practice.

Conclusion

Evolution in troponin assays has increased the complexity of the clinical estimation of coronary risk. The efficacy of anatomical coronary investigation among T2MI patients with high competing risks has not been adequately investigated and remains a point of substantial clinical equipoise, despite the greater prevalence of these patients than T1MI. Prospectively incorporating risk assessment into the decision algorithm will assist the translation of current therapies into effective outcomes and inform a large evidence-gap in national and international MI guidelines.

Table and Figure Legends

Table 1: Patient inclusion and exclusion criteria

Table 2: Study Outcomes Definitions

Figure 1: Contrasting cardiac and non-cardiac outcomes between Type 2 and Type 1 MI.

Figure 2: Study Schematic.

Footnote: APACHE: Acute Physiology, Age and Chronic Health Evaluation, GRACE: Global Registry for Acute Coronary Events: WCC: White Cell Count, CRP: C-reactive protein, BNP: Brain Natriuretic Peptide, Mx: management

Figure 3: Summary of diagnostic uncertainty, cardiac risk, competing risk and evidence of benefit with anatomic investigation and management of coronary artery disease.

Footnote: STE: ST Segment Elevation, NSTEMI: non-ST Segment Elevation. PROMISE: PROspective Multicenter Imaging Study for Evaluation of chest pain, SCOT-HEART: Scottish Computed Tomography of the HEART, COURAGE: Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluations

Acknowledgements and Disclosures

The authors are solely responsible for the design and conduct of this study including study analyses, drafting, editing and approval of the paper and its final contents. Support for this study was granted from National Health and Medical Research Council of Australia (APP1146512).

Conflicts of Interest: None

ACCEPTED MANUSCRIPT

References

1. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. 2018; 00:1-33. doi.org/10.1093/eurheartj/ehy462.
2. Hoenig MR ACSI. Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era (Review). 2014 Jan 1;:1–62.
3. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *European Heart Journal*. 2016 Jan 14;37(3):267–315.
4. Chew DP, Scott IA, Cullen L, French JK, Briffa TG, Tideman PA, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of acute coronary syndromes 2016. *Med J Aust*. 2016 Aug 1;205(3):128–33.
5. Chew DP, Briffa TG, Alhammad NJ, Horsfall M, Zhou J, Lou PW, et al. High sensitivity-troponin elevation secondary to non-coronary diagnoses and death and recurrent myocardial infarction: An examination against criteria of causality. *European Heart Journal: Acute Cardiovascular Care*. 2014 Dec 11.
6. Baron T, Hambraeus K, Sundström J, Erlinge D, Jernberg T, Lindahl B, et al. Type 2 myocardial infarction in clinical practice. *Heart*. 2015 Jan;101(2):101–6.
7. Sandoval Y, Smith SW, Thordsen SE, Apple FS. Supply/demand type 2 myocardial infarction: should we be paying more attention? *J Am Coll Cardiol*. 2014 May 27;63(20):2079–87.
8. McCarthy CP, Vaduganathan M, Januzzi JL Jr. Type 2 Myocardial Infarction—Diagnosis, Prognosis, and Treatment. *JAMA*. 2018 Jun 11;:1–2.
9. Alpert JS, Thygesen KA, White HD, Jaffe AS. Diagnostic and therapeutic implications of type 2 myocardial infarction: review and commentary. *Am J Med*. 2014 Feb;127(2):105–8.
10. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, de Werf Van F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006 Nov 25;333(7578):1091–1.
11. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest*. 1991 Dec;100(6):1619–36.
12. Chuang A, Hancock DG, Horsfall M, Alhammad NJ, Zhou J, Cullen L, et al. The predictive value of high sensitivity-troponin velocity within the first 6h of presentation

for cardiac outcomes regardless of acute coronary syndrome diagnosis. *Int J Cardiol.* Elsevier Ireland Ltd; 2016 Feb 1;204(C):106–11.

13. Giannitsis E, Becker M, Kurz K, Hess G, Zdunek D, Katus HA. High-sensitivity cardiac troponin T for early prediction of evolving non-ST-segment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin results on admission. *Clin Chem. Clinical Chemistry*; 2010 Apr;56(4):642–50.
14. Tan J, Lam C, Kasim SS, Aw TC, Heart JA, 2017. Asia-Pacific consensus statement on the optimal use of high-sensitivity troponin assays in acute coronary syndromes diagnosis: focus on hs-TnI. *heartasiabmj.com*
15. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA.* 2000 Aug 16;284(7):835–42.
16. Rockwood K, Song X, MacKnight C, Bergman H, Hogan D, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ.* 2005 Aug 1;173(5):489–95.
17. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res.* 2011 Dec;20(10):1727–36.
18. Glasziou P, Simes R, Gelber R. Quality adjusted survival analysis. *Stat Med.* 1990 Nov 1;9(11):1259–76.
19. Chew DP, Scott IA, Cullen L, French JK, Briffa TG, Tideman PA, et al. National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016. *Heart Lung Circ. Elsevier*; 2016 Sep;25(9):895–951.
20. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. 2011. pp. 2736–47.
21. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med.* 2015 Apr 2;372(14):1291–300.
22. Williams MC, Hunter A, Shah ASV, Assi V, Lewis S, Smith J, et al. Use of Coronary Computed Tomographic Angiography to Guide Management of Patients With Coronary Disease. *J Am Coll Cardiol.* 2016 Apr 19;67(15):1759–68.
23. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med.* 2007 Apr 12;356(15):1503–16.

Table 1: Patient Selection Criteria

Patient Inclusion Criteria	<p>The study will enrol in-hospital patients with at least one elevated (“rule-in”) troponin result using the local laboratory standards (Troponin T or I, with test sensitivity as implemented locally) defined as either (also see troponin pattern section):</p> <ol style="list-style-type: none"> i. Troponin T (Roche Elecsys): >52ng/L ii. Troponin I (Abbott Architect, Dimension Vista, Beckman Access): ≥ 5 times the assay-specific upper limit of normal <p>and:</p> <ol style="list-style-type: none"> a) A clinical presentation consistent with an acute clear non-coronary alternative diagnosis (see section below) <u>N.B.: In all cases medical stabilization of patient prior to angiography will be required.</u> b) Patient is 18 years of age or older; and c) Patient is willing to give his/her written informed consent; <p>Documentation of “acute non-coronary” presentation: For trial eligibility, all patients must have an unequivocal intercurrent diagnosis. Specifically:</p> <ol style="list-style-type: none"> d) Sepsis: Clinical evidence of a fever and/or a raised white cell count plus an elevation in C-reactive protein above the local laboratories reference limit and: <ol style="list-style-type: none"> a. Pneumonia: Cough, shortness of breath, positive sputum culture and radiological changes consistent with pneumonia on chest imaging b. Urosepsis: frequency, urgency or dysuria, with leukocytes in urinalysis and positive urine microscopy and culture c. Septicaemia: systemic symptoms of fevers, chills or sweats, and positive blood cultures thought not to be a contaminant. d. Systemic Inflammatory Response Syndrome (SIRS): With 3 or more of: <ol style="list-style-type: none"> i. Temperature, <36 °C (96.8 °F) or >38 °C (100.4 °F) ii. Heart rate, >90 beats/min iii. Respiratory rate, >20/min or PaCO₂<32 mmHg iv. While bleed cell count, <4x10⁹/L, >12x10⁹/L, or 10% bands e) Anaemia: haemoglobin <10mg/dL on at least 2 samples within 48 hours f) Thyrotoxicosis: TSH below the lower limit of normal g) Atrial tachycardias: evidence of sustained narrow complex tachycardia (Atrial fibrillation, atrial flutter, SVT) >120bpm for >20 min, documented on ECG monitoring (i.e. documentation of rate but not total duration of
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	<p>tachycardia).</p> <ul style="list-style-type: none"> h) Respiratory failure with an arterial oxygen tension <8 kPa (<60mmHg) and clinical signs of respiratory failure lasting >20 min. i) Arterial hypertension with a systolic blood pressure >160 mm Hg with or without concomitant left ventricular hypertrophy identified by echocardiography or electrocardiogram. j) Recent non-cardiac surgery, defined as surgical procedure requiring regional and general anaesthesia within 7 days prior to enrolment k) Traumatic fractured neck of femur demonstrated on x-ray, within the prior 7 days l) Acute kidney injury requiring dialysis or causing severe renal impairment (creatinine >150mmol/L) patients where dialysis remains a therapeutic consideration.
Patient Exclusion Criteria	<ul style="list-style-type: none"> a. Patients with clinically-defined TIMI: i.e. a rise and/or fall in troponin with at least 1 result above the 99th percentile of normal, with/without ECG changes consistent with ischaemia, and NO evidence of intercurrent illness. b. Patients with ST-segment elevation on the presenting ECG or new LBBB c. Haemodynamic instability including hypotension (Systolic BP<90mmHg, or requiring inotrope support), acute kidney injury where creatinine levels are not stable d. Patients with a prior angiogram within the last 6 months, regardless of the presence or absence of documented coronary artery disease on that investigation. e. New York Heart Association Class II-IV heart failure or Killip Class II-IV f. Symptomatic angina with a Canadian Cardiovascular Society class II or more classification g. Extensive frailty or co-morbidity in whom the treating physicians are unwilling to undertake a coronary angiogram (e.g. severe renal impairment in a patient unwilling to consider dialysis), or where life-expectancy is expected to be less than 2 years.

Table 2: Study Outcomes Definitions

Definitions	
All-cause mortality	Death from any cause
CV Mortality	CV death will be defined as any death resulting from acute myocardial infarction (MI), cardiogenic shock, cardiac arrhythmia/sudden cardiac death, heart failure/acute pulmonary oedema, stroke, CV procedures, CV hemorrhage, and any other CV causes which are documented as an antecedent cause of death on the death certificate.
New/Recurrent MI*	<p>Acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following;</p> <ul style="list-style-type: none"> ○ Symptoms of myocardial ischaemia; ○ New ischaemic ECG changes; ○ Development of pathological Q waves; ○ Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology; ○ Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs). <p>Post mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium (meets type 1 MI criteria).</p> <p>Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis (meets type 2 MI criteria).</p> <p>Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal (meets type 3 MI criteria).</p> <p><u>MI: In patients whom troponin is elevated and stable (<20% variation)</u></p> <p>If troponin values are stable or falling, then myocardial infarction diagnosis requires a $\geq 20\%$ increase (and $>$ URL) in troponin between the last sample recorded prior to randomisation and a further sample taken 3-6 hours later</p> <p><u>MI: In patients whose troponin is still rising</u></p>

	<p>If troponin values continue to rise after randomisation, there must be evidence of a $\geq 20\%$ increase between the last sample recorded prior to randomisation AND documentation of one of the following:</p> <ul style="list-style-type: none"> ○ New ischaemic ECG changes ○ Angiographic findings of a coronary thrombus <p><u>MI following PCI</u></p> <p>An MI after PCI will be defined as:</p> <ul style="list-style-type: none"> • Elevation of cTn values ($>5X$ 99th percentile URL) in patients with normal baseline values (≤ 99th percentile URL) or a $>5X$ increase in cTn values and a change of $\geq 20\%$ if the baseline values are elevated and are stable ($\leq 20\%$ variation) or falling. In addition to at least one of the following: <ul style="list-style-type: none"> ○ New ischemic ECG changes; ○ Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischemic etiology; ○ Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization. <p><u>MI following CABG</u></p> <p>In participants undergoing CABG, diagnosis of MI will require:</p> <ul style="list-style-type: none"> • Elevation of cTn ($>10X$ 99th percentile URL) in patients with normal baseline cTn values (≤ 99th percentile URL) or a $>10X$ increase in cTn values and a change of $>20\%$ if the baseline values are elevated and are stable ($\leq 20\%$ variation) or falling. In addition to at least one of the following: <ul style="list-style-type: none"> ○ Development of pathological Q waves; ○ Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization; ○ Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischemic etiology;
Unstable Angina	<p>Ischemic discomfort (angina, or symptoms thought to be equivalent) ≥ 10 minutes in duration occurring:</p> <ul style="list-style-type: none"> • At rest, or • In an accelerating pattern with frequent episodes associated with progressively decreased exercise

	<p>capacity</p> <p>AND</p> <p>Prompting an unscheduled hospitalization within 24 hours of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24 hour stay (or a change in calendar date if the hospital admission or discharge times are not available).</p> <p>AND</p> <p>At least one of the following:</p> <p>a. New or worsening ST or T wave changes on resting ECG (in the absence of cofounders, such as LBBB or LVH)</p> <p style="padding-left: 20px;">i. Transient ST elevation (duration <20 minutes) New ST elevation at the J point in two contiguous leads with the cut-point: $\geq 0.1\text{mV}$</p> <p style="padding-left: 40px;">in all leads other than leads V2-V3 where the following cut-points apply:</p> <p style="padding-left: 60px;">$\geq 0.2\text{mV}$ in men ≥ 40 years ($\geq 0.25\text{mV}$ in men <40 years) or</p> <p style="padding-left: 60px;">$\geq 0.15\text{mV}$ in women</p> <p style="padding-left: 20px;">ii. ST depression and T-wave changes New horizontal or down-sloping ST depression $\geq 0.05\text{mV}$ in two continuous leads with prominent R wave or R/S ratio >1.</p> <p style="padding-left: 40px;">The above ECF criteria illustrate patterns consistent with myocardial ischemia. It is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.</p> <p>b. Definite evidence of inducible myocardial ischemia as demonstrated by:</p> <p style="padding-left: 20px;">i. An early positive exercise stress test, defined as ST elevation or $\geq 2\text{mm}$ ST depression prior to 5 mets</p>
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	<p style="text-align: center;">OR</p> <ul style="list-style-type: none"> ii. Stress echocardiography (reversible wall motion abnormality) OR iii. Myocardial scintigraphy (reversible perfusion defect), OR iv. MRI (myocardial perfusion deficit under pharmacologic stress) v. AND believed to be responsible for the myocardial ischemic symptoms/signs <p>c. Angiographic evidence of new or worse $\geq 70\%$ lesion ($\geq 50\%$ for left main lesion) and/or thrombus in an epicardial coronary artery that is believe to be responsible for the myocardial ischemic symptoms/signs.</p> <p>d. Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent transfer to another institution without interceding home discharge.</p> <p>AND</p> <p>Negative cardiac troponin and no evidence of acute MI</p>
Unplanned hospital admission	Non-elective coronary revascularization; cerebrovascular accidents; atrial or ventricular arrhythmias; congestive cardiac failure without MI; as documented by a hospital discharge summary at 30 days, 12 months and 24 months.
Bleeding	<p>TIMI Major/minor/minimal bleed:</p> <ul style="list-style-type: none"> • Major: Overt clinical bleeding (or documented intracranial or retroperitoneal hemorrhage) associated with a drop in hemoglobin of greater than 5g/dl (50g/l) or a hematocrit of greater than 15% (absolute). • Minor: overt clinical bleeding associated with a fall in hemoglobin of 3g/dL to 5g/dL (50g/l) or a hematocrit of 9% to less than or equal to 15% (absolute). • Minimal: Any clinically overt sign of hemorrhage (including imaging) that is associated with a < 3 g/dl decrease in the hemoglobin concentration or $< 9\%$ decrease in the hematocrit <p>GUSTO Bleeding Classification</p> <ul style="list-style-type: none"> • Severe or life-threatening: Either intracranial hemorrhage or bleeding that causes hemodynamic

	<p>compromise and requires intervention</p> <ul style="list-style-type: none"> • Moderate: Bleeding that requires blood transfusion but does not result in hemodynamic compromise • Mild: Bleeding that does not meet criteria for either severe or moderate bleeding <p>ACUITY Bleeding Classification</p> <ul style="list-style-type: none"> • Intracranial or intraocular • Reduction in Hb of ≥ 4.0 g/dL without an overt source of bleeding, or of ≥ 3.0 g/dL with an overt source of bleeding • Use of any blood product transfusion • Hematoma ≥ 5cm in diameter, re-operation for bleeding, access site hemorrhage requiring intervention <p>Bleeding events will also be classified using the BARC Bleeding Classification (20)</p>
Health Economic Evaluation	<ul style="list-style-type: none"> ○ Measures of in-hospital care: stress testing, echocardiography, coronary angiography, cardiac medications at discharge consistent with guidelines ○ Health-related quality of life (EQ-5D) at 30 days, 12 and 24 months <p>Resource utilisation over 24 months: Medicare data among consenting patients using Medical Benefits Schedule (MBS), medication use from Pharmaceutical Benefits Schedule (PBS) and inpatient admissions from the AN-Diagnosis Related Group (DRG) version 6.0.</p>

* N.B. troponin elevations will undergo blinded adjudication for MI to confirm event time. All in-hospital MIs occurring during the index presentation will be excluded from the primary outcome. Adjudicated MIs will be sub-classified using the Fourth Universal definition of MI criteria(1).

Figure 1: Contrasting cardiac and non-cardiac outcomes between Type 2 and Type 1 MI. Adapted from reference ((5))

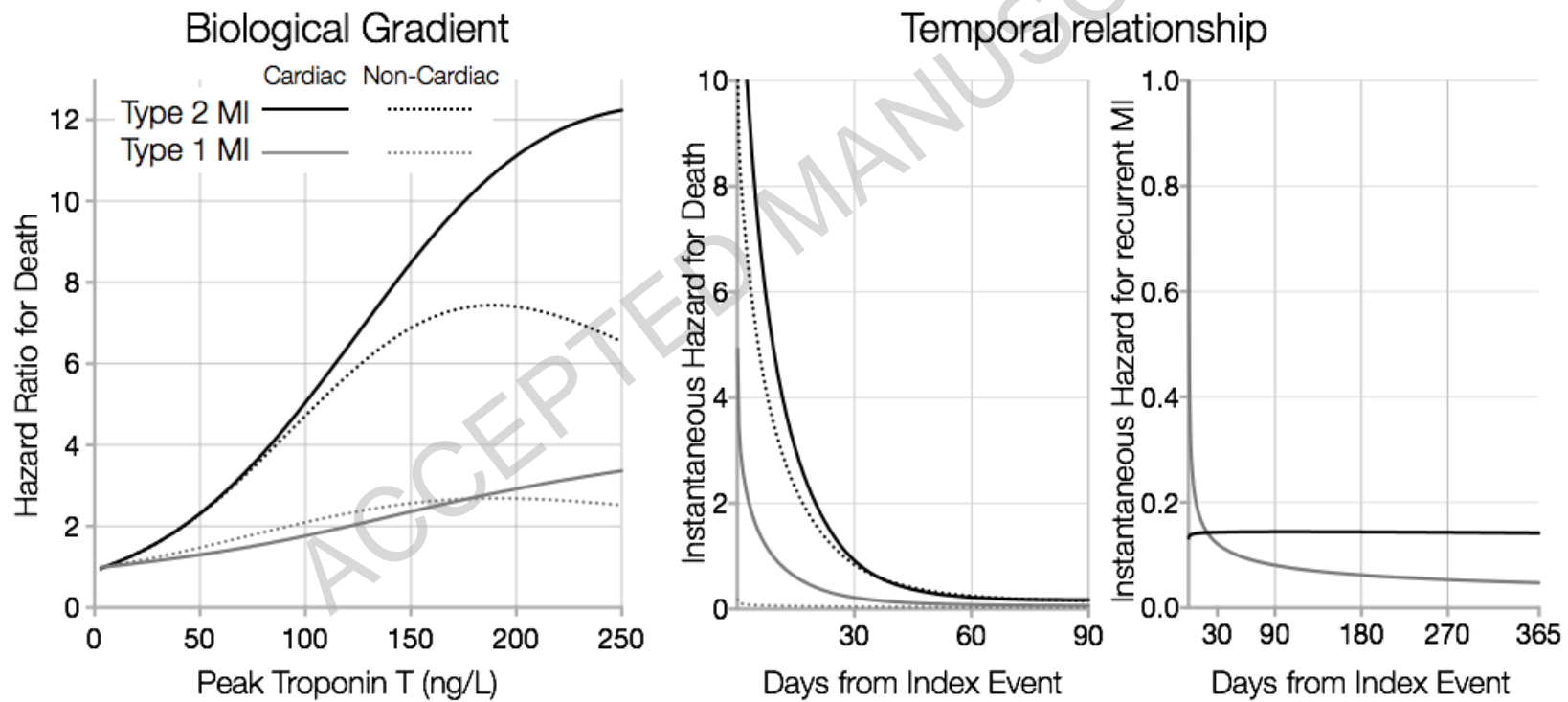


Figure 2: Study schematic

APACHE: Acute Physiology, Age and Chronic Health Evaluation, GRACE: Global Registry for Acute Coronary Events: WCC: White Cell Count, CRP: C-reactive protein, BNP: Brain Natriuretic Peptide, Mx: management

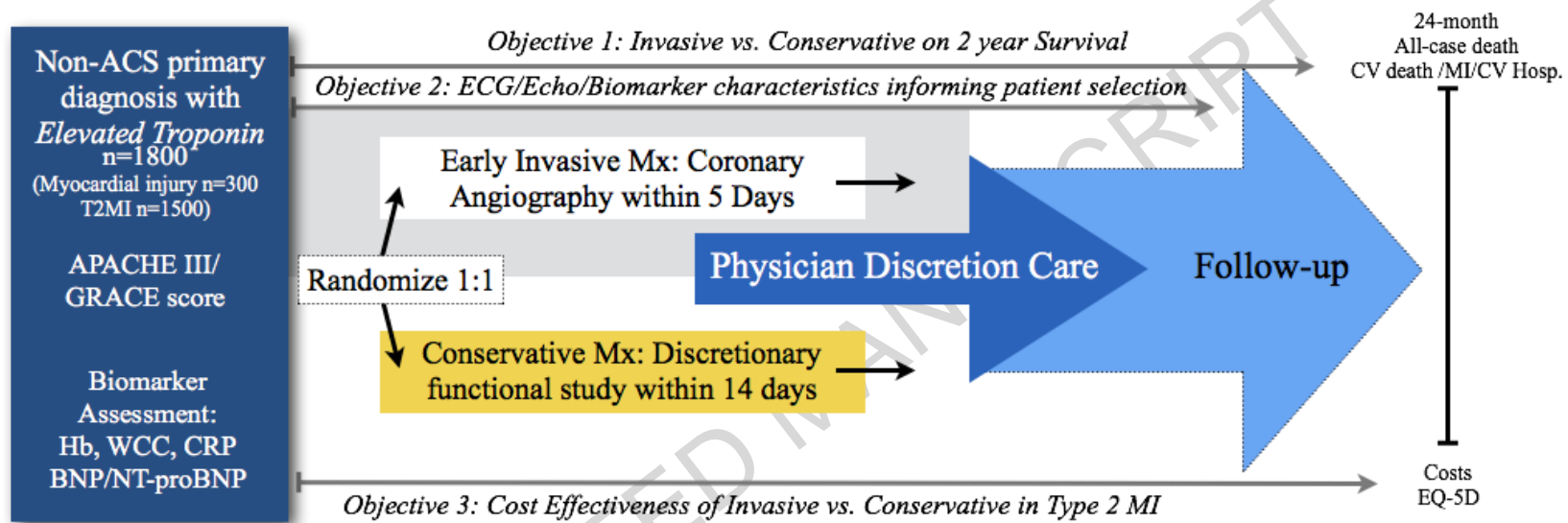
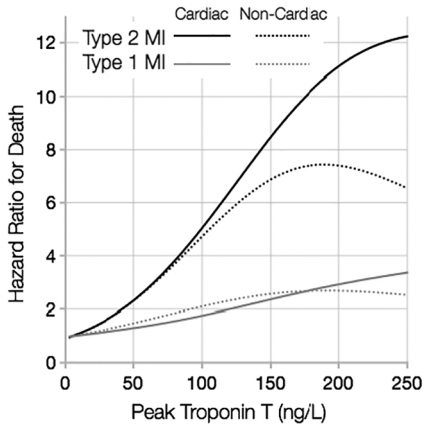


Figure 3: Summary of diagnostic uncertainty, cardiac risk, competing risk and evidence of benefit with anatomic investigation and management of coronary artery disease. (2,3,19,21-23)

ACCEPTED MANUSCRIPT

Biological Gradient



Temporal relationship

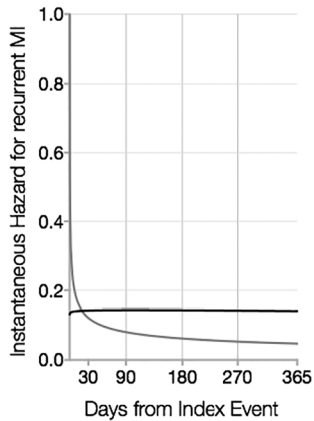
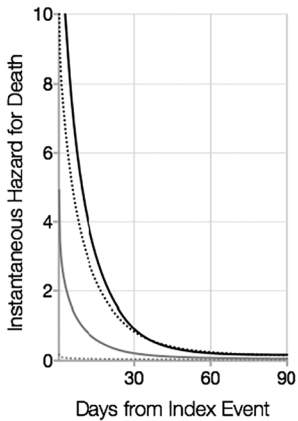


Figure 1

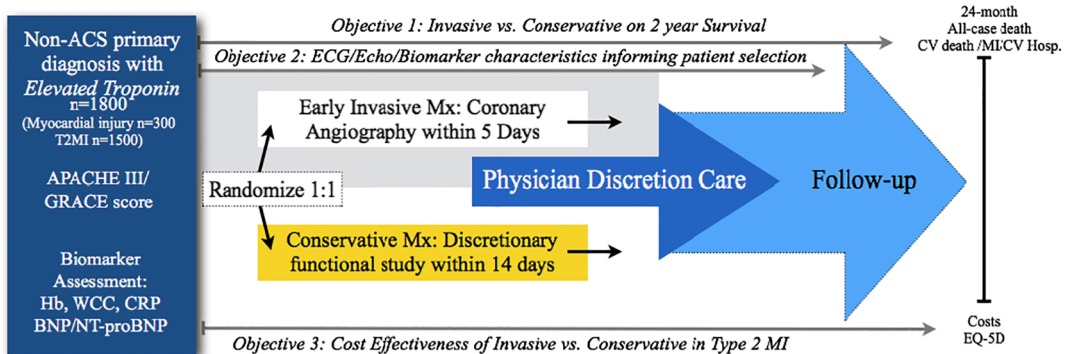


Figure 2

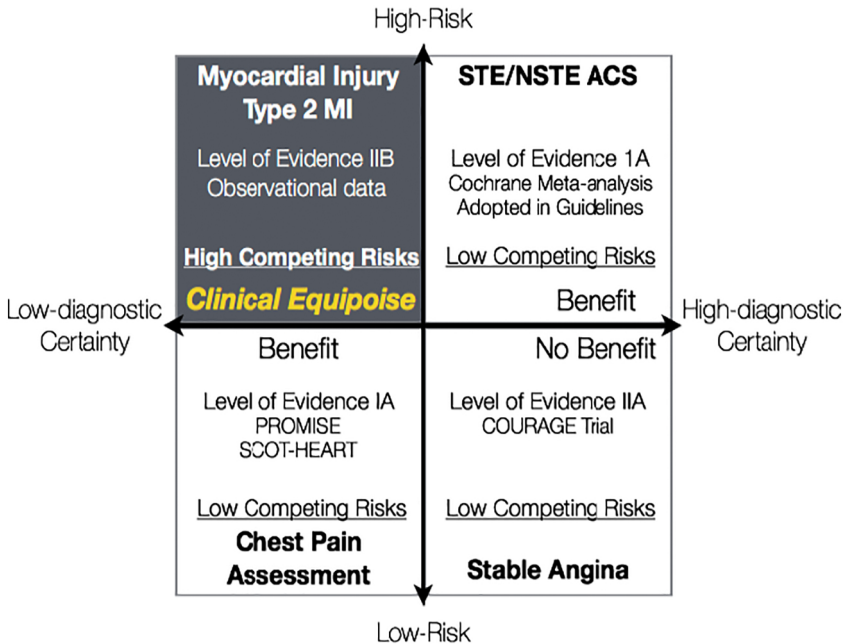


Figure 3