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A health economic assessment of diagnostic strategies using high sensitivity troponin for patients with possible acute coronary syndromes

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ABSTRACT

Objectives: To evaluate hospital-specific health economic implications of different protocols utilizing high sensitivity troponin I for assessment of patients with chest pain.

Design: A cost prediction model and an economic micro simulation were developed using a cohort recruited as part of the ASPECT Trial. This trial was a prospective observational trial conducted between 2008-2011. The model was populated with 40,000 bootstrapped samples in five high sensitivity troponin I-enabled algorithms versus usual care from a 30-day hospital perspective.

Setting: Adult Emergency Department of a tertiary referral hospital

Participants: Data were available for 938 patients who presented to the Emergency department with at least five minutes of symptoms suggestive of acute coronary syndrome. The analyses included 719 patients with complete data.

Main Outcome(s)/Measure(s): The primary outcome was total costs per correctly stratified patient. Other measures were referral to acute coronary syndrome management, and common emergency department performance measures.

Results: High sensitivity troponin I-supported algorithms increased diagnostic accuracy from 90.0% to 94.0% with an average cost reduction per patient compared to usual care of $490. Early rule-out criteria (limit of detection and the Modified 2-Hour ADAPT trial rules) avoided 7.5% of short stay unit admissions or 25% of admissions to a cardiac ward. Protocols utilizing high sensitivity troponin I alone or high sensitivity troponin I-enabled algorithms reduced length of stay by 6.2 hours and 13.6 hours respectively. Overnight stays decreased up to 43%. Results were seen for non-acute coronary syndrome patients, no difference was found for patients diagnosed with acute coronary syndrome.

Conclusions: High sensitivity troponin I algorithms are likely to be cost-effective on a hospital level compared to sensitive troponin protocols. The positive effect is conferred patients not diagnosed with acute coronary syndrome. Implementation could improve referral accuracy or facilitate safe discharge, and would provide significant benefits for the hospital.

Trial Registration: The original ADAPT trial was registered with the Australia-New Zealand Clinical trials Registry, ACTRN1261100106943.

Strengths and Limitations

- This study was based on an individual-level modeling design to allow for more realistic comparisons of different settings, assessment strategies, or risk stratification rules.
- As opposed to previous evaluations, costs and all management assumptions in this study were based on actual and individual patient information that was prospectively collected. The sampling strategy created a wide spectrum reflecting population heterogeneity and common variation in clinical practice
- Economic implications from breaching specific emergency department targets or access blocks were not taken into account but may have a significant impact; it appears likely that considering such aspects would strengthen the results in favor of accelerated protocols.

INTRODUCTION

Chest pain is a leading presenting complaint for adults seeking emergency department care,[1] with the most common serious underlying cause being acute coronary syndromes (ACS), including acute myocardial infarction and unstable angina. After detailed assessment, most patients are diagnosed with a non-cardiac cause (e.g. musculoskeletal pain or gastrointestinal causes) for their symptoms. In 2007–2008, 5.5 million people in the United States presented to emergency departments with chest pain and fewer than 15% were diagnosed with ACS.[2]

Accelerated assessment strategies for the rule-in and rule-out of acute myocardial infarction have recently been reported.[3-14] Under such strategies, a sizeable proportion of patients can be safely identified as low risk. Some protocols also accurately identify patients as high risk for acute myocardial infarction.[3-5, 15] The ADAPT and Modified ADAPT protocols utilizing sensitive and highly sensitive troponin assays support the identification of 20 and 40 % of patients respectively as low risk.

While research into novel accelerated strategies has usually reported clinical outcomes, few have assessed health economic implications of such protocols, or made comparisons to define optimum strategies. The incorporation of highly sensitive cardiac troponin I (hsTnI) assays into clinical practice may have additional health economic benefits on the hospital level; however, this aspect has not been explored to date. The aim of this study was to model strategies utilizing hsTnI alone and hsTnI within accelerated algorithms for assessment of emergency department patients with chest pain to determine the hospital-specific health economic implications compared to usual care.

METHODS

Study design and setting

This study utilized prospectively collected data from Brisbane, Australia. Participants were recruited as part of the Asia-Pacific Evaluation of Chest Pain Trial,[3] and included if they were aged 18 years or older, presented to the emergency department with at least five minutes' worth of chest pain suggestive of ACS (in accordance with American Heart Association case definitions),[16] and were being evaluated for ACS. Recruitment was performed by research staff in collaboration with the senior treating clinician. Patients were excluded if there was a clear non–ACS cause for their symptoms, they were unwilling or unable to provide informed consent, staff considered that recruitment was inappropriate, they were transferred from another hospital, were pregnant, were previously recruited to the study within the past 45 days, or were unable or unwilling to be contacted after discharge. Recruitment included consecutive eligible cases during working hours at each site. Enrolment occurred between January 2008 and November 2010. All patients were managed according to standard care, which included electrocardiogram and troponin testing on presentation and at greater than six hours after presentation to the emergency department. The clinical assay in use as the reference troponin assay was the Beckman Coulter second-generation AccuTnI (Beckman Coulter, Chaska, MN). A value above the 99th percentile of greater than 40ng/L was considered abnormal.

Original data were collected prospectively, using standardized case report forms.[17] Research nursing staff collected demographic and clinical data from patient interviews. Telephone follow-up and medical record review was conducted 30-days after initial attendance for the diagnosis of ACS. Information was obtained from the patient and from hospital databases about all additional cardiac events, investigations, or contact with any health care providers during the 30-day period. Follow-up information was verified through contact with the health care provider, and original copies of medical records and investigations were obtained. Ethical approval of the research project

HREC/14/QRBW/320 was obtained from the Royal Brisbane and Women's Hospital Human Research Ethics Committee (EC 00172) on 11th August, 2014.

All patients provided written informed consent for data collection and the ethics committee waived the requirement for consent for this analysis.

Each patient was assigned an endpoint occurring on presentation or within 30 days of admission. The ACS endpoint included cardiovascular death, cardiac arrest, revascularization procedure, cardiogenic shock, acute myocardial infarction, and unstable angina pectoris. Local cardiologists adjudicated the outcome independently using predefined standardized reporting guidelines. Cardiologists had knowledge of the clinical record, electrocardiogram and troponin results from standard care. A second cardiologist conducted a blind review of all ACS cases and 10% of non–ACS cases. In cases of disagreement, endpoints were agreed on by consensus. This was achieved for all endpoints.

In addition to sampling for routine clinical care, blood was drawn on presentation and two hours later. Samples were later tested with the ARCHITECT High Sensitive *STAT* Troponin-I assay (Abbott Laboratories, Abbott Park, IL). Laboratory technicians were blinded to patient data. The hsTnI assay has a 99th percentile concentration of 26.2ng/L with a corresponding co-efficient of variation of <5% and a limit of detection of 1.2ng/L.[18] Long-term stability of TnI has been demonstrated previously.[19]

Cost prediction model

As described previously,[20] individual cost data were extracted from hospital administration records and adjusted for inflation to 2011 Australian Dollars. To use a consistent cost matrix across all strategies, a prediction model was developed. Outliers, inconsistent or missing data were excluded

from the cohort. Patients with a hospital length of stay (LOS) greater than 12 days were excluded to reduce bias from long non-cardiac stays. A general Box-Cox transformed regression with data from 891 individuals (Selection criteria described in eTable 1) was used with the following predictors: emergency department time, inpatient time, performed activities (exercise stress test, myocardial perfusion scan, computed tomography coronary angiography, echocardiography, angiography), admission to short-stay unit, or admission to an inpatient ward.

Health economic model

A micro simulation cost-effectiveness model was developed with outcomes measured in terms of total hospital costs per correctly stratified patient based on the final adjudicated diagnosis (diagnostic accuracy). In addition, LOS and admission rates (emergency department, short stay unit, or inpatient unit) were evaluated. All model calculations followed a 30-day hospital perspective. Attributes (age, sex, clinical characteristics, adjudicated diagnosis, electrocardiogram status, and troponin values) from patients included for the analysis (eTable 2) were individually sampled from the cohort database by bootstrapping with 40,000 iterations.

The model compared six strategies as described in Table 1. Usual care was titled the "Standard" strategy, using sensitive cardiac troponin I (cTnI) at baseline and 6 hours. All other strategies utilized hsTnI values at 0 and 2 hour, alone (Strategy-2) or in combination with additional rule-in and rule-out rules (strategies 3 to 6). Individuals with a baseline hsTnI below the limit of detection (LoD) were ruled-out early in strategies 3, 5 and 6. Patients with hsTnI at presentation > 52ng/L were immediately admitted for ACS management in Strategy-6 (early rule-in). The Modified ADAPT accelerated diagnostic protocol (ADP) ruled-out individuals with hsTnI values below the diagnostic cut-off and a thrombolysis in myocardial infarction (TIMI) risk score ≤1.[5] This ADP rule was applied in strategies 4, 5, and 6.

Initial risk stratification was based on the first electrocardiogram and troponin taken in the emergency department. Individuals followed a standard pathway based on their assigned risk. Patients classified as high risk were admitted to inpatient cardiology. Low risk patients were kept in the emergency department to await final assessment. Intermediate-risk patients were referred to the short stay unit for further cardiac workup. Patients referred to the short stay unit or inpatient ward were classed as admitted.

If the final troponin was performed later than 6.30pm, patients stayed overnight. Total LOS comprised emergency department LOS, short stay unit LOS and inpatient stay. The maximum LOS was limited to 12 days in accordance with the assumptions made for the cost prediction model. Cost data for the index event and follow-up were predicted from the cost prediction model. We conducted one-way and probabilistic sensitivity analyses to test the robustness of the micro simulation results. Model structure, parameters and assumptions are described in detail in the supplement.

Patient Involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. Patients were asked whether they wished to receive a summary of these results. These individuals were posted a lay summary of the results.

RESULTS

Cost prediction and model validation

Characteristics of 719 patients meeting the minimum required dataset for the model and of the generated cohort of 40,000 patients are described in the supplement (eTable 5). The cost prediction

model showed excellent regression quality (R-square 88.3%; eTable 6). The model was validated for the standard strategy against actual statistics with good prediction accuracy for all patients (p-value vs. actual costs: 0.723) as well as for low-, intermediate- and high-risk patients (p= 0.761, 0.256, 0.946, respectively; Table 2).

Patient referral and management

During initial assessment, 1.3% of patients were classified as low risk and managed in the emergency department. 6.1% of patients met the criteria for an early rule-out (baseline hsTnI below the limit of detection) and were re-classified as low risk. The modified ADAPT accelerated diagnostic protocol (ADP) was effective for 49% of patients and reclassified 75% of intermediate risk patients to low risk. The early rule-in criteria (baseline hsTnI >52ng/L) applied to 7.2% of patients. These patients were classified as high risk and comprised 47% of all ACS patients (eTable 7).

Strategies considering LoD avoided short stay unit admissions for 4.9% of patients (-7.5% vs. usual care, Table 3). The number of ward admissions did not change with hsTnI alone. Utilising the LoD, ADP, or a combination of both, resulted in a stepwise and significant reduction of the ward admission rate from 49.6% to 37.1% (-25%; Table 3).

A 4-hour reduction in protocol time (cTnI vs. hsTnI: Mean 6.2h (Range 5.0 – 10.0h) vs. 2.3h (1.5 - 5.0h)) resulted in earlier management decisions (eFigure 4). Consequently, strategy-2 led to 30% fewer overnight stays compared to usual care (60.3% vs. 42.0%, Table 3). Incorporating additional rule-out logics to hsTnI further streamlined patient assessment, decreasing overnight stays by up to 43%.

3.2% of patients with a negative or stable cTnI status had a positive hsTnI status indicative of an acute event (eTable 8). Conversely, 3.0% of patients had an acute sensitive TnI finding but a negative

or stable troponin status with hsTnI. In total, the number of referrals to ACS management based on an acute troponin finding did not differ if replacing cTnI with hsTnI (cTnI: 11.9%; hsTnI: 12.1%; p=0.549). Patients with negative or stable troponin conditions were admitted for ACS management if further workup such as an exercise stress test or myocardial perfusion scan led to positive findings, resulting in a referral rate of 32% (Table 3). Strategies considering the LoD or ADP criteria respectively led to 5% or 35% fewer patients referred for ACS management compared to usual care, while the appropriateness of the referral to cardiology (referral accuracy) was increasingly improved (Strategy-1 to 4: 71.8%, 72.8%, 74.1%, 84.0%; Table 3). Switching from usual care to Strategy-4 thus reduced the number of unnecessary referrals to cardiology by 35%. Additional early rule-in criteria (Strategy-6 vs. 5) did not identify more patients requiring ACS management, but allowed for earlier management in 47% of ACS patients.

Length of stay and costs

A significant reduction in LOS was observed if hsTnI replaced cTnI with a mean saving of 6.2 hours (Table 3). Applying LoD or ADP rules to hsTnI saved an additional stay of 1.0 hours and 5.4 hours respectively. LOS times for ACS patients were stable between strategies (eTable 9). However, applying hsTnI to usual care resulted in a significant reduction of LOS for non-ACS patients as illustrated in Figure 1. Substantially decreased 75th percentiles of the LOS for all strategies considering ADPs indicated a considerable streamlining effect of ADP algorithms. Details for emergency department and short stay unit times are given in the supplement (eTable 10).

Significant cost reductions compared to usual care were found with all hsTnI strategies ($133-$491, p<0.001, Table 3). This effect was caused by substantial cost reductions for non-ACS patients. No difference between strategies was observed for ACS patients (eTable 9). As stated in Table 3, costs during the index stay as well as follow-up costs decreased for all hsTnI-supported strategies compared to usual care. The consideration of ADP and LoD alone, or in combination, in addition to

hsTnI protocols resulted in further significant cost savings. Applying an early rule-in strategy (Strategy-6) to a combination of hsTnT+ADP+LoD did not result in significant overall costs benefits.

Patient outcome and cost-effectiveness

The introduction of hsTnI into usual care did not alter overall diagnostic accuracy (p=0.86, Table 3, Figure 2), but increased the number of patients referred for ACS management with a final diagnosis of non-ACS (p=0.056; False-positives in Table 4). While all hsTnI supported strategies avoided false-negative diagnosis compared to usual care, a statistically significant reduction of the false-positive rate was observed for all strategies utilizing an ADP. Applying LoD and ADP to hsTnI reduced the number of false-positives by 6% (p=0.015) and 52% (p<0.001) respectively, whereas no effect was observed on the false-negative rate (Table 4).

Protocols utilizing hsTnI, ADP, and LoD, with, or without an early rule-in criteria were found to be superior to all other strategies, providing better accuracy at lower costs (Figure 2). Switching from usual care to Strategy-6 saved around $490 per patient and increased the diagnostic accuracy from 90.0% to 94.0%.

Conducting multiple runs in a probabilistic sensitivity analysis revealed consistent benefits confirming the robustness of micro simulation results (eFigure 6; eTable 11). hsTnI demonstrated equal or better diagnostic accuracy compared to cTnI in 79% of runs, with a stable average cost saving per patient ranging from $113 to $147. The hsTnI strategy helped to manage 82.6% of individuals at lower costs compared to usual care; 10.2% or 7.1% of patients were treated at equal or higher costs, respectively.

DISCUSSION

The cost-effectiveness of incorporating hsTnI into management protocols for patients presenting to the emergency department with chest pain has received increasing attention. hsTnI has been suggested to generate substantial benefits in the emergency department. Accelerated diagnostic protocols (ADPs) have been found to reduce the average emergency department length of stay in low risk patients while health outcomes were maintained.[6, 21] To the best of our knowledge, this is the first study evaluating health economic implications of several hsTnI enabled assessment algorithms in the emergency department from a distinct hospital perspective, thus complementing previous research that followed lifetime effects from a health systems perspective.[22-26]

Complex management algorithms that are based on individual patient attributes, plus the heterogeneity of the emergency department population, require an individual-level modeling design.[27] This allows for more realistic comparisons of different settings, assessment strategies, or risk stratification rules. As opposed to other evaluations, costs and all management assumptions in this study were based on actual and individual patient information of a single trial-based cohort. The sampling strategy created a wide spectrum reflecting population heterogeneity and common variation in clinical practice.[28] The clinical picture and additional information from objective testing were also considered in the simulation. We believe that this set the foundation for a consistent evaluation of the benefits that would accrue on the hospital level from implementing hsTnI-enabled algorithms.

We developed a cost prediction model for chest pain patients presenting to emergency department, and we conducted a patient-level economic analysis for comparing different hsTnI-enabled algorithms, validated against usual care. The analysis demonstrated that the implementation of hsTnI substantially reduced LOS and costs for patients enrolled in the chest pain pathway. Such benefits occurred without reducing diagnostic accuracy. The introduction of hsTnI allows for combining additional validated algorithms that enhanced the positive effect on common emergency

department performance metrics and clinical care. Hospital-level gains accrued from switching to hsTnI supported algorithms were caused by two effects: a) a substantial time reduction effect in troponin protocol time, and b) a significantly improved stratification efficiency of hsTnI enabled LoD and ADP protocols.

The significant decrease in overnight stays resulted in downstream effects of accelerated protocols on patient management. A 4-hour reduction in protocol time led to a 6.2-hour saving in LOS. By utilizing the ADP, the timeliness of the second hsTnI result freed an additional 7.4 hours per patient. This strategy saved around 60% of overnights stays and 15% of costs compared to usual care.

In line with the definition for a high-sensitive troponin assay,[18] measurable concentrations above the LoD were found for 94% of non-ACS patients; only 6% of individuals were eligible for an early rule-out considering the LoD criteria. This was modest compared to the ADP that captured almost 50% of patients. A combined strategy of utilizing hsTnI and LoD within the ADP helped to avoid 7.5% of short stay unit admissions and 25% of unnecessary inpatient ward admissions.

In our setting, most patients were managed in the short stay unit. Therefore, the impact of tested strategies on emergency department time was modest. In hospitals where no short stay unit is available, the demonstrated savings in short stay unit time may equally accumulate in the emergency department, thus helping to achieve time-based emergency department performance targets.

The referral of patients followed strict and standardized assumptions. Deviation from recommended pathways may occur probably due to individual preferences or logistic effects such as access block.[29] Some of the potential flow issues were addressed by assuming a wide range in the initial assessment time (6–118 minutes). Given the nature of a trial-based, individual level simulation, patient specific

data were limited to the actual cohort; e.g. the impact of variation in ACS prevalence could not be tested in a sensitivity analysis.

Management data extracted from administrative databases may have some inaccuracies. Each of the 719 individuals from the cohort were run through the model on average 55 times with consistent characteristics, but varied in terms of protocol, treatment times, and LOS. The thus generated cohort of 40,000 individuals reflected heterogeneity in patient management and addressed some of the uncertainty.

Economic implications from breaching specific emergency department targets or access blocks were not taken into account but may have a significant impact. Based on the findings of this study, it appears likely that considering such aspects would strengthen the results in favor of accelerated protocols. The cost prediction did not account for different costs of troponin assays. Compared to the magnitude of the difference between sensitive TnI and hsTnI strategies this effect was regarded as negligible.

CONCLUSION

This trial based economic modeling study demonstrates that emergency department assessment strategies utilizing hsTnI are very likely to be cost-effective on a hospital level when compared to sensitive TnI protocols for patients presenting with symptoms consistent with ACS. This is mainly due to a positive effect on the majority of patients not diagnosed with ACS. In particular, hsTnI-enabled algorithms considering early rule-out criteria (LoD, ADP) are expected to improve the accuracy of both referral to inpatient wards or safe discharge as appropriate. Implementation of these protocols would provide direct benefits for the hospital in terms of reduced admission rates, avoided overnight stays, and improvements in time-based emergency department performance measures,

thereby contributing to streamlined emergency department processes, more efficient use of resources, and overall cost savings.

Data sharing

Statistical code is available from the lead author.

Contributors

All authors had full access to the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. JG, LC and WP led the clinical study design as part of the Asia-Pacific Evaluation of Chest Pain Trial (ASPECT). JG extracted the dataset required for the modeling study. PJ developed the health economic model and run the analysis. Model design and assumptions were reviewed by all authors. All authors contributed in the interpretation of results, writing the manuscript, and critically reviewing each draft of the manuscript. The final version was approved by all authors. The study was supervised by LC.

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Conflicts of interest disclosures

All authors completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. PJ is a full-time employee of Abbott Diagnostics. JG has received funding from the Queensland Emergency Medicine Research Foundation. WP has received funding from the Queensland Emergency Medicine Research Foundation, Abbott Diagnostics, Roche, Alere, and Beckmann Coulter for research on diagnostic protocols; and honoraria, travel expenses, and consultancy fees from

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Transparency Declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1. Assessment strategies evaluated in the model

No	Strategy	Troponin assay	Protocol	Diagnostic cut-off [a]	Dynamic cut-off [b]	Early rule-in [c]	Early rule-out [d]	Accelerated rule-out [e]	Reference
1	Standard	cTnI	0 / 6hrs	> 40.0	delta < 10	No	No	No	Usual care
2	hsTnI	hsTnI	0 / 2hrs	> 26.2	delta < 2	No	No	No	11, 13
3	hsTnI+LoD	hsTnI	0 / 2hrs	> 26.2	delta < 2	No	Yes	No	11, 14
4	hsTnI+ADP	hsTnI	0 / 2hrs	> 26.2	delta < 2	No	No	Yes	5, 11
5	hsTnI+LoD+ADP	hsTnI	0 / 2hrs	> 26.2	delta < 2	No	Yes	Yes	5, 11, 14
6	hsTnI+LoD+ADP +early rule in	hsTnI	0 / 2hrs	> 26.2	delta < 2	Yes	Yes	Yes	5, 11, 14, 30

All values in ng/L.

cTnI= sensitive cardiac troponin I; hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP= ADAPT accelerated diagnostic protocol; ADAPT=2-Hour Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker trial

[a] A troponin value greater than the diagnostic cut-off was considered as elevated.

[b] A delta between troponin values at different time points of less than 10ng/L (cTnI) or 2ng/L (hsTnI) was used to distinguish and rule-out a rise and/or fall in troponin associated with acute cardiac conditions.

[c] Early rule-in of individuals with a hsTnI value at baseline above 52ng/L (early rule in).

[d] Early rule-out of individuals with a hsTnI value at baseline below the limit of detection of 1.2 ng/L (LoD).

[e] Referring to the Modified ADAPT accelerated diagnostic protocol (ADP). Accelerated rule-out applied to individuals with hsTnI values at 0 and 2h below the diagnostic cut-off and a TIMI risk score ≤1.

Table 2. Comparison of cost data and model validation.

Total costs, $	Item	Cullen 2015 [7]	Study cohort[a]	Model prediction[b]	Prediction vs. Cohort (p-value)
All	n (%)	926 (100%)	719 (100%)	719 (100%)	
	Mean cost (95%CI)	5272 (4835 - 5708)	5303 (4796 - 5810)	5437 (4897 - 5977)	0.72
	Median cost (25th-75th percentile)	2433 (1458 - 6778)	2497 (1449 - 6663)	2169 (1747 - 6384)	
Low Risk	n (%)	9 (1.0%)	9 (1.3%)	9 (1.3%)	
	Mean cost (95%CI)	2040 (1306 - 2774)	2040 (1125 - 2955)	2010 (1559 - 2460)	0.76
	Median cost (25th-75th percentile)	1530 (1298 - 3050)	1530 (1080 - 3359)	1907 (1569 - 2438)	
Intermediate Risk	n (%)	580 (62.6%)	468 (65.1%)	468 (65.1%)	
	Mean cost (95%CI)	3304 (2963 - 3644)	3413 (3050 - 3775)	3755 (3288 - 4223)	0.26
	Median cost (25th-75th percentile)	1849 (1376 - 3570)	1925 (1389 - 3628)	1946 (1668 - 3270)	
High Risk	n (%)	329 (35.5%)	242 (33.7%)	242 (33.7%)	
	Mean cost (95%CI)	8919 (7971 - 9867)	9081 (7878 - 10284)	8816 (7593 - 10040)	0.95
	Median cost (25th-75th percentile)	6452 (2650 - 11829)	6405 (2752 - 11309)	5566 (2355 - 11130)	

All costs referred to inflated costs in Australian dollars.

CI=confidence interval

a Excluded individuals not meeting the minimum required dataset for the model

b Excluded individuals with cost-outliers, missing and inconsistent data.

Table 3. Main model outcomes of different troponin supported assessment strategies

Indicator		Strategy 1 (Standard)	Strategy 2 (hsTnI)	Strategy 3 (hsTnI+LoD)	Strategy 4 (hsTnI+ADP)	Strategy 5 (hsTnI+LoD+ADP)	Strategy 6 (hsTnI+LoD+ADP+ early rule in)
Short stay unit admissions[a], %	Mean (95% CI)	65.3 (64.8 - 65.7)	65.3 (64.8 - 65.7)	60.4 (59.9 - 60.8)	65.3 (64.8 - 65.7)	60.4 (59.9 - 60.8)	60.4 (59.9 - 60.8)
	Incremental[b] (p-value)		0.0 (1.00)	-4.9 (<0.001)	4.9 (<0.001)	-4.9 (<0.001)	0.0 (1.00)
Ward admissions[a], %	Mean (95% CI)	49.7 (49.2 - 50.2)	49.6 (49.1 - 50.1)	47.4 (46.9 - 47.9)	38.4 (37.9 - 38.9)	37.1 (36.6 - 37.6)	37.1 (36.6 - 37.6)
	Incremental[b] (p-value)		-0.1 (0.81)	-2.3 (<0.001)	-9.0 (<0.001)	-1.3 (<0.001)	0.0 (1.00)
Overnight stays, %	Mean (95% CI)	60.3 (59.8 - 60.8)	42.0 (41.5 - 42.5)	39.8 (39.3 - 40.3)	24.4 (24.0 - 24.8)	23.9 (23.5 - 24.3)	24.1 (23.7 - 24.5)
	Incremental[b] (p-value)		-18.3 (<0.001)	-2.2 (<0.001)	-15.4 (<0.001)	-0.5 (0.08)	0.2 (0.51)
Referral to ACS management, %	Mean (95% CI)	32.4 (32.0 - 32.9)	32.2 (31.8 - 32.7)	30.9 (30.5 - 31.4)	21.0 (20.6 - 21.4)	20.7 (20.3 - 21.1)	20.9 (20.5 - 21.3)
	Incremental[b] (p-value)		-0.2 (0.56)	-1.3 (<0.001)	-9.9 (<0.001)	-0.3 (0.26)	0.3 (0.37)
Referral Accuracy, %	Mean (95% CI)	71.8 (71.4 - 72.2)	72.8 (72.3 - 73.2)	74.1 (73.6 - 74.5)	84.0 (83.6 - 84.3)	84.3 (83.9 - 84.6)	84.5 (84.2 - 84.9)
	Incremental[b] (p-value)		1.0 (0.004)	1.3 (<0.001)	9.9 (<0.001)	0.3 (0.001)	0.3 (0.35)
Length of stay, hours	Mean (95% CI)	34.0 (33.6 - 34.4)	27.8 (27.4 - 28.2)	26.8 (26.4 - 27.3)	20.4 (20.0 - 20.9)	20.1 (19.6 - 20.5)	20.4 (19.9 - 20.8)
	Incremental[b] (p-value)		-6.2 (<0.001)	-1.0 (0.002)	-6.4 (<0.001)	-0.4 (0.23)	0.3 (0.33)
Diagnostic accuracy (E), %	Mean (95% CI)	90.0 (89.7 - 90.3)	90.0 (89.7 - 90.3)	90.5 (90.2 - 90.8)	93.6 (93.4 - 93.8)	93.7 (93.5 - 93.9)	94 (93.7 - 94.2)
	Incremental[b] (p-value)		0.0 (0.86)	0.4 (0.04)	3.1 (<0.001)	0.1 (0.54)	0.3 (0.13)
Index costs per patient, $	Mean (95% CI)	3029 (3001 - 3058)	2923 (2894 - 2952)	2846 (2816 - 2875)	2621 (2592 - 2649)	2568 (2539 - 2596)	2582 (2553 - 2610)
	Incremental[b] (p-value)		-106 (<0.001)	-77 (<0.001)	-225 (<0.001)	-53 (0.01)	14 (0.51)
Follow-Up costs per patient, $	Mean (95% CI)	238 (225 - 250)	211 (199 - 223)	211 (199 - 223)	213 (201 - 225)	213 (201 - 225)	195 (183 - 206)
	Incremental[b] (p-value)		-26 (0.003)	0 (1.00)	2 (0.82)	0 (1.00)	-18 (0.03)
Total costs per patient (C), $	Mean (95% CI)	3267 (3236 - 3297)	3134 (3103 - 3165)	3057 (3026 - 3088)	2834 (2804 - 2864)	2781 (2751 - 2811)	2776 (2746 - 2807)
	Incremental[b] (p-value)		-133 (<0.001)	-77 (0.001)	-223 (<0.001)	-53 (0.02)	-5 (0.83)

hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP= ADAPT accelerated diagnostic protocol; ACS=acute coronary syndrome

All stated costs are in Australian dollars. (E) and (C) used as main measures of outcome.

[a] Patients could be admitted to the short stay unit before being referred to inpatient ward; numbers may not sum up to 100%.

[b] Incremental values compared to next best alternative to the left.

Table 4. False-negative and false-positive diagnosis of different assessment strategies

Strategy	False positives, %			False negatives, %		
	Mean	(95% CI)	p-value	Mean	(95% CI)	p-value
(1) Standard	6.6	(6.4 - 6.9)		3.4	(3.2 - 3.6)	
(2) hsTnI	7.0	(6.7 - 7.2)	0.06[a]	3.0	(2.8 - 3.2)	0.002[a]
(3) hsTnI+LoD	6.5	(6.3 - 6.8)	0.62[a]; 0.02[b]	3.0	(2.8 - 3.2)	0.002[a]; 1.00[b]
(4) hsTnI+ ADP	3.4	(3.2 - 3.5)	<0.001[a,b]	3.0	(2.9 - 3.2)	0.005[a]; 0.84[b]
(5) hsTnI+LoD+ADP	3.3	(3.1 - 3.4)	<0.001[a,b]	3.0	(2.9 - 3.2)	0.005[a]; 0.84[b]
(6) hsTnI+LoD+ADP+early rule in	3.3	(3.1 - 3.4)	<0.001[a,b]	2.8	(2.6 - 2.9)	<0.001[a]; 0.05[b]

False positives: Number of patients admitted for ACS management with a 30-days final diagnosis of non-ACS.

False negatives: Number of patients not admitted for ACS management with a 30-days final diagnosis of ACS.

hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP= ADAPT accelerated diagnostic protocol; ACS=acute coronary syndrome

[a] p-value vs. Strategy-1 (Usual care)

[b] p-value vs. Strategy-2 (hsTnI)

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Figure 1. Total LOS per strategy for patients finally diagnosed with non-ACS

Strategy code: (1) Standard, (2) hsTnI, (3) hsTnI+LoD, (4) hsTnI+ADP, (5) hsTnI+LoD+ADP, (6) hsTnI+LoD+ADP+early rule in.

LOS=Length of stay; ACS=Acute coronary syndrome; hsTnI=Highly sensitive cardiac troponin I; LoD=Limit of detection; ADP=ADAPT accelerated diagnostic protocol

Figure 2. Cost-effectiveness matrix

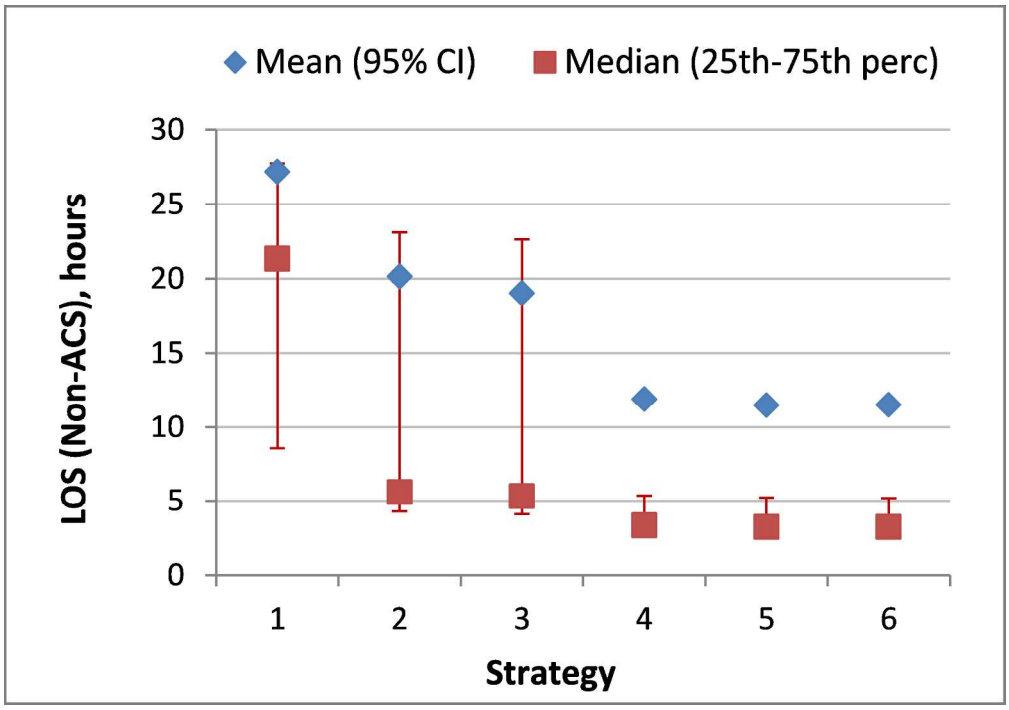
Strategy code: (1) Standard, (2) hsTnI, (3) hsTnI+LoD, (4) hsTnI+ADP, (5) hsTnI+LoD+ADP, (6) hsTnI+LoD+ADP+early rule in.

Costs include index costs and 30-days follow-up costs from the hospital perspective.

Diagnostic accuracy refers to the adjudicated final diagnosis of ACS within 30 days after presentation to the emergency department.

Each data-point reflects the strategy specific mean value and 95% confidence interval of 40,000 iterations.

hsTnI=Highly sensitive cardiac troponin I; LoD=Limit of detection; ADP=ADAPT accelerated diagnostic protocol



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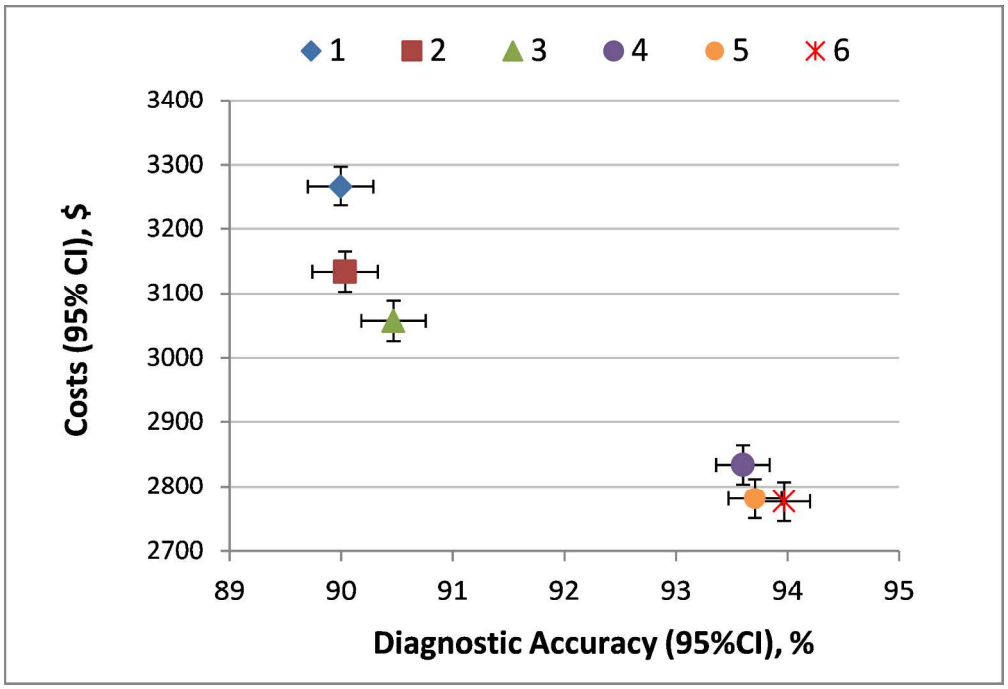

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706x479mm (96 x 96 DPI)

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report,** *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	TITLE PAGE
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	PAGE 1-2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	PAGES 1-4
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	PAGE 5
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	PAGE 5
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	PAGES 6-7
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	PAGE 7
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	PAGE 6
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	N/A
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	PAGE 7
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	PAGE 12

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A PAGE 5
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	PAGES 6-7
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	PAGES 5-6
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	PAGES 6-7, 8
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	SUPPLEMENT
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	PAGES 7-8,
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	SUPPLEMENT
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	PAGES 8-11
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	PAGES 8-11
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	PAGE 11

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	PAGES 12-14
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	PAGE 16
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	PAGE 16

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

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The organizational value of diagnostic strategies using high sensitivity troponin for patients with possible acute coronary syndromes: A trial-based cost-effectiveness analysis

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The organizational value of diagnostic strategies using high sensitivity troponin for patients with possible acute coronary syndromes: A trial-based cost-effectiveness analysis

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Keywords: Acute Coronary Syndrome; Health Care Economics and Organizations; Health Planning; Emergency Service, Hospital

Word Count: 3785

ABSTRACT

Objectives: To evaluate hospital-specific health economic implications of different protocols utilizing high sensitivity troponin I for assessment of patients with chest pain.

Design: A cost prediction model and an economic microsimulation were developed using a cohort from a single centre recruited as part of the ADAPT Trial, a prospective observational trial conducted from 2008-2011. The model was populated with 40,000 bootstrapped samples in five high sensitivity troponin I-enabled algorithms versus standard care.

Setting: Adult Emergency Department of a tertiary referral hospital

Participants: Data were available for 938 patients who presented to the Emergency department with at least five minutes of symptoms suggestive of acute coronary syndrome. The analyses included 719 patients with complete data.

Main Outcome(s)/Measure(s): The primary outcome was total costs. Other measures were referral to acute coronary syndrome management, and common emergency department performance measures.

Results: High sensitivity troponin I-supported algorithms increased diagnostic accuracy from 90.0% to 94.0% with an average cost reduction per patient compared to standard care of $490. The inclusion of additional criteria for accelerated rule-out (limit of detection and the Modified 2-Hour ADAPT trial rules) avoided 7.5% of short-stay unit admissions or 25% of admissions to a cardiac ward. Protocols utilizing high sensitivity troponin I alone, or high sensitivity troponin I within accelerated diagnostic algorithms reduced length of stay by 6.2 hours and 13.6 hours respectively. Overnight stays decreased up to 43%. Results were seen for non-acute coronary syndrome patients, no difference was found for patients diagnosed with acute coronary syndrome.

Conclusions: High sensitivity troponin I algorithms are likely to be cost-effective on a hospital level compared to sensitive troponin protocols. The positive effect is conferred by patients not diagnosed with acute coronary syndrome. Implementation could improve referral accuracy or facilitate safe discharge. It would decrease costs, and provide significant benefits for the hospital.

Trial Registration: The original ADAPT trial was registered with the Australia-New Zealand Clinical trials Registry, ACTRN12611001069943.

Strengths

- This study was based on an individual-level modeling design to allow for more realistic comparisons of different settings, assessment strategies, or risk stratification rules.
- As opposed to previous evaluations, costs and all management assumptions were based on actual patient information that was prospectively collected. In addition, we considered realistic management rules. For example, if patients were not discharged before 6:30pm, they required an overnight stay.
- Model results were based on a sampling strategy that created a large cohort with a wide spectrum of individual information, thus reflecting population heterogeneity and common variation in clinical practice.

Limitations

- Cost data were based on information from an administrative database. The cost prediction was limited to activities during the assessment period. Information about inpatient treatment other than time was not available.
- Economic implications from breaching specific emergency department targets or access blocks were not taken into account but may have a significant impact; it appears likely that considering such aspects would strengthen the results in favor of accelerated protocols.

INTRODUCTION

Chest pain is a leading presenting complaint for adults seeking emergency department (ED) care. [1] The most common serious underlying causes are acute coronary syndromes (ACS), including acute myocardial infarction and unstable angina. After detailed assessment, most patients are diagnosed with a non-cardiac cause (e.g. musculoskeletal pain or gastrointestinal causes) for their symptoms. In Australia, over 500,000 persons per year present with chest pain, but fewer than 20% were diagnosed with ACS.[2, 3] The identification of the majority of chest pain presentations at low-risk for ACS remains an organizational challenge for emergency departments.

Accelerated assessment strategies for the rule-in and rule-out of acute myocardial infarction have recently been reported.[3-12] Such strategies utilize clinical decision rules and/or troponin testing to identify a sizeable proportion of patients as low risk. Some protocols also accurately identify patients as high-risk for acute myocardial infarction.[3,4] The use of high sensitivity troponin on presentation or within two hours is a key feature of several accelerated assessment strategies[6-10]. For example, the Modified ADAPT accelerated diagnostic protocol (ADP) utilizes highly sensitive troponin assays to support the identification of 40 % of patients as low risk.[4]

While research into novel accelerated strategies has usually reported clinical outcomes, few studies have assessed the health economic implications of such protocols, or made comparisons to define optimum strategies. The incorporation of highly sensitive cardiac troponin I (hsTnI) assays into clinical practice may have additional health economic benefits on the hospital level; however, this aspect has not been explored to date. The aim of this study was to evaluate the hospital-specific health economic implications of different protocols utilizing hsTnI for assessment of emergency department patients with chest pain, compared to standard care.

METHODS

Study design and setting

This study utilized data from a prospective, single centre observational study in Brisbane, Australia. Participants were recruited as part of the ADAPT Trial,[3] and included if they were aged 18 years or older, presented to the emergency department with at least five minutes' worth of chest pain suggestive of ACS (in accordance with American Heart Association case definitions),[13] and were being evaluated for ACS. Recruitment was performed by research staff in collaboration with the senior treating clinician. Patients were excluded if there was a clear non–ACS cause for their symptoms (e.g., findings of pneumonia) they were unwilling or unable to provide informed consent, staff considered that recruitment was inappropriate (e.g., patients undergoing palliative treatment) , they were transferred from another hospital, were pregnant, were previously recruited to the study within the past 45 days, or were unable or unwilling to be contacted after discharge. Recruitment included consecutive eligible cases during working hours at each site. Enrolment occurred between January 2008 and November 2010. All patients were managed according to standard care, which included electrocardiogram and troponin testing on presentation and at greater than six hours after presentation to the emergency department. Patients were classified into risk groups according to the Heart Foundation of Australia/Cardiac Society of Australia and New Zealand guidelines.[14] The clinical assay in use as the reference troponin assay was the Beckman Coulter second-generation AccuTnI (Beckman Coulter, Chaska, MN). A value above the 99th percentile of greater than 40ng/L was considered abnormal.

Original data were collected prospectively, using standardized case report forms.[15] Research nursing staff collected demographic and clinical data from patient interviews. Telephone follow-up and medical record review was conducted 30-days after initial attendance for the diagnosis of ACS. Information was obtained from the patient and from hospital databases about all additional cardiac events, investigations, or contact with any health care providers during the 30-day period. Follow-up information was verified through contact with the health care provider, and original copies of

medical records and investigations were obtained. Ethical approval of the research project HREC/14/QRBW/320 was obtained from the Royal Brisbane and Women's Hospital Human Research Ethics Committee (EC 00172) on 11th August, 2014. All patients provided written informed consent for data collection and the ethics committee waived the requirement for consent for this analysis.

Each patient was assigned one or more endpoints to explain the reason for their index presentation, or any events occurring within 30 days of admission. There were fifteen possible endpoints, including both cardiovascular and non-cardiovascular endpoints. Patients were considered to meet the definition for ACS if they were assigned any of the following endpoints; cardiovascular death, cardiac arrest, revascularization procedure, cardiogenic shock, acute myocardial infarction, or unstable angina pectoris. One cardiologist from a group of three potential cardiologists adjudicated the outcome independently. Cardiologists had knowledge of the clinical record, electrocardiogram and troponin results from standard care and used such information to determine whether the patient met the predefined criteria for the cardiovascular endpoints[15]. Patients not meeting such endpoints were classed as having a non-cardiovascular problem. A second cardiologist from the group conducted a blind review of all ACS cases and 10% of non–ACS cases. In cases of disagreement, endpoints were agreed on by consensus by the two cardiologists involved in endpoint adjudication and one emergency physician. This was achieved for all endpoints.

In addition to sampling for routine clinical care, blood was drawn on presentation and two hours later. Samples were later tested with the ARCHITECT High Sensitive *STAT* Troponin-I assay (Abbott Laboratories, Abbott Park, IL). Laboratory technicians were blinded to patient data. The hsTnI assay has a 99th percentile concentration of 26.2ng/L with a corresponding co-efficient of variation of <5% and a limit of detection of 1.2ng/L.[16]

Cost prediction model

As described previously,[17] individual cost data were extracted from hospital administration records and adjusted for inflation to 2011 Australian Dollars. To use a consistent cost matrix across all strategies, a prediction model was developed in four steps. First, we analyzed the data and predefined exclusion criteria (eTable1). Patients who received coronary bypass surgery (CABG) were excluded because they were transferred to another hospital for surgery with no available outcome data and unknown accuracy of cost information. Cases with inconsistent or missing costs were excluded. Patients with a hospital length of stay (LOS) greater than 12 days were excluded to reduce bias from non-cardiac stays. Second, we considered key activities for evaluating an acute coronary syndrome in a generalized Box-Cox transformed model. Third, we dropped non-significant variables (2^{nd} troponin, p=0.9; stress echocardiography, p=0.6) from the predictor variables, checked for relevant multicollinearity between variables, and excluded cases that showed extreme discrepancies to the predicted results (n=4; eTable1). Fourth, we run the final analysis that led to the cost prediction model and the 95% confidence intervals for each predictor (eTable6). The final model was based on data from 891 individuals. The following predictors were used: ED time, inpatient time, performed activities (exercise stress test, myocardial perfusion scan, computed tomography coronary angiography, echocardiography, and angiography), admission to short-stay unit, or admission to an inpatient ward. More information is given in the supplement (eMethods).

Health economic model

We developed a microsimulation cost-effectiveness model that compared six assessment strategies (Table 1). The standard of care was based on a protocol using cardiac troponin I (cTnI) at baseline and 6 hours after arrival (Strategy 1). All other strategies utilized hsTnI at presentation and 2 hours. Strategy 2 (termed hsTnI) was the same as standard care except that a 2-hour highly sensitive troponin was used rather than a 6-hour sensitive troponin. Strategy 3 (hsTnI+LoD) also utilised a 2 hour hsTnI, but allowed a patient to be directly ruled out on admission with no further work-up if

their baseline hsTnI was below the assay's limit of detection (LoD). Strategy 4 (hsTnI+ADP) utilised baseline and 2 hour hsTnI but enabled patients to be directly ruled out with no further work-up using the modified ADAPT ADP. That is, patients could be ruled out if their TIMI risk score was <=1, their baseline and 2 hour troponin were below the diagnostic cutoff and their presentation ECG was non ischaemic. Strategy 5 (hsTnI+LoD+ADP) was a combination of Strategies 3 and 4 in that patients could be ruled out if their baseline hsTnI was below the LoD or if they met the criteria according to the modified ADAPT ADP. Finally, Strategy 6 (hsTnI+LoD+ADP+direct rule in) employed the same rule -out criteria as Strategy 5, but also enabled patients with hsTnI at presentation >52ng/L to be directly ruled-in and admitted for ACS management (strategy 6).[18]

The model structure and the evaluation pathway are described in Figure 1 and eFigure 1, respectively. Individuals entering the model were stratified in the ED based on individual characteristics, first electrocardiogram, and baseline troponin. Patients classified as high-risk were admitted to inpatient cardiology. Low-risk patients were kept in the emergency department to await final assessment. Intermediate-risk patients were referred to the short stay unit (SSU) for further cardiac workup. Patients referred to the SSU or inpatient ward were counted as admitted.

If the final troponin was performed later than 6.30pm, patients stayed overnight. Total LOS comprised emergency department LOS, short stay unit LOS and inpatient stay. The maximum LOS was limited to 12 days in accordance with the assumptions made for the cost prediction model. A 30-day follow-up event was assumed for individuals who were ruled-out by the respective strategy, and who had a reported 30-day clinical outcome of ACS.

A minimum required dataset was defined for the cohort used in the model (eTable 2), and 219 patients with missing troponin values were excluded. Work-up, work-up duration, and length of stay were analyzed from the model cohort and transformed into statistical distributions. Patient

attributes (age, sex, clinical characteristics, adjudicated diagnosis, electrocardiogram status, and troponin values) were individually sampled from the model cohort by bootstrapping. This created a hypothetical cohort of 40,000 patients who followed the model for each of the strategies. Work-up and times for each patient were randomly sampled from distributions. Costs were estimated by considering attributes, work-up activities, work-up duration, and length of stay in the cost prediction model with coefficients individually sampled from the 95% confidence interval of the respective predictor. The model followed a 30-day hospital perspective. Costs for the index event and follow-up were estimated from the cost prediction model.

Differences between strategies were expressed in terms of total hospital costs per patient and diagnostic accuracy. Diagnostic accuracy was defined as the percentage of correctly diagnosed patients compared to the final adjudicated diagnosis. In addition, LOS, referral rates, admission rates, and overnight stays were evaluated. We conducted one-way and probabilistic sensitivity analyses to test the robustness of the micro simulation results. Model structure, parameters and assumptions are described in detail in the supplement.

Patient Involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. Patients were asked whether they wished to receive a summary of these results. These individuals were posted a lay summary of the results.

RESULTS

Cost prediction and model validation

Characteristics of 719 patients meeting the minimum required dataset for the model and of the generated cohort of 40,000 patients are described in the supplement (eTable 5). The cost prediction model showed excellent regression quality (R-square 88.3%; eTable 6). The model was validated for the standard strategy against actual statistics with good prediction accuracy for all patients (p-value vs. actual costs: 0.723) as well as for low-, intermediate- and high-risk patients (p= 0.946, 0.256, 0.761, respectively; Table 2).

Patient referral and management

During initial assessment, 1.3% of patients were classified as low-risk and managed in the emergency department. 6.1% of patients met the criteria for a direct rule-out (baseline hsTnI below the limit of detection) and were re-classified as low-risk. The modified ADAPT accelerated diagnostic protocol (ADP) was effective for 49% of patients and reclassified 75% of intermediate-risk patients to low risk. The direct rule-in criteria (baseline hsTnI >52ng/L) applied to 7.2% of patients.

Strategies considering LoD avoided short-stay unit admissions for 4.9% of patients (-7.5% vs. standard care, Table 3). The number of ward admissions did not change with hsTnI alone. Utilising the LoD, ADP, or a combination of both, resulted in a stepwise and significant reduction of the ward admission rate from 49.6% to 37.1% (-25%; Table 3).

A 4-hour reduction in protocol time (cTnI vs. hsTnI: Mean 6.2h (Range 5.0 – 10.0h) vs. 2.3h (1.5 - 5.0h)) resulted in earlier management decisions (eFigure 4). Consequently, strategy-2 led to 30% fewer overnight stays compared to standard care (60.3% vs. 42.0%, Table 3). Incorporating additional rule-out to hsTnI options further streamlined patient assessment, decreasing overnight stays by up to 43%.

3.2% of patients with a negative or stable cTnI status had a positive hsTnI status indicative of an acute event (eTable 8). Conversely, 3.0% of patients had an acute sensitive TnI finding but a negative or stable troponin status with hsTnI. In total, the number of referrals to ACS management based on an acute troponin finding did not differ if replacing cTnI with hsTnI (cTnI: 11.9%; hsTnI: 12.1%; p=0.549). Patients with negative or stable troponin conditions were admitted for ACS management and further workup if such as an exercise stress test or myocardial perfusion scan led to positive findings, resulting in a referral rate of 32% (Table 3). Strategies considering the LoD or ADP rules respectively led to 5% or 35% fewer patients referred for ACS management compared to standard care. Additional direct rule-in criteria (Strategy-6 vs. 5) did not identify more patients requiring ACS management but allowed for earlier cardiac intervention for 46.6% of ACS patients.

Length of stay and costs

A significant reduction in LOS was observed if hsTnI replaced cTnI, with a mean saving of 6.2 hours (Table 3). Applying LoD or ADP rules to hsTnI saved an additional stay of 1.0 and 5.4 hours respectively. LOS times for ACS patients were stable between strategies (eTable 9). However, applying hsTnI to standard care resulted in a significant reduction of LOS for non-ACS patients. Substantially decreased 75th percentiles of the LOS for all strategies considering the ADP indicated its considerable streamlining effect. Details for emergency department and SSU times are given in the supplement (eTable 10).

Significant cost reductions compared to standard care were found with all hsTnI strategies ($133-$491, p<0.001, Table 3). This effect was caused by substantial cost reductions for non-ACS patients. No difference between strategies was observed for ACS patients (eTable 9). As stated in Table 3, costs during the index stay and follow-up decreased for all hsTnI-supported strategies compared to standard care. The consideration of ADP and LoD alone, or in combination, in addition to hsTnI

protocols resulted in further significant cost savings. Applying an direct rule-in strategy (Strategy-6) to a combination of hsTnT+ADP+LoD did not result in significant overall costs benefits.

Patient outcome and cost-effectiveness

The introduction of hsTnI into standard care did not alter overall diagnostic accuracy (p=0.86, Table 3, Figure 2), but increased the number of patients referred for ACS management who had a final diagnosis of non-ACS (p=0.056; False-positives in Table 4). While all hsTnI supported strategies avoided false-negative diagnoses compared to standard care, a statistically significant reduction of the false-positive rate was observed for all strategies utilizing an ADP. Applying LoD and ADP to hsTnI reduced the number of false-positives by 6% (p=0.015) and 52% (p<0.001) respectively, whereas no effect was observed on the false-negative rate (Table 4).

Strategy-5 (a protocol utitilizing hsTnI, ADP, and LoD) was found to be the dominant strategy in the study, providing better accuracy at lower costs (Figure 2).[19] Switching from standard care to Strategy 5 saved $486 per patient (p<0.001) and increased the diagnostic accuracy from 90.0% to 94.0% (p<0.001).

Conducting multiple runs in a probabilistic sensitivity analysis revealed consistent benefits confirming the robustness of micro simulation results (eFigure 6; eTable 11). hsTnI demonstrated equal or better diagnostic accuracy compared to cTnI in 79% of runs, with a stable average cost saving per patient ranging from $113 to $147. The hsTnI strategy helped to manage 82.6% of individuals at lower costs compared to standard care; 10.2% or 7.1% of patients were treated at equal or higher costs, respectively.

DISCUSSION

The cost-effectiveness of incorporating hsTnI into management protocols for patients presenting to the emergency department with chest pain has received increasing attention. HsTnI has been suggested to generate substantial benefits in the emergency department. Accelerated diagnostic protocols (ADPs) have been found to reduce the average emergency department length of stay in low-risk patients while health outcomes were maintained.[5, 11] To the best of our knowledge, this is the first study evaluating health economic implications of several hsTnI enabled assessment algorithms in the emergency department from a hospital perspective, thus complementing previous research that followed lifetime effects from a health systems perspective. [20-24]

Complex management algorithms that are based on individual patient attributes, plus the heterogeneity of the emergency department population, require an individual-level modeling design. [25] This allows for more realistic comparisons of different settings, assessment strategies, or risk stratification rules. As opposed to other evaluations, costs and all management assumptions in this study were based on actual and individual patient information of a single trial-based cohort. The sampling strategy created a wide spectrum reflecting population heterogeneity and common variation in clinical practice. [26] The clinical picture and additional information from objective testing were also considered in the simulation. We believe that this set the foundation for a consistent evaluation of the benefits that would accrue on the hospital level from implementing hsTnI-enabled algorithms.

We developed a cost prediction model for chest pain patients presenting to ED, and we conducted a patient-level economic analysis for comparing different hsTnI-enabled algorithms, validated against standard care. The analysis demonstrated that the implementation of hsTnI substantially reduced LOS and costs for patients enrolled in the chest pain pathway compared to standard care. Such benefits occurred without reducing diagnostic accuracy. Moreover, the introduction of hsTnI allows for combining additional validated management rules (LoD, ADP). The overall organizational

benefits of the dominant strategy (Strategy-5) compared to standard care were caused by two effects: a) a substantial time reduction in protocol time, and b) significantly improved stratification efficiency.

The significant decrease in overnight stays resulted in downstream effects of accelerated protocols on patient management. A 4-hour reduction in protocol time led to a 6.2-hour saving in LOS. By utilizing the ADP, the timeliness of the second hsTnI result freed an additional 7.4 hours per patient. This strategy saved around 60% of overnights stays and 15% of costs compared to standard care.

In line with the definition for a high-sensitive troponin assay, [16] measurable concentrations above the LoD were found for 94% of non-ACS patients; only 6% of individuals were eligible for a direct rule-out considering the LoD criteria. This proportion appeared to be modest compared to the ADP that captured almost 50% of patients. Nevertheless, switching from Strategy-4 (hsTnI+ADP) to Strategy-5 (hsTnI+ADP+LOD) resulted in a significant reduction in the number of admissions to the short-stay unit and wards. This was caused by the fact that the LoD-rule moved 4.7% of patients from an accelerated rule-out after the 2nd troponin (ADP), to a direct rule-out after the baseline troponin (LoD). In addition, the strategy including LOD classified 1.4% of patients, who were not captured by the ADP, as eligible for a direct rule-out. As a result, a total costs were significantly reduced for Strategy 5 compared to Strategy 4 (p=0.02). The combined strategy of utilizing hsTnI and LoD within the ADP helped to avoid 7.5% of short stay unit admissions and 25% of unnecessary inpatient ward admissions.

Strategy-6 (including a direct rule in) did not significantly differ from Strategy-5 in terms of costs and diagnostic accuracy. All patients meeting the criteria of a highly elevated baseline hsTnI (≥52mg/L) were classified as high-risk and admitted to inpatient cardiology by all other strategies. Therefore, Strategy-6 did not result in a change in admission rates. However, the key value of Strategy-6 was

the immediate referral to cardiology: 46.6% of patients finally diagnosed with ACS would receive earlier cardiac intervention. Given the fact that all patients in the underlying observational study were managed by standard care, data on potential outcome effects of an earlier cardiac treatment were not available, and thus not captured in the health economic evaluation.

Some limitations deserve attention. The analysis was based on a single-center cohort, which may limit the generalizability of the findings. Given the nature of a trial-based, individual level simulation, patient attributes were limited to the actual cohort; e.g. the impact of variation in ACS prevalence could not be tested in a sensitivity analysis. Management and cost data extracted from administrative databases may have some inaccuracies. Each of the 719 individuals from the cohort were run through the model on average 55 times with consistent characteristics, but varied in terms of protocol, treatment times, LOS, optional work-up decisions, and accrued costs. The thus generated cohort of 40,000 individuals reflected heterogeneity in patient management and addressed some of the uncertainty. The referral of patients followed strict and standardized assumptions. Deviation from recommended pathways may occur probably due to individual preferences or logistic effects such as access block.[27] Some of the potential flow issues were addressed by assuming a wide range in the initial assessment time (6–118 minutes). The predictors used in the cost model were limited to information about risk assessment and stratification; information about inpatient management other than inpatient time was not available. Patients with a long-term stay were excluded from the analysis in order to mitigate this potential risk of bias.

Economic implications from breaching specific emergency department targets or access blocks were not taken into account but may have a significant impact. Based on the findings of this study, it appears likely that considering such aspects would strengthen the results in favor of accelerated protocols. The model compared a sensitive troponin assay at 6 hours to highly sensitive assay at 2 hours. For the models not utilizing the LoD, it is unclear whether a sensitive troponin taken at 2 hours would provide the same benefits outlined here with a highly sensitive assay. The cost

prediction did not account for different costs of troponin assays. Compared to the magnitude of the difference between sensitive TnI and hsTnI strategies this effect was regarded as negligible.

CONCLUSION

This trial based economic modeling study demonstrates that emergency department assessment strategies utilizing hsTnI are very likely to be cost-effective on a hospital level when compared to sensitive TnI protocols for patients presenting with symptoms consistent with ACS. This is mainly due to a positive effect on the majority of patients not diagnosed with ACS. In particular, hsTnI-enabled algorithms considering additional rule-out criteria (LoD, ADP) are expected to improve the accuracy of both referral to inpatient wards or safe discharge as appropriate. Implementation of these protocols would provide direct benefits for the hospital in terms of reduced admission rates, avoided overnight stays, and improvements in time-based emergency department performance measures, thereby contributing to streamlined emergency department processes, more efficient use of resources, and overall cost savings.

Data sharing

Statistical code is available from the lead author.

Contributors

All authors had full access to the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. JG, LC and WP led the clinical study design as part of the Asia-Pacific Evaluation of Chest Pain Trial (ASPECT). JG extracted the dataset required for the modeling study. PJ developed the health economic model and run the analysis. Model design and assumptions were reviewed by all authors. All authors contributed in the interpretation of results, writing the manuscript, and critically reviewing each draft of the manuscript. The final version was approved by all authors. The study was supervised by LC.

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Transparency Declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1. Assessment strategies evaluated in the model

No	Strategy	Troponin assay	Protocol	Diagnostic cut-off [a]	Dynamic cut-off [b]	Direct rule-in [c]	Direct rule-out [d]	Accelerated rule-out [e]	Reference
1	Standard	cTnI	0 / 6hrs	> 40.0	delta < 10	No	No	No	Standard Care
2	hsTnI	hsTnI	0 / 2hrs	> 26.2	delta < 2	No	No	No	9, 11
3	hsTnI+LoD	hsTnI	0 / 2hrs	> 26.2	delta < 2	No	Yes	No	9, 12
4	hsTnI+ADP	hsTnI	0 / 2hrs	> 26.2	delta < 2	No	No	Yes	4, 9
5	hsTnI+LoD+ADP	hsTnI	0 / 2hrs	> 26.2	delta < 2	No	Yes	Yes	4, 9, 12
6	hsTnI+LoD+ADP +direct rule in	hsTnI	0 / 2hrs	> 26.2	delta < 2	Yes	Yes	Yes	4, 9, 12, 18

All values in ng/L.

cTnI= sensitive cardiac troponin I; hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP= Modified ADAPT accelerated diagnostic protocol; ADAPT=2-Hour Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker trial

[a] A troponin value greater than the diagnostic cut-off was considered as elevated.

[b] A delta between troponin values at different time points of less than 10ng/L (cTnI) or 2ng/L (hsTnI) was used to distinguish and rule-out a rise and/or fall in troponin associated with acute cardiac conditions.

[c] Direct rule-in of individuals with a hsTnI value at baseline above 52ng/L.

[d] Direct rule-out of individuals with a hsTnI value at baseline below the limit of detection of 1.2 ng/L (LoD).

[e] Referring to the Modified ADAPT accelerated diagnostic protocol (ADP). Accelerated rule-out applied to individuals with hsTnI values at 0 and 2h below the diagnostic cut-off and a TIMI risk score ≤1.

Table 2. Comparison of cost data and model validation.

Total costs, $	Item	Cullen 2015 [7]	Model cohort[a]	Model prediction[b]	Prediction vs. Cohort (p-value)
All	n (%)	926 (100%)	719 (100%)	719 (100%)	
	Mean cost (95%CI)	5272 (4835 - 5708)	5303 (4796 - 5810)	5437 (4897 - 5977)	0.72
	Median cost (25th-75th percentile)	2433 (1458 - 6778)	2497 (1449 - 6663)	2169 (1747 - 6384)	
Low Risk	n (%)	9 (1.0%)	9 (1.3%)	9 (1.3%)	
	Mean cost (95%CI)	2040 (1306 - 2774)	2040 (1125 - 2955)	2010 (1559 - 2460)	0.95
	Median cost (25th-75th percentile)	1530 (1298 - 3050)	1530 (1080 - 3359)	1907 (1569 - 2438)	
Intermediate Risk	n (%)	580 (62.6%)	468 (65.1%)	468 (65.1%)	
	Mean cost (95%CI)	3304 (2963 - 3644)	3413 (3050 - 3775)	3755 (3288 - 4223)	0.26
	Median cost (25th-75th percentile)	1849 (1376 - 3570)	1925 (1389 - 3628)	1946 (1668 - 3270)	
High Risk	n (%)	329 (35.5%)	242 (33.7%)	242 (33.7%)	
	Mean cost (95%CI)	8919 (7971 - 9867)	9081 (7878 - 10284)	8816 (7593 - 10040)	0.76
	Median cost (25th-75th percentile)	6452 (2650 - 11829)	6405 (2752 - 11309)	5566 (2355 - 11130)	

All costs referred to inflated costs in Australian dollars.

CI=confidence interval

a Excluded individuals not meeting the minimum required dataset for the model

b Excluded individuals with cost-outliers, missing and inconsistent data.

Table 3. Main model outcomes of different troponin supported assessment strategies

Indicator		Strategy 1 (Standard)	Strategy 2 (hsTnI)	Strategy 3 (hsTnI+LoD)	Strategy 4 (hsTnI+ADP)	Strategy 5 (hsTnI+LoD+ADP)	Strategy 6 (hsTnI+LoD+ADP+ direct rule- in)
Short stay unit admissions[a], %	Mean (95% CI)	65.3 (64.8 - 65.7)	65.3 (64.8 - 65.7)	60.4 (59.9 - 60.8)	65.3 (64.8 - 65.7)	60.4 (59.9 - 60.8)	60.4 (59.9 - 60.8)
	Incremental[b] (p-value)		0.0 (1.00)	-4.9 (<0.001)	4.9 (<0.001)	-4.9 (<0.001)	0.0 (1.00)
Ward admissions[a], %	Mean (95% CI)	49.7 (49.2 - 50.2)	49.6 (49.1 - 50.1)	47.4 (46.9 - 47.9)	38.4 (37.9 - 38.9)	37.1 (36.6 - 37.6)	37.1 (36.6 - 37.6)
	Incremental[b] (p-value)		-0.1 (0.81)	-2.3 (<0.001)	-9.0 (<0.001)	-1.3 (<0.001)	0.0 (1.00)
Overnight stays, %	Mean (95% CI)	60.3 (59.8 - 60.8)	42.0 (41.5 - 42.5)	39.8 (39.3 - 40.3)	24.4 (24.0 - 24.8)	23.9 (23.5 - 24.3)	24.1 (23.7 - 24.5)
	Incremental[b] (p-value)		-18.3 (<0.001)	-2.2 (<0.001)	-15.4 (<0.001)	-0.5 (0.08)	0.2 (0.51)
Referral to ACS management, %	Mean (95% CI)	32.4 (32.0 - 32.9)	32.2 (31.8 - 32.7)	30.9 (30.5 - 31.4)	21.0 (20.6 - 21.4)	20.7 (20.3 - 21.1)	20.9 (20.5 - 21.3)
	Incremental[b] (p-value)		-0.2 (0.56)	-1.3 (<0.001)	-9.9 (<0.001)	-0.3 (0.26)	0.3 (0.37)
Length of stay, hours	Mean (95% CI)	34.0 (33.6 - 34.4)	27.8 (27.4 - 28.2)	26.8 (26.4 - 27.3)	20.4 (20.0 - 20.9)	20.1 (19.6 - 20.5)	20.4 (19.9 - 20.8)
	Incremental[b] (p-value)		-6.2 (<0.001)	-1.0 (0.002)	-6.4 (<0.001)	-0.4 (0.23)	0.3 (0.33)
Diagnostic accuracy (E), %	Mean (95% CI)	90.0 (89.7 - 90.3)	90.0 (89.7 - 90.3)	90.5 (90.2 - 90.8)	93.6 (93.4 - 93.8)	93.7 (93.5 - 93.9)	94 (93.7 - 94.2)
	Incremental[b] (p-value)		0.0 (0.86)	0.4 (0.04)	3.1 (<0.001)	0.1 (0.54)	0.3 (0.13)
Index costs per patient, $	Mean (95% CI)	3029 (3001 - 3058)	2923 (2894 - 2952)	2846 (2816 - 2875)	2621 (2592 - 2649)	2568 (2539 - 2596)	2582 (2553 - 2610)
	Incremental[b] (p-value)		-106 (<0.001)	-77 (<0.001)	-225 (<0.001)	-53 (0.01)	14 (0.51)
Follow-Up costs per patient, $	Mean (95% CI)	238 (225 - 250)	211 (199 - 223)	211 (199 - 223)	213 (201 - 225)	213 (201 - 225)	195 (183 - 206)
	Incremental[b] (p-value)		-26 (0.003)	0 (1.00)	2 (0.82)	0 (1.00)	-18 (0.03)
Total costs per patient (C), $	Mean (95% CI)	3267 (3236 - 3297)	3134 (3103 - 3165)	3057 (3026 - 3088)	2834 (2804 - 2864)	2781 (2751 - 2811)	2776 (2746 - 2807)
	Incremental[b] (p-value)		-133 (<0.001)	-77 (0.001)	-223 (<0.001)	-53 (0.02)	-5 (0.83)

hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP= Modified ADAPT accelerated diagnostic protocol; ACS=acute coronary syndrome

All stated costs are in Australian dollars. (E) and (C) used as main measures of outcome.

[a] Patients could be admitted to the short stay unit before being referred to inpatient ward; numbers may not sum up to 100%.

[b] Incremental values compared to next best alternative to the left.

Table 4. False-negative and false-positive diagnosis of different assessment strategies

Strategy	False positives, %			False negatives, %		
	Mean	(95% CI)	p-value	Mean	(95% CI)	p-value
(1) Standard	6.6	(6.4 - 6.9)		3.4	(3.2 - 3.6)	
(2) hsTnI	7.0	(6.7 - 7.2)	0.06[a]	3.0	(2.8 - 3.2)	0.002[a]
(3) hsTnI+LoD	6.5	(6.3 - 6.8)	0.62[a]; 0.02[b]	3.0	(2.8 - 3.2)	0.002[a]; 1.00[b]
(4) hsTnI+ ADP	3.4	(3.2 - 3.5)	<0.001[a,b]	3.0	(2.9 - 3.2)	0.005[a]; 0.84[b]
(5) hsTnI+LoD+ADP	3.3	(3.1 - 3.4)	<0.001[a,b]	3.0	(2.9 - 3.2)	0.005[a]; 0.84[b]
(6) hsTnI+LoD+ADP+direct rule-in	3.3	(3.1 - 3.4)	<0.001[a,b]	2.8	(2.6 - 2.9)	<0.001[a]; 0.05[b]

False positives: Number of patients admitted for ACS management with a 30-days final diagnosis of non-ACS.

False negatives: Number of patients not admitted for ACS management with a 30-days final diagnosis of ACS.

hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP= Modified ADAPT accelerated diagnostic protocol; ACS=acute coronary syndrome

[a] p-value vs. Strategy-1 (Standard Care)

[b] p-value vs. Strategy-2 (hsTnI)

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Figure 1. Basic model structure

[a] In strategy 6: if hsTnI at baseline ≥52ng/L.

[b] In strategies 3,5, and 6: if hsTnI at baseline ≤1.2ng/L (limit of detection).

[c] In strategies 4,5, and 6: if hsTnI values at baseline and 2h are below the diagnostic cut-off of 26.2ng/L, and TIMI risk score ≤1, according to the Modified ADAPT accelerated diagnostic protocol (ADP).

Figure 2. Cost-effectiveness matrix

Strategy code: (1) Standard, (2) hsTnI, (3) hsTnI+LoD, (4) hsTnI+ADP, (5) hsTnI+LoD+ADP, (6) hsTnI+LoD+ADP+direct rule -in.

Costs include index costs and 30-days follow-up costs from the hospital perspective.

Diagnostic accuracy refers to the adjudicated final diagnosis of ACS within 30 days after presentation to the emergency department.

Each data-point reflects the strategy specific mean value and 95% confidence interval of 40,000 iterations.

hsTnI=Highly sensitive cardiac troponin I; LoD=Limit of detection; ADP=Modified ADAPT accelerated diagnostic protocol

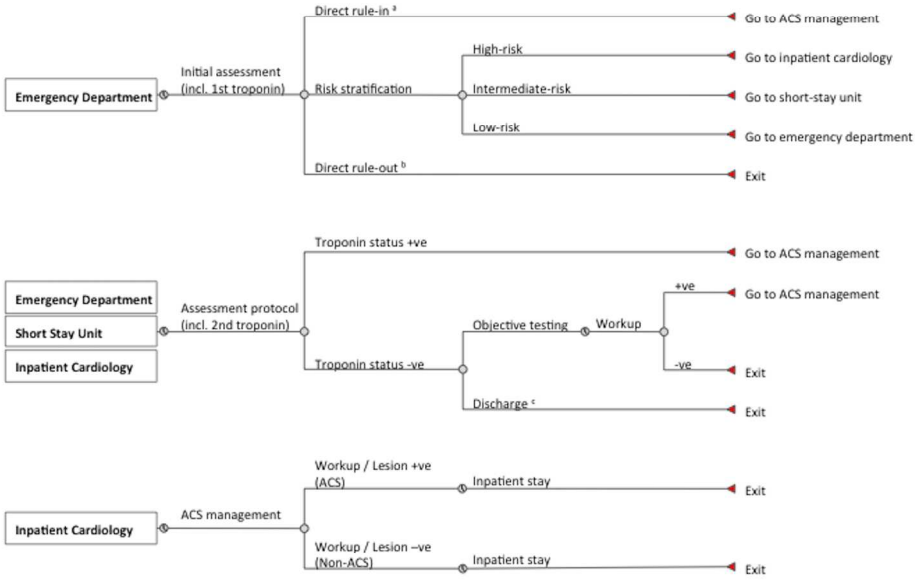

Figure 1. Basic model structure

‼ ┼ a In strategy 6: if hsTnI at baseline ≥52ng/L%

b In strategies 3,5, and 6: if hsTnI at baseline ≤1.2ng/L (limit of detection).

┼ c In strategies 4,5, and 6: if hsTnI values at baseline and 2h are below the diagnostic cut-off of 26.2ng/L, and TIMI risk score ≤1, according to the Modified ADAPT accelerated diagnostic protocol (ADP).

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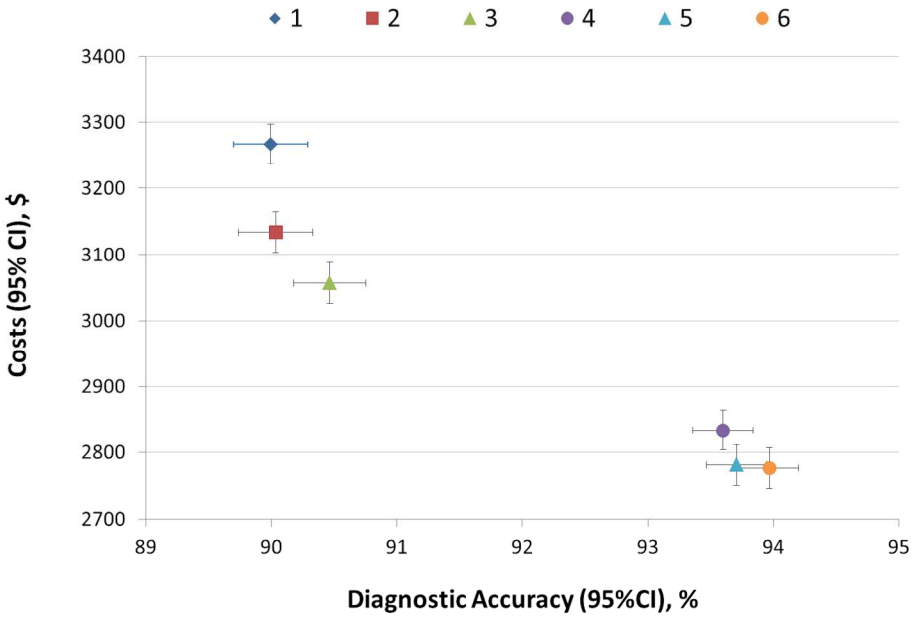

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The organizational value of diagnostic strategies using high sensitivity troponin for patients with possible acute coronary syndromes: A trial-based cost-effectiveness analysis

SUPPLEMENTARY ONLINE CONTENT

Contents

eMethods 1. Micro simulation model

Troponin testing

After blood was drawn, samples for hsTnI testing were immediately centrifuged. Serum and EDTA plasma were separated and stored frozen at -80°C, within two hours. During March and April, 2012, previously unthawed samples were thawed, mixed, and centrifuged prior to analysis. The assay used was the final pre-commercial release version of the ARCHITECT High Sensitive STAT Troponin-I assay (Abbott Laboratories, Abbott Park, IL). The hsTnI assay has a 99th percentile concentration of 26.2ng/L with a corresponding co-efficient of variation of <5% and a limit of detection of 1.2ng/L. [1] Long-term stability of TnI has been demonstrated previously. [2]

Cost prediction model

In alignment with the study focus, activities that were available by patient were limited to the risk assessment and stratification period (ECG, stress test, troponin testing, MPS, CTCA, angiography, etc.). Information about inpatient treatment and management other than inpatient time were not available. Thus, the prediction of total costs based on the available data was expected to be biased with increasing inpatient time. In fact, the average costs per inpatient day decreased with increasing stay until a slight increase appeared for patients staying more than 15 days. This was regarded as an indicator for costs accrued from activities not captured in the collected data. By further analyzing the data, we excluded 2.5% of patients with an inpatient stay of more than 12 days, as this was the maximum length of stay threshold that did not affect quartiles, median, and the 95th percentile of the cost distribution of the original data, but also excluded effects of unknown inpatient activities from the prediction model.

Patient pathway

Patients were classified into risk groups according to the Queensland chest pain pathway (eFigure 1).[3] Low-risk patients were treated in the ED; intermediate-risk patients were managed in the ED with admission to the ED short-stay unit. High-risk patients were referred to inpatient cardiology. Patients requiring CABG were transferred to another institution.

Health economic model

The model distinguished five troponin statuses (eTable 3). On a positive troponin status, patients were referred to inpatient cardiology. Patients with a negative troponin status underwent further testing for coronary ischemia.

Further testing included the evaluation of the troponin status after the second test and additional objective testing (exercise stress test, myocardial perfusion scan, stress echocardiography, computed tomography coronary angiography or angiography). If objective testing was negative, patients were eligible for discharge from the chest pain pathway and exit the model. If objective testing or troponin results were positive, patients were referred for acute coronary syndrome (ACS) management in the inpatient ward.

In the accelerated diagnostic protocol (ADP) scenarios, patients meeting the Modified 2-hour Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker trial (ADAPT) criteria for low risk patients (thrombosis in myocardial infarction (TIMI) score ≤1 and hsTnI ≤ upper limit of normal (ULN)) were discharged and exited the model without further testing and workup.

Diagnosis was compared to the final adjudicated 30-days diagnosis for calculating the diagnostic accuracy. A follow-up event within 30 days was assumed for individuals ruled-out by the respective strategy, and a reported 30-days clinical outcome of ACS (False-negative patients).

Occurrences and results of workup testing per individual were randomly sampled from binomial distributions on the basis of the troponin status using actual probabilities derived from the study cohort. Duration of workup was analyzed from the model cohort and transformed into statistical distributions. Times were randomly sampled from these distributions individually during simulation. To reflect the heterogeneity of hospital stay, LOS data of the

model cohort were analyzed by final diagnosis (ACS, Non-ACS) and electrocardiogram status (normal, ischemic, abnormal).

Hospital LOS times were randomly sampled per individual from distributions with values limited between the observed minimum and maximum of the cohort. Inpatient stay was calculated by deducting all inpatient activities from the sampled LOS times. Inpatient time was only considered for individuals that were referred to ACS management. All next day discharges were counted as overnight stays.

Regression coefficients for predicting index costs were randomly sampled per individual case with a uniform distribution between the lower and upper bound of the 95% confidence interval. Follow up cost data were estimated by assuming that the patient was admitted to cardiology for angiography with an emergency department-LOS of one hour, 3 inpatient days, no exercise stress test, no myocardial perfusion scan, no computed tomography coronary angiography, and no echocardiography. Follow-up costs were assigned by randomly sampling from a uniform distribution between the upper and lower limit of the 95% CI of the predicated costs of this scenario ($5402-$8628).

The appropriate number of samples was estimated by conducting several pilot runs estimating the effect size. A reasonable distinction between confidence intervals for costs, an acceptable consistency between multiple run (n=5) and single run results, and a between-run variability of below 10% were used as criteria.[4] We regarded the latter as particularly important since it would allow for meaningful comparisons between different scenarios, settings and assumptions in subsequent evaluations. Based on results of the pilot runs (eFigure 2A-B) the sample size was set to 40,000 patients.

For the probabilistic sensitivity analysis Strategy-2 was compared against Strategy-1 by repeating the micro simulation 250 times with 40,000 patients each. Mean results and 95% confidence intervals for costs, referral accuracy, and diagnostic accuracy were compared to the micro simulation results (eFigure 6; eTable 11).

The impact of protocol time on costs was tested by running Strategy-2 and assuming constant troponin values and increasing but fixed protocol times. Variation in the discharge threshold between 6pm and 10pm were tested and compared to a scenario with no daytime restriction for discharge.

Model was developed in TreeAge Pro 2015, R1.0 (TreeAge Software, Williamstown, MA, USA). Statistical analyses were done in Minitab 16.1.0. A significance level of 0.05 was used in all analyses. Continuous data were analyzed conducting a 2-Sample t-test and Mann-Whitney test. For categorical data Fisher's exact test was used.

Additional information

By randomly sampling from the database, each of the 719 individual patients was sampled on average 55 to 56 times (Range 36 – 78). Each sample of a patient was consistent in age, sex, characteristics, ACS status and troponin values, but varied in terms of arrival time, protocol time, treatment times, additional cardiac testing if required, total inpatient LOS if referred for ACS management, and costs predictors. This generated a huge cohort of patients that reflected variation and heterogeneity in decision making, severity, and management. The result of the sampling approach is demonstrated in eFigure 3 which shows distribution of costs of the first 10 individuals as an example. Given the fact that cardiac testing such as exercise stress testing or myocardial perfusion scanning could potentially lead to positive results in patients with negative ACS condition (eTable 4A) some repetitions generated positive workup results that led to ACS management referrals (Italic numbers in eFigure 3). The inpatient stay after stratification and workup was by assumption only considered for patients referred to ACS management. Therefore, the observed variation in costs for patients referred to ACS management is mainly driven by variation in length of stay reflecting different treatments, underlying diseases, severity or management decisions. There was a potential risk that this variation would superimpose the focus of the study to evaluate different assessment strategies.

In line with a long-term perspective, previous research did not consider short term effects for hospitals or variation in troponin protocol time.[5-9] This model used a distribution around the recommended target derived from actual data reflecting a more realistic scenario (eFigure 4A).

eFigure 5 provides histograms of SSU times. The majority of patients were admitted to short stay unit (65% with short stay unit time > 0hrs, eFigure 5A); in the standard strategy utilizing cTnI some patients were managed around a mean of 7.5 hours, some required additional observation with a mean of 25.0 hours indicating overnight stays. Replacing cTnI with hsTnI resulted in a substantial shift to lower short stay unit times as shown by mean

values of 4.0 hours and 22.5 hours for those staying overnight (eFigure 5B). An additional direct rule-out strategy (limit of detection, LoD) decreased the number of short stay unit admissions significantly as indicated by an increased proportion of patients at 0h in eFigure 5B. As illustrated in eFigure 5C accelerated rule-out protocols for low risk patients (ADP) moved the SSU time distribution to distinctly lower values.

Testing the influence of different protocol times revealed that protocols with lower time targets would be less affected by variation and delays (eFigure 7). As a practical consequence, accelerated algorithms could be expected to result in more stable and more predictable emergency department processes, thus allowing for better management and resource allocation.

Patients may not be discharged immediately even if they are regarded as low risk. Prolonged protocol times could cause some clinically unnecessary overnight stays at the hospital's expense. We used the discharge threshold time to reflect such specific management rules. Since the threshold may not be fixed in real life we tested the impact of some flexibility. Data in eFigure 8 reveal no significant observable effect of a flexible threshold time on Strategy 2 (hsTnI) whereas Strategy 1 (cTnI, standard care) was strongly affected between 6 and 8pm. Although these findings depend on emergency department arrival pattern results suggested that hsTnI enabled algorithms would be less affected by variation. Given the fact that arrival pattern used in the model was derived from actual data accelerated protocols would likely lead to more stable and predictable emergency department processes.

eTable 1. Patient selection criteria: Cost prediction model

Criteria	Excluded	N
All data		938
Exclude patients with CABG*	-14	924
Exclude long-stay outliers >12d (incl. non-cardiac complications)	-23	901
Exclude inconsistent or missing data	-6	895
Analyze extreme outliers	-4	891

*Patients receiving coronary bypass surgery (CABG) were excluded for the cost prediction model. Costs were unknown as patients were transferred to another hospital for surgery.
CABG=Coronary artery bypass graft

eTable 2. Patient selection criteria: Micro simulation model

Minimum required dataset	Excluded	N
Basic characteristics	0	938
Time points stated	0	938
ECG information available	0	938
Baseline cTnI	0	928
Baseline hsTnI	-145	793
Second cTn (6hrs)	-57	736
Second hsTnI (2hrs)	-17	719
Final endpoint	0	719

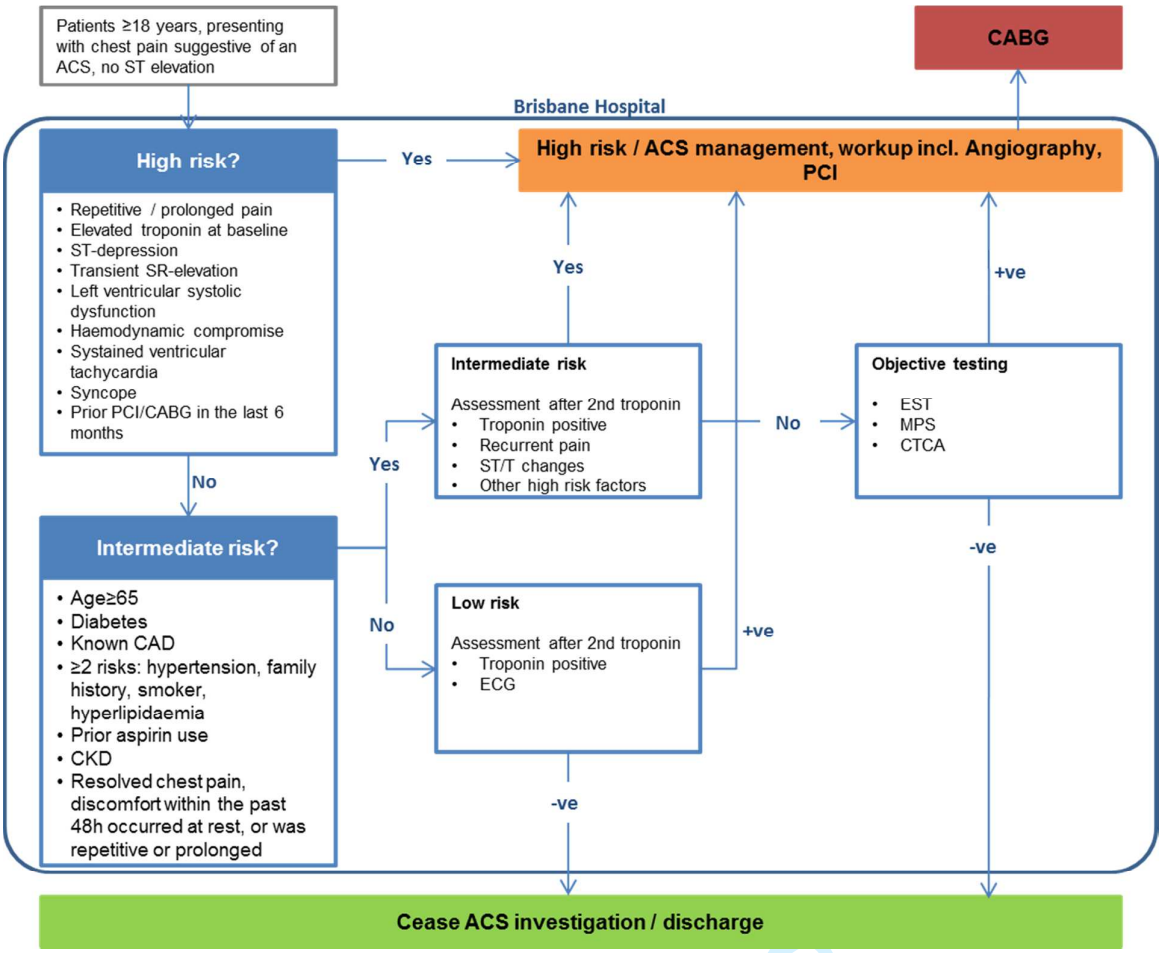
Individuals with missing data in the minimum required dataset were excluded from the analysis.
ECG=echocardiogram, cTnI=sensitive cardiac troponin I, hsTnI=highly sensitive cardiac troponin I

eTable 3. Troponin statuses considered in the model

Status	Description	Evaluation for ACS
1	1st troponin & 2nd troponin ≤ ULN	Negative
2	1st troponin ≤ ULN & 2nd troponin > ULN	Positive
3	1st troponin > ULN & 2nd troponin ≤ ULN	Positive
4	1st troponin & 2nd troponin > ULN; difference < delta cut-off	Negative (Stable)
5	1st troponin & 2nd troponin > ULN; difference ≥ delta cut-off	Positive

ULN=Upper limit of normal, 99th percentile of the reference population; ACS=Acute coronary syndrome

eFigure 1. Risk stratification and process of care for possible acute coronary syndrome



Risk stratification according to [3].

eTable 4A. Model parameter and assumptions: Objective testing probabilities.

Workup	Troponin status	N	Occurence	Result +-ve
Exercise Stress Test	1	582	60.1%	5.4%
	2	31	29.0%	11.1%
	3	15	33.3%	20.0%
	4	40	12.5%	40.0%
	5	51	2.0%	0.0%
Myocardial perfusion scan	1	582	14.3%	18.1%
	2	31	12.9%	75.0%
	3	15	20.0%	33.3%
	4	40	7.5%	0.0%
	5	51	2.0%	0.0%
Echocardiography	1	582	17.0%	data not available
	2	31	48.4%	
	3	15	20.0%	
	4	40	50.0%	
	5	51	70.6%	
Computed tomography coronary angiography	1	582	3.1%	data not available
	2	31	0.0%	
	3	15	6.7%	
	4	40	5.0%	
	5	51	0.0%	

Statistical evaluation of the model cohort (N=719)

eTable 4B. Model parameter and assumptions: Probabilities for angiography.

Workup	Troponin status	N	Occurrence	Result +ve (ACS patients)	Result +ve (non-ACS patients)
Angiography	1	582	11.9%	50.0%	31.3%
	2	31	35.5%	100.0%	0.0%
	3	15	13.3%	0.0%	0.0%
	4	40	27.5%	83.3%	40.0%
	5	51	70.6%	96.8%	20.0%

Statistical evaluation of the model cohort (N=719)
ACS=Acute coronary syndrome

eTable 4C. Model parameter and assumptions: Cardiac workup duration

Variable	Mean time, hours	Distribution
Arrival time (decimal time format)	0.45	Normal
Initial assessment time	0.45	Gamma
Protocol time cTnI	6.3	Gamma
Protocol time hsTnI	2.3	Gamma
Workup time (2nd Tn after 6.30pm)	17.1	Gamma
Probability of short workup time (2nd Tn before 6.30pm)	0.79	Binomial
Workup time (short; 2nd Tn before 6.30pm)	1.78	Gamma
Workup time (long; 2nd Tn before 6.30pm)	20.3	Gamma
Angiography	3.0	Gamma

cTnI=sensitive cardiac troponin I; hsTnI=highly sensitive cardiac troponin I

eTable 4D. Model parameter and assumptions: Hospital length of stay

Hospital LOS, hours	Mean	SD	Q1	Median	Q3	Min	Max	Distribution
ACS / ECG normal	154.4	99.6	66.5	100.6	273.4	48.7	280.4	Gamma
ACS / ECG ischemic	125.4	87.6	56.7	92.8	209.6	20.5	288.0	Gamma
ACS / ECG abnormal	110.3	81.5	59.3	85.5	166.0	15.8	283.9	Gamma
Non-ACS / ECG normal	33.1	49.7	6.0	19.6	27.6	0.0	284.0	Gamma
Non-ACS / ECG ischemic	91.9	90.5	25.0	64.7	121.3	0.0	284.0	Gamma
Non-ACS / ECG abnormal	58.9	71.7	8.0	25.3	80.5	0.0	282.4	Gamma

Statistical evaluation of the model cohort (N=719)
LOS=length of stay; ACS=acute coronary syndrome; ECG=electrocardiogram

eTable 5. Patient characteristics of the selected and generated model cohort.

Demographics	Cohort (N = 719)	Generated cohort[a] (N = 40,000)	p-value
Sex (% women)	39.4	39.5	0.94
Age, yrs. Mean (Range)	55 (19 - 97)	55 (19-97)	0.94
Risk factors			
Dyslipidaemia, %	42.1	Sampled and used for estimating the assessment status	
Diabetes, %	12.8		
Hypertension, %	43.3		
Tachycardia, %	1.7		
Obesity (BMI>30), %	35.5		
Smoking, %	26.8		
Medical History			
Angina, %	22.5	Sampled and used for estimating the assessment status	
Coronary artery disease, %	20.5		
Myocardial infarction, %	16.3		
Family coronary artery disease, %	46.6		
Arrhythmia, %	9.0		
Congestive heart failure, %	4.2		
CABG surgery, %	6.5		
Prior angioplasty, %	10.3		
Peripheral artery disease, %	1.8		
Aspirin use, %	25.3		
Stroke, %	9.0		
Initial assessment & final diagnosis			
ACS, %	11.0	11.0	1.00
ECG normal, %	49.5	49.1	0.85
ECG ischemic, %	7.8	7.7	0.94
ECG abnormal, %	42.7	43.2	0.82
TIMI 0, %	24.5	25.0	0.75
TIMI 1, %	33.0	33.9	0.61
TIMI 2, %	17.9	17.2	0.58
TIMI 3, %	12.2	12.1	0.86
TIMI 4, %	6.4	6.5	1.00
TIMI ≥5, %	6.0	5.4	0.51
High risk, %	33.7	33.5	0.94
Intermediate risk, %	65.1	65.3	0.94
Low risk, %	1.3	1.3	1.00
Baseline cTnI, ng/L (Mean, range)	118 (10 - 31000)	119 (10 - 31000)	0.97
Baseline hsTnI, ng/L (Mean, Range)	117.5 (0.3 - 38685)	119.2 (0.3 - 38685)	0.98
hsTnI < LoD at baseline[b], %	5.1	6.1	0.34

TIMI and risk assignment based on standard strategy
[a] Samples per individuals: Mean 55.6; Range 36-78; Mode: 52.
[b] Limit of detection for hsTnI 1.2ng/L
BMI=Body mass index; CABG=coronary artery bypass graft; ACS=acute coronary syndrome; ECG=electrocardiogram; TIMI=Thrombolysis in myocardial infarction; cTnI=sensitive cardiac troponin I; hsTnI=highly sensitive cardiac troponin I, LoD=limit of detection

eTable 6. Cost prediction model regression analysis

Term	Coef	SE Coeff	T	P-value	(95% CI)	VIF
Constant	3.57	0.04	101.5	<0.001	(3.51 – 3.64)	
ED time, hours	0.02	0.00	8.8	<0.001	(0.02 – 0.03)	1.15
Inpatient stay, days	0.19	0.01	37.7	<0.001	(0.18 – 0.20)	1.78
Exercise stress test	-0.09	0.02	-4.3	<0.001	(-0.13 – -0.05)	1.37
Myocardial perfusion scan	0.25	0.04	6.7	<0.001	(0.18 – 0.32)	1.22
Computed tomography coronary angiography	0.27	0.07	4.0	<0.001	(0.14 – 0.40)	1.02
Angiography	0.65	0.03	21.8	<0.001	(0.59 – 0.71)	1.34
Echocardiography	0.32	0.03	11.4	<0.001	(0.26 – 0.37)	1.49
Admission	0.39	0.03	11.6	<0.001	(0.33 – 0.46)	1.21

VIF: Variance inflation factor

Box-Cox transformation with Lambda= 0.189 (95%CI 0.135 – 0.245)

S	0.264
PRESS	63.4
R-Sq	88.3%
R-Sq(adj)	88.2%
R-Sq(pred)	88.0%

Admission considers admission to short-stay unit or inpatient ward

eTable 7. Risk assignment of patients

Strategy			Initial risk assignement, %		
			Low-risk	Intermediate -risk	High- risk
Standard			**1.3**	**65.3**	**33.5**
hsTnI			**1.3**	**65.3**	**33.5**
Direct rule-out if baseline hsTnI < LoD (LoD)	No direct rule-out	**All**	**1.3**	**60.4**	**32.3**
	Direct rule-out[a]	**All**	**0.0**	**4.9**	**1.2**
		ACS	0.0	0.0	0.0
		No ACS	0.0	4.9	1.2
Accelerated rule-out if hsTnI values below the diagnostic cut-off and TIMI ≤1 (ADP)	No accelerated rule-out	**All**	**0.5**	**16.4**	**33.5**
	Accelerated rule-out[a]	**All**	**0.7**	**48.8**	**0.0**
		ACS	0.0	0.2	0.0
		No ACS	0.7	48.7	0.0
Direct rule-in if baseline hsTnI >52ng/L	No direct rule-in	**All**	**1.3**	**65.3**	**26.3**
	Direct rule-in[b]	**All**	**0.0**	**0.0**	**7.2**
		ACS	0.0	0.0	5.1
		No ACS	0.0	0.0	2.0

LoD=Limit of detection; ACS= Acute coronary syndrome;
TIMI=Thrombolysis in myocardial infarction;
ADP=Accelerated diagnostic protocol;
hsTnI=highly sensitive cardiac troponin I
[a] classified as low-risk
[b] classified as high-risk

eTable 8. Troponin status by assay used

	hsTnI			Sum (cTnI), %
cTnI	**Negative, %**	**Stable, %**	**Positive, %**	
Negative, %	84.0	0.1	0.3	**84.4**
Stable, %	0.6	0.3	2.9	**3.4**
Positive, %	2.4	0.6	9.0	**11.9**
Sum (hsTnI), %	**86.9**	**1.0**	**12.1**	**100.0**

Troponin status interpretation according to eTable3
cTnI=sensitive cardiac troponin I; hsTnI=highly sensitive cardiac TnI

eTable 9. Total length of stay and costs per strategy and final diagnosis

Strategy	Category	Total costs, $				Total LOSs, hours			
		Median	(25th - 75th perc)	Mean	(95% CI)	Median	(25th - 75th perc)	Mean	(95% CI)
1	**All**	**2135**	**(1741 - 3109)**	**3267**	**(3236 - 3297)**	**22.6**	**(8.7 - 29.8)**	**34.0**	**(33.6 - 34.4)**
	No ACS	2022	(1708 - 2669)	2570	(2550 - 2590)	21.3	(8.6 - 27.7)	27.2	(26.9 - 27.5)
	ACS	8421	(5863 - 10248)	8895	(8756 - 9034)	74.8	(25.5 - 137)	89.2	(87 - 91.3)
2	**All**	**1983**	**(1597 - 2951)**	**3134**	**(3103 - 3165)**	**6.0**	**(4.4 - 25.3)**	**27.8**	**(27.4 - 28.2)**
	No ACS	1860	(1567 - 2478)	2417[a]	(2397 - 2436)	5.6	(4.3 - 23.1)	20.2[a]	(19.8 - 20.5)
	ACS	8269	(5827 - 10210)	8930	(8788 - 9073)	79.0	(23 - 139.2)	89.6	(87.4 - 91.8)
3	**All**	**1921**	**(1548 - 2878)**	**3057**	**(3026 - 3088)**	**3.6**	**(2.7 - 10.1)**	**20.4**	**(20 - 20.9)**
	No ACS	1805	(1517 - 2427)	2330[a]	(2310 - 2350)	3.3	(2.6 - 5.4)	11.9[a]	(11.6 - 12.2)
	ACS	8269	(5827 - 10210)	8930	(8788 - 9073)	78.7	(22.8 - 139.1)	89.3	(87.1 - 91.5)
4	**All**	**1695**	**(1560 - 2260)**	**2834**	**(2804 - 2864)**	**5.6**	**(4.2 - 24.8)**	**26.8**	**(26.4 - 27.3)**
	No ACS	1663	(1544 - 1862)	2079[a]	(2062 - 2096)	5.3	(4.1 - 22.6)	19.0[a]	(18.7 - 19.4)
	ACS	8268	(5851 - 10198)	8932	(8790 - 9074)	79.0	(23 - 139.2)	89.6	(87.4 - 91.8)
5	**All**	**1681**	**(1532 - 2231)**	**2781**	**(2751 - 2811)**	**3.5**	**(2.6 - 8.3)**	**20.1**	**(19.6 - 20.5)**
	No ACS	1648	(1514 - 1845)	2020[a]	(2002 - 2037)	3.2	(2.5 - 5.2)	11.5[a]	(11.2 - 11.8)
	ACS	8268	(5851 - 10198)	8932	(8790 - 9074)	78.7	(22.8 - 139.1)	89.3	(87.1 - 91.5)
6	**All**	**1681**	**(1532 - 2230)**	**2776**	**(2746 - 2807)**	**3.5**	**(2.6 - 8.8)**	**20.4**	**(19.9 - 20.8)**
	No ACS	1648	(1514 - 1845)	2020[a]	(2003 - 2037)	3.2	(2.5 - 5.2)	11.5[a]	(11.2 - 11.8)
	ACS	8151	(5702 - 10194)	8885	(8740 - 9029)	82.0	(24.8 - 140.5)	91.9	(89.7 - 94.1)

Strategy code: (1) Standard, (2) hsTnI, (3) hsTnI+LoD, (4) hsTnI+ADP, (5) hsTnI+LoD+ADP, (6) hsTnI+LoD+ADP+Rule in.
Total costs include index costs and 30 days follow-up costs.
All costs stated are in Australian dollars.
[a] p-value vs. Standard < 0.001
ACS=Acute coronary syndrome; hsTnI=highly sensitive troponin I; LoD=limit of detection; ADP=accelerated diagnostic protocol; LOS=Length of stay

eTable 10A. Emergency department performance by strategy

Emergency department time, hours	Mean	(95% CI)	Median	(25th - 75th perc)	97.5th perc	≤4hrs
1) Standard	0.68	(0.66 - 0.7)	0.41	(0.26 - 0.63)	1.4	98.7%
2) hsTnI	0.58	(0.57 - 0.6)	0.41	(0.26 - 0.63)	1.4	99.0%
3) hsTnI+LoD	0.58	(0.57 - 0.6)	0.41	(0.26 - 0.63)	1.4	99.0%
4) hsTnI+ADP	0.54	(0.53 - 0.55)	0.41	(0.26 - 0.63)	1.4	99.6%
5) hsTnI+LoD+ADP	0.54	(0.53 - 0.55)	0.41	(0.26 - 0.63)	1.4	99.6%
6) hsTnI+LoD+ADP+Direct rule-in	0.54	(0.53 - 0.55)	0.41	(0.26 - 0.63)	1.4	99.6%

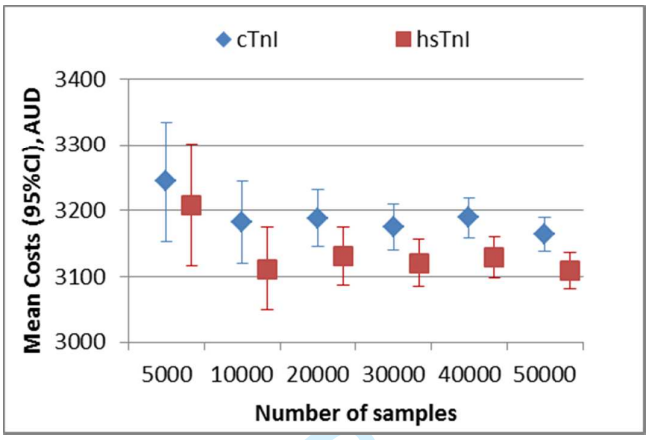
hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP=accelerated diagnostic protocol.

eTable 10B. Short Stay Unit times per patient by strategy

SSU time, hours	Mean	(95% CI)	Median	(25th - 75th perc)	90th perc
1) Standard	9.9	(9.8 - 10)	7.54	(0.0 - 20.8)	25.7
2) hsTnI	5.1	(5.1 - 5.2)	3.49	(0.0 - 4.7)	21.2
3) hsTnI+LoD	4.7	(4.7 - 4.8)	3.31	(0.0 - 4.5)	20.7
4) hsTnI+ADP	2.4	(2.3 - 2.4)	2.06	(0.0 - 2.6)	3.8
5) hsTnI+LoD+ADP	2.2	(2.2 - 2.3)	1.99	(0.0 - 2.6)	3.8
6) hsTnI+LoD+ADP+Rule in	2.2	(2.2 - 2.3)	1.99	(0.0 - 2.6)	3.8

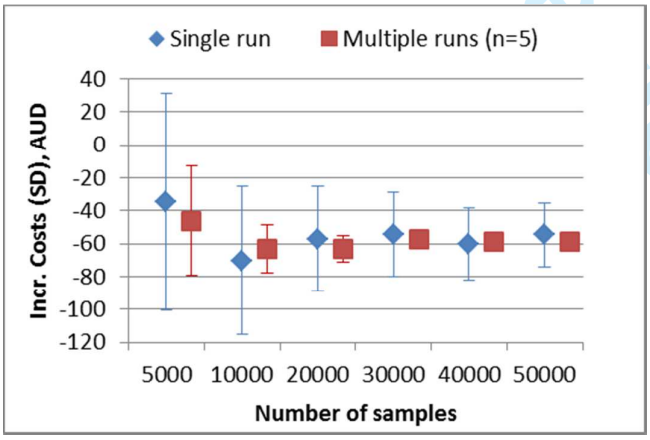
hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP=accelerated diagnostic protocol.

eFigure 2A. Mean costs based on number of samples in the micro simulation



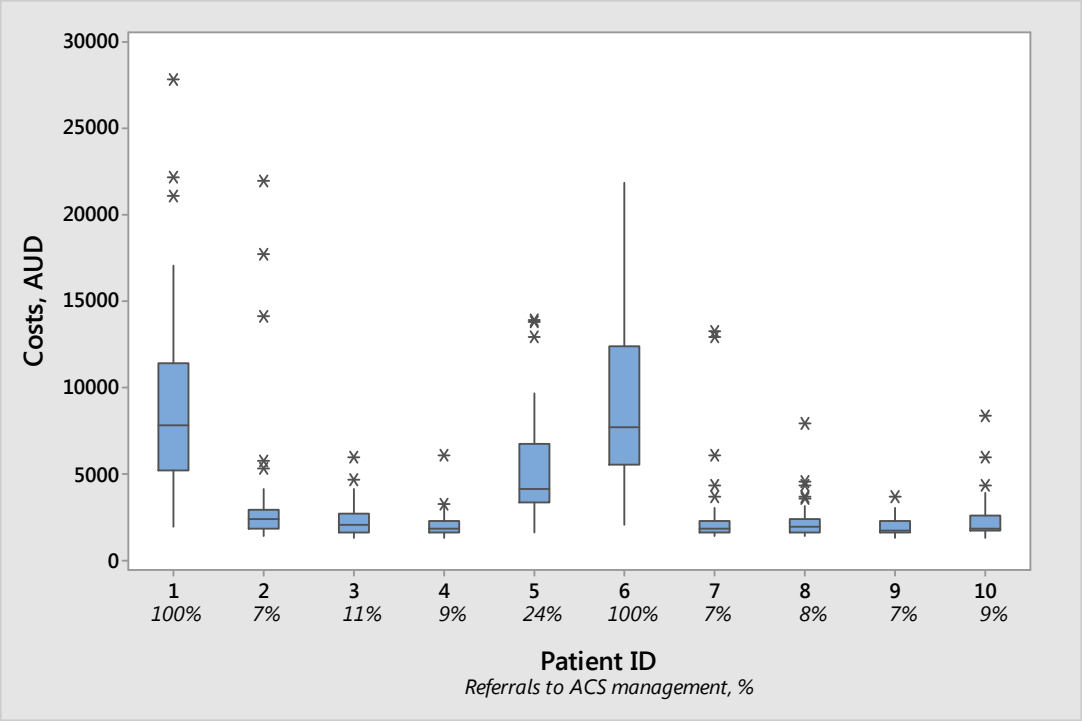
cTnI=sensitive cardiac troponin; hsTnI=highly sensitive cardiac troponin I

eFigure 2B. Incremental costs based on different number of samples in the micro simulation



Incremental costs refer to Strategy-2 – Strategy 1

eFigure 3. Total costs variation as a result of the sampling strategy illustrated for ten selected individuals

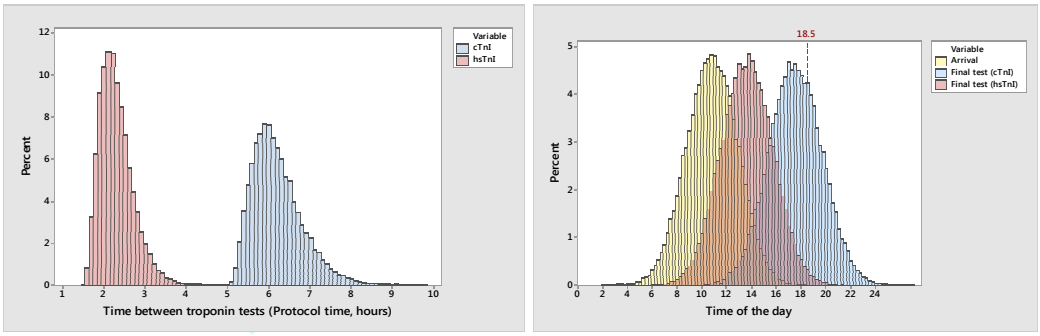


Box plots illustrate the variability in costs from multiple samples of the same individual as an example for the first 10 patients (Patient-ID 1 to 10).

By running 40,000 iterations, each of the 719 individuals was sampled on average 55 to 56 times (Range 36 – 78). This generated a huge cohort of patients that reflected variation and heterogeneity in decision making, severity, and management.

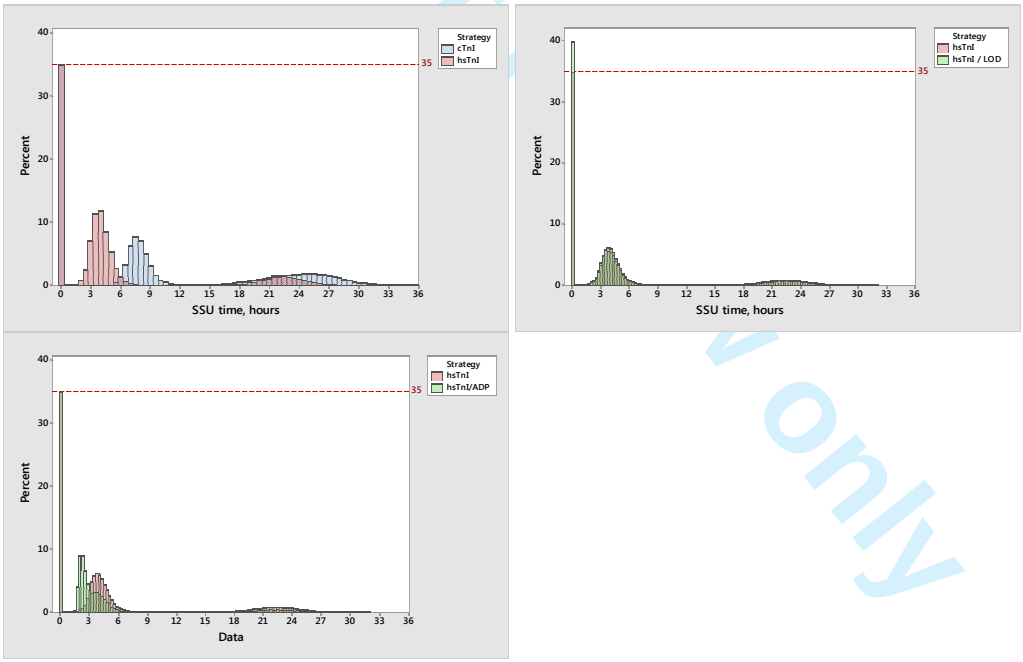
Each sample of an individual was consistent in age, sex, characteristics, ACS status and troponin values, but varied in terms of arrival time, protocol time, treatment times, additional cardiac testing if required, total inpatient LOS if referred for ACS management, and costs predictors. This resulted in a range of costs as demonstrated in the chart.
For individuals with non-ACS conditions, variation in subjective decision making or results from cardiac testing (exercise stress test or myocardial perfusion scan) led to admittance for ACS management in some cases (Patient ID 2-4, and 7-10). Italic numbers indicate the proportion of referrals to ACS management per patient. Patients with ACS were admitted for ACS management in 100% of iterations (Patient ID 1 and 6). Variation in costs between ACS patients was caused by sampling different LOS assumptions.

eFigure 4. Simulated troponin protocol times (A), patient arrival times, and times of final results for sensitive troponin I and highly sensitive troponin I (B).



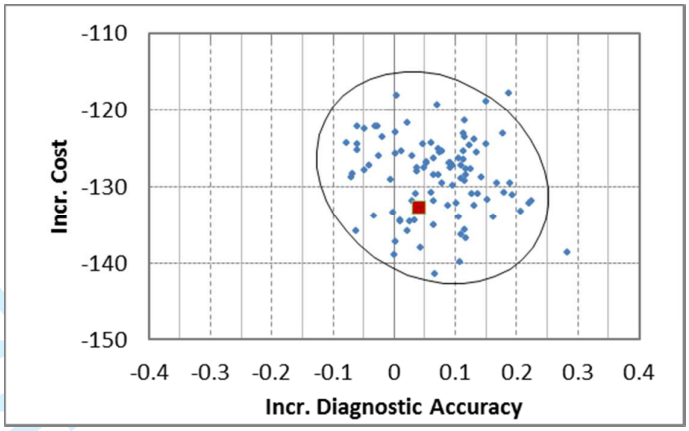
cTnI=sensitive cardiac troponin; hsTnI=highly sensitive cardiac troponin I

eFigure 5 A-C. Histograms of Short Stay Unit times for different strategies



A: Standard strategy (cTnI) vs. hsTnI;
B: hsTnI strategy vs. hsTnI / LoD strategy; C: hsTnI strategy vs. hsTnI / ADP strategy.
The reference line at 35% indicates the proportion of patients that were not admitted to Short Stay Unit in the standard strategy.
hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP=accelerated diagnostic protocol.

eFigure 6. Incremental cost and effectiveness of Strategy 2 (hsTnI) vs. Strategy 1 (cTnI, usual care).



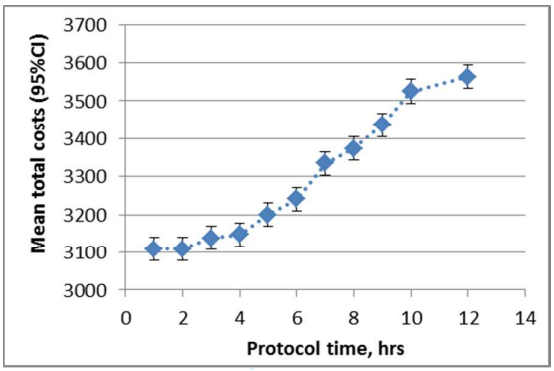
Results from multiple runs in a probabilistic sensitivity analysis (n=250). Each point represents results of a run with 40,000 sampled patients. The ellipse reflects the 95% confidence interval. Red box represents the result from the micro simulation.

eTable 11. Comparison of results from single and multiple run micro simulations

Strategy	Analysis	Total costs		Referral Accuracy, %		Diagnostic Accuracy	
		A$	(95%CI)	Mean	(95%CI)	Mean	(95%CI)
Standard	MS	3267	(3236 - 3297)	71.8	(71.4 - 72.2)	90.00	(89.7 - 90.3)
	PSA	3253	(3251 - 3255)	72.0	(71.97 - 72.02)	90.21	(90.2 - 90.23)
hsTnI	MS	3134	(3103 - 3165)	72.8	(72.3 - 73.2)	90.04	(89.7 - 90.3)
	PSA	3124	(3122 - 3126)	73.0	(72.95 – 73.00)	90.3	(90.26 - 90.29)

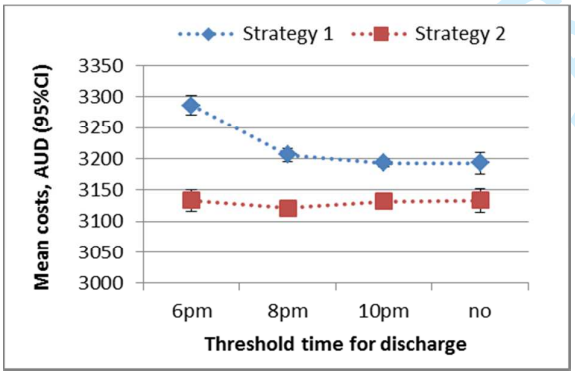
MS: Micro simulation (n=1 runs)
PSA: Probabilistic sensitivity analysis (n=250 runs)

eFigure 7. Impact of protocol time on costs.



Analysis of strategy 2 (hsTnI) assuming constant troponin values and a fixed protocol time.

eFigure 8. Impact of threshold time for discharge on costs.



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CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1 / Title page
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Pages 2-3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Page 5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Pages 5-7
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Pages 5-7
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 10
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Pages 8-9
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 9, 10
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Not appropriate
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 10
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Pages 6-7

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Pages 6-7
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 8; Supplement page 65
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 8
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 14; Figure 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Pages 8-10; Supplement
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Pages 8-10; Suppl. pages 65-67; 78
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Pages 10-13; Table 3; Supplement
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 3
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	Page 12; Supplement Suppl. pages 28, 80,81

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Pages 13-16
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 18
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Pages 18-19

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.

BMJ Open

The organizational value of diagnostic strategies using high sensitivity troponin for patients with possible acute coronary syndromes: A trial-based cost-effectiveness analysis

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Primary Subject Heading:	Health economics
Secondary Subject Heading:	Emergency medicine, Cardiovascular medicine
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The organizational value of diagnostic strategies using high sensitivity troponin for patients with possible acute coronary syndromes: A trial-based cost-effectiveness analysis

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Keywords: Acute Coronary Syndrome; Health Care Economics and Organizations; Health Planning; Emergency Service, Hospital

Word Count: 3785

ABSTRACT

Objectives: To evaluate hospital-specific health economic implications of different protocols utilizing high sensitivity troponin I for assessment of patients with chest pain.

Design: A cost prediction model and an economic microsimulation were developed using a cohort from a single centre recruited as part of the ADAPT Trial, a prospective observational trial conducted from 2008-2011. The model was populated with 40,000 bootstrapped samples in five high sensitivity troponin I-enabled algorithms versus standard care.

Setting: Adult Emergency Department of a tertiary referral hospital

Participants: Data were available for 938 patients who presented to the Emergency department with at least five minutes of symptoms suggestive of acute coronary syndrome. The analyses included 719 patients with complete data.

Main Outcome(s)/Measure(s): This study examined direct hospital costs, number of false negative and number of false positive cases in the assessment of acute coronary syndrome.

Results: High sensitivity troponin I-supported algorithms increased diagnostic accuracy from 90.0% to 94.0% with an average cost reduction per patient compared to standard care of $490. The inclusion of additional criteria for accelerated rule-out (limit of detection and the Modified 2-Hour ADAPT trial rules) avoided 7.5% of short-stay unit admissions or 25% of admissions to a cardiac ward. Protocols utilising high sensitivity troponin I alone, or high sensitivity troponin I within accelerated diagnostic algorithms reduced length of stay by 6.2 hours and 13.6 hours respectively. Overnight stays decreased up to 43%. Results were seen for non-acute coronary syndrome patients, no difference was found for patients with acute coronary syndrome.

Conclusions: High sensitivity troponin I algorithms are likely to be cost-effective on a hospital level compared to sensitive troponin protocols. The positive effect is conferred by patients not diagnosed with acute coronary syndrome. Implementation could improve referral accuracy or facilitate safe discharge. It would decrease costs, and provide significant hospital benefits.

Trial Registration: The original ADAPT trial was registered with the Australia-New Zealand Clinical trials Registry, ACTRN12611001069943.

Strengths

- This study was based on an individual-level modelling design to allow for more realistic comparisons of different settings, assessment strategies, or risk stratification rules.
- As opposed to previous evaluations, costs and all management assumptions were based on actual patient information that was prospectively collected. In addition, we considered realistic management rules. For example, if patients were not discharged before 6:30pm, they required an overnight stay.
- Model results were based on a sampling strategy that created a large cohort with a wide spectrum of individual information, thus reflecting population heterogeneity and common variation in clinical practice.

Limitations

- Cost data were based on information from an administrative database. The cost prediction was limited to activities during the assessment period. Information about inpatient treatment other than time was not available.
- Economic implications from breaching specific emergency department targets or access blocks were not taken into account but may have a significant impact; it appears likely that considering such aspects would strengthen the results in favour of accelerated protocols.

INTRODUCTION

Chest pain is a leading presenting complaint for adults seeking emergency department (ED) care.[1] The most common serious underlying causes are acute coronary syndromes (ACS), including acute myocardial infarction and unstable angina. After detailed assessment, most patients are diagnosed with a non-cardiac cause (e.g. musculoskeletal pain or gastrointestinal causes) for their symptoms. In Australia, over 500,000 persons per year present with chest pain, but fewer than 20% were diagnosed with ACS.[2, 3] The identification of the majority of chest pain presentations at low-risk for ACS remains an organizational challenge for emergency departments.

Accelerated assessment strategies for the rule-in and rule-out of acute myocardial infarction have recently been reported.[3-12] Such strategies utilise clinical decision rules and/or troponin testing to identify a sizeable proportion of patients as low risk. Some protocols also accurately identify patients as high-risk for acute myocardial infarction.[3,4] The use of high sensitivity troponin on presentation or within two hours is a key feature of several accelerated assessment strategies[6-10]. For example, the Modified ADAPT accelerated diagnostic protocol (ADP) utilises highly sensitive troponin assays to support the identification of 40% of patients as low risk.[4]

While research into novel accelerated strategies has usually reported clinical outcomes, few studies have assessed the health economic implications of such protocols, or made comparisons to define optimum strategies. The incorporation of highly sensitive cardiac troponin I (hsTnI) assays into clinical practice may have additional health economic benefits on the hospital level; however, this aspect has not been explored to date. The aim of this study was to evaluate the hospital-specific costs of different protocols utilising hsTnI for assessment of emergency department patients with chest pain, compared to standard care. The hypothesis was that hsTnI enabled algorithms would streamline ED processes with equal or better diagnostic accuracy, thus leaving to savings in direct hospital costs when compared to standard care.

METHODS

Study design and setting

This study utilised data from a prospective, single centre observational study in Brisbane, Australia. Participants were recruited as part of the ADAPT Trial,[3] and included if they were aged 18 years or older, presented to the emergency department with at least five minutes' worth of chest pain suggestive of ACS, and were being evaluated for ACS. Pain suggestive of ACS was defined in accordance with American Heart Association case definitions.[13] Recruitment was performed by research staff in collaboration with the senior treating clinician. Patients were excluded if there was a clear non–ACS cause for their symptoms (e.g., findings of pneumonia), they were unwilling or unable to provide informed consent, staff considered that recruitment was inappropriate (e.g., patients undergoing palliative treatment), they were transferred from another hospital, were pregnant, were previously recruited to the study within the past 45 days, or were unable or unwilling to be contacted after discharge. Recruitment included consecutive eligible cases during working hours at each site. Enrolment occurred between January 2008 and November 2010. All patients were managed according to standard care, which included electrocardiogram and troponin testing on presentation and at greater than six hours after presentation to the emergency department. Patients were classified into risk groups according to the Heart Foundation of Australia/Cardiac Society of Australia and New Zealand guidelines.[14] The clinical assay in use as the reference troponin assay was the Beckman Coulter second-generation AccuTnI (Beckman Coulter, Chaska, MN). A value above the 99th percentile of greater than 40ng/L was considered abnormal.

Original data were collected prospectively, using standardised case report forms.[15] Research nursing staff collected demographic and clinical data from patient interviews. Telephone follow-up and medical record review was conducted 30-days after initial attendance for the diagnosis of ACS. Information was obtained from the patient and from hospital databases about all additional cardiac

events, investigations, or contact with any health care providers during the 30-day period. Follow-up information was verified through contact with the health care provider, and original copies of medical records and investigations were obtained. Ethical approval of the research project HREC/14/QRBW/320 was obtained from the Royal Brisbane and Women's Hospital Human Research Ethics Committee (EC 00172) on 11th August, 2014. All patients provided written informed consent for data collection and the ethics committee waived the requirement for consent for this analysis.

Each patient was assigned one or more endpoints to explain the reason for their index presentation, or any events occurring within 30 days of admission. There were fifteen possible endpoints, including both cardiovascular and non-cardiovascular endpoints. Patients were considered to meet the definition for ACS if they were assigned any of the following endpoints; cardiovascular death, cardiac arrest, revascularisation procedure, cardiogenic shock, acute myocardial infarction, or unstable angina pectoris. One cardiologist from a group of three potential cardiologists adjudicated the outcome independently. Cardiologists had knowledge of the clinical record, electrocardiogram and troponin results from standard care and used such information to determine whether the patient met the predefined criteria for the cardiovascular endpoints[15]. Patients not meeting such endpoints were classed as having a non-cardiovascular problem. A second cardiologist from the group conducted a blind review of all ACS cases and 10% of non–ACS cases. In cases of disagreement, endpoints were agreed on by consensus by the two cardiologists involved in endpoint adjudication and one emergency physician. This was achieved for all endpoints.

In addition to sampling for routine clinical care, blood was drawn on presentation and two hours later. Samples were later tested with the ARCHITECT High Sensitive *STAT* Troponin-I assay (Abbott Laboratories, Abbott Park, IL). Laboratory technicians were blinded to patient data. The hsTnI assay has a 99th percentile concentration of 26.2ng/L with a corresponding co-efficient of variation of <5% and a limit of detection of 1.2ng/L.[16]

Cost prediction model

As described previously,[17] individual cost data were extracted from hospital administration records and adjusted for inflation to 2011 Australian Dollars. To use a consistent cost matrix across all strategies, a prediction model was developed in four steps. First, we analysed the data and predefined exclusion criteria (eTable1). Patients who received coronary bypass surgery (CABG) were excluded because they were transferred to another hospital for surgery with no available outcome data and unknown accuracy of cost information. Cases with inconsistent or missing costs were excluded. Patients with a hospital length of stay (LOS) greater than 12 days were excluded to reduce bias from non-cardiac stays. Second, we considered key activities for evaluating an acute coronary syndrome in a generalized Box-Cox transformed model. Third, we dropped non-significant variables (2nd troponin, p=0.9; stress echocardiography, p=0.6) from the predictor variables, checked for relevant multicollinearity between variables, and excluded cases that showed extreme discrepancies to the predicted results (n=4; eTable1). Fourth, we run the final analysis that led to the cost prediction model and the 95% confidence intervals for each predictor (eTable6). The final model was based on data from 891 individuals. The following predictors were used: ED time, inpatient time, performed activities (exercise stress test, myocardial perfusion scan, computed tomography coronary angiography, echocardiography, and angiography), admission to short-stay unit, or admission to an inpatient ward. More information is given in the supplement (eMethods).

Health economic model

We developed a microsimulation cost-effectiveness model that compared six assessment strategies (Table 1). The standard of care was based on a protocol using cardiac troponin I (cTnI) at baseline and 6 hours after arrival (Strategy 1). All other strategies utilised hsTnI at presentation and 2 hours. Strategy 2 (termed hsTnI) was the same as standard care except that a 2-hour highly sensitive

troponin was used rather than a 6-hour sensitive troponin. Strategy 3 (hsTnI+LoD) also utilised a 2 hour hsTnI, but allowed a patient to be directly ruled out on admission with no further work-up if their baseline hsTnI was below the assay's limit of detection (LoD). Strategy 4 (hsTnI+ADP) utilised baseline and 2 hour hsTnI but enabled patients to be directly ruled out with no further work-up using the modified ADAPT ADP. That is, patients could be ruled out if their TIMI risk score was <=1, their baseline and 2 hour troponin were below the diagnostic cut off, and their presentation ECG was non ischaemic. Strategy 5 (hsTnI+LoD+ADP) was a combination of Strategies 3 and 4 in that patients could be ruled out if their baseline hsTnI was below the LoD or if they met the criteria according to the modified ADAPT ADP. Finally, Strategy 6 (hsTnI+LoD+ADP+direct rule in) employed the same rule -out criteria as Strategy 5, but also enabled patients with hsTnI at presentation >52ng/L to be directly ruled-in and admitted for ACS management.[18]

The model structure and the evaluation pathway are described in Figure 1 and eFigure 1, respectively. Individuals entering the model were stratified in the ED based on individual characteristics, first electrocardiogram, and baseline troponin. Patients classified as high-risk were admitted to inpatient cardiology. Low-risk patients were kept in the emergency department to await final assessment. Intermediate-risk patients were referred to the short stay unit (SSU) for further cardiac workup. Patients referred to the SSU or inpatient ward were counted as admitted.

If the final troponin was performed later than 6.30pm, patients stayed overnight. Total LOS comprised emergency department LOS, short stay unit LOS and inpatient stay. The maximum LOS was limited to 12 days to avoid bias in the effects from prolonged stays in patients with non-cardiac diagnoses. A 30-day follow-up event was assumed for individuals who were ruled-out by the respective strategy, and who had a reported 30-day clinical outcome of ACS.

A minimum required dataset was defined for the cohort used in the model (eTable 2), and 219 patients with missing troponin values were excluded. Work-up, work-up duration, and length of stay were analysed from the model cohort and transformed into statistical distributions. Patient attributes (age, sex, clinical characteristics, adjudicated diagnosis, electrocardiogram status, and troponin values) were individually sampled from the model cohort by bootstrapping. This created a hypothetical cohort of 40,000 patients who followed the model for each of the strategies. Work-up and times for each patient were randomly sampled from distributions. Costs were estimated by considering attributes, work-up activities, work-up duration, and length of stay in the cost prediction model with coefficients individually sampled from the 95% confidence interval of the respective predictor. The model followed a 30-day hospital perspective. Costs for the index event and follow-up were estimated from the cost prediction model.

Differences between strategies were expressed in terms of total hospital costs per patient and diagnostic accuracy. Diagnostic accuracy was defined as the percentage of correctly diagnosed patients compared to the final adjudicated diagnosis. In addition, LOS, referral rates, admission rates, and overnight stays were evaluated. We conducted one-way and probabilistic sensitivity analyses to test the robustness of the micro simulation results. Model structure, parameters and assumptions are described in detail in the supplement.

Patient Involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. Patients were asked whether they wished to receive a summary of these results. These individuals were posted a lay summary of the results.

RESULTS

Cost prediction and model validation

Characteristics of 719 patients meeting the minimum required dataset for the model and of the generated cohort of 40,000 patients are described in the supplement (eTable 5). The cost prediction model showed excellent regression quality (R-square 88.3%; eTable 6). The model was validated for the standard strategy against actual statistics with good prediction accuracy for all patients (p-value vs. actual costs: 0.723) as well as for low-, intermediate- and high-risk patients (p= 0.946, 0.256, 0.761, respectively; Table 2).

Patient referral and management

During initial assessment, 1.3% of patients were classified as low-risk and managed in the emergency department. 6.1% of patients met the criteria for a direct rule-out (baseline hsTnI below the limit of detection) and were re-classified as low-risk. The modified ADAPT accelerated diagnostic protocol (ADP) was effective for 49% of patients and reclassified 75% of intermediate-risk patients to low risk. The direct rule-in criteria (baseline hsTnI>52ng/L) applied to 7.2% of patients.

Strategies considering LoD avoided short-stay unit admissions for 4.9% of patients (-7.5% vs. standard care, Table 3). The number of ward admissions did not change with hsTnI alone. Utilising the LoD, ADP, or a combination of both, resulted in a stepwise and significant reduction of the ward admission rate from 49.6% to 37.1% (-25%; Table 3).

A 4-hour reduction in protocol time (cTnI vs. hsTnI: Mean 6.2h (Range 5.0 – 10.0h) vs. 2.3h (1.5 - 5.0h)) resulted in earlier management decisions (eFigure 4). Consequently, strategy-2 led to 30% fewer overnight stays compared to standard care (60.3% vs. 42.0%, Table 3). Incorporating additional rule-out to hsTnI options further streamlined patient assessment, decreasing overnight stays by up to 43%.

3.2% of patients with a negative or stable cTnI status had a positive hsTnI status indicative of an acute event (eTable 8). Conversely, 3.0% of patients had an acute sensitive TnI finding but a negative or stable troponin status with hsTnI. In total, the number of referrals to ACS management based on an acute troponin finding did not differ if replacing cTnI with hsTnI (cTnI: 11.9%; hsTnI: 12.1%; p=0.549). Patients with negative or stable troponin conditions were admitted for ACS management and further workup if such as an exercise stress test or myocardial perfusion scan led to positive findings, resulting in a referral rate of 32% (Table 3). Strategies considering the LoD or ADP rules respectively led to 5% or 35% fewer patients referred for ACS management compared to standard care. Additional direct rule-in criteria (Strategy-6 vs. 5) did not identify more patients requiring ACS management but allowed for earlier cardiac intervention for 46.6% of ACS patients.

Length of stay and costs

A significant reduction in LOS was observed if hsTnI replaced cTnI, with a mean saving of 6.2 hours (p<0.001, Table 3). Applying LoD or ADP rules to hsTnI saved an additional stay of 1.0 and 5.4 hours respectively. LOS times for ACS patients were stable between strategies (eTable 9). However, applying hsTnI to standard care resulted in a significant reduction of LOS for non-ACS patients. Substantially decreased 75th percentiles of the LOS for all strategies considering the ADP indicated its considerable streamlining effect. Details for emergency department and SSU times are given in the supplement (eTable 10).

Significant cost reductions compared to standard care were found with all hsTnI strategies ($133-$491, p<0.001, Table 3). This effect was caused by substantial cost reductions for non-ACS patients. No difference between strategies was observed for ACS patients (eTable 9). As stated in Table 3, costs during the index stay and follow-up decreased for all hsTnI-supported strategies compared to standard care. The consideration of ADP and LoD alone, or in combination, in addition to hsTnI

protocols resulted in further significant cost savings. Applying a direct rule-in strategy (Strategy-6) to a combination of hsTnT+ LoD+ADP did not result in significant overall costs benefits.

Patient outcome and cost-effectiveness

The introduction of hsTnI into standard care did not alter overall diagnostic accuracy (p=0.86, Table 3, Figure 2), but increased the number of patients referred for ACS management who had a final diagnosis of non-ACS (p=0.056; False-positives in Table 4). While all hsTnI supported strategies avoided false-negative diagnoses compared to standard care, a statistically significant reduction of the false-positive rate was observed for all strategies utilizing an ADP. Applying LoD and ADP to hsTnI reduced the number of false-positives by 6% (p=0.015) and 52% (p<0.001) respectively, whereas no effect was observed on the false-negative rate (Table 4).

Strategy-5 (a protocol utilising hsTnI, ADP, and LoD) was found to be the dominant strategy in the study, providing better accuracy at lower costs (Figure 2).[19] Switching from standard care to Strategy 5 saved $486 per patient (p<0.001) and increased the diagnostic accuracy from 90.0% to 94.0% (p<0.001).

Conducting multiple runs in a probabilistic sensitivity analysis revealed consistent benefits confirming the robustness of micro simulation results (eFigure 6; eTable 11). HsTnI demonstrated equal or better diagnostic accuracy compared to cTnI in 79% of runs, with a stable average cost saving per patient ranging from $113 to $147. The hsTnI strategy helped to manage 82.6% of individuals at lower costs compared to standard care; 10.2% or 7.1% of patients were treated at equal or higher costs, respectively.

DISCUSSION

The cost-effectiveness of incorporating hsTnI into management protocols for patients presenting to the emergency department with chest pain has received increasing attention. HsTnI has been suggested to generate substantial benefits in the emergency department. Accelerated diagnostic protocols (ADPs) have been found to reduce the average emergency department length of stay in low-risk patients while health outcomes were maintained.[5, 11] To the best of our knowledge, this is the first study evaluating health economic implications of several hsTnI enabled assessment algorithms in the emergency department from a hospital perspective, thus complementing previous research that followed lifetime effects from a health systems perspective.[20-24]

Complex management algorithms that are based on individual patient attributes, plus the heterogeneity of the emergency department population, require an individual-level modelling design. [25] This allows for more realistic comparisons of different settings, assessment strategies, or risk stratification rules. As opposed to other evaluations, costs and all management assumptions in this study were based on actual and individual patient information of a single trial-based cohort. The sampling strategy created a wide spectrum reflecting population heterogeneity and common variation in clinical practice. [26] The clinical picture and additional information from objective testing were also considered in the simulation. We believe that this set the foundation for a consistent evaluation of the benefits that would accrue on the hospital level from implementing hsTnI-enabled algorithms.

We developed a cost prediction model for chest pain patients presenting to ED, and we conducted a patient-level economic analysis for comparing different hsTnI-enabled algorithms, validated against standard care. The analysis demonstrated that the implementation of hsTnI substantially reduced LOS and costs for patients enrolled in the chest pain pathway compared to standard care. Such benefits occurred without reducing diagnostic accuracy. Moreover, the introduction of hsTnI allows for combining additional validated management rules (LoD, ADP). The overall organizational benefits

of the dominant strategy (Strategy-5) compared to standard care were caused by two effects: a) a substantial time reduction in protocol time, and b) significantly improved stratification efficiency.

The significant decrease in overnight stays resulted in downstream effects of accelerated protocols on patient management. A 4-hour reduction in protocol time led to a 6.2-hour saving in LOS. By utilizing the ADP, the timeliness of the second hsTnI result freed an additional 7.4 hours per patient. This strategy saved around 60% of overnights stays and 15% of costs compared to standard care.

In line with the definition for a high-sensitive troponin assay, [16] measurable concentrations above the LoD were found for 94% of non-ACS patients; only 6% of individuals were eligible for a direct rule-out considering the LoD criteria. This proportion appeared to be modest compared to the ADP that captured almost 50% of patients. Nevertheless, switching from Strategy-4 (hsTnI+ADP) to Strategy-5 (hsTnI+LoD+ADP) resulted in a significant reduction in the number of admissions to the short-stay unit and wards. This was caused by the fact that the LoD-rule moved 4.7% of patients from an accelerated rule-out after the 2nd troponin (ADP), to a direct rule-out after the baseline troponin (LoD). In addition, the strategy including LOD classified 1.4% of patients, who were not captured by the ADP, as eligible for a direct rule-out. As a result, a total costs were significantly reduced for Strategy 5 compared to Strategy 4 (p=0.02). The combined strategy of utilizing hsTnI and LoD within the ADP helped to avoid 7.5% of short stay unit admissions and 25% of unnecessary inpatient ward admissions.

Strategy-6 (including a direct rule in) did not significantly differ from Strategy-5 in terms of costs and diagnostic accuracy. All patients meeting the criteria of a highly elevated baseline hsTnI (≥52mg/L) were classified as high-risk and admitted to inpatient cardiology by all other strategies. Therefore, Strategy-6 did not result in a change in admission rates. However, the key value of Strategy-6 was the immediate referral to cardiology: 46.6% of patients finally diagnosed with ACS would receive

earlier cardiac intervention. Given the fact that all patients in the underlying observational study were managed by standard care, data on potential outcome effects of an earlier cardiac treatment were not available, and thus not captured in the health economic evaluation.

Some limitations deserve attention. The analysis was based on a single-centre cohort, which may limit the generalizability of the findings. Given the nature of a trial-based, individual level simulation, patient attributes were limited to the actual cohort; e.g. the impact of variation in ACS prevalence could not be tested in a sensitivity analysis. Management and cost data extracted from administrative databases may have some inaccuracies. Each of the 719 individuals from the cohort were run through the model on average 55 times with consistent characteristics, but varied in terms of protocol, treatment times, LOS, optional work-up decisions, and accrued costs. The generated cohort of 40,000 individuals reflected heterogeneity in patient management and addressed some of the uncertainty. The referral of patients followed strict and standardised assumptions. Deviation from recommended pathways may occur probably due to individual preferences or logistic effects such as access block.[27]Some of the potential flow issues were addressed by assuming a wide range in the initial assessment time (6–118 minutes). The predictors used in the cost model were limited to information about risk assessment and stratification; information about inpatient management other than inpatient time was not available. Patients with a long-term stay were excluded from the analysis in order to mitigate this potential risk of bias.

Economic implications from breaching specific emergency department targets or access blocks were not taken into account but may have a significant impact. Based on the findings of this study, it appears likely that considering such aspects would strengthen the results in favour of accelerated protocols. The model compared a sensitive troponin assay at 6 hours to highly sensitive assay at 2 hours. For the models not utilizing the LoD, it is unclear whether a sensitive troponin taken at 2 hours would provide the same benefits outlined here with a highly sensitive assay. The cost

prediction did not account for different costs of troponin assays. Compared to the magnitude of the difference between sensitive TnI and hsTnI strategies this effect was regarded as negligible.

CONCLUSION

This trial based economic modelling study sought to the impact of different hsTnI protocols on direct hospital costs and diagnostic accuracy compared to standard care. We found that emergency department assessment strategies utilising hsTnI are very likely to be cost-effective and provide cost savings on a hospital level when compared to sensitive TnI protocols for patients presenting with symptoms consistent with ACS. This is mainly due to a positive effect on the majority of patients not diagnosed with ACS. In particular, hsTnI-enabled algorithms considering additional rule-out criteria (LoD, ADP) are expected to improve the accuracy of both referral to inpatient wards or safe discharge as appropriate. Implementation of these protocols would provide direct benefits for the hospital in terms of reduced admission rates, avoided overnight stays, and improvements in time-based emergency department performance measures, thereby contributing to streamlined emergency department processes, more efficient use of resources, and overall cost savings.

Data sharing

Statistical code is available from the lead author.

Contributors

All authors had full access to the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. JG, LC and WP led the clinical study design as part of the Asia-Pacific Evaluation of Chest Pain Trial (ASPECT). JG extracted the dataset required for the modelling study. PJ developed the health economic model and run the analysis. Model design and assumptions were reviewed by all authors. All authors contributed in the interpretation of results, writing the manuscript, and critically reviewing each draft of the manuscript. The final version was approved by all authors. The study was supervised by LC.

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Conflicts of interest disclosures

All authors completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. PJ is a full-time employee of Abbott Diagnostics. JG has received funding from the Queensland Emergency Medicine Research Foundation. WP has received funding from the Queensland Emergency Medicine Research Foundation, Abbott Diagnostics, Roche, Alere, and Beckmann Coulter for research on diagnostic protocols; and honoraria, travel expenses, and consultancy fees from

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Transparency Declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1. Assessment strategies evaluated in the model

No	Strategy	Troponin assay	Protocol	Diagnostic cut-off [a]	Dynamic cut-off [b]	Direct rule-in [c]	Direct rule-out [d]	Accelerated rule-out [e]	Reference
1	Standard	cTnI	0 / 6hrs	> 40.0	delta < 10	No	No	No	Standard Care
2	hsTnI	hsTnI	0 / 2hrs	> 26.2	delta < 2	No	No	No	9, 11
3	hsTnI+LoD	hsTnI	0 / 2hrs	> 26.2	delta < 2	No	Yes	No	9, 12
4	hsTnI+ADP	hsTnI	0 / 2hrs	> 26.2	delta < 2	No	No	Yes	4, 9
5	hsTnI+LoD+ADP	hsTnI	0 / 2hrs	> 26.2	delta < 2	No	Yes	Yes	4, 9, 12
6	hsTnI+LoD+ADP +direct rule in	hsTnI	0 / 2hrs	> 26.2	delta < 2	Yes	Yes	Yes	4, 9, 12, 18

All values in ng/L.

cTnI= sensitive cardiac troponin I; hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP= Modified ADAPT accelerated diagnostic protocol; ADAPT=2-Hour Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker trial

[a] A troponin value greater than the diagnostic cut-off was considered as elevated.

[b] A delta between troponin values at different time points of less than 10ng/L (cTnI) or 2ng/L (hsTnI) was used to distinguish and rule-out a rise and/or fall in troponin associated with acute cardiac conditions.

[c] Direct rule-in of individuals with a hsTnI value at baseline above 52ng/L.

[d] Direct rule-out of individuals with a hsTnI value at baseline below the limit of detection of 1.2 ng/L (LoD).

[e] Referring to the Modified ADAPT accelerated diagnostic protocol (ADP). Accelerated rule-out applied to individuals with hsTnI values at 0 and 2h below the diagnostic cut-off and a TIMI risk score ≤1.

Table 2. Comparison of cost data and model validation.

Total costs, $	Item	Cullen 2015 [7]	Model cohort[a]	Model prediction[b]	Prediction vs. Cohort (p-value)
All	n (%)	926 (100%)	719 (100%)	719 (100%)	
	Mean cost (95%CI)	5272 (4835 - 5708)	5303 (4796 - 5810)	5437 (4897 - 5977)	0.72
	Median cost (25th-75th percentile)	2433 (1458 - 6778)	2497 (1449 - 6663)	2169 (1747 - 6384)	
Low Risk	n (%)	9 (1.0%)	9 (1.3%)	9 (1.3%)	
	Mean cost (95%CI)	2040 (1306 - 2774)	2040 (1125 - 2955)	2010 (1559 - 2460)	0.95
	Median cost (25th-75th percentile)	1530 (1298 - 3050)	1530 (1080 - 3359)	1907 (1569 - 2438)	
Intermediate Risk	n (%)	580 (62.6%)	468 (65.1%)	468 (65.1%)	
	Mean cost (95%CI)	3304 (2963 - 3644)	3413 (3050 - 3775)	3755 (3288 - 4223)	0.26
	Median cost (25th-75th percentile)	1849 (1376 - 3570)	1925 (1389 - 3628)	1946 (1668 - 3270)	
High Risk	n (%)	329 (35.5%)	242 (33.7%)	242 (33.7%)	
	Mean cost (95%CI)	8919 (7971 - 9867)	9081 (7878 - 10284)	8816 (7593 - 10040)	0.76
	Median cost (25th-75th percentile)	6452 (2650 - 11829)	6405 (2752 - 11309)	5566 (2355 - 11130)	

All costs referred to inflated costs in Australian dollars.

CI=confidence interval

a Excluded individuals not meeting the minimum required dataset for the model

b Excluded individuals with cost-outliers, missing and inconsistent data.

Table 3. Main model outcomes of different troponin supported assessment strategies

Indicator		Strategy 1 (Standard)	Strategy 2 (hsTnI)	Strategy 3 (hsTnI+LoD)	Strategy 4 (hsTnI+ADP)	Strategy 5 (hsTnI+LoD+ADP)	Strategy 6 (hsTnI+LoD+ADP+ direct rule- in)
Short stay unit admissions[a], %	Mean (95% CI)	65.3 (64.8 - 65.7)	65.3 (64.8 - 65.7)	60.4 (59.9 - 60.8)	65.3 (64.8 - 65.7)	60.4 (59.9 - 60.8)	60.4 (59.9 - 60.8)
	Incremental[b] (p-value)		0.0 (1.00)	-4.9 (<0.001)	4.9 (<0.001)	-4.9 (<0.001)	0.0 (1.00)
Ward admissions[a], %	Mean (95% CI)	49.7 (49.2 - 50.2)	49.6 (49.1 - 50.1)	47.4 (46.9 - 47.9)	38.4 (37.9 - 38.9)	37.1 (36.6 - 37.6)	37.1 (36.6 - 37.6)
	Incremental[b] (p-value)		-0.1 (0.81)	-2.3 (<0.001)	-9.0 (<0.001)	-1.3 (<0.001)	0.0 (1.00)
Overnight stays, %	Mean (95% CI)	60.3 (59.8 - 60.8)	42.0 (41.5 - 42.5)	39.8 (39.3 - 40.3)	24.4 (24.0 - 24.8)	23.9 (23.5 - 24.3)	24.1 (23.7 - 24.5)
	Incremental[b] (p-value)		-18.3 (<0.001)	-2.2 (<0.001)	-15.4 (<0.001)	-0.5 (0.08)	0.2 (0.51)
Referral to ACS management, %	Mean (95% CI)	32.4 (32.0 - 32.9)	32.2 (31.8 - 32.7)	30.9 (30.5 - 31.4)	21.0 (20.6 - 21.4)	20.7 (20.3 - 21.1)	20.9 (20.5 - 21.3)
	Incremental[b] (p-value)		-0.2 (0.56)	-1.3 (<0.001)	-9.9 (<0.001)	-0.3 (0.26)	0.3 (0.37)
Length of stay, hours	Mean (95% CI)	34.0 (33.6 - 34.4)	27.8 (27.4 - 28.2)	26.8 (26.4 - 27.3)	20.4 (20.0 - 20.9)	20.1 (19.6 - 20.5)	20.4 (19.9 - 20.8)
	Incremental[b] (p-value)		-6.2 (<0.001)	-1.0 (0.002)	-6.4 (<0.001)	-0.4 (0.23)	0.3 (0.33)
Diagnostic accuracy (E), %	Mean (95% CI)	90.0 (89.7 - 90.3)	90.0 (89.7 - 90.3)	90.5 (90.2 - 90.8)	93.6 (93.4 - 93.8)	93.7 (93.5 - 93.9)	94 (93.7 - 94.2)
	Incremental[b] (p-value)		0.0 (0.86)	0.4 (0.04)	3.1 (<0.001)	0.1 (0.54)	0.3 (0.13)
Index costs per patient, $	Mean (95% CI)	3029 (3001 - 3058)	2923 (2894 - 2952)	2846 (2816 - 2875)	2621 (2592 - 2649)	2568 (2539 - 2596)	2582 (2553 - 2610)
	Incremental[b] (p-value)		-106 (<0.001)	-77 (<0.001)	-225 (<0.001)	-53 (0.01)	14 (0.51)
Follow-Up costs per patient, $	Mean (95% CI)	238 (225 - 250)	211 (199 - 223)	211 (199 - 223)	213 (201 - 225)	213 (201 - 225)	195 (183 - 206)
	Incremental[b] (p-value)		-26 (0.003)	0 (1.00)	2 (0.82)	0 (1.00)	-18 (0.03)
Total costs per patient (C), $	Mean (95% CI)	3267 (3236 - 3297)	3134 (3103 - 3165)	3057 (3026 - 3088)	2834 (2804 - 2864)	2781 (2751 - 2811)	2776 (2746 - 2807)
	Incremental[b] (p-value)		-133 (<0.001)	-77 (0.001)	-223 (<0.001)	-53 (0.02)	-5 (0.83)

hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP= Modified ADAPT accelerated diagnostic protocol; ACS=acute coronary syndrome

All stated costs are in Australian dollars. (E) and (C) used as main measures of outcome.

[a] Patients could be admitted to the short stay unit before being referred to inpatient ward; numbers may not sum up to 100%.

[b] Incremental values compared to next best alternative to the left.

Table 4. False-negative and false-positive diagnosis of different assessment strategies

Strategy	False positives, %			False negatives, %		
	Mean	(95% CI)	p-value	Mean	(95% CI)	p-value
(1) Standard	6.6	(6.4 - 6.9)		3.4	(3.2 - 3.6)	
(2) hsTnI	7.0	(6.7 - 7.2)	0.06[a]	3.0	(2.8 - 3.2)	0.002[a]
(3) hsTnI+LoD	6.5	(6.3 - 6.8)	0.62[a]; 0.02[b]	3.0	(2.8 - 3.2)	0.002[a]; 1.00[b]
(4) hsTnI+ ADP	3.4	(3.2 - 3.5)	<0.001[a,b]	3.0	(2.9 - 3.2)	0.005[a]; 0.84[b]
(5) hsTnI+LoD+ADP	3.3	(3.1 - 3.4)	<0.001[a,b]	3.0	(2.9 - 3.2)	0.005[a]; 0.84[b]
(6) hsTnI+LoD+ADP+direct rule-in	3.3	(3.1 - 3.4)	<0.001[a,b]	2.8	(2.6 - 2.9)	<0.001[a]; 0.05[b]

False positives: Number of patients admitted for ACS management with a 30-days final diagnosis of non-ACS.

False negatives: Number of patients not admitted for ACS management with a 30-days final diagnosis of ACS.

hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP= Modified ADAPT accelerated diagnostic protocol; ACS=acute coronary syndrome

[a] p-value vs. Strategy-1 (Standard Care)

[b] p-value vs. Strategy-2 (hsTnI)

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Figure 1. Basic model structure

[a] In strategy 6: if hsTnI at baseline ≥52ng/L.

[b] In strategies 3,5, and 6: if hsTnI at baseline ≤1.2ng/L (limit of detection).

[c] In strategies 4,5, and 6: if hsTnI values at baseline and 2h are below the diagnostic cut-off of 26.2ng/L, and TIMI risk score ≤1, according to the Modified ADAPT accelerated diagnostic protocol (ADP).

Figure 2. Cost-effectiveness matrix

Strategy code: (1) Standard, (2) hsTnI, (3) hsTnI+LoD, (4) hsTnI+ADP, (5) hsTnI+LoD+ADP, (6) hsTnI+LoD+ADP+direct rule-in.

Costs include index costs and 30-days follow-up costs from the hospital perspective.

Diagnostic accuracy refers to the adjudicated final diagnosis of ACS within 30 days after presentation to the emergency department.

Each data-point reflects the strategy specific mean value and 95% confidence interval of 40,000 iterations.

hsTnI=Highly sensitive cardiac troponin I; LoD=Limit of detection; ADP=Modified ADAPT accelerated diagnostic protocol

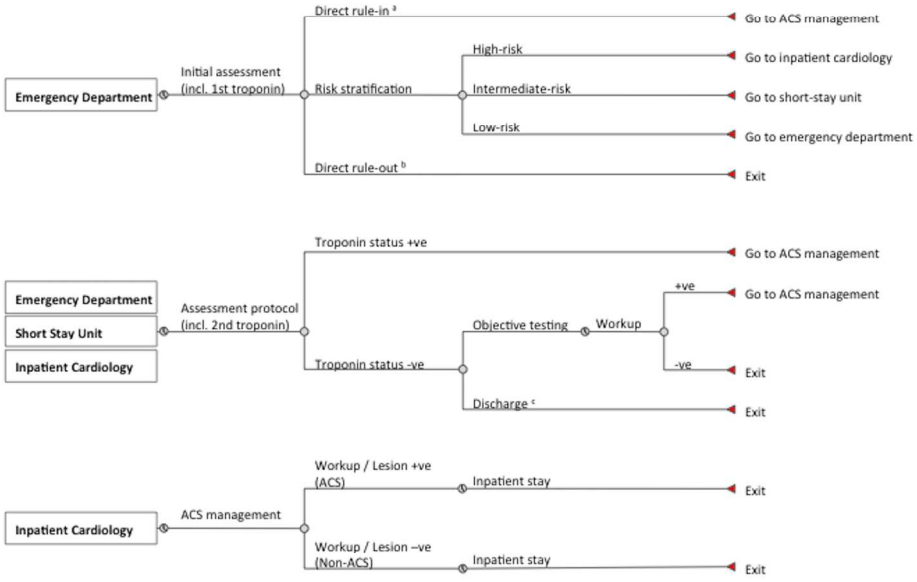

Figure 1. Basic model structure

‼ ┼ a In strategy 6: if hsTnI at baseline ≥52ng/L%

b In strategies 3,5, and 6: if hsTnI at baseline ≤1.2ng/L (limit of detection).

┼ c In strategies 4,5, and 6: if hsTnI values at baseline and 2h are below the diagnostic cut-off of 26.2ng/L, and TIMI risk score ≤1, according to the Modified ADAPT accelerated diagnostic protocol (ADP).

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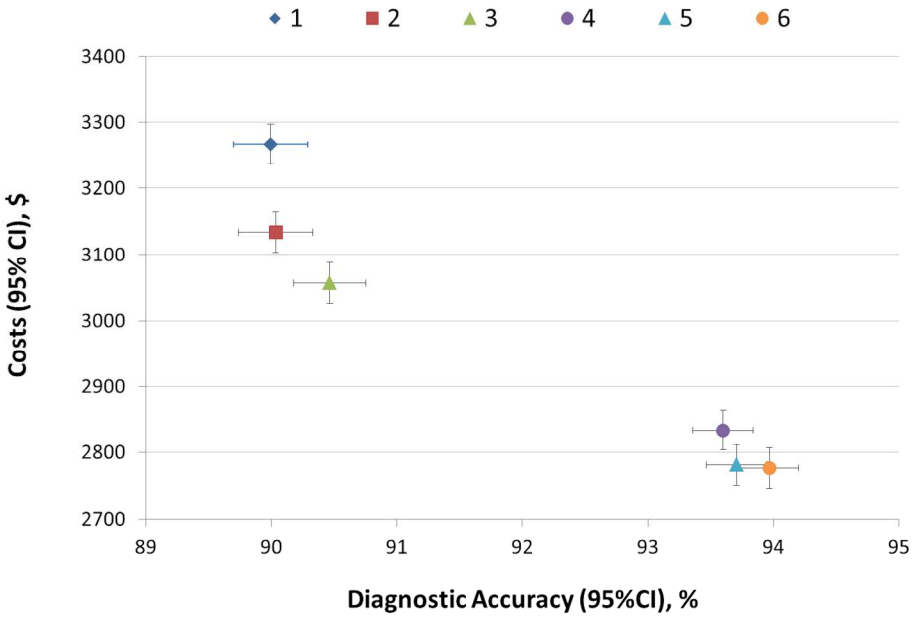

Strategy code: (1) Standard, (2) hsTnI, (3) hsTnI+LoD, (4) hsTnI+ADP, (5) hsTnI+LoD+ADP, (6) hsTnI+LoD+ADP+direct rule -in.┼ Costs include index costs and 30-days follow-up costs from the hospital perspective.┼ Diagnostic accuracy refers to the adjudicated final diagnosis of ACS within 30 days after presentation to the emergency department.┼ Each data-point reflects the strategy specific mean value and 95% confidence interval of 40,000 iterations.┼ hsTnI=Highly sensitive cardiac troponin I; LoD=Limit of detection; ADP=Modified ADAPT accelerated diagnostic protocol┼

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The organizational value of diagnostic strategies using high sensitivity troponin for patients with possible acute coronary syndromes: A trial-based cost-effectiveness analysis

SUPPLEMENTARY ONLINE CONTENT

Contents

eMethods 1. Micro simulation model

Troponin testing

After blood was drawn, samples for hsTnI testing were immediately centrifuged. Serum and EDTA plasma were separated and stored frozen at -80°C, within two hours. During March and April, 2012, previously unthawed samples were thawed, mixed, and centrifuged prior to analysis. The assay used was the final pre-commercial release version of the ARCHITECT High Sensitive STAT Troponin-I assay (Abbott Laboratories, Abbott Park, IL). The hsTnI assay has a 99th percentile concentration of 26.2ng/L with a corresponding co-efficient of variation of <5% and a limit of detection of 1.2ng/L. [1] Long-term stability of TnI has been demonstrated previously. [2]

Cost prediction model

In alignment with the study focus, activities that were available by patient were limited to the risk assessment and stratification period (ECG, stress test, troponin testing, MPS, CTCA, angiography, etc.). Information about inpatient treatment and management other than inpatient time were not available. Thus, the prediction of total costs based on the available data was expected to be biased with increasing inpatient time. In fact, the average costs per inpatient day decreased with increasing stay until a slight increase appeared for patients staying more than 15 days. This was regarded as an indicator for costs accrued from activities not captured in the collected data. By further analyzing the data, we excluded 2.5% of patients with an inpatient stay of more than 12 days, as this was the maximum length of stay threshold that did not affect quartiles, median, and the 95th percentile of the cost distribution of the original data, but also excluded effects of unknown inpatient activities from the prediction model.

Patient pathway

Patients were classified into risk groups according to the Queensland chest pain pathway (eFigure 1).[3] Low-risk patients were treated in the ED; intermediate-risk patients were managed in the ED with admission to the ED short-stay unit. High-risk patients were referred to inpatient cardiology. Patients requiring CABG were transferred to another institution.

Health economic model

The model distinguished five troponin statuses (eTable 3). On a positive troponin status, patients were referred to inpatient cardiology. Patients with a negative troponin status underwent further testing for coronary ischemia.

Further testing included the evaluation of the troponin status after the second test and additional objective testing (exercise stress test, myocardial perfusion scan, stress echocardiography, computed tomography coronary angiography or angiography). If objective testing was negative, patients were eligible for discharge from the chest pain pathway and exit the model. If objective testing or troponin results were positive, patients were referred for acute coronary syndrome (ACS) management in the inpatient ward.

In the accelerated diagnostic protocol (ADP) scenarios, patients meeting the Modified 2-hour Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker trial (ADAPT) criteria for low risk patients (thrombosis in myocardial infarction (TIMI) score ≤1 and hsTnI ≤ upper limit of normal (ULN)) were discharged and exited the model without further testing and workup.

Diagnosis was compared to the final adjudicated 30-days diagnosis for calculating the diagnostic accuracy. A follow-up event within 30 days was assumed for individuals ruled-out by the respective strategy, and a reported 30-days clinical outcome of ACS (False-negative patients).

Occurrences and results of workup testing per individual were randomly sampled from binomial distributions on the basis of the troponin status using actual probabilities derived from the study cohort. Duration of workup was analyzed from the model cohort and transformed into statistical distributions. Times were randomly sampled from these distributions individually during simulation. To reflect the heterogeneity of hospital stay, LOS data of the

model cohort were analyzed by final diagnosis (ACS, Non-ACS) and electrocardiogram status (normal, ischemic, abnormal).

Hospital LOS times were randomly sampled per individual from distributions with values limited between the observed minimum and maximum of the cohort. Inpatient stay was calculated by deducting all inpatient activities from the sampled LOS times. Inpatient time was only considered for individuals that were referred to ACS management. All next day discharges were counted as overnight stays.

Regression coefficients for predicting index costs were randomly sampled per individual case with a uniform distribution between the lower and upper bound of the 95% confidence interval. Follow up cost data were estimated by assuming that the patient was admitted to cardiology for angiography with an emergency department-LOS of one hour, 3 inpatient days, no exercise stress test, no myocardial perfusion scan, no computed tomography coronary angiography, and no echocardiography. Follow-up costs were assigned by randomly sampling from a uniform distribution between the upper and lower limit of the 95% CI of the predicated costs of this scenario ($5402-$8628).

The appropriate number of samples was estimated by conducting several pilot runs estimating the effect size. A reasonable distinction between confidence intervals for costs, an acceptable consistency between multiple run (n=5) and single run results, and a between-run variability of below 10% were used as criteria.[4] We regarded the latter as particularly important since it would allow for meaningful comparisons between different scenarios, settings and assumptions in subsequent evaluations. Based on results of the pilot runs (eFigure 2A-B) the sample size was set to 40,000 patients.

For the probabilistic sensitivity analysis Strategy-2 was compared against Strategy-1 by repeating the micro simulation 250 times with 40,000 patients each. Mean results and 95% confidence intervals for costs, referral accuracy, and diagnostic accuracy were compared to the micro simulation results (eFigure 6; eTable 11).

The impact of protocol time on costs was tested by running Strategy-2 and assuming constant troponin values and increasing but fixed protocol times. Variation in the discharge threshold between 6pm and 10pm were tested and compared to a scenario with no daytime restriction for discharge. Both analyses were done by sampling 40,000 individuals in 5 independent runs.

Model was developed in TreeAge Pro 2015, R1.0 (TreeAge Software, Williamstown, MA, USA). Statistical analyses were done in Minitab 16.1.0. A significance level of 0.05 was used in all analyses. Continuous data were analyzed conducting a 2-Sample t-test and Mann-Whitney test. For categorical data Fisher's exact test was used.

Additional information

By randomly sampling from the database, each of the 719 individual patients was sampled on average 55 to 56 times (Range 36 – 78). Each sample of a patient was consistent in age, sex, characteristics, ACS status and troponin values, but varied in terms of arrival time, protocol time, treatment times, additional cardiac testing if required, total inpatient LOS if referred for ACS management, and costs predictors. This generated a huge cohort of patients that reflected variation and heterogeneity in decision making, severity, and management. The result of the sampling approach is demonstrated in eFigure 3 which shows distribution of costs of the first 10 individuals as an example. Given the fact that cardiac testing such as exercise stress testing or myocardial perfusion scanning could potentially lead to positive results in patients with negative ACS condition (eTable 4A) some repetitions generated positive workup results that led to ACS management referrals (Italic numbers in eFigure 3). The inpatient stay after stratification and workup was by assumption only considered for patients referred to ACS management. Therefore, the observed variation in costs for patients referred to ACS management is mainly driven by variation in length of stay reflecting different treatments, underlying diseases, severity or management decisions. There was a potential risk that this variation would superimpose the focus of the study to evaluate different assessment strategies.

In line with a long-term perspective, previous research did not consider short term effects for hospitals or variation in troponin protocol time.[5-9] This model used a distribution around the recommended target derived from actual data reflecting a more realistic scenario (eFigure 4A).

eFigure 5 provides histograms of SSU times. The majority of patients were admitted to short stay unit (65% with short stay unit time > 0hrs, eFigure 5A); in the standard strategy utilizing cTnI some patients were managed around a mean of 7.5 hours, some required additional observation with a mean of 25.0 hours indicating overnight

stays. Replacing cTnI with hsTnI resulted in a substantial shift to lower short stay unit times as shown by mean values of 4.0 hours and 22.5 hours for those staying overnight (eFigure 5B). An additional direct rule-out strategy (limit of detection, LoD) decreased the number of short stay unit admissions significantly as indicated by an increased proportion of patients at 0h in eFigure 5B. As illustrated in eFigure 5C accelerated rule-out protocols for low risk patients (ADP) moved the SSU time distribution to distinctly lower values.

Testing the influence of different protocol times revealed that protocols with lower time targets would be less affected by variation and delays (eFigure 7). As a practical consequence, accelerated algorithms could be expected to result in more stable and more predictable emergency department processes, thus allowing for better management and resource allocation.

Patients may not be discharged immediately even if they are regarded as low risk. Prolonged protocol times could cause some clinically unnecessary overnight stays at the hospital's expense. We used the discharge threshold time to reflect such specific management rules. Since the threshold may not be fixed in real life we tested the impact of some flexibility. Data in eFigure 8 reveal no significant observable effect of a flexible threshold time on Strategy 2 (hsTnI) whereas Strategy 1 (cTnI, standard care) was strongly affected between 6 and 8pm. Although these findings depend on emergency department arrival pattern results suggested that hsTnI enabled algorithms would be less affected by variation. Given the fact that arrival pattern used in the model was derived from actual data accelerated protocols would likely lead to more stable and predictable emergency department processes.

eTable 1. Patient selection criteria: Cost prediction model

Criteria	Excluded	N
All data		938
Exclude patients with CABG*	-14	924
Exclude long-stay outliers >12d (incl. non-cardiac complications)	-23	901
Exclude inconsistent or missing data	-6	895
Analyze extreme outliers	-4	891

*Patients receiving coronary bypass surgery (CABG) were excluded for the cost prediction model. Costs were unknown as patients were transferred to another hospital for surgery.
CABG=Coronary artery bypass graft

eTable 2. Patient selection criteria: Micro simulation model

Minimum required dataset	Excluded	N
Basic characteristics	0	938
Time points stated	0	938
ECG information available	0	938
Baseline cTnI	0	928
Baseline hsTnI	-145	793
Second cTn (6hrs)	-57	736
Second hsTnI (2hrs)	-17	719
Final endpoint	0	719

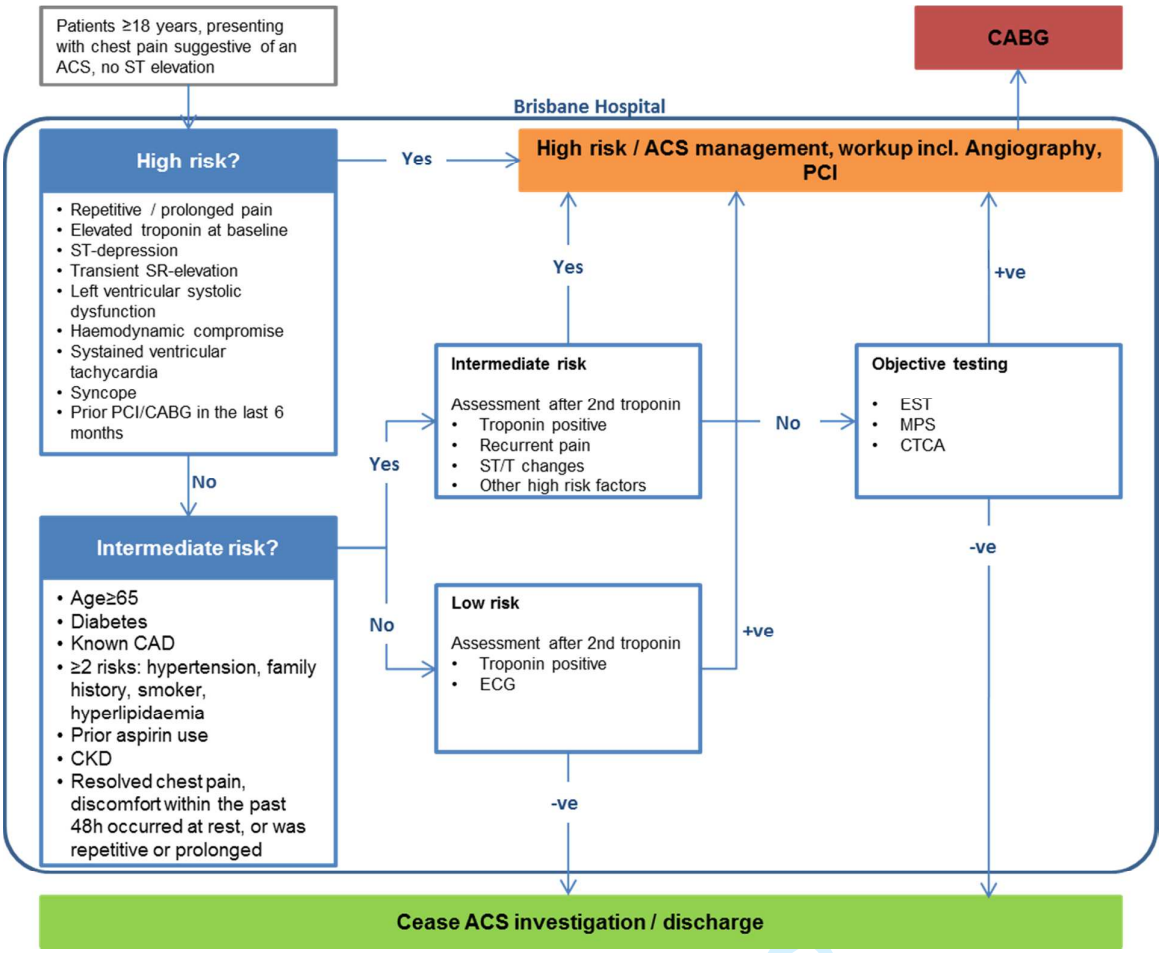
Individuals with missing data in the minimum required dataset were excluded from the analysis.
ECG=echocardiogram, cTnI=sensitive cardiac troponin I, hsTnI=highly sensitive cardiac troponin I

eTable 3. Troponin statuses considered in the model

Status	Description	Evaluation for ACS
1	1st troponin & 2nd troponin ≤ ULN	Negative
2	1st troponin ≤ ULN & 2nd troponin > ULN	Positive
3	1st troponin > ULN & 2nd troponin ≤ ULN	Positive
4	1st troponin & 2nd troponin > ULN; difference < delta cut-off	Negative (Stable)
5	1st troponin & 2nd troponin > ULN; difference ≥ delta cut-off	Positive

ULN=Upper limit of normal, 99th percentile of the reference population; ACS=Acute coronary syndrome

eFigure 1. Risk stratification and process of care for possible acute coronary syndrome



Risk stratification according to [3].

eTable 4A. Model parameter and assumptions: Objective testing probabilities.

Workup	Troponin status	N	Occurence	Result +-ve
Exercise Stress Test	1	582	60.1%	5.4%
	2	31	29.0%	11.1%
	3	15	33.3%	20.0%
	4	40	12.5%	40.0%
	5	51	2.0%	0.0%
Myocardial perfusion scan	1	582	14.3%	18.1%
	2	31	12.9%	75.0%
	3	15	20.0%	33.3%
	4	40	7.5%	0.0%
	5	51	2.0%	0.0%
Echocardiography	1	582	17.0%	data not available
	2	31	48.4%	
	3	15	20.0%	
	4	40	50.0%	
	5	51	70.6%	
Computed tomography coronary angiography	1	582	3.1%	data not available
	2	31	0.0%	
	3	15	6.7%	
	4	40	5.0%	
	5	51	0.0%	

Statistical evaluation of the model cohort (N=719)

eTable 4B. Model parameter and assumptions: Probabilities for angiography.

Workup	Troponin status	N	Occurrence	Result +ve (ACS patients)	Result +ve (non-ACS patients)
Angiography	1	582	11.9%	50.0%	31.3%
	2	31	35.5%	100.0%	0.0%
	3	15	13.3%	0.0%	0.0%
	4	40	27.5%	83.3%	40.0%
	5	51	70.6%	96.8%	20.0%

Statistical evaluation of the model cohort (N=719)
ACS=Acute coronary syndrome

eTable 4C. Model parameter and assumptions: Cardiac workup duration

Variable	Mean time, hours	Distribution
Arrival time (decimal time format)	0.45	Normal
Initial assessment time	0.45	Gamma
Protocol time cTnI	6.3	Gamma
Protocol time hsTnI	2.3	Gamma
Workup time (2nd Tn after 6.30pm)	17.1	Gamma
Probability of short workup time (2nd Tn before 6.30pm)	0.79	Binomial
Workup time (short; 2nd Tn before 6.30pm)	1.78	Gamma
Workup time (long; 2nd Tn before 6.30pm)	20.3	Gamma
Angiography	3.0	Gamma

cTnI=sensitive cardiac troponin I; hsTnI=highly sensitive cardiac troponin I

eTable 4D. Model parameter and assumptions: Hospital length of stay

Hospital LOS, hours	Mean	SD	Q1	Median	Q3	Min	Max	Distribution
ACS / ECG normal	154.4	99.6	66.5	100.6	273.4	48.7	280.4	Gamma
ACS / ECG ischemic	125.4	87.6	56.7	92.8	209.6	20.5	288.0	Gamma
ACS / ECG abnormal	110.3	81.5	59.3	85.5	166.0	15.8	283.9	Gamma
Non-ACS / ECG normal	33.1	49.7	6.0	19.6	27.6	0.0	284.0	Gamma
Non-ACS / ECG ischemic	91.9	90.5	25.0	64.7	121.3	0.0	284.0	Gamma
Non-ACS / ECG abnormal	58.9	71.7	8.0	25.3	80.5	0.0	282.4	Gamma

Statistical evaluation of the model cohort (N=719)
LOS=length of stay; ACS=acute coronary syndrome; ECG=electrocardiogram

eTable 5. Patient characteristics of the selected and generated model cohort.

Demographics	Cohort (N = 719)	Generated cohort[a] (N = 40,000)	p-value
Sex (% women)	39.4	39.5	0.94
Age, yrs. Mean (Range)	55 (19 - 97)	55 (19-97)	0.94
Risk factors			
Dyslipidaemia, %	42.1	Sampled and used for estimating the assessment status	
Diabetes, %	12.8		
Hypertension, %	43.3		
Tachycardia, %	1.7		
Obesity (BMI>30), %	35.5		
Smoking, %	26.8		
Medical History			
Angina, %	22.5	Sampled and used for estimating the assessment status	
Coronary artery disease, %	20.5		
Myocardial infarction, %	16.3		
Family coronary artery disease, %	46.6		
Arrhythmia, %	9.0		
Congestive heart failure, %	4.2		
CABG surgery, %	6.5		
Prior angioplasty, %	10.3		
Peripheral artery disease, %	1.8		
Aspirin use, %	25.3		
Stroke, %	9.0		
Initial assessment & final diagnosis			
ACS, %	11.0	11.0	1.00
ECG normal, %	49.5	49.1	0.85
ECG ischemic, %	7.8	7.7	0.94
ECG abnormal, %	42.7	43.2	0.82
TIMI 0, %	24.5	25.0	0.75
TIMI 1, %	33.0	33.9	0.61
TIMI 2, %	17.9	17.2	0.58
TIMI 3, %	12.2	12.1	0.86
TIMI 4, %	6.4	6.5	1.00
TIMI ≥5, %	6.0	5.4	0.51
High risk, %	33.7	33.5	0.94
Intermediate risk, %	65.1	65.3	0.94
Low risk, %	1.3	1.3	1.00
Baseline cTnI, ng/L (Mean, range)	118 (10 - 31000)	119 (10 - 31000)	0.97
Baseline hsTnI, ng/L (Mean, Range)	117.5 (0.3 - 38685)	119.2 (0.3 - 38685)	0.98
hsTnI < LoD at baseline[b], %	5.1	6.1	0.34

TIMI and risk assignment based on standard strategy

[a] Samples per individuals: Mean 55.6; Range 36-78; Mode: 52.

[b] Limit of detection for hsTnI 1.2ng/L

BMI=Body mass index; CABG=coronary artery bypass graft; ACS=acute coronary syndrome; ECG=electrocardiogram; TIMI=Thrombolysis in myocardial infarction; cTnI=sensitive cardiac troponin I; hsTnI=highly sensitive cardiac troponin I, LoD=limit of detection

eTable 6. Cost prediction model regression analysis

Term	Coef	SE Coeff	T	P-value	(95% CI)	VIF
Constant	3.57	0.04	101.5	<0.001	(3.51 – 3.64)	
ED time, hours	0.02	0.00	8.8	<0.001	(0.02 – 0.03)	1.15
Inpatient stay, days	0.19	0.01	37.7	<0.001	(0.18 – 0.20)	1.78
Exercise stress test	-0.09	0.02	-4.3	<0.001	(-0.13 – -0.05)	1.37
Myocardial perfusion scan	0.25	0.04	6.7	<0.001	(0.18 – 0.32)	1.22
Computed tomography coronary angiography	0.27	0.07	4.0	<0.001	(0.14 – 0.40)	1.02
Angiography	0.65	0.03	21.8	<0.001	(0.59 – 0.71)	1.34
Echocardiography	0.32	0.03	11.4	<0.001	(0.26 – 0.37)	1.49
Admission	0.39	0.03	11.6	<0.001	(0.33 – 0.46)	1.21

VIF: Variance inflation factor

Box-Cox transformation with Lambda= 0.189 (95%CI 0.135 – 0.245)

S	0.264
PRESS	63.4
R-Sq	88.3%
R-Sq(adj)	88.2%
R-Sq(pred)	88.0%

Admission considers admission to short-stay unit or inpatient ward

eTable 7. Risk assignment of patients

Strategy			Initial risk assignement, %		
			Low-risk	Intermediate -risk	High-risk
Standard			**1.3**	**65.3**	**33.5**
hsTnI			**1.3**	**65.3**	**33.5**
Direct rule-out if baseline hsTnI < LoD (LoD)	No direct rule-out	**All**	**1.3**	**60.4**	**32.3**
	Direct rule-out[a]	**All**	**0.0**	**4.9**	**1.2**
		ACS	0.0	0.0	0.0
		No ACS	0.0	4.9	1.2
Accelerated rule-out if hsTnI values below the diagnostic cut-off and TIMI ≤1 (ADP)	No accelerated rule-out	**All**	**0.5**	**16.4**	**33.5**
	Accelerated rule-out[a]	**All**	**0.7**	**48.8**	**0.0**
		ACS	0.0	0.2	0.0
		No ACS	0.7	48.7	0.0
Direct rule-in if baseline hsTnI >52ng/L	No direct rule-in	**All**	**1.3**	**65.3**	**26.3**
	Direct rule-in[b]	**All**	**0.0**	**0.0**	**7.2**
		ACS	0.0	0.0	5.1
		No ACS	0.0	0.0	2.0

LoD=Limit of detection; ACS= Acute coronary syndrome;
TIMI=Thrombolysis in myocardial infarction;
ADP=Accelerated diagnostic protocol;
hsTnI=highly sensitive cardiac troponin I
[a] classified as low-risk
[b] classified as high-risk

eTable 8. Troponin status by assay used

	hsTnI			Sum (cTnI), %
cTnI	**Negative, %**	**Stable, %**	**Positive, %**	
Negative, %	84.0	0.1	0.3	**84.4**
Stable, %	0.6	0.3	2.9	**3.4**
Positive, %	2.4	0.6	9.0	**11.9**
Sum (hsTnI), %	**86.9**	**1.0**	**12.1**	**100.0**

Troponin status interpretation according to eTable3
cTnI=sensitive cardiac troponin I; hsTnI=highly sensitive cardiac TnI

eTable 9. Total length of stay and costs per strategy and final diagnosis

Strategy	Category	Total costs, $				Total LOSs, hours			
		Median	(25th - 75th perc)	Mean	(95% CI)	Median	(25th - 75th perc)	Mean	(95% CI)
1	**All**	**2135**	**(1741 - 3109)**	**3267**	**(3236 - 3297)**	**22.6**	**(8.7 - 29.8)**	**34.0**	**(33.6 - 34.4)**
	No ACS	2022	(1708 - 2669)	2570	(2550 - 2590)	21.3	(8.6 - 27.7)	27.2	(26.9 - 27.5)
	ACS	8421	(5863 - 10248)	8895	(8756 - 9034)	74.8	(25.5 - 137)	89.2	(87 - 91.3)
2	**All**	**1983**	**(1597 - 2951)**	**3134**	**(3103 - 3165)**	**6.0**	**(4.4 - 25.3)**	**27.8**	**(27.4 - 28.2)**
	No ACS	1860	(1567 - 2478)	2417[a]	(2397 - 2436)	5.6	(4.3 - 23.1)	20.2[a]	(19.8 - 20.5)
	ACS	8269	(5827 - 10210)	8930	(8788 - 9073)	79.0	(23 - 139.2)	89.6	(87.4 - 91.8)
3	**All**	**1921**	**(1548 - 2878)**	**3057**	**(3026 - 3088)**	**3.6**	**(2.7 - 10.1)**	**20.4**	**(20 - 20.9)**
	No ACS	1805	(1517 - 2427)	2330[a]	(2310 - 2350)	3.3	(2.6 - 5.4)	11.9[a]	(11.6 - 12.2)
	ACS	8269	(5827 - 10210)	8930	(8788 - 9073)	78.7	(22.8 - 139.1)	89.3	(87.1 - 91.5)
4	**All**	**1695**	**(1560 - 2260)**	**2834**	**(2804 - 2864)**	**5.6**	**(4.2 - 24.8)**	**26.8**	**(26.4 - 27.3)**
	No ACS	1663	(1544 - 1862)	2079[a]	(2062 - 2096)	5.3	(4.1 - 22.6)	19.0[a]	(18.7 - 19.4)
	ACS	8268	(5851 - 10198)	8932	(8790 - 9074)	79.0	(23 - 139.2)	89.6	(87.4 - 91.8)
5	**All**	**1681**	**(1532 - 2231)**	**2781**	**(2751 - 2811)**	**3.5**	**(2.6 - 8.3)**	**20.1**	**(19.6 - 20.5)**
	No ACS	1648	(1514 - 1845)	2020[a]	(2002 - 2037)	3.2	(2.5 - 5.2)	11.5[a]	(11.2 - 11.8)
	ACS	8268	(5851 - 10198)	8932	(8790 - 9074)	78.7	(22.8 - 139.1)	89.3	(87.1 - 91.5)
6	**All**	**1681**	**(1532 - 2230)**	**2776**	**(2746 - 2807)**	**3.5**	**(2.6 - 8.8)**	**20.4**	**(19.9 - 20.8)**
	No ACS	1648	(1514 - 1845)	2020[a]	(2003 - 2037)	3.2	(2.5 - 5.2)	11.5[a]	(11.2 - 11.8)
	ACS	8151	(5702 - 10194)	8885	(8740 - 9029)	82.0	(24.8 - 140.5)	91.9	(89.7 - 94.1)

Strategy code: (1) Standard, (2) hsTnI, (3) hsTnI+LoD, (4) hsTnI+ADP, (5) hsTnI+LoD+ADP, (6) hsTnI+LoD+ADP+Rule in.
Total costs include index costs and 30 days follow-up costs.
All costs stated are in Australian dollars.
[a] p-value vs. Standard < 0.001
ACS=Acute coronary syndrome; hsTnI=highly sensitive troponin I; LoD=limit of detection; ADP=accelerated diagnostic protocol; LOS=Length of stay

eTable 10A. Emergency department performance by strategy

Emergency department time, hours	Mean	(95% CI)	Median	(25th - 75th perc)	97.5th perc	≤4hrs
1) Standard	0.68	(0.66 - 0.7)	0.41	(0.26 - 0.63)	1.4	98.7%
2) hsTnI	0.58	(0.57 - 0.6)	0.41	(0.26 - 0.63)	1.4	99.0%
3) hsTnI+LoD	0.58	(0.57 - 0.6)	0.41	(0.26 - 0.63)	1.4	99.0%
4) hsTnI+ADP	0.54	(0.53 - 0.55)	0.41	(0.26 - 0.63)	1.4	99.6%
5) hsTnI+LoD+ADP	0.54	(0.53 - 0.55)	0.41	(0.26 - 0.63)	1.4	99.6%
6) hsTnI+LoD+ADP+Direct rule-in	0.54	(0.53 - 0.55)	0.41	(0.26 - 0.63)	1.4	99.6%

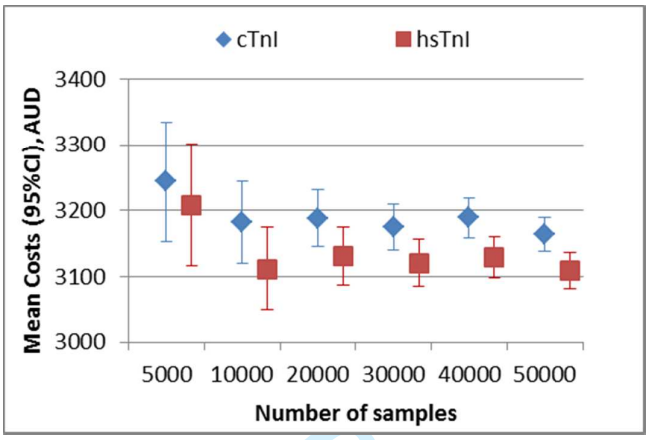
hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP=accelerated diagnostic protocol.

eTable 10B. Short Stay Unit times per patient by strategy

SSU time, hours	Mean	(95% CI)	Median	(25th - 75th perc)	90th perc
1) Standard	9.9	(9.8 - 10)	7.54	(0.0 - 20.8)	25.7
2) hsTnI	5.1	(5.1 - 5.2)	3.49	(0.0 - 4.7)	21.2
3) hsTnI+LoD	4.7	(4.7 - 4.8)	3.31	(0.0 - 4.5)	20.7
4) hsTnI+ADP	2.4	(2.3 - 2.4)	2.06	(0.0 - 2.6)	3.8
5) hsTnI+LoD+ADP	2.2	(2.2 - 2.3)	1.99	(0.0 - 2.6)	3.8
6) hsTnI+LoD+ADP+Rule in	2.2	(2.2 - 2.3)	1.99	(0.0 - 2.6)	3.8

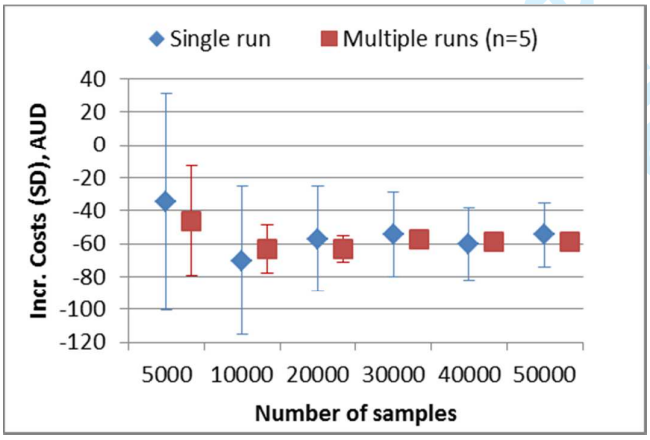
hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP=accelerated diagnostic protocol.

eFigure 2A. Mean costs based on number of samples in the micro simulation



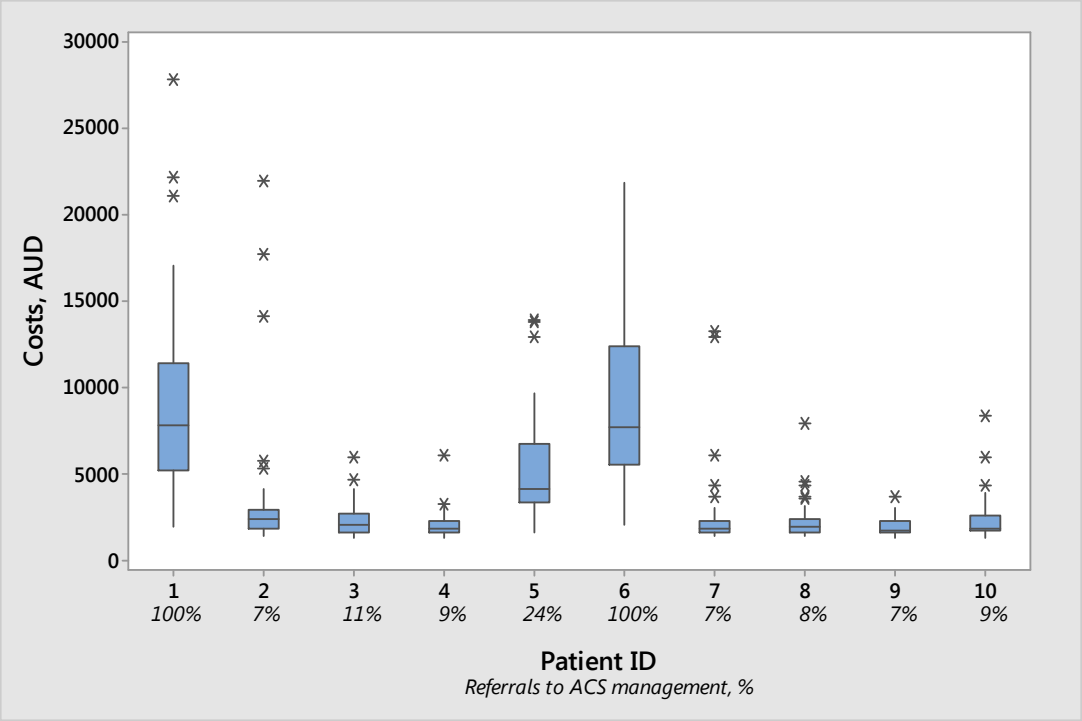
cTnI=sensitive cardiac troponin; hsTnI=highly sensitive cardiac troponin I

eFigure 2B. Incremental costs based on different number of samples in the micro simulation



Incremental costs refer to Strategy-2 – Strategy 1

eFigure 3. Cost variation as a result of the sampling strategy illustrated for ten selected individuals

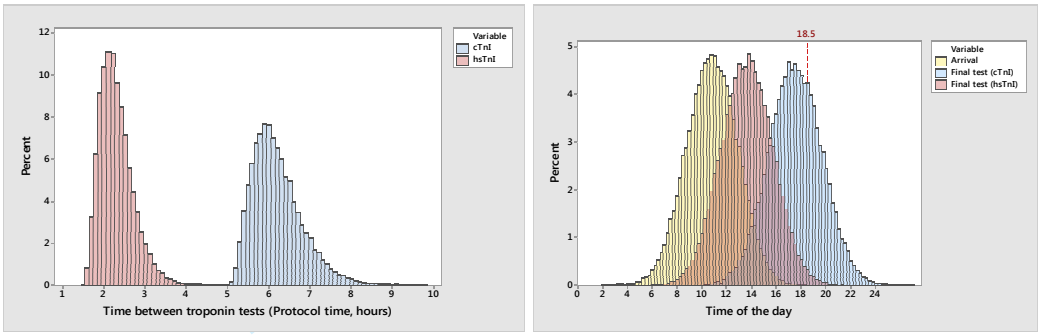


Box plots illustrate the variability in costs from multiple samples of the same individual as an example for the first 10 patients (Patient-ID 1 to 10).

By running 40,000 iterations, each of the 719 individuals was sampled on average 55 to 56 times (Range 36 – 78). This generated a huge cohort of patients that reflected variation and heterogeneity in decision making, severity, and management.

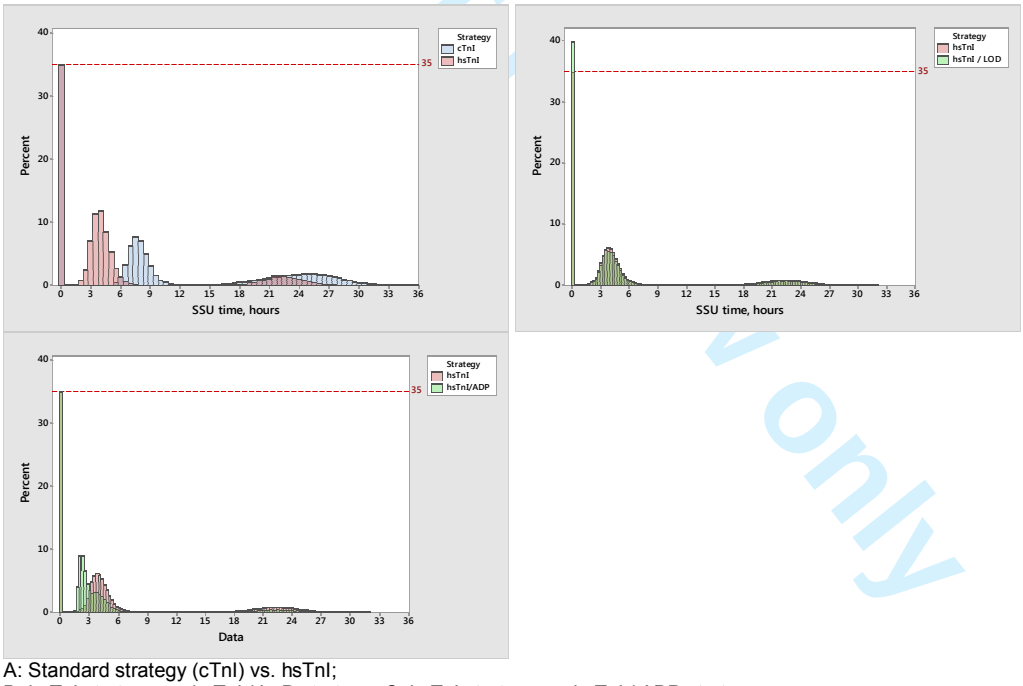
Each sample of an individual was consistent in age, sex, characteristics, ACS status and troponin values, but varied in terms of arrival time, protocol time, treatment times, additional cardiac testing if required, total inpatient LOS if referred for ACS management, and costs predictors. This resulted in a range of costs as demonstrated in the chart.
For individuals with non-ACS conditions, variation in subjective decision making or results from cardiac testing (exercise stress test or myocardial perfusion scan) led to admittance for ACS management in some cases (Patient ID 2-4, and 7-10). Italic numbers indicate the proportion of referrals to ACS management per patient. Patients with ACS were admitted for ACS management in 100% of iterations (Patient ID 1 and 6). Variation in costs between ACS patients was caused by sampling different LOS assumptions.

eFigure 4. Simulated troponin protocol times (A), patient arrival times, and times of final results for sensitive troponin I and highly sensitive troponin I (B).



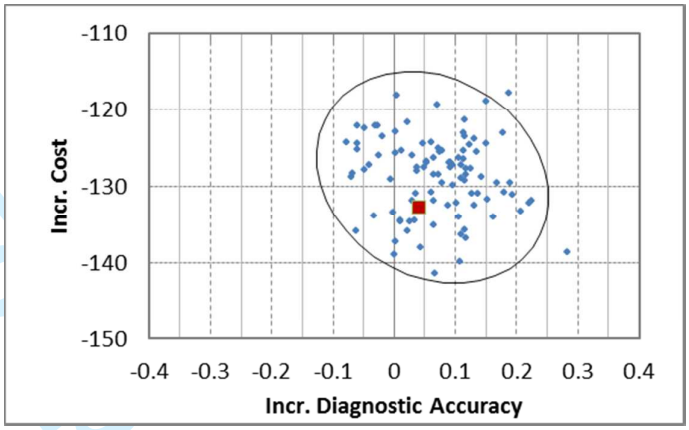
cTnI=sensitive cardiac troponin; hsTnI=highly sensitive cardiac troponin I

eFigure 5 A-C. Histograms of Short Stay Unit times for different strategies



A: Standard strategy (cTnI) vs. hsTnI;
B: hsTnI strategy vs. hsTnI / LoD strategy; C: hsTnI strategy vs. hsTnI / ADP strategy.
The reference line at 35% indicates the proportion of patients that were not admitted to Short Stay Unit in the standard strategy.
hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP=accelerated diagnostic protocol.

eFigure 6. Incremental cost and effectiveness of Strategy 2 (hsTnI) vs. Strategy 1 (cTnI, usual care).



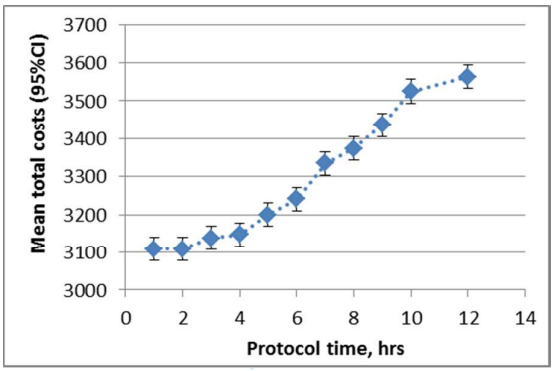
Results from multiple runs in a probabilistic sensitivity analysis (n=250). Each point represents results of a run with 40,000 sampled patients. The ellipse reflects the 95% confidence interval. Red box represents the result from the micro simulation.

eTable 11. Comparison of results from single and multiple run micro simulations

Strategy	Analysis	Total costs		Referral Accuracy, %		Diagnostic Accuracy	
		A$	(95%CI)	Mean	(95%CI)	Mean	(95%CI)
Standard	MS	3267	(3236 - 3297)	71.8	(71.4 - 72.2)	90.00	(89.7 - 90.3)
	PSA	3253	(3251 - 3255)	72.0	(71.97 - 72.02)	90.21	(90.2 - 90.23)
hsTnI	MS	3134	(3103 - 3165)	72.8	(72.3 - 73.2)	90.04	(89.7 - 90.3)
	PSA	3124	(3122 - 3126)	73.0	(72.95 – 73.00)	90.3	(90.26 - 90.29)

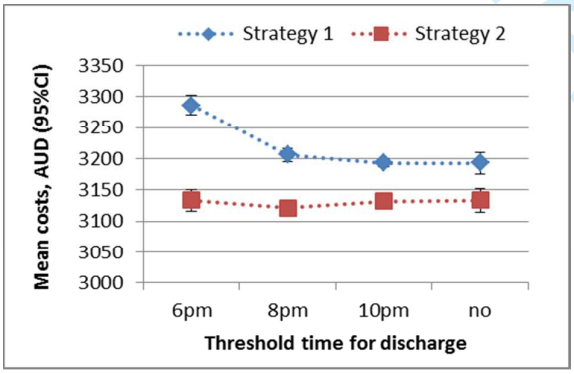
MS: Micro simulation (n=1 runs)
PSA: Probabilistic sensitivity analysis (n=250 runs)

eFigure 7. Impact of protocol time on costs.



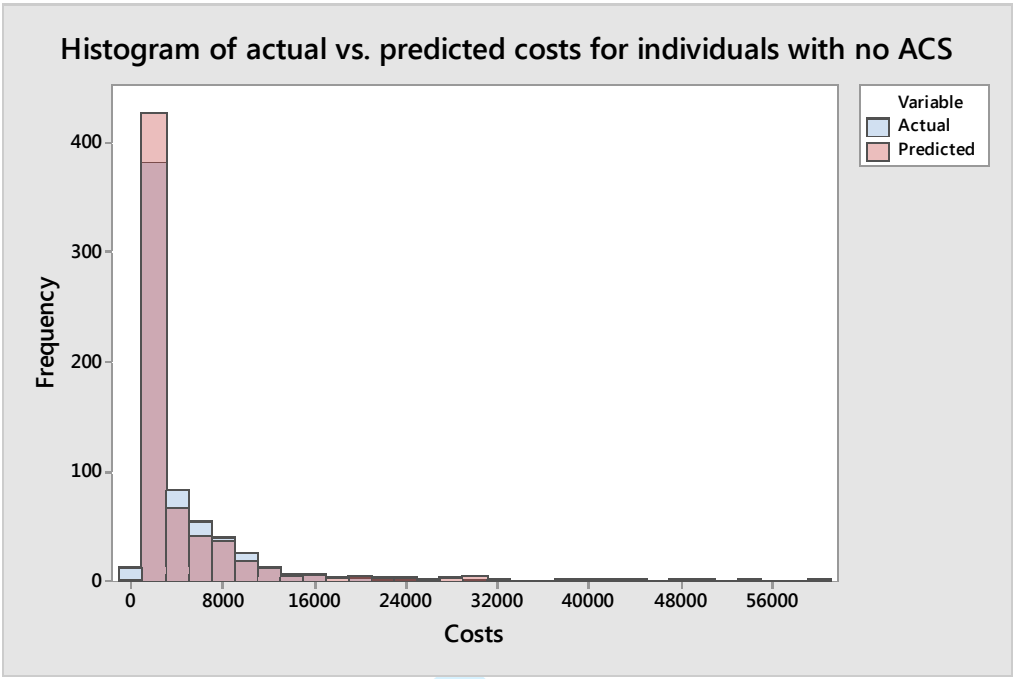
Analysis of strategy 2 (hsTnI) assuming constant troponin values and a fixed protocol time. Each data point represents the result of 5 independent runs with 40,000 patients per run.

eFigure 8. Impact of threshold time for discharge on costs.

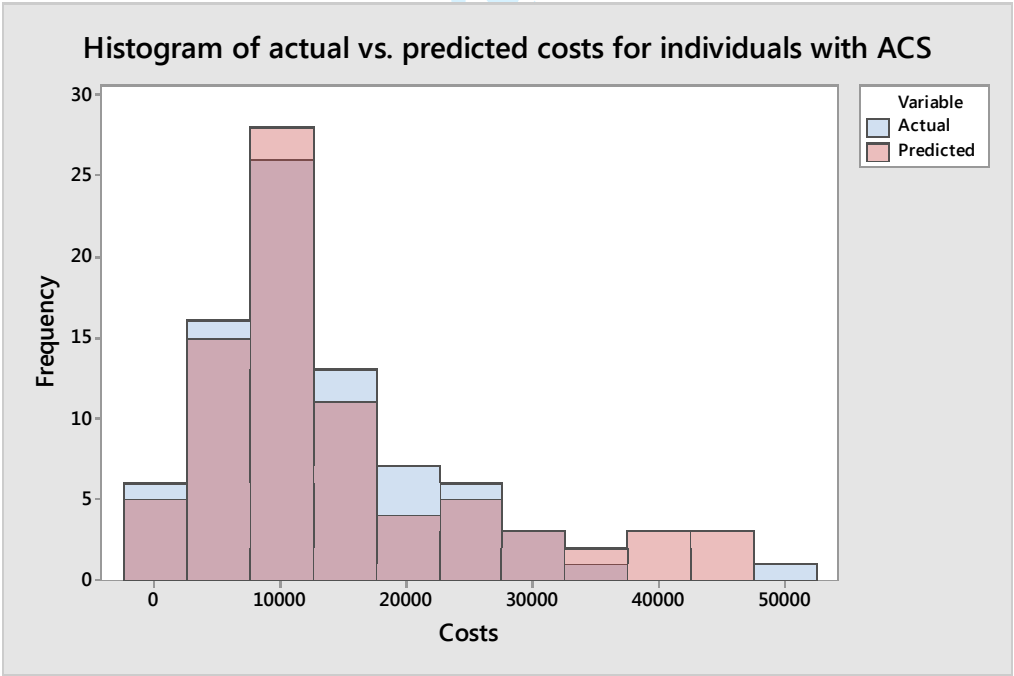


Each data point represents the result of 5 independent runs with 40,000 patients per run.

eFigure 9 A/B. Comparison of actual vs. predicted costs.



Data based on individuals with a final diagnosis of Non-ACS (640/719); p-value for Mean: 0.97



Data based on individuals with a final diagnosis of ACS (79/719); p-value for Mean: 0.39

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CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1 / Title page
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Pages 2-3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Page 5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Pages 5-7
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Pages 5-7
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 10
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Pages 8-9
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 9, 10
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Not appropriate
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 10
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Pages 6-7

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Pages 6-7
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 8; Supplement page 65
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 8
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 14; Figure 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Pages 8-10; Supplement
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Pages 8-10; Suppl. pages 65-67; 78
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Pages 10-13; Table 3; Supplement
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 3
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	Page 12; Supplement Suppl. pages 28, 80,81

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Pages 13-16
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 18
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Pages 18-19

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:
Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.

BMJ Open

The organizational value of diagnostic strategies using high sensitivity troponin for patients with possible acute coronary syndromes: A trial-based cost-effectiveness analysis

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Primary Subject Heading:	Health economics
Secondary Subject Heading:	Emergency medicine, Cardiovascular medicine
Keywords:	ACCIDENT & EMERGENCY MEDICINE, Myocardial infarction < CARDIOLOGY, HEALTH ECONOMICS

The organizational value of diagnostic strategies using high sensitivity troponin for patients with possible acute coronary syndromes: A trial-based cost-effectiveness analysis

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Keywords: Acute Coronary Syndrome; Health Care Economics and Organizations; Health Planning; Emergency Service, Hospital

Word Count: 3785

ABSTRACT

Objectives: To evaluate hospital-specific health economic implications of different protocols utilizing high sensitivity troponin I for assessment of patients with chest pain.

Design: A cost prediction model and an economic microsimulation were developed using a cohort from a single centre recruited as part of the ADAPT Trial, a prospective observational trial conducted from 2008-2011. The model was populated with 40,000 bootstrapped samples in five high sensitivity troponin I-enabled algorithms versus standard care.

Setting: Adult Emergency Department of a tertiary referral hospital

Participants: Data were available for 938 patients who presented to the Emergency department with at least five minutes of symptoms suggestive of acute coronary syndrome. The analyses included 719 patients with complete data.

Main Outcome(s)/Measure(s): This study examined direct hospital costs, number of false negative and number of false positive cases in the assessment of acute coronary syndrome.

Results: High sensitivity troponin I-supported algorithms increased diagnostic accuracy from 90.0% to 94.0% with an average cost reduction per patient compared to standard care of $490. The inclusion of additional criteria for accelerated rule-out (limit of detection and the Modified 2-Hour ADAPT trial rules) avoided 7.5% of short-stay unit admissions or 25% of admissions to a cardiac ward. Protocols utilizing high sensitivity troponin I alone, or high sensitivity troponin I within accelerated diagnostic algorithms reduced length of stay by 6.2 hours and 13.6 hours respectively. Overnight stays decreased up to 43%. Results were seen for non-acute coronary syndrome patients, no difference was found for patients with acute coronary syndrome.

Conclusions: High sensitivity troponin I algorithms are likely to be cost-effective on a hospital level compared to sensitive troponin protocols. The positive effect is conferred by patients not diagnosed with acute coronary syndrome. Implementation could improve referral accuracy or facilitate safe discharge. It would decrease costs, and provide significant hospital benefits.

Trial Registration: The original ADAPT trial was registered with the Australia-New Zealand Clinical trials Registry, ACTRN12611001069943.

Strengths

- This study was based on an individual-level modeling design to allow for more realistic comparisons of different settings, assessment strategies, or risk stratification rules.
- As opposed to previous evaluations, costs and all management assumptions were based on actual patient information that was prospectively collected. In addition, we considered realistic management rules. For example, if patients were not discharged before 6:30pm, they required an overnight stay.
- Model results were based on a sampling strategy that created a large cohort with a wide spectrum of individual information, thus reflecting population heterogeneity and common variation in clinical practice.
- Troponin results must be interpreted in concert with clinical presentation, ECG changes and other available information. Diagnostic accuracy used in this study refers to results of the complete pathway consisting of troponin results, ECG and cardiac workup. All hospital costs accrued from assessment, management and events during 30-days follow-up were considered in the analysis.

Limitations

- Cost data were based on information from an administrative database. The cost prediction was limited to activities during the assessment period. Information about inpatient treatment other than time was not available.
- Economic implications from breaching specific emergency department targets or access blocks were not taken into account but may have a significant impact; it appears likely that considering such aspects would strengthen the results in favor of accelerated protocols.
- Generalizability might be hindered by the variety of assessment processes. Exploiting the value of hsTnI relies on the appropriateness of testing and the implementation of adequate protocols.

INTRODUCTION

Chest pain is a leading presenting complaint for adults seeking emergency department (ED) care. [1] The most common serious underlying causes are acute coronary syndromes (ACS), including acute myocardial infarction and unstable angina. After detailed assessment, most patients are diagnosed with a non-cardiac cause (e.g. musculoskeletal pain or gastrointestinal causes) for their symptoms. In Australia, over 500,000 persons per year present with chest pain, but fewer than 20% were diagnosed with ACS.[2, 3] The identification of the majority of chest pain presentations at low-risk for ACS remains an organizational challenge for emergency departments.

Accelerated assessment strategies for the rule-in and rule-out of acute myocardial infarction have recently been reported.[3-12] Such strategies utilize clinical decision rules and/or troponin testing to identify a sizeable proportion of patients as low risk. Some protocols also accurately identify patients as high-risk for acute myocardial infarction.[3,4] The use of high sensitivity troponin on presentation or within two hours is a key feature of several accelerated assessment strategies[6-10]. For example, the Modified ADAPT accelerated diagnostic protocol (ADP) utilizes highly sensitive troponin assays to support the identification of 40 % of patients as low risk.[4]

While research into novel accelerated strategies has usually reported clinical outcomes, few studies have assessed the health economic implications of such protocols, or made comparisons to define optimum strategies. The incorporation of highly sensitive cardiac troponin I (hsTnI) assays into clinical practice may have additional health economic benefits on the hospital level; however, this aspect has not been explored to date. The aim of this study was to evaluate the hospital-specific costs of different protocols utilizing hsTnI for assessment of emergency department patients with chest pain, compared to standard care. The hypothesis was that hsTnI enabled algorithms would streamline ED processes with equal or better diagnostic accuracy, thus leading to savings in direct hospital costs when compared to standard care.

METHODS

Study design and setting

This study utilized data from a prospective, single centre observational study in Brisbane, Australia. Participants were recruited as part of the ADAPT Trial,[3] and included if they were aged 18 years or older, presented to the emergency department with at least five minutes' worth of chest pain suggestive of ACS, and were being evaluated for ACS. Pain suggestive of ACS was defined in accordance with American Heart Association case definitions.[13] Recruitment was performed by research staff in collaboration with the senior treating clinician. Patients were excluded if there was a clear non–ACS cause for their symptoms (e.g., findings of pneumonia), they were unwilling or unable to provide informed consent, staff considered that recruitment was inappropriate (e.g., patients undergoing palliative treatment), they were transferred from another hospital, were pregnant, were previously recruited to the study within the past 45 days, or were unable or unwilling to be contacted after discharge. Recruitment included consecutive eligible cases during working hours at each site. Enrolment occurred between January 2008 and November 2010. All patients were managed according to standard care, which included electrocardiogram and troponin testing on presentation and at greater than six hours after presentation to the emergency department. Patients were classified into risk groups according to the Heart Foundation of Australia/Cardiac Society of Australia and New Zealand guidelines.[14] The clinical assay in use as the reference troponin assay was the Beckman Coulter second-generation AccuTnI (Beckman Coulter, Chaska, MN). A value above the 99th percentile of greater than 40ng/L was considered abnormal.

Original data were collected prospectively, using standardized case report forms.[15] Research nursing staff collected demographic and clinical data from patient interviews. Telephone follow-up and medical record review was conducted 30-days after initial attendance for the diagnosis of ACS. Information was obtained from the patient and from hospital databases about all additional cardiac

events, investigations, or contact with any health care providers during the 30-day period. Follow-up information was verified through contact with the health care provider, and original copies of medical records and investigations were obtained. Ethical approval of the research project HREC/14/QRBW/320 was obtained from the Royal Brisbane and Women's Hospital Human Research Ethics Committee (EC 00172) on 11th August, 2014. All patients provided written informed consent for data collection and the ethics committee waived the requirement for consent for this analysis.

Each patient was assigned one or more endpoints to explain the reason for their index presentation, or any events occurring within 30 days of admission. There were fifteen possible endpoints, including both cardiovascular and non-cardiovascular endpoints. Patients were considered to meet the definition for ACS if they were assigned any of the following endpoints; cardiovascular death, cardiac arrest, revascularization procedure, cardiogenic shock, acute myocardial infarction, or unstable angina pectoris. One cardiologist from a group of three potential cardiologists adjudicated the outcome independently. Cardiologists had knowledge of the clinical record, electrocardiogram and troponin results from standard care and used such information to determine whether the patient met the predefined criteria for the cardiovascular endpoints[15]. Patients not meeting such endpoints were classed as having a non-cardiovascular problem. A second cardiologist from the group conducted a blind review of all ACS cases and 10% of non–ACS cases. In cases of disagreement, endpoints were agreed on by consensus by the two cardiologists involved in endpoint adjudication and one emergency physician. This was achieved for all endpoints.

In addition to sampling for routine clinical care, blood was drawn on presentation and two hours later. Samples were later tested with the ARCHITECT High Sensitive *STAT* Troponin-I assay (Abbott Laboratories, Abbott Park, IL). Laboratory technicians were blinded to patient data. The hsTnI assay has a 99th percentile concentration of 26.2ng/L with a corresponding co-efficient of variation of <5% and a limit of detection of 1.2ng/L.[16]

Cost prediction model

As described previously,[17] individual cost data were extracted from hospital administration records and adjusted for inflation to 2011 Australian Dollars. To use a consistent cost matrix across all strategies, a prediction model was developed in four steps. First, we analyzed the data and predefined exclusion criteria (eTable1). Patients who received coronary bypass surgery (CABG) were excluded because they were transferred to another hospital for surgery with no available outcome data and unknown accuracy of cost information. Cases with inconsistent or missing costs were excluded. Patients with a hospital length of stay (LOS) greater than 12 days were excluded to reduce bias from non-cardiac stays. Second, we considered key activities for evaluating an acute coronary syndrome in a generalized Box-Cox transformed model. Third, we dropped non-significant variables (2^{nd} troponin, p=0.9; stress echocardiography, p=0.6) from the predictor variables, checked for relevant multicollinearity between variables, and excluded cases that showed extreme discrepancies to the predicted results (n=4; eTable1). Fourth, we run the final analysis that led to the cost prediction model and the 95% confidence intervals for each predictor (eTable6). The final model was based on data from 891 individuals. The following predictors were used: ED time, inpatient time, performed activities (exercise stress test, myocardial perfusion scan, computed tomography coronary angiography, echocardiography, and angiography), admission to short-stay unit, or admission to an inpatient ward. More information is given in the supplement (eMethods).

Health economic model

We developed a microsimulation cost-effectiveness model that compared six assessment strategies (Table 1). The standard of care was based on a protocol using cardiac troponin I (cTnI) at baseline and 6 hours after arrival (Strategy 1). All other strategies utilized hsTnI at presentation and 2 hours. Strategy 2 (termed hsTnI) was the same as standard care except that a 2-hour highly sensitive

troponin was used rather than a 6-hour sensitive troponin. Strategy 3 (hsTnI+LoD) also utilised a 2 hour hsTnI, but allowed a patient to be directly ruled out on admission with no further work-up if their baseline hsTnI was below the assay's limit of detection (LoD). Strategy 4 (hsTnI+ADP) utilised baseline and 2 hour hsTnI but enabled patients to be directly ruled out with no further work-up using the modified ADAPT ADP. That is, patients could be ruled out if their TIMI risk score was <=1, their baseline and 2 hour troponin were below the diagnostic cutoff and their presentation ECG was non ischaemic. Strategy 5 (hsTnI+LoD+ADP) was a combination of Strategies 3 and 4 in that patients could be ruled out if their baseline hsTnI was below the LoD or if they met the criteria according to the modified ADAPT ADP. Finally, Strategy 6 (hsTnI+LoD+ADP+direct rule in) employed the same rule -out criteria as Strategy 5, but also enabled patients with hsTnI at presentation >52ng/L to be directly ruled-in and admitted for ACS management (strategy 6).[18]

The model structure and the evaluation pathway are described in Figure 1 and eFigure 1, respectively. Individuals entering the model were stratified in the ED based on individual characteristics, first electrocardiogram, and baseline troponin. Patients classified as high-risk were admitted to inpatient cardiology. Low-risk patients were kept in the emergency department to await final assessment. Intermediate-risk patients were referred to the short stay unit (SSU) for further cardiac workup. Patients referred to the SSU or inpatient ward were counted as admitted.

If the final troponin was performed later than 6.30pm, patients stayed overnight. Total LOS comprised emergency department LOS, short stay unit LOS and inpatient stay. The maximum LOS was limited to 12 days to avoid bias in the effects from prolonged stays in patients with non-cardiac diagnoses. A 30-day follow-up event was assumed for individuals who were ruled-out by the respective strategy, and who had a reported 30-day clinical outcome of ACS.

A minimum required dataset was defined for the cohort used in the model (eTable 2), and 219 patients with missing troponin values were excluded. Work-up, work-up duration, and length of stay were analyzed from the model cohort and transformed into statistical distributions. Patient attributes (age, sex, clinical characteristics, adjudicated diagnosis, electrocardiogram status, and troponin values) were individually sampled from the model cohort by bootstrapping. This created a hypothetical cohort of 40,000 patients who followed the model for each of the strategies. Work-up and times for each patient were randomly sampled from distributions. Costs were estimated by considering attributes, work-up activities, work-up duration, and length of stay in the cost prediction model with coefficients individually sampled from the 95% confidence interval of the respective predictor. The model followed a 30-day hospital perspective. Costs for the index event and follow-up were estimated from the cost prediction model.

Differences between strategies were expressed in terms of total hospital costs per patient and diagnostic accuracy. Diagnostic accuracy was defined as the percentage of correctly diagnosed patients compared to the final adjudicated diagnosis. In addition, LOS, referral rates, admission rates, and overnight stays were evaluated. We conducted one-way and probabilistic sensitivity analyses to test the robustness of the micro simulation results. Model structure, parameters and assumptions are described in detail in the supplement.

Patient Involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. Patients were asked whether they wished to receive a summary of these results. These individuals were posted a lay summary of the results.

RESULTS

Cost prediction and model validation

Characteristics of 719 patients meeting the minimum required dataset for the model and of the generated cohort of 40,000 patients are described in the supplement (eTable 5). The cost prediction model showed excellent regression quality (R-square 88.3%; eTable 6). The model was validated for the standard strategy against actual statistics with good prediction accuracy for all patients (p-value vs. actual costs: 0.723) as well as for low-, intermediate- and high-risk patients (p= 0.946, 0.256, 0.761, respectively; Table 2).

Patient referral and management

During initial assessment, 1.3% of patients were classified as low-risk and managed in the emergency department. 6.1% of patients met the criteria for a direct rule-out (baseline hsTnI below the limit of detection) and were re-classified as low-risk. The modified ADAPT accelerated diagnostic protocol (ADP) was effective for 49% of patients and reclassified 75% of intermediate-risk patients to low risk. The direct rule-in criteria (baseline hsTnI >52ng/L) applied to 7.2% of patients.

Strategies considering LoD avoided short-stay unit admissions for 4.9% of patients (-7.5% vs. standard care, Table 3). The number of ward admissions did not change with hsTnI alone. Utilising the LoD, ADP, or a combination of both, resulted in a stepwise and significant reduction of the ward admission rate from 49.6% to 37.1% (-25%; Table 3).

A 4-hour reduction in protocol time (cTnI vs. hsTnI: Mean 6.2h (Range 5.0 – 10.0h) vs. 2.3h (1.5 - 5.0h)) resulted in earlier management decisions (eFigure 4). Consequently, strategy-2 led to 30% fewer overnight stays compared to standard care (60.3% vs. 42.0%, Table 3). Incorporating additional rule-out to hsTnI options further streamlined patient assessment, decreasing overnight stays by up to 43%.

3.2% of patients with a negative or stable cTnI status had a positive hsTnI status indicative of an acute event (eTable 8). Conversely, 3.0% of patients had an acute cTnI finding but a negative or stable troponin status with hsTnI. In total, the number of referrals to ACS management based on an acute troponin finding did not differ if replacing cTnI with hsTnI (cTnI: 11.9%; hsTnI: 12.1%; p=0.549). Patients with negative or stable troponin conditions were admitted for ACS management and further workup if such as an exercise stress test or myocardial perfusion scan led to positive findings, resulting in a referral rate of 32% (Table 3). Strategies considering the LoD or ADP rules respectively led to 5% or 35% fewer patients referred for ACS management compared to standard care. Additional direct rule-in criteria (Strategy-6 vs. 5) did not identify more patients requiring ACS management but allowed for earlier cardiac intervention for 46.6% of ACS patients.

Length of stay and costs

A significant reduction in LOS was observed if hsTnI replaced cTnI, with a mean saving of 6.2 hours (p<0.001, Table 3). Applying LoD or ADP rules to hsTnI saved an additional stay of 1.0 and 5.4 hours respectively. LOS times for ACS patients were stable between strategies (eTable 9). However, applying hsTnI to standard care resulted in a significant reduction of LOS for non-ACS patients. Substantially decreased 75th percentiles of the LOS for all strategies considering the ADP indicated its considerable streamlining effect. Details for emergency department and SSU times are given in the supplement (eTable 10).

Significant cost reductions compared to standard care were found with all hsTnI strategies ($133-$491, p<0.001, Table 3). This effect was caused by substantial cost reductions for non-ACS patients. No difference between strategies was observed for ACS patients (eTable 9). As stated in Table 3, costs during the index stay and follow-up decreased for all hsTnI-supported strategies compared to standard care. The consideration of ADP and LoD alone, or in combination, in addition to hsTnI

protocols resulted in further significant cost savings. Applying a direct rule-in strategy (Strategy-6) to a combination of hsTnT+ADP+LoD did not result in significant overall costs benefits.

Patient outcome and cost-effectiveness

The introduction of hsTnI into standard care did not alter overall diagnostic accuracy (p=0.86, Table 3, Figure 2), but tend to increase the number of patients with a false positive diagnosis of ACS (p=0.056; Table 4). While all hsTnI supported strategies avoided false-negative diagnoses compared to standard care, a statistically significant reduction of the false-positive rate was observed for all strategies utilizing an ADP. Applying LoD and ADP to hsTnI reduced the number of false-positives by 6% (p=0.015) and 52% (p<0.001) respectively, whereas no effect was observed on the false-negative rate (Table 4).

Strategy-5 (a protocol utitilizing hsTnI, ADP, and LoD) was found to be the dominant strategy in the study, providing better accuracy at lower costs (Figure 2).[19] Switching from standard care to Strategy 5 saved $486 per patient (p<0.001) and increased the diagnostic accuracy from 90.0% to 94.0% (p<0.001).

Conducting multiple runs in a probabilistic sensitivity analysis revealed consistent benefits confirming the robustness of micro simulation results (eFigure 6; eTable 11). hsTnI demonstrated equal or better diagnostic accuracy compared to cTnI in 79% of runs, with a stable average cost saving per patient ranging from $113 to $147. The hsTnI strategy helped to manage 82.6% of individuals at lower costs compared to standard care; 10.2% or 7.1% of patients were treated at equal or higher costs, respectively.

DISCUSSION

The cost-effectiveness of incorporating hsTnI into management protocols for patients presenting to the emergency department with chest pain has received increasing attention. HsTnI has been suggested to generate substantial benefits in the emergency department. Accelerated diagnostic protocols (ADPs) have been found to reduce the average emergency department length of stay in low-risk patients while health outcomes were maintained.[5, 11] To the best of our knowledge, this is the first study evaluating health economic implications of several hsTnI enabled assessment algorithms in the emergency department from a hospital perspective, thus complementing previous research that followed lifetime effects from a health systems perspective. [20-24]

Complex management algorithms that are based on individual patient attributes, plus the heterogeneity of the emergency department population, require an individual-level modeling design. [25] This allows for more realistic comparisons of different settings, assessment strategies, or risk stratification rules. As opposed to other evaluations, costs and all management assumptions in this study were based on actual and individual patient information of a single trial-based cohort. The sampling strategy created a wide spectrum reflecting population heterogeneity and common variation in clinical practice. [26] The clinical picture and additional information from objective testing were also considered in the simulation. We believe that this set the foundation for a consistent evaluation of the benefits that would accrue on the hospital level from implementing hsTnI-enabled algorithms.

We developed a cost prediction model for chest pain patients presenting to ED, and we conducted a patient-level economic analysis for comparing different hsTnI-enabled algorithms, validated against standard care. The analysis demonstrated that the implementation of hsTnI substantially reduced LOS and costs for patients enrolled in the chest pain pathway compared to standard care. Such benefits occurred without reducing diagnostic accuracy. Moreover, the introduction of hsTnI allows for combining additional validated management rules (LoD, ADP). The overall organizational benefits

of the dominant strategy (Strategy-5) compared to standard care were caused by two effects: a) a substantial time reduction in protocol time, and b) significantly improved stratification efficiency.

The significant decrease in overnight stays resulted in downstream effects of accelerated protocols on patient management. A 4-hour reduction in protocol time led to a 6.2-hour saving in LOS. By utilizing the ADP, the timeliness of the second hsTnI result freed an additional 7.4 hours per patient. This strategy saved around 60% of overnights stays and 15% of costs compared to standard care.

In line with the definition for a high-sensitive troponin assay, [16] measurable concentrations above the LoD were found for 94% of non-ACS patients; only 6% of individuals were eligible for a direct rule-out considering the LoD criteria. This proportion appeared to be modest compared to the ADP that captured almost 50% of patients. Nevertheless, switching from Strategy-4 (hsTnI+ADP) to Strategy-5 (hsTnI+ADP+LOD) resulted in a significant reduction in the number of admissions to the short-stay unit and wards. This was caused by the fact that the LoD-rule moved 4.7% of patients from an accelerated rule-out after the 2nd troponin (ADP), to a direct rule-out after the baseline troponin (LoD). In addition, the strategy including LOD classified 1.4% of patients, who were not captured by the ADP, as eligible for a direct rule-out. As a result, a total costs were significantly reduced for Strategy 5 compared to Strategy 4 (p=0.02). The combined strategy of utilizing hsTnI and LoD within the ADP helped to avoid 7.5% of short stay unit admissions and 25% of unnecessary inpatient ward admissions.

A false positive troponin status can result in unnecessary referrals. In our study 12.1% of individuals were categorized with an hsTnI status indicative for an acute event (eTable 8). 32% of individuals were referred for ACS management; this number was not different between Strategy 1 and 2. Most of the referrals were based on a negative troponin finding followed by a positive cardiac work-up. Although we considered a conservative criteria with an absolute delta change between serial hsTnI

tests of 2ng/L, an increase in total referrals for ACS management could not be found. However, a tendency for an increased number of patients with a false positive diagnosis of ACS was observed. It is however important to note that costs accrued from such interventions were considered in the analysis.

Strategy-6 (including a direct rule in) did not significantly differ from Strategy-5 in terms of costs and diagnostic accuracy. All patients meeting the criteria of a highly elevated baseline hsTnI (≥52mg/L) were classified as high-risk and admitted to inpatient cardiology by all other strategies. Therefore, Strategy-6 did not result in a change in admission rates. However, the key value of Strategy-6 was the immediate referral to cardiology: 46.6% of patients finally diagnosed with ACS would receive earlier cardiac intervention. Given the fact that all patients in the underlying observational study were managed by standard care, data on potential outcome effects of an earlier cardiac treatment were not available, and thus not captured in the health economic evaluation.

Some limitations deserve attention. The analysis was based on a single-center cohort, which may limit the generalizability of the findings. Given the nature of a trial-based, individual level simulation, patient attributes were limited to the actual cohort; e.g. the impact of variation in ACS prevalence could not be tested in a sensitivity analysis. Follow-up was limited to 30 days. Events happening after 30 days were not considered but may have an impact on the number of false-positives diagnosis. Troponin results must be interpreted in concert with clinical presentation, ECG changes and other available information. Diagnostic accuracy in this study refers to results of the complete assessment pathway consisting of troponin results, ECG and cardiac workup. In an approach to emphasize safety, we used a conservative dynamic cut-off between serial troponin tests. The impact of different absolute or relative changes was not evaluated. Age or gender specific troponin reference values may further improve the diagnostic accuracy but were not considered.

Management and cost data extracted from administrative databases may have some inaccuracies. Each of the 719 individuals from the cohort were run through the model on average 55 times with consistent characteristics, but varied in terms of protocol, treatment times, LOS, optional work-up decisions, and accrued costs. The thus generated cohort of 40,000 individuals reflected heterogeneity in patient management and addressed some of the uncertainty. The referral of patients followed strict and standardized assumptions. Deviation from recommended pathways may occur probably due to individual preferences or logistic effects such as access block. [27] Some of the potential flow issues were addressed by assuming a wide range in the initial assessment time (6–118 minutes). The predictors used in the cost model were limited to information about risk assessment and stratification; information about inpatient management other than inpatient time was not available. Patients with a long-term stay were excluded from the analysis in order to mitigate this potential risk of bias.

Economic implications from breaching specific emergency department targets or access blocks were not taken into account but may have a significant impact. Based on the findings of this study, it appears likely that considering such aspects would strengthen the results in favor of accelerated protocols. The model compared a sensitive troponin assay at 6 hours to highly sensitive assay at 2 hours. For the models not utilizing the LoD, it is unclear whether a sensitive troponin taken at 2 hours would provide the same benefits outlined here with a highly sensitive assay. The cost prediction did not account for different costs of troponin assays. Compared to the magnitude of the difference between sensitive TnI and hsTnI strategies this effect was regarded as negligible.
It should be noted that exploiting the value of hsTnI fully relies on the appropriateness of testing and the implementation of adequate protocols.

CONCLUSION

This trial based economic modeling study sought to evaluate the impact of different hsTnI protocols on direct costs and diagnostic accuracy compared to standard care. We found that emergency department assessment strategies utilizing hsTnI are very likely to be cost-effective and provide cost savings on a hospital level when compared to sensitive TnI protocols for patients presenting with symptoms consistent with ACS. This is mainly due to a positive effect on the majority of patients not diagnosed with ACS. In particular, hsTnI-enabled algorithms considering additional rule-out criteria (LoD, ADP) are expected to improve the accuracy of both referral to inpatient wards or safe discharge as appropriate. Implementation of these protocols would provide direct benefits for the hospital in terms of reduced admission rates, avoided overnight stays, and improvements in time-based emergency department performance measures, thereby contributing to streamlined emergency department processes, more efficient use of resources, and overall cost savings.

Data sharing

Statistical code is available from the lead author.

Contributors

All authors had full access to the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. JG, LC and WP led the clinical study design as part of the Asia-Pacific Evaluation of Chest Pain Trial (ASPECT). JG extracted the dataset required for the modeling study. PJ developed the health economic model and run the analysis. Model design and assumptions were reviewed by all authors. All authors contributed in the interpretation of results, writing the manuscript, and critically reviewing each draft of the manuscript. The final version was approved by all authors. The study was supervised by LC.

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Conflicts of interest disclosures

All authors completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. PJ is a full-time employee of Abbott Diagnostics. JG has received funding from the Queensland Emergency Medicine Research Foundation. WP has received funding from the Queensland Emergency Medicine Research Foundation, Abbott Diagnostics, Roche, Alere, and Beckmann Coulter for research on diagnostic protocols; and honoraria, travel expenses, and consultancy fees from

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Transparency Declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1. Assessment strategies evaluated in the model

No	Strategy	Troponin assay	Protocol	Diagnostic cut-off [a]	Dynamic cut-off [b]	Direct rule-in [c]	Direct rule-out [d]	Accelerated rule-out [e]	Reference
1	Standard	cTnI	0 / 6hrs	> 40.0	delta < 10	No	No	No	Standard Care
2	hsTnI	hsTnI	0 / 2hrs	> 26.2	delta < 2	No	No	No	9, 11
3	hsTnI+LoD	hsTnI	0 / 2hrs	> 26.2	delta < 2	No	Yes	No	9, 12
4	hsTnI+ADP	hsTnI	0 / 2hrs	> 26.2	delta < 2	No	No	Yes	4, 9
5	hsTnI+LoD+ADP	hsTnI	0 / 2hrs	> 26.2	delta < 2	No	Yes	Yes	4, 9, 12
6	hsTnI+LoD+ADP +direct rule in	hsTnI	0 / 2hrs	> 26.2	delta < 2	Yes	Yes	Yes	4, 9, 12, 18

All values in ng/L.

cTnI= sensitive cardiac troponin I; hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP= Modified ADAPT accelerated diagnostic protocol; ADAPT=2-Hour Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker trial

[a] A troponin value greater than the diagnostic cut-off was considered as elevated.

[b] A delta between troponin values at different time points of less than 10ng/L (cTnI) or 2ng/L (hsTnI) was used to distinguish and rule-out a rise and/or fall in troponin associated with acute cardiac conditions.

[c] Direct rule-in of individuals with a hsTnI value at baseline above 52ng/L.

[d] Direct rule-out of individuals with a hsTnI value at baseline below the limit of detection of 1.2 ng/L (LoD).

[e] Referring to the Modified ADAPT accelerated diagnostic protocol (ADP). Accelerated rule-out applied to individuals with hsTnI values at 0 and 2h below the diagnostic cut-off and a TIMI risk score ≤1.

Table 2. Comparison of cost data and model validation.

Total costs, $	Item	Cullen 2015 [7]	Model cohort[a]	Model prediction[b]	Prediction vs. Cohort (p-value)
All	n (%)	926 (100%)	719 (100%)	719 (100%)	
	Mean cost (95%CI)	5272 (4835 - 5708)	5303 (4796 - 5810)	5437 (4897 - 5977)	0.72
	Median cost (25th-75th percentile)	2433 (1458 - 6778)	2497 (1449 - 6663)	2169 (1747 - 6384)	
Low Risk	n (%)	9 (1.0%)	9 (1.3%)	9 (1.3%)	
	Mean cost (95%CI)	2040 (1306 - 2774)	2040 (1125 - 2955)	2010 (1559 - 2460)	0.95
	Median cost (25th-75th percentile)	1530 (1298 - 3050)	1530 (1080 - 3359)	1907 (1569 - 2438)	
Intermediate Risk	n (%)	580 (62.6%)	468 (65.1%)	468 (65.1%)	
	Mean cost (95%CI)	3304 (2963 - 3644)	3413 (3050 - 3775)	3755 (3288 - 4223)	0.26
	Median cost (25th-75th percentile)	1849 (1376 - 3570)	1925 (1389 - 3628)	1946 (1668 - 3270)	
High Risk	n (%)	329 (35.5%)	242 (33.7%)	242 (33.7%)	
	Mean cost (95%CI)	8919 (7971 - 9867)	9081 (7878 - 10284)	8816 (7593 - 10040)	0.76
	Median cost (25th-75th percentile)	6452 (2650 - 11829)	6405 (2752 - 11309)	5566 (2355 - 11130)	

All costs referred to inflated costs in Australian dollars.

CI=confidence interval

a Excluded individuals not meeting the minimum required dataset for the model

b Excluded individuals with cost-outliers, missing and inconsistent data.

Table 3. Main model outcomes of different troponin supported assessment strategies

Indicator		Strategy 1 (Standard)	Strategy 2 (hsTnI)	Strategy 3 (hsTnI+LoD)	Strategy 4 (hsTnI+ADP)	Strategy 5 (hsTnI+LoD+ADP)	Strategy 6 (hsTnI+LoD+ADP+ direct rule- in)
Short stay unit admissions[a], %	Mean (95% CI)	65.3 (64.8 - 65.7)	65.3 (64.8 - 65.7)	60.4 (59.9 - 60.8)	65.3 (64.8 - 65.7)	60.4 (59.9 - 60.8)	60.4 (59.9 - 60.8)
	Incremental[b] (p-value)		0.0 (1.00)	-4.9 (<0.001)	4.9 (<0.001)	-4.9 (<0.001)	0.0 (1.00)
Ward admissions[a], %	Mean (95% CI)	49.7 (49.2 - 50.2)	49.6 (49.1 - 50.1)	47.4 (46.9 - 47.9)	38.4 (37.9 - 38.9)	37.1 (36.6 - 37.6)	37.1 (36.6 - 37.6)
	Incremental[b] (p-value)		-0.1 (0.81)	-2.3 (<0.001)	-9.0 (<0.001)	-1.3 (<0.001)	0.0 (1.00)
Overnight stays, %	Mean (95% CI)	60.3 (59.8 - 60.8)	42.0 (41.5 - 42.5)	39.8 (39.3 - 40.3)	24.4 (24.0 - 24.8)	23.9 (23.5 - 24.3)	24.1 (23.7 - 24.5)
	Incremental[b] (p-value)		-18.3 (<0.001)	-2.2 (<0.001)	-15.4 (<0.001)	-0.5 (0.08)	0.2 (0.51)
Referral to ACS management, %	Mean (95% CI)	32.4 (32.0 - 32.9)	32.2 (31.8 - 32.7)	30.9 (30.5 - 31.4)	21.0 (20.6 - 21.4)	20.7 (20.3 - 21.1)	20.9 (20.5 - 21.3)
	Incremental[b] (p-value)		-0.2 (0.56)	-1.3 (<0.001)	-9.9 (<0.001)	-0.3 (0.26)	0.3 (0.37)
Length of stay, hours	Mean (95% CI)	34.0 (33.6 - 34.4)	27.8 (27.4 - 28.2)	26.8 (26.4 - 27.3)	20.4 (20.0 - 20.9)	20.1 (19.6 - 20.5)	20.4 (19.9 - 20.8)
	Incremental[b] (p-value)		-6.2 (<0.001)	-1.0 (0.002)	-6.4 (<0.001)	-0.4 (0.23)	0.3 (0.33)
Diagnostic accuracy (E), %	Mean (95% CI)	90.0 (89.7 - 90.3)	90.0 (89.7 - 90.3)	90.5 (90.2 - 90.8)	93.6 (93.4 - 93.8)	93.7 (93.5 - 93.9)	94 (93.7 - 94.2)
	Incremental[b] (p-value)		0.0 (0.86)	0.4 (0.04)	3.1 (<0.001)	0.1 (0.54)	0.3 (0.13)
Index costs per patient, $	Mean (95% CI)	3029 (3001 - 3058)	2923 (2894 - 2952)	2846 (2816 - 2875)	2621 (2592 - 2649)	2568 (2539 - 2596)	2582 (2553 - 2610)
	Incremental[b] (p-value)		-106 (<0.001)	-77 (<0.001)	-225 (<0.001)	-53 (0.01)	14 (0.51)
Follow-Up costs per patient, $	Mean (95% CI)	238 (225 - 250)	211 (199 - 223)	211 (199 - 223)	213 (201 - 225)	213 (201 - 225)	195 (183 - 206)
	Incremental[b] (p-value)		-26 (0.003)	0 (1.00)	2 (0.82)	0 (1.00)	-18 (0.03)
Total costs per patient (C), $	Mean (95% CI)	3267 (3236 - 3297)	3134 (3103 - 3165)	3057 (3026 - 3088)	2834 (2804 - 2864)	2781 (2751 - 2811)	2776 (2746 - 2807)
	Incremental[b] (p-value)		-133 (<0.001)	-77 (0.001)	-223 (<0.001)	-53 (0.02)	-5 (0.83)

hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP= Modified ADAPT accelerated diagnostic protocol; ACS=acute coronary syndrome

All stated costs are in Australian dollars. (E) and (C) used as main measures of outcome.

[a] Patients could be admitted to the short stay unit before being referred to inpatient ward; numbers may not sum up to 100%.

[b] Incremental values compared to next best alternative to the left.

Table 4. False-negative and false-positive diagnosis of different assessment strategies

Strategy	False positives, %			False negatives, %		
	Mean	(95% CI)	p-value	Mean	(95% CI)	p-value
(1) Standard	6.6	(6.4 - 6.9)		3.4	(3.2 - 3.6)	
(2) hsTnI	7.0	(6.7 - 7.2)	0.06[a]	3.0	(2.8 - 3.2)	0.002[a]
(3) hsTnI+LoD	6.5	(6.3 - 6.8)	0.62[a]; 0.02[b]	3.0	(2.8 - 3.2)	0.002[a]; 1.00[b]
(4) hsTnI+ ADP	3.4	(3.2 - 3.5)	<0.001[a,b]	3.0	(2.9 - 3.2)	0.005[a]; 0.84[b]
(5) hsTnI+LoD+ADP	3.3	(3.1 - 3.4)	<0.001[a,b]	3.0	(2.9 - 3.2)	0.005[a]; 0.84[b]
(6) hsTnI+LoD+ADP+direct rule-in	3.3	(3.1 - 3.4)	<0.001[a,b]	2.8	(2.6 - 2.9)	<0.001[a]; 0.05[b]

False positives: Number of patients diagnosed with ACS and a 30-days adjudicated diagnosis of non-ACS.

False negatives: Number of patients not diagnosed with ACS and a 30-days adjudicated diagnosis of ACS.

hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP= Modified ADAPT accelerated diagnostic protocol; ACS=acute coronary syndrome

[a] p-value vs. Strategy-1 (Standard Care)

[b] p-value vs. Strategy-2 (hsTnI)

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Figure 1. Basic model structure

[a] In strategy 6: if hsTnI at baseline ≥52ng/L.

[b] In strategies 3,5, and 6: if hsTnI at baseline ≤1.2ng/L (limit of detection).

[c] In strategies 4,5, and 6: if hsTnI values at baseline and 2h are below the diagnostic cut-off of 26.2ng/L, and TIMI risk score ≤1, according to the Modified ADAPT accelerated diagnostic protocol (ADP).

Figure 2. Cost-effectiveness matrix

Strategy code: (1) Standard, (2) hsTnI, (3) hsTnI+LoD, (4) hsTnI+ADP, (5) hsTnI+LoD+ADP, (6) hsTnI+LoD+ADP+direct rule -in.

Costs include index costs and 30-days follow-up costs from the hospital perspective.

Diagnostic accuracy refers to the adjudicated final diagnosis of ACS within 30 days after presentation to the emergency department.

Each data-point reflects the strategy specific mean value and 95% confidence interval of 40,000 iterations.

hsTnI=Highly sensitive cardiac troponin I; LoD=Limit of detection; ADP=Modified ADAPT accelerated diagnostic protocol

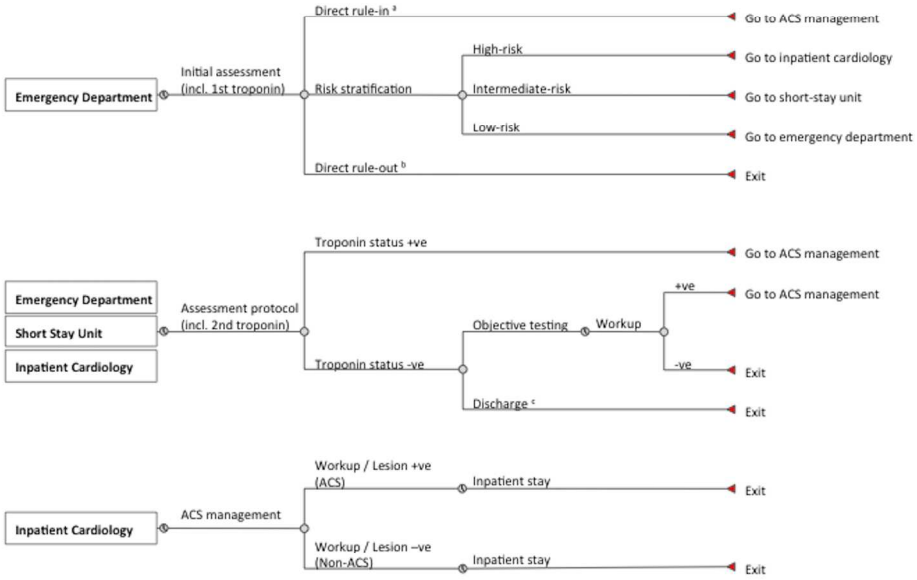

Figure 1. Basic model structure

‼ ┼ a In strategy 6: if hsTnI at baseline ≥52ng/L%

b In strategies 3,5, and 6: if hsTnI at baseline ≤1.2ng/L (limit of detection).

┼ c In strategies 4,5, and 6: if hsTnI values at baseline and 2h are below the diagnostic cut-off of 26.2ng/L, and TIMI risk score ≤1, according to the Modified ADAPT accelerated diagnostic protocol (ADP).

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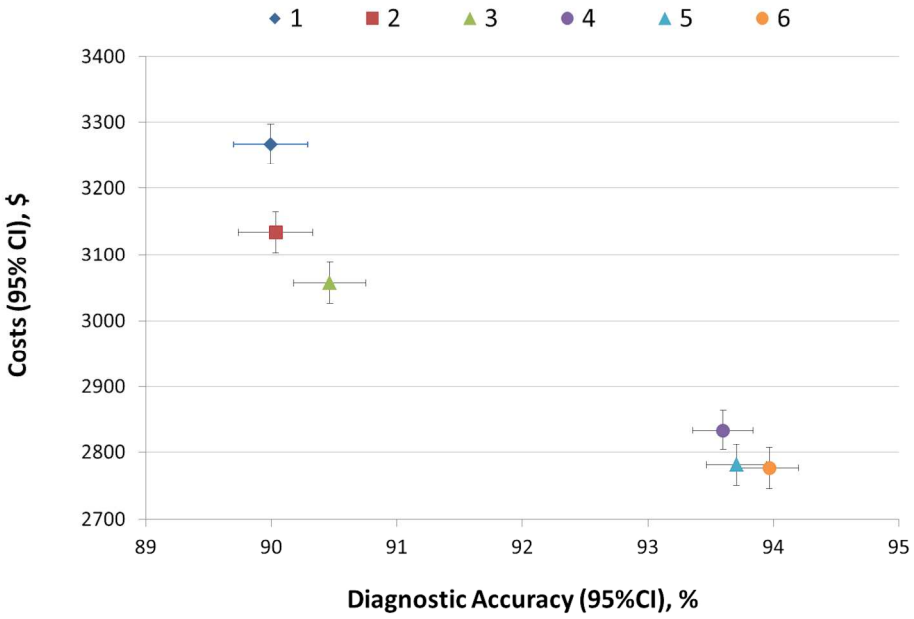

Strategy code: (1) Standard, (2) hsTnI, (3) hsTnI+LoD, (4) hsTnI+ADP, (5) hsTnI+LoD+ADP, (6) hsTnI+LoD+ADP+direct rule -in.┼ Costs include index costs and 30-days follow-up costs from the hospital perspective.┼ Diagnostic accuracy refers to the adjudicated final diagnosis of ACS within 30 days after presentation to the emergency department.┼ Each data-point reflects the strategy specific mean value and 95% confidence interval of 40,000 iterations.┼ hsTnI=Highly sensitive cardiac troponin I; LoD=Limit of detection; ADP=Modified ADAPT accelerated diagnostic protocol┼

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The organizational value of diagnostic strategies using high sensitivity troponin for patients with possible acute coronary syndromes: A trial-based cost-effectiveness analysis

SUPPLEMENTARY ONLINE CONTENT

Contents

eMethods 1. Micro simulation model

Troponin testing

After blood was drawn, samples for hsTnI testing were immediately centrifuged. Serum and EDTA plasma were separated and stored frozen at -80°C, within two hours. During March and April, 2012, previously unthawed samples were thawed, mixed, and centrifuged prior to analysis. The assay used was the final pre-commercial release version of the ARCHITECT High Sensitive STAT Troponin-I assay (Abbott Laboratories, Abbott Park, IL). The hsTnI assay has a 99th percentile concentration of 26.2ng/L with a corresponding co-efficient of variation of <5% and a limit of detection of 1.2ng/L. [1] Long-term stability of TnI has been demonstrated previously. [2]

Cost prediction model

In alignment with the study focus, activities that were available by patient were limited to the risk assessment and stratification period (ECG, stress test, troponin testing, MPS, CTCA, angiography, etc.). Information about inpatient treatment and management other than inpatient time were not available. Thus, the prediction of total costs based on the available data was expected to be biased with increasing inpatient time. In fact, the average costs per inpatient day decreased with increasing stay until a slight increase appeared for patients staying more than 15 days. This was regarded as an indicator for costs accrued from activities not captured in the collected data. By further analyzing the data, we excluded 2.5% of patients with an inpatient stay of more than 12 days, as this was the maximum length of stay threshold that did not affect quartiles, median, and the 95th percentile of the cost distribution of the original data, but also excluded effects of unknown inpatient activities from the prediction model.

Patient pathway

Patients were classified into risk groups according to the Queensland chest pain pathway (eFigure 1).[3] Low-risk patients were treated in the ED; intermediate-risk patients were managed in the ED with admission to the ED short-stay unit. High-risk patients were referred to inpatient cardiology. Patients requiring CABG were transferred to another institution.

Health economic model

The model distinguished five troponin statuses (eTable 3). On a positive troponin status, patients were referred to inpatient cardiology. Patients with a negative troponin status underwent further testing for coronary ischemia.

Further testing included the evaluation of the troponin status after the second test and additional objective testing (exercise stress test, myocardial perfusion scan, stress echocardiography, computed tomography coronary angiography or angiography). If objective testing was negative, patients were eligible for discharge from the chest pain pathway and exit the model. If objective testing or troponin results were positive, patients were referred for acute coronary syndrome (ACS) management in the inpatient ward.

In the accelerated diagnostic protocol (ADP) scenarios, patients meeting the Modified 2-hour Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker trial (ADAPT) criteria for low risk patients (thrombosis in myocardial infarction (TIMI) score ≤1 and hsTnI ≤ upper limit of normal (ULN)) were discharged and exited the model without further testing and workup.

Diagnosis was compared to the final adjudicated 30-days diagnosis for calculating the diagnostic accuracy. A follow-up event within 30 days was assumed for individuals ruled-out by the respective strategy, and a reported 30-days clinical outcome of ACS (False-negative patients).

Occurrences and results of workup testing per individual were randomly sampled from binomial distributions on the basis of the troponin status using actual probabilities derived from the study cohort. Duration of workup was analyzed from the model cohort and transformed into statistical distributions. Times were randomly sampled from these distributions individually during simulation. To reflect the heterogeneity of hospital stay, LOS data of the

model cohort were analyzed by final diagnosis (ACS, Non-ACS) and electrocardiogram status (normal, ischemic, abnormal).

Hospital LOS times were randomly sampled per individual from distributions with values limited between the observed minimum and maximum of the cohort. Inpatient stay was calculated by deducting all inpatient activities from the sampled LOS times. Inpatient time was only considered for individuals that were referred to ACS management. All next day discharges were counted as overnight stays.

Regression coefficients for predicting index costs were randomly sampled per individual case with a uniform distribution between the lower and upper bound of the 95% confidence interval. Follow up cost data were estimated by assuming that the patient was admitted to cardiology for angiography with an emergency department-LOS of one hour, 3 inpatient days, no exercise stress test, no myocardial perfusion scan, no computed tomography coronary angiography, and no echocardiography. Follow-up costs were assigned by randomly sampling from a uniform distribution between the upper and lower limit of the 95% CI of the predicated costs of this scenario ($5402-$8628).

The appropriate number of samples was estimated by conducting several pilot runs estimating the effect size. A reasonable distinction between confidence intervals for costs, an acceptable consistency between multiple run (n=5) and single run results, and a between-run variability of below 10% were used as criteria.[4] We regarded the latter as particularly important since it would allow for meaningful comparisons between different scenarios, settings and assumptions in subsequent evaluations. Based on results of the pilot runs (eFigure 2A-B) the sample size was set to 40,000 patients.

For the probabilistic sensitivity analysis Strategy-2 was compared against Strategy-1 by repeating the micro simulation 250 times with 40,000 patients each. Mean results and 95% confidence intervals for costs, referral accuracy, and diagnostic accuracy were compared to the micro simulation results (eFigure 6; eTable 11).

The impact of protocol time on costs was tested by running Strategy-2 and assuming constant troponin values and increasing but fixed protocol times. Variation in the discharge threshold between 6pm and 10pm were tested and compared to a scenario with no daytime restriction for discharge. Both analyses were done by sampling 40,000 individuals in 5 independent runs.

Model was developed in TreeAge Pro 2015, R1.0 (TreeAge Software, Williamstown, MA, USA). Statistical analyses were done in Minitab 16.1.0. A significance level of 0.05 was used in all analyses. Continuous data were analyzed conducting a 2-Sample t-test and Mann-Whitney test. For categorical data Fisher's exact test was used.

Additional information

By randomly sampling from the database, each of the 719 individual patients was sampled on average 55 to 56 times (Range 36 – 78). Each sample of a patient was consistent in age, sex, characteristics, ACS status and troponin values, but varied in terms of arrival time, protocol time, treatment times, additional cardiac testing if required, total inpatient LOS if referred for ACS management, and costs predictors. This generated a huge cohort of patients that reflected variation and heterogeneity in decision making, severity, and management. The result of the sampling approach is demonstrated in eFigure 3 which shows distribution of costs of the first 10 individuals as an example. Given the fact that cardiac testing such as exercise stress testing or myocardial perfusion scanning could potentially lead to positive results in patients with negative ACS condition (eTable 4A) some repetitions generated positive workup results that led to ACS management referrals (Italic numbers in eFigure 3). The inpatient stay after stratification and workup was by assumption only considered for patients referred to ACS management. Therefore, the observed variation in costs for patients referred to ACS management is mainly driven by variation in length of stay reflecting different treatments, underlying diseases, severity or management decisions. There was a potential risk that this variation would superimpose the focus of the study to evaluate different assessment strategies.

In line with a long-term perspective, previous research did not consider short term effects for hospitals or variation in troponin protocol time.[5-9] This model used a distribution around the recommended target derived from actual data reflecting a more realistic scenario (eFigure 4A).

eFigure 5 provides histograms of SSU times. The majority of patients were admitted to short stay unit (65% with short stay unit time > 0hrs, eFigure 5A); in the standard strategy utilizing cTnI some patients were managed around a mean of 7.5 hours, some required additional observation with a mean of 25.0 hours indicating overnight

stays. Replacing cTnI with hsTnI resulted in a substantial shift to lower short stay unit times as shown by mean values of 4.0 hours and 22.5 hours for those staying overnight (eFigure 5B). An additional direct rule-out strategy (limit of detection, LoD) decreased the number of short stay unit admissions significantly as indicated by an increased proportion of patients at 0h in eFigure 5B. As illustrated in eFigure 5C accelerated rule-out protocols for low risk patients (ADP) moved the SSU time distribution to distinctly lower values.

Testing the influence of different protocol times revealed that protocols with lower time targets would be less affected by variation and delays (eFigure 7). As a practical consequence, accelerated algorithms could be expected to result in more stable and more predictable emergency department processes, thus allowing for better management and resource allocation.

Patients may not be discharged immediately even if they are regarded as low risk. Prolonged protocol times could cause some clinically unnecessary overnight stays at the hospital's expense. We used the discharge threshold time to reflect such specific management rules. Since the threshold may not be fixed in real life we tested the impact of some flexibility. Data in eFigure 8 reveal no significant observable effect of a flexible threshold time on Strategy 2 (hsTnI) whereas Strategy 1 (cTnI, standard care) was strongly affected between 6 and 8pm. Although these findings depend on emergency department arrival pattern results suggested that hsTnI enabled algorithms would be less affected by variation. Given the fact that arrival pattern used in the model was derived from actual data accelerated protocols would likely lead to more stable and predictable emergency department processes.

eTable 1. Patient selection criteria: Cost prediction model

Criteria	Excluded	N
All data		938
Exclude patients with CABG*	-14	924
Exclude long-stay outliers >12d (incl. non-cardiac complications)	-23	901
Exclude inconsistent or missing data	-6	895
Analyze extreme outliers	-4	891

*Patients receiving coronary bypass surgery (CABG) were excluded for the cost prediction model. Costs were unknown as patients were transferred to another hospital for surgery.
CABG=Coronary artery bypass graft

eTable 2. Patient selection criteria: Micro simulation model

Minimum required dataset	Excluded	N
Basic characteristics	0	938
Time points stated	0	938
ECG information available	0	938
Baseline cTnI	0	928
Baseline hsTnI	-145	793
Second cTn (6hrs)	-57	736
Second hsTnI (2hrs)	-17	719
Final endpoint	0	719

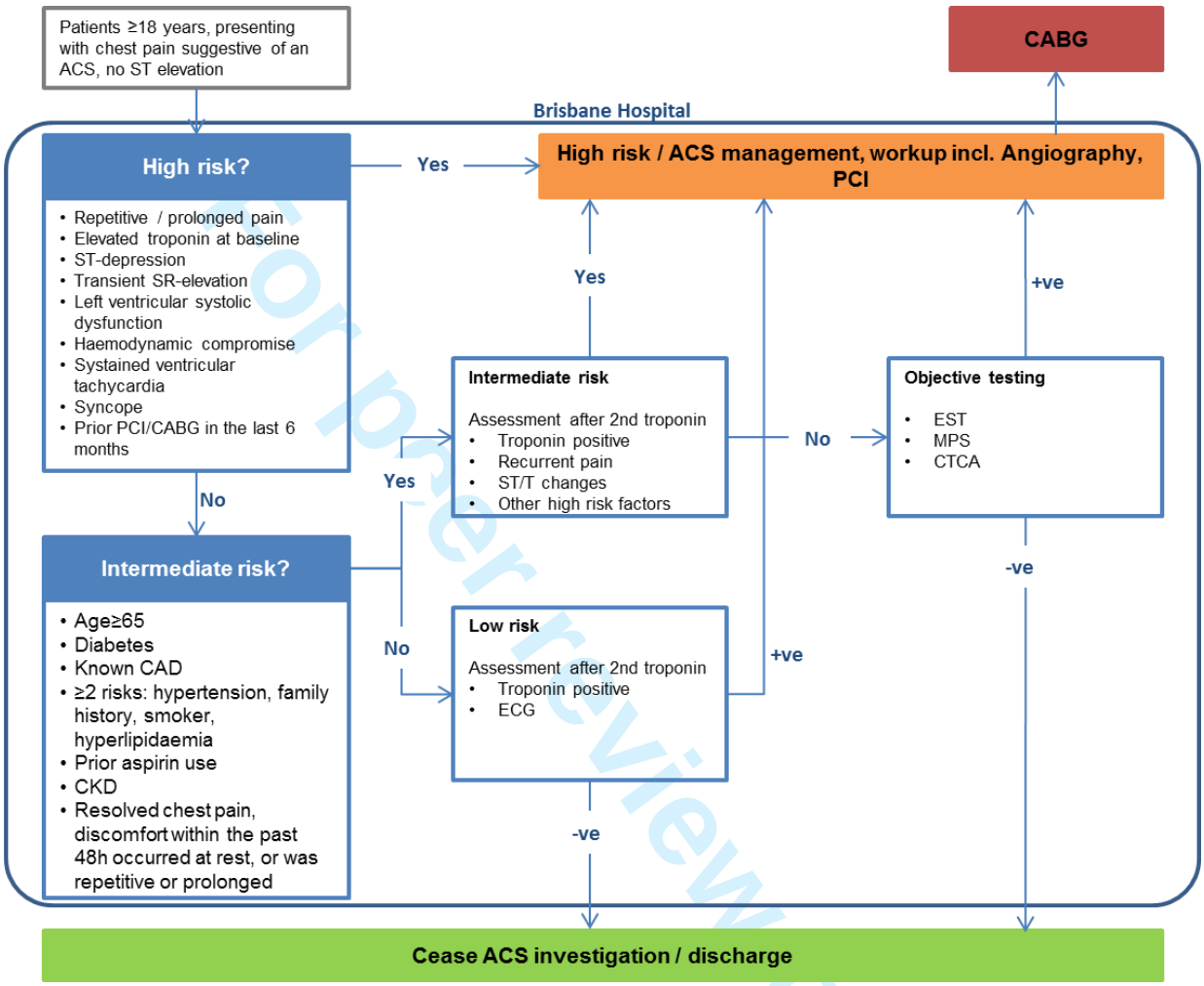
Individuals with missing data in the minimum required dataset were excluded from the analysis.
ECG=echocardiogram, cTnI=sensitive cardiac troponin I, hsTnI=highly sensitive cardiac troponin I

eTable 3. Troponin statuses considered in the model

Status	Description	Evaluation for ACS
1	1^{st} troponin & 2^{nd} troponin ≤ ULN	Negative
2	1^{st} troponin ≤ ULN & 2^{nd} troponin > ULN	Positive
3	1^{st} troponin > ULN & 2^{nd} troponin ≤ ULN	Positive
4	1^{st} troponin & 2^{nd} troponin > ULN; difference < delta cut-off	Negative (Stable)
5	1^{st} troponin & 2^{nd} troponin > ULN; difference ≥ delta cut-off	Positive

ULN=Upper limit of normal, 99^{th} percentile of the reference population; ACS=Acute coronary syndrome

eFigure 1. Risk stratification and process of care for possible acute coronary syndrome



Risk stratification according to [3].

eTable 4A. Model parameter and assumptions: Objective testing probabilities.

Workup	Troponin status	N	Occurence	Result +-ve
Exercise Stress Test	1	582	60.1%	5.4%
	2	31	29.0%	11.1%
	3	15	33.3%	20.0%
	4	40	12.5%	40.0%
	5	51	2.0%	0.0%
Myocardial perfusion scan	1	582	14.3%	18.1%
	2	31	12.9%	75.0%
	3	15	20.0%	33.3%
	4	40	7.5%	0.0%
	5	51	2.0%	0.0%
Echocardiography	1	582	17.0%	data not available
	2	31	48.4%	
	3	15	20.0%	
	4	40	50.0%	
	5	51	70.6%	
Computed tomography coronary angiography	1	582	3.1%	data not available
	2	31	0.0%	
	3	15	6.7%	
	4	40	5.0%	
	5	51	0.0%	

Statistical evaluation of the model cohort (N=719)

eTable 4B. Model parameter and assumptions: Probabilities for angiography.

Workup	Troponin status	N	Occurrence	Result +ve (ACS patients)	Result +ve (non-ACS patients)
Angiography	1	582	11.9%	50.0%	31.3%
	2	31	35.5%	100.0%	0.0%
	3	15	13.3%	0.0%	0.0%
	4	40	27.5%	83.3%	40.0%
	5	51	70.6%	96.8%	20.0%

Statistical evaluation of the model cohort (N=719)
ACS=Acute coronary syndrome

eTable 4C. Model parameter and assumptions: Cardiac workup duration

Variable	Mean time, hours	Distribution
Arrival time (decimal time format)	0.45	Normal
Initial assessment time	0.45	Gamma
Protocol time cTnI	6.3	Gamma
Protocol time hsTnI	2.3	Gamma
Workup time (2nd Tn after 6.30pm)	17.1	Gamma
Probability of short workup time (2nd Tn before 6.30pm)	0.79	Binomial
Workup time (short; 2nd Tn before 6.30pm)	1.78	Gamma
Workup time (long; 2nd Tn before 6.30pm)	20.3	Gamma
Angiography	3.0	Gamma

cTnI=sensitive cardiac troponin I; hsTnI=highly sensitive cardiac troponin I

eTable 4D. Model parameter and assumptions: Hospital length of stay

Hospital LOS, hours	Mean	SD	Q1	Median	Q3	Min	Max	Distribution
ACS / ECG normal	154.4	99.6	66.5	100.6	273.4	48.7	280.4	Gamma
ACS / ECG ischemic	125.4	87.6	56.7	92.8	209.6	20.5	288.0	Gamma
ACS / ECG abnormal	110.3	81.5	59.3	85.5	166.0	15.8	283.9	Gamma
Non-ACS / ECG normal	33.1	49.7	6.0	19.6	27.6	0.0	284.0	Gamma
Non-ACS / ECG ischemic	91.9	90.5	25.0	64.7	121.3	0.0	284.0	Gamma
Non-ACS / ECG abnormal	58.9	71.7	8.0	25.3	80.5	0.0	282.4	Gamma

Statistical evaluation of the model cohort (N=719)
LOS=length of stay; ACS=acute coronary syndrome; ECG=electrocardiogram

eTable 5. Patient characteristics of the selected and generated model cohort.

Demographics	Cohort (N = 719)	Generated cohort[a] (N = 40,000)	p-value
Sex (% women)	39.4	39.5	0.94
Age, yrs. Mean (Range)	55 (19 - 97)	55 (19-97)	0.94
Risk factors			
Dyslipidaemia, %	42.1	Sampled and used for estimating the assessment status	
Diabetes, %	12.8		
Hypertension, %	43.3		
Tachycardia, %	1.7		
Obesity (BMI>30), %	35.5		
Smoking, %	26.8		
Medical History			
Angina, %	22.5	Sampled and used for estimating the assessment status	
Coronary artery disease, %	20.5		
Myocardial infarction, %	16.3		
Family coronary artery disease, %	46.6		
Arrhythmia, %	9.0		
Congestive heart failure, %	4.2		
CABG surgery, %	6.5		
Prior angioplasty, %	10.3		
Peripheral artery disease, %	1.8		
Aspirin use, %	25.3		
Stroke, %	9.0		
Initial assessment & final diagnosis			
ACS, %	11.0	11.0	1.00
ECG normal, %	49.5	49.1	0.85
ECG ischemic, %	7.8	7.7	0.94
ECG abnormal, %	42.7	43.2	0.82
TIMI 0, %	24.5	25.0	0.75
TIMI 1, %	33.0	33.9	0.61
TIMI 2, %	17.9	17.2	0.58
TIMI 3, %	12.2	12.1	0.86
TIMI 4, %	6.4	6.5	1.00
TIMI ≥5, %	6.0	5.4	0.51
High risk, %	33.7	33.5	0.94
Intermediate risk, %	65.1	65.3	0.94
Low risk, %	1.3	1.3	1.00
Baseline cTnI, ng/L (Mean, range)	118 (10 - 31000)	119 (10 - 31000)	0.97
Baseline hsTnI, ng/L (Mean, Range)	117.5 (0.3 - 38685)	119.2 (0.3 - 38685)	0.98
hsTnI < LoD at baseline[b], %	5.1	6.1	0.34

TIMI and risk assignment based on standard strategy
[a] Samples per individuals: Mean 55.6; Range 36-78; Mode: 52.
[b] Limit of detection for hsTnI 1.2ng/L
BMI=Body mass index; CABG=coronary artery bypass graft; ACS=acute coronary syndrome; ECG=electrocardiogram; TIMI=Thrombolysis in myocardial infarction; cTnI=sensitive cardiac troponin I; hsTnI=highly sensitive cardiac troponin I, LoD=limit of detection

eTable 6. Cost prediction model regression analysis

Term	Coef	SE Coeff	T	P-value	(95% CI)	VIF
Constant	3.57	0.04	101.5	<0.001	(3.51 – 3.64)	
ED time, hours	0.02	0.00	8.8	<0.001	(0.02 – 0.03)	1.15
Inpatient stay, days	0.19	0.01	37.7	<0.001	(0.18 – 0.20)	1.78
Exercise stress test	-0.09	0.02	-4.3	<0.001	(-0.13 – -0.05)	1.37
Myocardial perfusion scan	0.25	0.04	6.7	<0.001	(0.18 – 0.32)	1.22
Computed tomography coronary angiography	0.27	0.07	4.0	<0.001	(0.14 – 0.40)	1.02
Angiography	0.65	0.03	21.8	<0.001	(0.59 – 0.71)	1.34
Echocardiography	0.32	0.03	11.4	<0.001	(0.26 – 0.37)	1.49
Admission	0.39	0.03	11.6	<0.001	(0.33 – 0.46)	1.21

VIF: Variance inflation factor

Box-Cox transformation with Lambda= 0.189 (95%CI 0.135 – 0.245)

S	0.264
PRESS	63.4
R-Sq	88.3%
R-Sq(adj)	88.2%
R-Sq(pred)	88.0%

Admission considers admission to short-stay unit or inpatient ward

eTable 7. Risk assignment of patients

Strategy			Initial risk assignement, %		
			Low-risk	Intermediate -risk	High- risk
Standard			**1.3**	**65.3**	**33.5**
hsTnI			**1.3**	**65.3**	**33.5**
Direct rule-out if baseline hsTnI < LoD (LoD)	No direct rule-out	**All**	**1.3**	**60.4**	**32.3**
	Direct rule-out[a]	**All**	**0.0**	**4.9**	**1.2**
		ACS	0.0	0.0	0.0
		No ACS	0.0	4.9	1.2
Accelerated rule-out if hsTnI values below the diagnostic cut-off and TIMI ≤1 (ADP)	No accelerated rule-out	**All**	**0.5**	**16.4**	**33.5**
	Accelerated rule-out[a]	**All**	**0.7**	**48.8**	**0.0**
		ACS	0.0	0.2	0.0
		No ACS	0.7	48.7	0.0
Direct rule-in if baseline hsTnI >52ng/L	No direct rule-in	**All**	**1.3**	**65.3**	**26.3**
	Direct rule-in[b]	**All**	**0.0**	**0.0**	**7.2**
		ACS	0.0	0.0	5.1
		No ACS	0.0	0.0	2.0

LoD=Limit of detection; ACS= Acute coronary syndrome;
TIMI=Thrombolysis in myocardial infarction;
ADP=Accelerated diagnostic protocol;
hsTnI=highly sensitive cardiac troponin I
[a] classified as low-risk
[b] classified as high-risk

eTable 8. Troponin status by assay used

	hsTnI			Sum (cTnI), %
cTnI	**Negative, %**	**Stable, %**	**Positive, %**	
Negative, %	84.0	0.1	0.3	**84.4**
Stable, %	0.6	0.3	2.9	**3.4**
Positive, %	2.4	0.6	9.0	**11.9**
Sum (hsTnI), %	**86.9**	**1.0**	**12.1**	**100.0**

Troponin status interpretation according to eTable3
cTnI=sensitive cardiac troponin I; hsTnI=highly sensitive cardiac TnI

eTable 9. Total length of stay and costs per strategy and final diagnosis

Strategy	Category	Total costs, $				Total LOSs, hours			
		Median	(25th - 75th perc)	Mean	(95% CI)	Median	(25th - 75th perc)	Mean	(95% CI)
1	**All**	**2135**	**(1741 - 3109)**	**3267**	**(3236 - 3297)**	**22.6**	**(8.7 - 29.8)**	**34.0**	**(33.6 - 34.4)**
	No ACS	2022	(1708 - 2669)	2570	(2550 - 2590)	21.3	(8.6 - 27.7)	27.2	(26.9 - 27.5)
	ACS	8421	(5863 - 10248)	8895	(8756 - 9034)	74.8	(25.5 - 137)	89.2	(87 - 91.3)
2	**All**	**1983**	**(1597 - 2951)**	**3134**	**(3103 - 3165)**	**6.0**	**(4.4 - 25.3)**	**27.8**	**(27.4 - 28.2)**
	No ACS	1860	(1567 - 2478)	2417[a]	(2397 - 2436)	5.6	(4.3 - 23.1)	20.2[a]	(19.8 - 20.5)
	ACS	8269	(5827 - 10210)	8930	(8788 - 9073)	79.0	(23 - 139.2)	89.6	(87.4 - 91.8)
3	**All**	**1921**	**(1548 - 2878)**	**3057**	**(3026 - 3088)**	**3.6**	**(2.7 - 10.1)**	**20.4**	**(20 - 20.9)**
	No ACS	1805	(1517 - 2427)	2330[a]	(2310 - 2350)	3.3	(2.6 - 5.4)	11.9[a]	(11.6 - 12.2)
	ACS	8269	(5827 - 10210)	8930	(8788 - 9073)	78.7	(22.8 - 139.1)	89.3	(87.1 - 91.5)
4	**All**	**1695**	**(1560 - 2260)**	**2834**	**(2804 - 2864)**	**5.6**	**(4.2 - 24.8)**	**26.8**	**(26.4 - 27.3)**
	No ACS	1663	(1544 - 1862)	2079[a]	(2062 - 2096)	5.3	(4.1 - 22.6)	19.0[a]	(18.7 - 19.4)
	ACS	8268	(5851 - 10198)	8932	(8790 - 9074)	79.0	(23 - 139.2)	89.6	(87.4 - 91.8)
5	**All**	**1681**	**(1532 - 2231)**	**2781**	**(2751 - 2811)**	**3.5**	**(2.6 - 8.3)**	**20.1**	**(19.6 - 20.5)**
	No ACS	1648	(1514 - 1845)	2020[a]	(2002 - 2037)	3.2	(2.5 - 5.2)	11.5[a]	(11.2 - 11.8)
	ACS	8268	(5851 - 10198)	8932	(8790 - 9074)	78.7	(22.8 - 139.1)	89.3	(87.1 - 91.5)
6	**All**	**1681**	**(1532 - 2230)**	**2776**	**(2746 - 2807)**	**3.5**	**(2.6 - 8.8)**	**20.4**	**(19.9 - 20.8)**
	No ACS	1648	(1514 - 1845)	2020[a]	(2003 - 2037)	3.2	(2.5 - 5.2)	11.5[a]	(11.2 - 11.8)
	ACS	8151	(5702 - 10194)	8885	(8740 - 9029)	82.0	(24.8 - 140.5)	91.9	(89.7 - 94.1)

Strategy code: (1) Standard, (2) hsTnI, (3) hsTnI+LoD, (4) hsTnI+ADP, (5) hsTnI+LoD+ADP, (6) hsTnI+LoD+ADP+Rule in.
Total costs include index costs and 30 days follow-up costs.
All costs stated are in Australian dollars.
[a] p-value vs. Standard < 0.001
ACS=Acute coronary syndrome; hsTnI=highly sensitive troponin I; LoD=limit of detection; ADP=accelerated diagnostic protocol; LOS=Length of stay

eTable 10A. Emergency department performance by strategy

Emergency department time, hours	Mean	(95% CI)	Median	(25th - 75th perc)	97.5th perc	≤4hrs
1) Standard	0.68	(0.66 - 0.7)	0.41	(0.26 - 0.63)	1.4	98.7%
2) hsTnI	0.58	(0.57 - 0.6)	0.41	(0.26 - 0.63)	1.4	99.0%
3) hsTnI+LoD	0.58	(0.57 - 0.6)	0.41	(0.26 - 0.63)	1.4	99.0%
4) hsTnI+ADP	0.54	(0.53 - 0.55)	0.41	(0.26 - 0.63)	1.4	99.6%
5) hsTnI+LoD+ADP	0.54	(0.53 - 0.55)	0.41	(0.26 - 0.63)	1.4	99.6%
6) hsTnI+LoD+ADP+Direct rule-in	0.54	(0.53 - 0.55)	0.41	(0.26 - 0.63)	1.4	99.6%

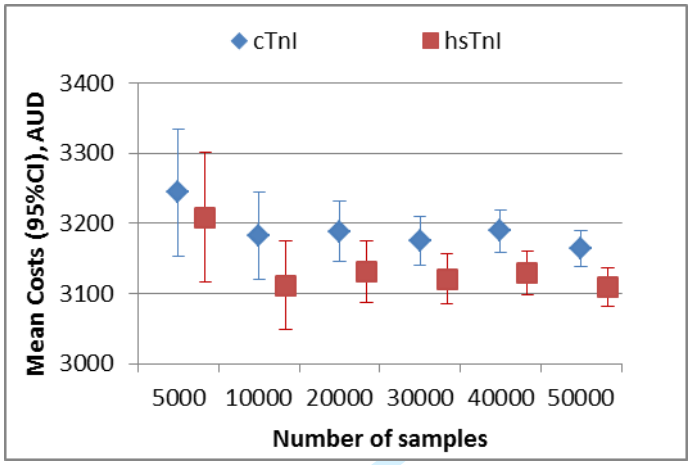
hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP=accelerated diagnostic protocol.

eTable 10B. Short Stay Unit times per patient by strategy

SSU time, hours	Mean	(95% CI)	Median	(25th - 75th perc)	90th perc
1) Standard	9.9	(9.8 - 10)	7.54	(0.0 - 20.8)	25.7
2) hsTnI	5.1	(5.1 - 5.2)	3.49	(0.0 - 4.7)	21.2
3) hsTnI+LoD	4.7	(4.7 - 4.8)	3.31	(0.0 - 4.5)	20.7
4) hsTnI+ADP	2.4	(2.3 - 2.4)	2.06	(0.0 - 2.6)	3.8
5) hsTnI+LoD+ADP	2.2	(2.2 - 2.3)	1.99	(0.0 - 2.6)	3.8
6) hsTnI+LoD+ADP+Rule in	2.2	(2.2 - 2.3)	1.99	(0.0 - 2.6)	3.8

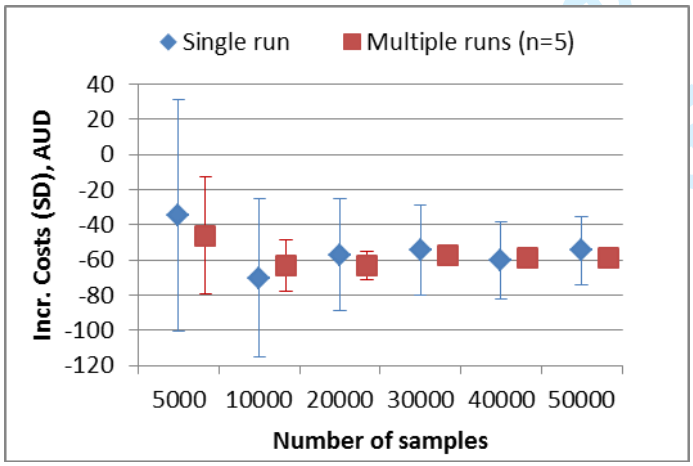
hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP=accelerated diagnostic protocol.

eFigure 2A. Mean costs based on number of samples in the micro simulation



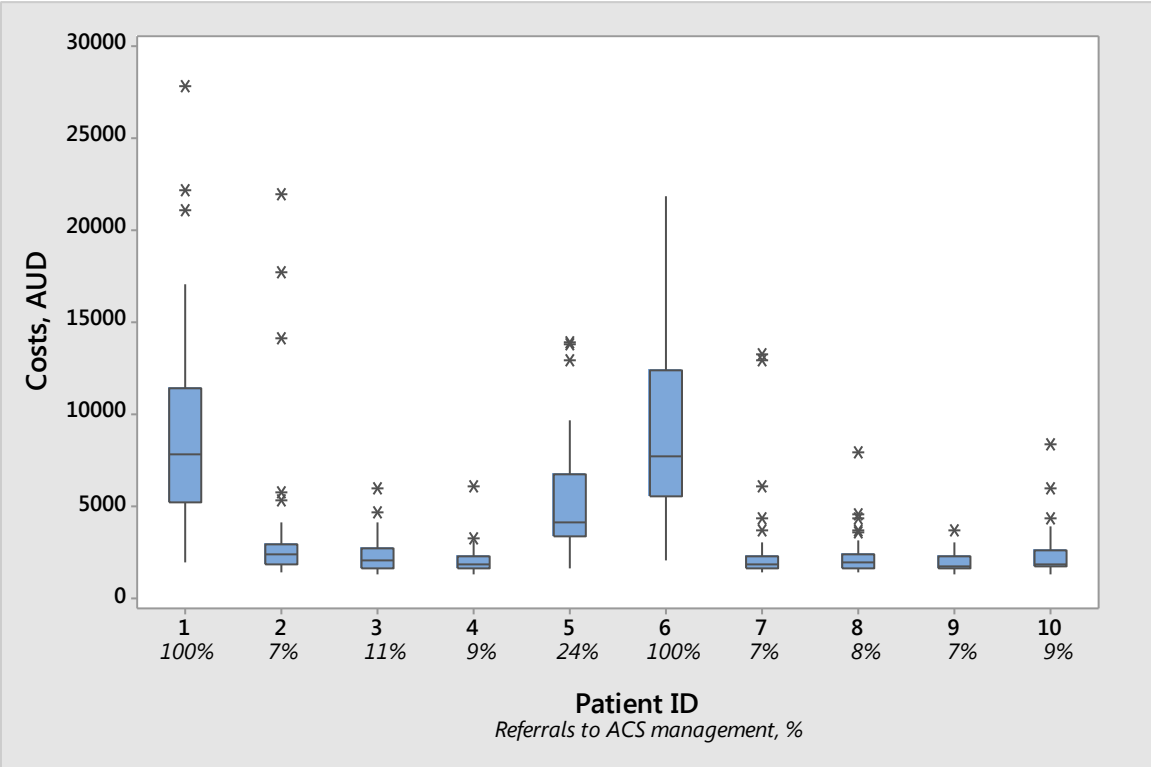
cTnI=sensitive cardiac troponin; hsTnI=highly sensitive cardiac troponin I

eFigure 2B. Incremental costs based on different number of samples in the micro simulation



Incremental costs refer to Strategy-2 – Strategy 1

eFigure 3. Cost variation as a result of the sampling strategy illustrated for ten selected individuals

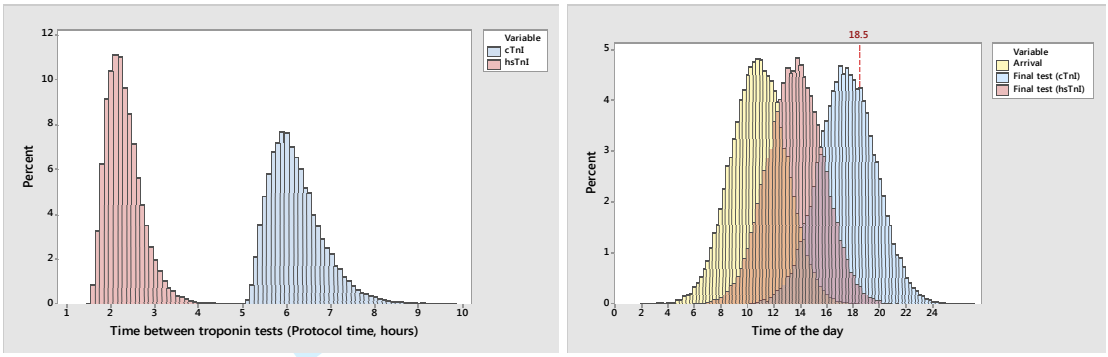


Box plots illustrate the variability in costs from multiple samples of the same individual as an example for the first 10 patients (Patient-ID 1 to 10).

By running 40,000 iterations, each of the 719 individuals was sampled on average 55 to 56 times (Range 36 – 78). This generated a huge cohort of patients that reflected variation and heterogeneity in decision making, severity, and management.

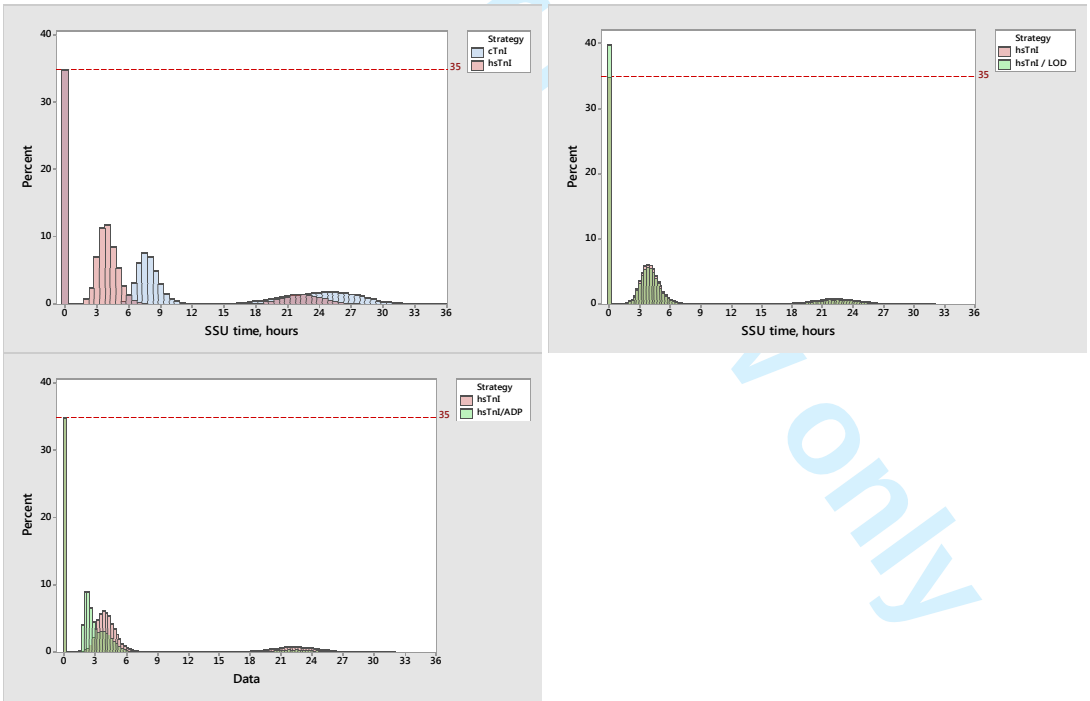
Each sample of an individual was consistent in age, sex, characteristics, ACS status and troponin values, but varied in terms of arrival time, protocol time, treatment times, additional cardiac testing if required, total inpatient LOS if referred for ACS management, and costs predictors. This resulted in a range of costs as demonstrated in the chart.
For individuals with non-ACS conditions, variation in subjective decision making or results from cardiac testing (exercise stress test or myocardial perfusion scan) led to admittance for ACS management in some cases (Patient ID 2-4, and 7-10). Italic numbers indicate the proportion of referrals to ACS management per patient. Patients with ACS were admitted for ACS management in 100% of iterations (Patient ID 1 and 6). Variation in costs between ACS patients was caused by sampling different LOS assumptions.

eFigure 4. Simulated troponin protocol times (A), patient arrival times, and times of final results for sensitive troponin I and highly sensitive troponin I (B).



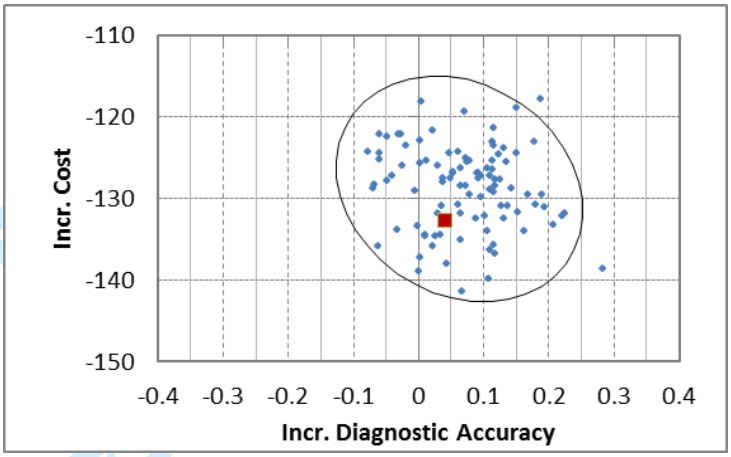
cTnI=sensitive cardiac troponin; hsTnI=highly sensitive cardiac troponin I

eFigure 5 A-C. Histograms of Short Stay Unit times for different strategies



A: Standard strategy (cTnI) vs. hsTnI;
B: hsTnI strategy vs. hsTnI / LoD strategy; C: hsTnI strategy vs. hsTnI / ADP strategy.
The reference line at 35% indicates the proportion of patients that were not admitted to Short Stay Unit in the standard strategy.
hsTnI=highly sensitive cardiac troponin I; LoD=limit of detection; ADP=accelerated diagnostic protocol.

eFigure 6. Incremental cost and effectiveness of Strategy 2 (hsTnI) vs. Strategy 1 (cTnI, usual care).



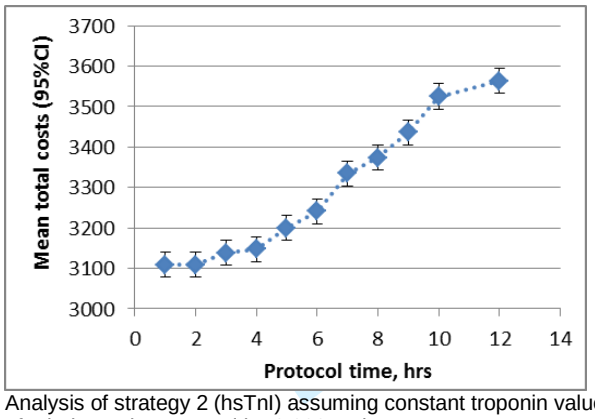
Results from multiple runs in a probabilistic sensitivity analysis (n=250). Each point represents results of a run with 40,000 sampled patients. The ellipse reflects the 95% confidence interval. Red box represents the result from the micro simulation.

eTable 11. Comparison of results from single and multiple run micro simulations

Strategy	Analysis	Total costs		Referral Accuracy, %		Diagnostic Accuracy	
		A$	(95%CI)	Mean	(95%CI)	Mean	(95%CI)
Standard	MS	3267	(3236 - 3297)	71.8	(71.4 - 72.2)	90.00	(89.7 - 90.3)
	PSA	3253	(3251 - 3255)	72.0	(71.97 - 72.02)	90.21	(90.2 - 90.23)
hsTnI	MS	3134	(3103 - 3165)	72.8	(72.3 - 73.2)	90.04	(89.7 - 90.3)
	PSA	3124	(3122 - 3126)	73.0	(72.95 – 73.00)	90.3	(90.26 - 90.29)

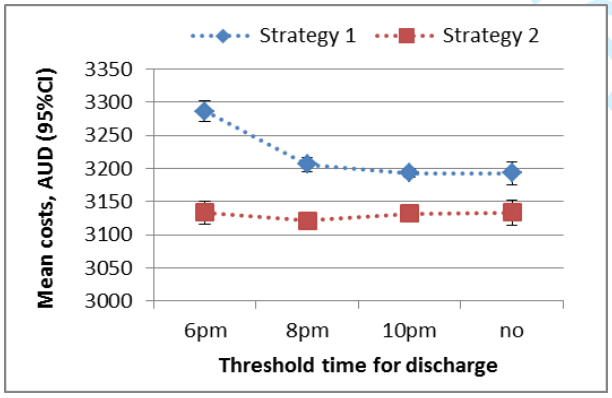
MS: Micro simulation (n=1 runs)
PSA: Probabilistic sensitivity analysis (n=250 runs)

eFigure 7. Impact of protocol time on costs.



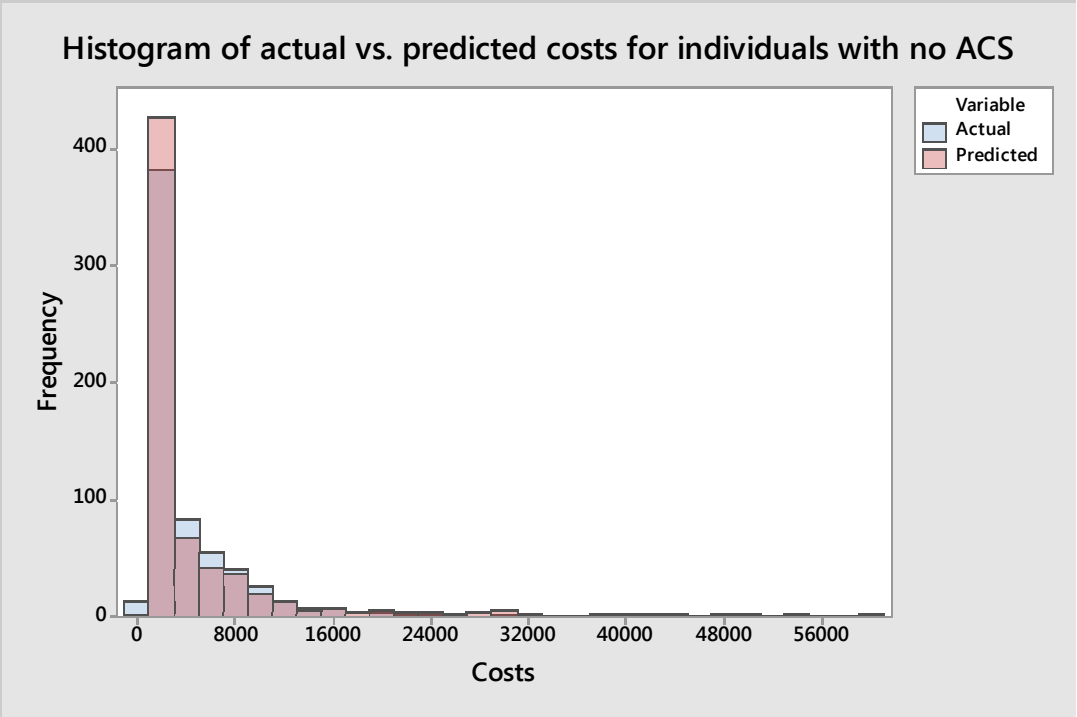
Analysis of strategy 2 (hsTnI) assuming constant troponin values and a fixed protocol time. Each data point represents the result of 5 independent runs with 40,000 patients per run.

eFigure 8. Impact of threshold time for discharge on costs.

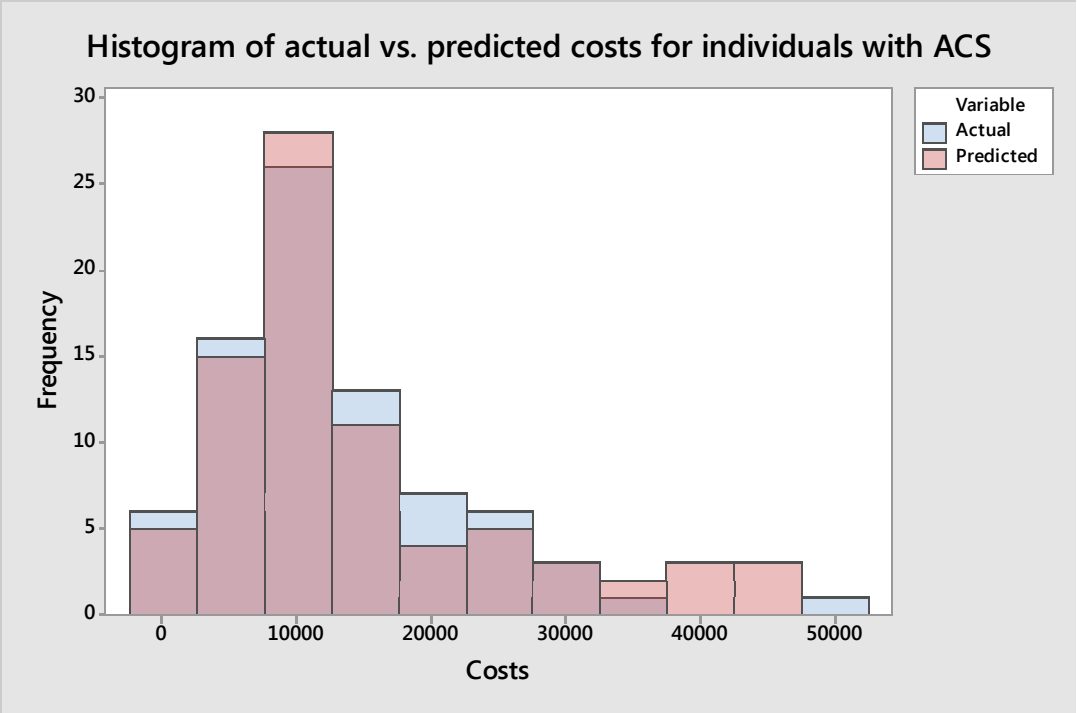


Each data point represents the result of 5 independent runs with 40,000 patients per run.

eFigure 9 A/B. Comparison of actual vs. predicted costs.



Data based on individuals with a final diagnosis of Non-ACS (640/719); p-value for Mean: 0.97



Data based on individuals with a final diagnosis of ACS (79/719); p-value for Mean: 0.39

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CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1 / Title page
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Pages 2-3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Page 5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Pages 5-7
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Pages 5-7
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 10
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Pages 8-9
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 9, 10
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Not appropriate
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 10
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Pages 6-7

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Pages 6-7
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 8; Supplement page 65
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 8
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 14; Figure 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Pages 8-10; Supplement
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Pages 8-10; Suppl. pages 65-67; 78
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Pages 10-13; Table 3; Supplement
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 3
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	Page 12; Supplement Suppl. pages 28, 80,81

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Pages 13-16
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 18
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Pages 18-19

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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