Using expert elicitation to estimate the potential impact of improved diagnostic performance of laboratory tests: a case study on rapid discharge of suspected NSTEMI patients

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Running title: Using expert's judgment in a health economic model

Key words: cost-effectiveness, early health technology assessment, acute myocardial infarction, high-sensitive troponin, copeptin, H-FABP

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Abstract:

Objectives

Early health technology assessment can provide insight in the potential cost-effectiveness of new tests to guide further development decisions. This can increase their potential benefit but often requires evidence which is lacking in early test development stages. Then, expert elicitation may be used to generate evidence on the impact of tests on patient management. This is illustrated in a case study on a new triple biomarker test (copeptin, heart-fatty acid binding protein, and high-sensitive troponin [HsTn]) at hospital admission. The elicited evidence enables estimating the impact of using the triple biomarker on time to exclusion of non ST-elevation myocardial infarction (NSTEMI) compared to current serial HsTn measurement (performed 0, 2 and 6 hours after admission).

Methods

Cardiologists were asked to estimate the effect of the triple biomarker on patient's discharge rates and interventions performed, depending on its diagnostic performance. This elicited evidence was combined with Dutch reimbursement data and published evidence into a decision analytic model. Direct hospital costs and patient's discharge rates were assessed for three testing strategies including this triple biomarker (i.e. only at admission or combined with HsTn measurements after two and six hours).

Results

Direct hospital costs of suspected NSTEMI patients using serial HsTn measurements are estimated at €1,825/patient. Combining this triple biomarker with HsTn measurements after two and six hours is

expected to be the most cost-effective strategy. Depending on the diagnostic performance of the triple biomarker, this strategy is estimated to reduce costs with €66-205/patient (i.e. 3.6%-11.3% reduction).

Conclusions

Expert elicitation can be a valuable tool for early health technology assessment to provide an initial estimate of the cost-effectiveness of new tests prior to their implementation in clinical practice. As demonstrated in our case study, improved diagnostic performance of the triple biomarker may have benefits that should be further explored.

Introduction:

Over the last several decades, there has been a major increase in both the utilization of existing laboratory tests and the development of new tests [1, 2]. Although new laboratory diagnostics may provide additional information for clinicians and patients, their development also raises concerns about overutilization, potential negative effects of over-testing on patient outcomes, and rising healthcare costs [3, 4]. Therefore, the potential benefits of new tests, in terms of health outcomes and costs, should be thoroughly investigated prior to their implementation in clinical practice [5-12].

Compared to the evaluation of treatment strategies, the most important difference with diagnostic testing is that tests influence health outcomes indirectly, by changing the clinical decisions made and management of the disease guided by the test results [9, 12]. Consequently, to estimate the potential added value of a new test, the role of the new test in the existing diagnostic pathway first needs to be assessed. Bossuyt et al. (2006) proposed three roles of the new test: (1) replacing an existing test in the diagnostic pathway (e.g. because the new test is more accurate), (2) preceding the pathway as a triage test, to safely rule out patients for further testing, or (3) after the pathway as add-on (e.g. to reduce the proportion of false positive test results) [6].

The diagnostic performance of a new test will depend to a large extent on its intended role, and on the performance of other tests it is combined with [6]. For example, if it is used as an add-on, the combined performance of all tests should be determined, recognizing that the performance of the new test depends on the selection of patients it is actually used in (i.e. patients with positive preceding tests).

Evidence concerning the effect of new tests (alone or in combination) on a patient's diagnostic pathway is commonly very limited in early stages of product development. A randomized controlled trial (RCT) is accepted to provide the highest quality of evidence to quantify the consequences of laboratory testing strategies, but is often not feasible for ethical, financial, or other reasons, in particular in early stages of product development [8, 13-15]. In those situations, Van den Bruel et al. (2007) suggest that evidence on changes in diagnosis or intended management by the physician, before and after the test result has been disclosed, may serve as a proxy [9]. In addition, such evidence may be used to inform the potential cost-effectiveness of a new test and the drivers of diagnostic performance. One way to deal with this would be to perform a model based early health technology assessment where part of the evidence is determined by expert elicitations [16-18]. Elicitation involves a process by which experts formulate a quantitative judgement based on their own beliefs, independent of the quality of such knowledge, for an uncertain quantity [19]. Those elicitations can be used as input for a decision analytic model. Such models are particularly helpful in early health economic modeling, where uncertain and unknown priors are used to populate a model. Such early assessments can guide decisions about whether or not to continue test development, and ideally to optimize this process [20, 21].

In this paper we will therefore illustrate how expert's judgment about improved test performance can be incorporated into an early model for estimating cost-effectiveness. The case is about adding a copeptin and heart-fatty acid binding protein (H-FABP) test to conventional serial high-sensitive troponin (HsTn) measurement, to allow rapid exclusion of acute myocardial infarction (specifically NSTEMI) in the

coronary pain unit (CPU), which is a specialized emergency unit for patients presenting with chest pain. The described approach can further guide test development and optimization, and can serve as initial evidence on the likely added value of combinations of tests. In addition, this approach can be used to estimate the likely impact of different implementation strategies of this triple biomarker.

Case description

Patients with chest pain represent a large proportion of acute hospitalizations [22, 23], yet distinguishing patients with acute coronary syndrome (ACS) remains a diagnostic challenge. ACS encompasses both unstable angina (UA), ST-elevation myocardial infarction (STEMI), and non-ST-elevation myocardial infarction (NSTEMI). Although STEMI can be diagnosed based on persistent ST-elevation on the ECG, in-vitro laboratory tests have great diagnostic value to distinguish NSTEMI from both UA and other (non-cardiac) causes of chest pain [22, 23].

Currently, HsTn is the preferred laboratory test for diagnosing NSTEMI because it allows both earlier and more sensitive detection of elevated troponin levels compared to the conventional troponin tests [22]. Although this new generation of tests has improved the early diagnosis of NSTEMI, current guidelines still recommend to monitor the majority of patients for several hours and perform serial troponin measurements [22, 24]. Although recommended in the guidelines, such prolonged duration of hospital stay accounts for about two third of direct hospital costs in chest pain patients [25]. Early exclusion of NSTEMI can therefore greatly enhance efficient use of hospital resources.

As reported in previous studies, combining a HsTn measurement with other early cardiac markers might contribute to an early and safe discharge [26-35]. Two potential markers that are elevated rapid after an AMI, are copeptin and H-FABP [36-39]. Hence, adding those markers to the conventional HsTn measurement is expected to improve the overall diagnostic performance in the first hours after chest pain onset. This may then increase the diagnostic certainty of cardiologists, and facilitate early discharge of those patients. The combination of three markers will hereafter be referred to as 'triple biomarker'.

Methods

Model description

A decision tree was constructed which was populated with a hypothetical sample of 1,000 patients presenting with symptoms suggestive of ACS at the CPU. The population eligible for the current simulation was defined as patients (1) with an onset of chest pain in the last twelve hours; (2) not having persistent ST-elevation on the ECG; (3) not presenting at the CPU with cardiac arrest requiring immediate reperfusion.

The current diagnostic pathway consists of serial HsTn measurements at regular intervals, i.e. at the time of a patient's presentation at the CPU (t0), and repeated after two and six hours (t2 and t6, respectively). To analyze the most cost-effective strategy of implementing the triple biomarker, three alternative diagnostic strategies were evaluated in the model: (I) the triple biomarker only at t0 and without follow-up HsTn measurements, (II) the triple biomarker at t0 followed by repeat testing of HsTn at t2, and (III)

the triple biomarker at t0 followed by repeat testing of HsTn at t2 and t6 (figure 1). The decision tree for each of the three strategies is provided in Additional file 1.

--- Figure 1 - Diagnostic strategies evaluated in the model ---

Because the diagnostic performance of the triple biomarker in any of these combinations is unknown, the cost-effectiveness of the three strategies was evaluated for three potential diagnostic performances of the triple biomarker. This allows prediction of the minimum diagnostic performance that is required for this triple biomarker to be considered cost-effective.

The primary effectiveness measure in the model was defined as the percentage of patients correctly discharged from hospital at each time point (t0, t2, t6, or after overnight admission). Incremental effectiveness was expressed as the difference in the number of patients discharged (per 1,000 patients) when using the triple biomarker compared to serial HsTn measurement alone. A direct hospital cost perspective was taken, including all costs that occur from the moment a patient presents at the CPU until hospital discharge. Costs were expressed in 2015 Euros. Incremental cost was defined as the difference in direct hospital costs per patient. The incremental cost-effectiveness ratio (ICER) was obtained by dividing the incremental costs by the incremental effectiveness. Because the length of a patient's hospital stay was shorter than one year, discounting of costs and effects was not required.

Estimation of diagnostic performance of the markers

We performed a literature review to estimate the diagnostic performance of HsTn measurement at t0. Details of this literature review are described in Additional file 2. .Keller et al. (2010) reported a sensitivity of 98.3% and NPV of 99.0% for the combination of HsTn and copeptin [27]. Based on this study, the maximum performance of the triple biomarker that can realistically be achieved after the addition of a third marker was estimated at a sensitivity and NPV of both 99.0%. Furthermore, an increase in sensitivity of the triple biomarker of at least 5% was considered necessary to change clinical management. Therefore, based on those assumptions and the results of the literature review, the sensitivity and NPV of HsTn at t0 in patients with suspected NSTEMI were set at 85%, and 95%, respectively [27, 40-42]. The three potential diagnostic performances of the triple biomarker that were evaluated in the model, were set at a sensitivity of 90%, 95%, and 99%, with a corresponding NPV of 96%, 98% and 99% (table 1).

--- Table 1 - sensitivities and negative predictive values (NPV) used in the questionnaire, for both serial high-sensitive troponin measurement (current practice) as well as for the three scenarios for the performance of the triple biomarker. NPV = negative predictive value ---

The specificity of high-sensitive troponin, was derived from a review by Goodacre et al. (2013) [41-44]. The specificity of the triple biomarker at t0 (49.8%) was calculated by multiplying the individual specificities of H-FABP (80.0%) [43, 45-52], copeptin (70.0%) [27, 43], and HsTn (89.0%) [41-44, 53]. Those diagnostic performances were used to determine the flow of patients through the model (table 2). Furthermore, although the specificity of HsTn is expected to decrease during follow-up measurements (at t2 and t6), as caused by the discharge of patients without NSTEMI, the specificity of HsTn was assumed not to change during those follow-up measurements. As a higher specificity at t2 and t6 would improve model outcomes more for the serial HsTn measurement than for the triple biomarker strategy, because less individuals are discharged at t0 and thus more individuals are tested at t2 and t6, this assumption prevents overestimating the potential impact of this triple biomarker.

--- Table 2 - specificities used to calculate the flow of patients through the model. ---

Questionnaire

The improved diagnostic performance as achieved by the triple biomarker might impact the patient's diagnostic pathway as well as the treatment received. However, the clinical utility of the marker in suspected NSTEMI patients is unknown. First, patients might be discharged earlier, and secondly they might have to undergo less diagnostic and therapeutic interventions. Besides laboratory tests, the most commonly performed interventions considered in this study, involve a stress ECG, a catheterization, and drug treatment. We developed a closed-ended paper-and-pencil questionnaire to evaluate the clinical utility of the triple biomarker to affect clinical decisions, as well as how an improved diagnostic

performance may change clinical management. In this questionnaire, we presented cardiologists the (hypothetical) result of a HsTn assay at both t0, t2 and t6, in patients with suspected ACS. They were then asked to estimate the patient's discharge rates at each point in time, as well as the interventions to be given. Following this, they estimated to what extent an improvement in diagnostic performance, as achieved by the triple biomarker, would affect those decisions. Answer options to both questions consisted of percentages with a range of 25%, and including 0% and 100% (i.e. 0%, 0-25%, 25-50%, 50-75%, 75-100%, 100%). The results from this questionnaire served as input for the health economic model.

The participating cardiologists (n = 10) had on average 17 years of experience in the field of cardiology. Respondents were derived from the Jeroen Bosch Hospital (Den Bosch, the Netherlands), and from Medisch Spectrum Twente (Enschede, the Netherlands). Both are large (730 and 1,070 beds, respectively) teaching hospitals offering acute coronary interventions. As cardiologists were asked for their opinion and experiences, they were told that no wrong answers could be given and that the answers would be treated anonymously. When filling out the questionnaires, no interaction between experts was possible. All percentages were averaged. The full questionnaire is included in Additional file 3.

Assumptions

The decision analytical model contains a few important assumptions. First, it is assumed that STEMI is diagnosed primarily based on the result of the ECG, indicating that the triple biomarker will not be of added value in those patients. Those patients will undergo a coronary intervention immediately, and are

therefore excluded from this analysis. Secondly, based on qualitative interviews with four cardiologists it was assumed that no diagnosis of NSTEMI will be missed at the CPU. Third, it is assumed that none of the patients with a negative HsTn at t0, but a positive H-FABP and/or copeptin will be discharged at this time point. An extensive description of all model assumptions is described in Additional file 4.

Cost data

The direct hospital costs of NSTEMI patients are based on a study by Polder et al. (2006) [54]. Unit costs of hospital stay and a patient's therapy were obtained from the Dutch Healthcare Authority, and from the costs manual by Hakkaart-van Roijen et al. (2013) [55, 56]. Unit costs for medication were obtained from www.medicijnkosten.nl (carbaspirin calcium, heparin, metoprolol, and clopidogrel)[57]. Tariffs for laboratory tests, including HsTn measurement, were derived from the Dutch Healthcare Authority [56]. Costs for the H-FABP test were based on published literature[58], while costs of the copeptin test were based on the laboratory tariff of a Dutch university medical center[59]. Direct hospital costs were estimated by summing all different elements of a patient's hospital stay, and the probability of each element occurring. All costs were converted to 2015 Euros.

Analysis of the results

Descriptive statistics were used to report means and percentages. 95% confidence intervals were determined for the probabilities obtained from the questionnaire using Microsoft Excel 2010. Deterministic sensitivity analysis is applied to test the robustness of the model to changes in one variable. The minimum performance at which the additional upfront costs of the triple biomarker are offset by savings further downstream the diagnostic pathway and in subsequent treatment (i.e. break-

even point) was estimated. Similarly, the maximum allowable total costs of the two additional tests (i.e. H-FABP and copeptin), that could be justified by their expected increased performance as compared to current practice, was assessed. The results were presented for both a negative and a slightly elevated HsTn level.

Sensitivity analysis

All probability parameters were assigned a beta distribution utilizing a standard error derived from the results of the questionnaire or from literature[60], while all cost parameters were assigned a gamma distribution and an assumed standard error of 25%. A probabilistic sensitivity analysis was performed by means of Monte Carlo simulations, using 10,000 model iterations for each of the nine scenarios. Mean outcomes of the probabilistic sensitivity analysis were used as our base case outcomes.

One-way sensitivity analyses were performed to test the robustness of the model outcomes to changes in input parameters. All model input parameters were varied along their 95% confidence interval. As Keller et al. (2010) reported a sensitivity of 98.3% and NPV of 99.0% for the combination of HsTn and copeptin [27], this one-way sensitivity analysis was only performed for the scenario concerning a sensitivity and NPV of both 99.0%, and only for the strategy (I, II or III) that is found to be most cost-effective. The results are visualized in a tornado diagram, showing both the effect of changes in input parameters on costs and on outcomes (i.e. the incremental discharge rate).

Results

Figure 2 shows the impact of the triple biomarker as compared to serial HsTn measurement on the effectiveness (expressed as patient's discharge rates), as elicited by the cardiologists at each point in time (t0, t2 and t6). Results from the questionnaire indicate that in the current diagnostic pathway cardiologists estimate to discharge 12% of all suspected NSTEMI patients from the CPU following a negative HsTn result at t0. An increase in sensitivity and NPV of the triple biomarker is expected to increase the percentage of patients' correctly discharged (figure 2). In addition, if the performance of the triple biomarker improves, cardiologists may decide not to perform further interventions as shown in figure 3.

--- Figure 2 – Expected discharge rates according to experts as a function of diagnostic performance ---

--- Figure 3 – Interventions performed according to experts as a function of diagnostic performance ---

If sensitivity and NPV of the triple biomarker would be 99% at t0, cardiologists estimate to discharge 30% of suspected NSTEMI patients following the laboratory results at t0. If a triple biomarker with this diagnostic performance is combined with HsTn measurements at t2 and t6 (strategy III), the percentage of patients without NSTEMI that is admitted overnight might decrease from 39% in current practice, to 27%. Regardless of the performance of the triple biomarker, this third strategy incurs the highest patients' discharge rates at the lowest cost. In current practice, direct hospital cost per suspected

NSTEMI patient at the CPU are estimated to be €1,825. Strategy III could decrease those costs to €1,758 (-3.6%), €1,703 (-6.6%), or €1,618-11.3%), depending on the performance of the triple biomarker at t0 (table 3). In this strategy, a 5% increase in sensitivity of the triple biomarker (at t0) from 85% to 90%, and an accompanying increase in NPV from 95% to 96% is already expected to result in higher patient discharge rates and lower costs compared to serial HsTn measurement. In this same strategy, a sensitivity and NPV of 99% of the triple biomarker with additional HsTn measurements at t2 and t6 (strategy III), is expected to result in an additional discharge of 120 patients per 1,000 following the laboratory results at t6, with accompanying cost savings of €205 per patient. Estimating that 137,000 people in the Netherlands each year present at the hospital with chest pain, this strategy could involve costs savings ranging from 9 up to 28 million Euros per year, depending on the performance of the triple biomarker [61, 62]. As shown in table 3, an increase in the performance of the triple biomarker also increases cost savings.

--- Table 3: costs and effects of the alternative strategies compared to the current serial HsTn analysis. ---

After excluding the estimated number of NSTEMI patients in the hypothetical cohort of 1,000 patients, the remaining patients are divided in two subgroups, i.e. with and without a slightly elevated HsTn level. These subgroup results indicate that the greatest cost savings per patient can be achieved in patients with a slightly elevated HsTn level (table 3). In both subgroups, strategy III is expected to incur most cost savings and involve the highest incremental patient discharge rates as compared to the two other strategies.

As the results indicate that strategy III is most cost-effective, a one-way sensitivity analysis was performed for this strategy, assuming a sensitivity and NPV of the triple biomarker of both 99%. As shown in figures 4a and 4b, results indicate that the costs per patient are mainly driven by the specificity of HsTn at t2, the costs of overnight hospital stay, and the specificity of HsTn at t0, while the incremental effect on time to discharge was mainly driven by the specificity of HsTn at t0 and t6. However, those changes in model outcomes regarding both costs and discharge rates would not have changed the overall conclusion.

--- Figure 4a and b – Results of one-way sensitivity analysis ---

Figure 5 shows the results of the probabilistic sensitivity analysis for each of the nine scenarios evaluated in the model. For each scenario, an ellipse is shown which covers 95% of the cost-effectiveness outcomes of the triple biomarker strategy as compared to current serial HsTn measurement. Each ellipse is based on 10,000 model iterations of a hypothetical cohort of 1,000 patients. Results indicate that, for strategy III, the probability that the triple biomarker strategy dominates current serial HsTn measurement increases from 61.7%, to 84.1%, to 96.0%, depending on the performance of the triple biomarker.

--- Figure 5 – Ellipse plot ---

To decrease uncertainty around cost estimates, the maximum costs of both H-FABP and copeptin are determined, in order for the triple biomarker to break-even compared to current practice. For a triple biomarker with a sensitivity of 90% and accompanying NPV of 96%, costs of copeptin and H-FABP together may rise to €109 when combined with two follow-up HsTn measurements (strategy III). In case of a sensitivity of 95% and an NPV of 98% of the triple biomarker, those costs may rise to €164. In this same strategy, costs may rise to €250 in case the triple biomarker increases both the sensitivity and NPV to 99%. Thus, when the diagnostic performance would increase, this would in turn enhance rapid discharge rates and lead to cost savings. Therefore, the addition of those two tests would still be cost-effective even when their costs would be higher than assumed in our analysis.

Discussion

In this paper we illustrate the value of using expert elicitations in the early assessment of new medical tests, using a case of a triple biomarker to inform early exclusion of NSTEMI at the CPU. Previous studies already investigated the diagnostic accuracy in excluding AMI using combinations of those markers [26-35, 49, 63, 64]. However, this study is the first study that provides an initial estimate of the cost-effectiveness of this triple biomarker in suspected NSTEMI patients on referral rates and on subsequent interventions.

In our case study, the results of the expert elicitations indicate that an increase in diagnostic performance achieved by the use of a triple biomarker as compared to conventional serial HsTn measurement alone, may lead to earlier patient discharge, a reduction in the interventions performed in those patients and, consequently, a decrease in direct hospital costs. Results indicate that the triple biomarker with additional HsTn measurements after two and six hours (strategy III), is expected to be the most cost-effective strategy compared to serial HsTn measurement. Regardless of the diagnostic performance of the triple biomarker (i.e., a sensitivity of 90%, 95%, and 99%, combined with an NPV of 96%, 98%, and 99%, respectively), time until hospital discharge, interventions performed, and hospital costs are expected to be reduced in this strategy. In addition, results of the sensitivity analyses indicate that the uncertainty in model input parameters is unlikely to change those conclusions. Also, as long as the costs of copeptin and H-FABP together do not exceed €109, this strategy is cost-saving or cost-neutral from the perspective of the hospital. For reference, one HsTn measurement costs about €9.55, indicating there is large headroom to achieve a cost-saving outcome.

Limitations of the case study analysis

This study has certain limitations. First, we assumed that all patients with NSTEMI are diagnosed as such at the CPU. This assumption was based on open interviews with cardiologists (n = 5), who stated that the risk-averse approach in excluding NSTEMI ensures that no patient with this diagnosis is inadvertently discharged from the hospital. In addition, they stated that using this triple biomarker would not affect this because regardless of the performance of a laboratory test, a patient's signs and symptoms are

always considered in the decision to discharge a patient. However, further research is necessary to test the validity of those assumptions in clinical practice.

Second, the number of experts who completed the questionnaire was small (n = 10). However, a previous systematic review by Johnson et al. (2010), reports a median sample size of 11 participants included in expert elicitations [65], indicating that our sample is not unusually small. Also, the variation in the probabilities of patient's discharge rates and interventions performed, as derived from the cardiologists' elicitations, was substantial. This variation is often inevitable in early health technology assessment, and incorporating this uncertainty in the model's input parameters ensures that the real effect of an intervention is not systematically overestimated or underestimated. As the model outcome was shown to be robust against changes in input parameters, this uncertainty is unlikely to change our conclusions.

Third, based on our literature review, we applied a sensitivity of 85% and an NPV of 95% for the HsTn measurement at t0 in our questionnaire. However, a more recently published review reported a lower sensitivity of HsTn of 77%, while the authors mention that the diagnostic performance varied strongly due to substantial heterogeneity between studies [43]. Although this may limit the generalizability of the results, this lower sensitivity also increases the potential benefit of the triple biomarker.

Fourth, although this add-on strategy of the triple biomarker increases sensitivity, this comes at the cost of the specificity [6, 63]. In the current study, the disjunctive positivity criterion was used (as described by Felder and Mayrhofer, 2011), which implies that the composite test result is positive when at least one of the tests of the triple biomarker is positive [66]. In our case study, this results in a larger proportion of

patients with a positive test result at t0 in case the triple biomarker is used, as compared to when a single HsTn test is used. Consequently, this will prevent discharge in patients with a positive H-FABP and/or copeptin, and may simultaneously increase discharge rates in individuals with a triple negative result. The decrease in specificity, however, may be smaller than assumed in the current study as the real life specificity of the triple biomarker likely exceeds the assumed specificity as based on multiplying the specificities of the three individual tests. For example, Lippi et al. found a combined specificity of troponin and H-FABP of 82%, while multiplying the individual specificities resulted in a combined specificity of 78% [63].

The rapid increase in the number of available laboratory tests complicates decisions regarding test implementation in clinical practice. When high-grade evidence studies (for example RCTs) are not available in early stages of laboratory test development, model based early health technology assessment can be recommended to guide decisions whether or not to continue test development, for which diagnostic setting and/or in which patient (sub)group the test should be used, and at what cost. The major advantage of such a model based analyses is that the results can be updated when new evidence becomes available, for example about real world effects of the new test on a patient's diagnostic pathway. In our study we illustrated such an assessment by developing a decision analytic model combining evidence on the expected (combined) diagnostic accuracy of new tests with cardiologists' elicitations on the impact of this test on a patient's diagnostic pathway and subsequent treatment. This study shows the added value of expert elicitations in guiding decisions about whether or not to continue product development, if possible, to optimize this process, and to estimate the cost-effectiveness of those tests prior to their implementation in daily practice [20]. However, because

guidelines concerning the process of expert elicitation are currently lacking, different approaches are used which may lead to different results. Further research into the pros and cons of different methods of expert elicitation is therefore recommended to allow standardization of this process.

Our study illustrates how model based early health technology assessment combined with expert elicitations can be valuable when estimating the potential cost-effectiveness of a laboratory test, at different diagnostic performances. This was achieved by combining evidence on test performance retrieved from literature, with elicitations from clinicians on the impact of new tests on a patient's diagnostic pathway and subsequent treatment. Our case study suggests that a triple biomarker, consisting of a copeptin, H-FAPB, and a HsTn measurement at the time of a patient's admission at the CPU, when combined with follow-up HsTn measurements at t2 and t6, may have the potential to safely inform the decision for early discharge and may reduce the number of interventions performed, resulting in lower costs.

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Figure legends

Figure 1 - Diagnostic strategies evaluated in the model. This figure shows the current diagnostic work-up in suspected NSTEMI patients, as well as the three alternative diagnostic strategies evaluated. The current work-up consists of serial high-sensitive troponin (HsTn) measurements 0, 2 and 6 hours after hospital admission (t0, t2, and t6, respectively). The three alternative diagnostic strategies involve: (I) the triple biomarker only at t0 and without follow-up HsTn measurements, (II) the triple biomarker at t0 followed by repeat testing of HsTn at t2, and (III) the triple biomarker at t0 followed by repeat testing of HsTn at t2 and t6.

Figure 2 – Expected discharge rates according to experts as a function of diagnostic performance. This figure shows the impact of the triple biomarker as compared to serial high-sensitive troponin (HsTn) measurement on the percentage of patients discharged as indicated by the cardiologists at each point in time (t0, t2 and t6), including the 95% confidence interval. NPV = negative predictive value, sens. = sensitivity.

Figure 3 – Interventions performed according to experts as a function of diagnostic performance. This figure shows the percentage of patients in whom diagnostic or therapeutic interventions (stress ECG, catheterization, and administering medication) are performed during their hospital admission, as

indicated by the cardiologists, including the 95% confidence interval. ECG = electrocardiogram, NPV = negative predictive value, sens. = sensitivity.

Figure 4a - Result of one-way sensitivity analysis, showing the difference in the effect on the probability of being discharged more early when using the triple biomarker (strategy III), with a sensitivity and NPV of both 99%, as compared to serial high-sensitive troponin (HsTn) measurement. All probabilities were varied according the 95% confidence interval. ECG = electrocardiogram.

Figure 4b - Result of one-way sensitivity analysis, showing the difference in costs of triple biomarker (strategy III), with a sensitivity and NPV of both 99%, as compared to serial high-sensitive troponin (HsTn) measurement. All probabilities were varied according the 95% confidence interval, all costs were varied 25% below and above the mean. ECG = electrocardiogram, NSTEMI = non-ST elevation myocardial infarction.

Figure 5. Ellipse plot. The ellipses cover 95% of the cost-effectiveness outcomes of the triple biomarker strategy as compared to current serial HsTn measurement, for each of the nine scenarios evaluated in the model. Each ellipse is based on 10,000 model iterations using probabilistic sensitivity analysis. All probability parameters were assigned a beta distribution utilizing a standard error derived from the

results of the questionnaire or from literature, while all cost parameters were assigned a gamma distribution and an assumed standard error of 25%. Sens. = sensitivity.

Tables:

Table 1: sensitivities and negative predictive values (NPV) used in the questionnaire, for both serial high-sensitive troponin measurement (current practice) as well as for the three scenarios for the performance of the triple biomarker. NPV = negative predictive value

Work-up		**Sensitivity at t0**	**NPV at t0**
Serial high-sensitive troponin measurement		85%	95%
Triple biomarker	Scenario 1	90%	96%
	Scenario 2	95%	98%
	Scenario 3	99%	99%

Table 2: specificities used to calculate the flow of patients through the model. *the specificity of high-sensitive troponin is assumed not to change at t2 and t6. H-FABP = heart-fatty acid binding protein.

Test performance at t0	**Specificity**	**Source**
High-sensitive troponin*	89.0%	Review Goodacre et al, 2013 [41-44]
H-FABP	80.0%	Review Goodacre et al, 2013 [43, 45-52]
Copeptin	70.0%	Review Goodacre et al, 2013 [27, 43]
Triple biomarker	49.8%	Calculated [53]

Table 3: costs and effects of the alternative strategies compared to the current serial HsTn analysis.

			Effectiveness (number of patients discharged)	Incremental effectiveness	Costs (per patient)	Incremental costs	ICER
All patients, n = 1000 (NSTEMI: n = 84)							
Serial HsTn analysis			616	-	€ 1,825	-	-
Triple biomarker	Strategy I	Sens. 90%	101	-512	€ 2,217	€ 393	- 768
		Sens. 95%	177	-435	€ 2,119	€ 296	- 679
		Sens. 99%	298	-314	€ 1,972	€ 148	- 473
	Strategy II	Sens. 90%	433	-179	€ 1,944	€ 120	- 672
		Sens. 95%	477	-135	€ 1,873	€ 49	- 365
		Sens. 99%	549	-63	€ 1,764	- € 60	957
	Strategy III	Sens. 90%	671	58	€ 1,758	- € 66	- 1,132
		Sens. 95%	694	81	€ 1,703	- € 121	- 1,488
		Sens. 99%	733	120	€ 1,618	- € 205	- 1,706
All patients with negative HsTn result at t0, n = 815							
Serial HsTn analysis			604	-	€ 1,036	-	-
Triple biomarker	Strategy I	Sens. 90%	97	-507	€ 1,520	€ 484	- 955
		Sens. 95%	166	-438	€ 1,416	€ 380	- 868
		Sens. 99%	275	-328	€ 1,257	€ 221	- 674
	Strategy II	Sens. 90%	421	-183	€ 1,209	€ 173	- 943
		Sens. 95%	458	-146	€ 1,137	€ 101	- 690
		Sens. 99%	520	-84	€ 1,024	- € 12	149
	Strategy III	Sens. 90%	632	28	€ 994	- € 42	- 1,475
		Sens. 95%	651	48	€ 941	- € 95	- 1,990
		Sens. 99%	684	80	€ 859	- € 177	- 2,215
All patients with a slightly elevated HsTn result at t0 without NSTEMI, n = 101							
Serial HsTn analysis			12	-	€ 1,850	-	-
Triple biomarker	Strategy I	Sens. 90%	3	-8	€ 1,776	- € 74	9,042
		Sens. 95%	11	-1	€ 1,651	- € 200	220,990
		Sens. 99%	23	11	€ 1,471	- € 379	- 34,251
	Strategy II	Sens. 90%	12	1	€ 1,589	- € 262	- 321,508
		Sens. 95%	19	7	€ 1,468	- € 383	- 55,597
		Sens. 99%	29	17	€ 1,291	- € 559	- 32,211
	Strategy III	Sens. 90%	38	27	€ 1,477	- € 373	- 13,999
		Sens. 95%	42	30	€ 1,356	- € 494	- 16,207

		Sens. 99%	49	37	€ 1,180	- € 671	- 17,981

Sens. = sensitivity, ICER = incremental cost-effectiveness ratio. A sensitivity of 90, 95, and 99% corresponds with an NPV of 96, 98 and 99% respectively.

Figures

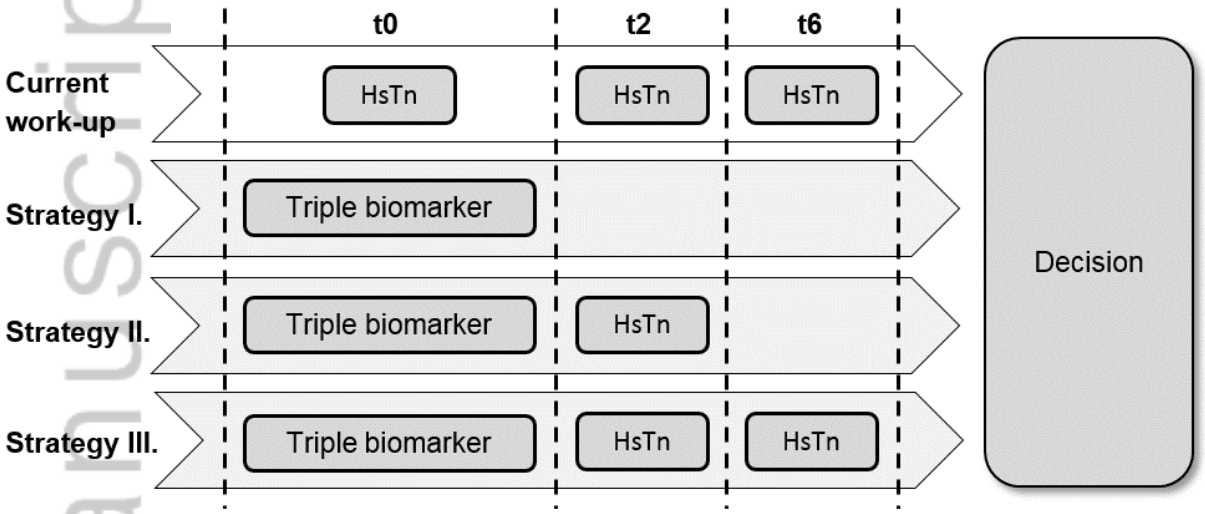


Figure 1 – Diagnostic strategies

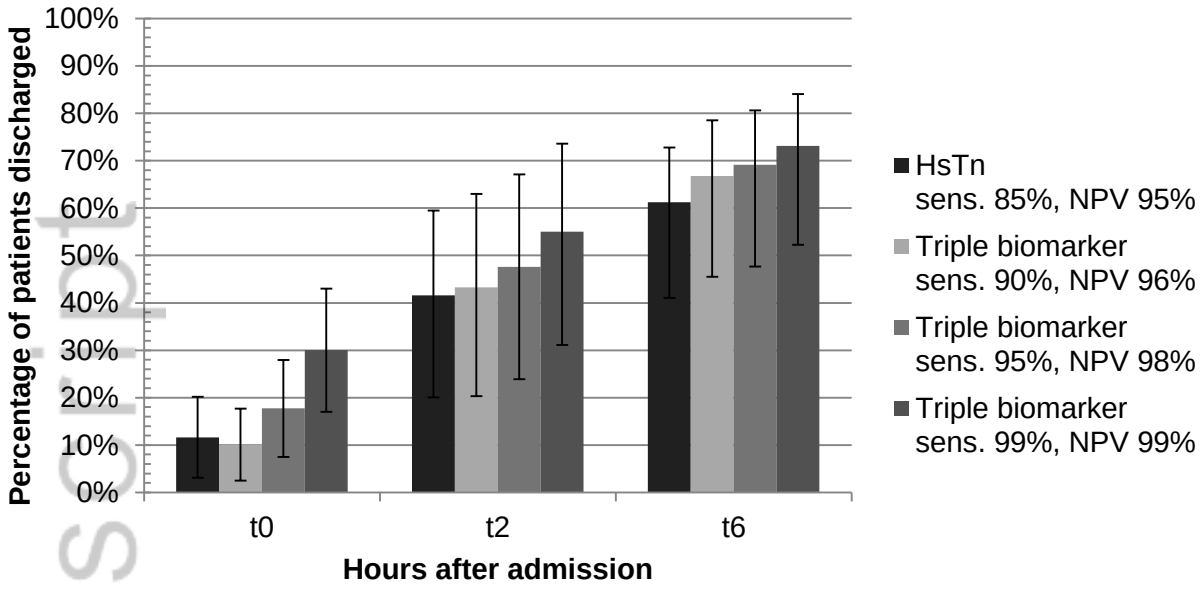


Figure 2 – Discharge of patients

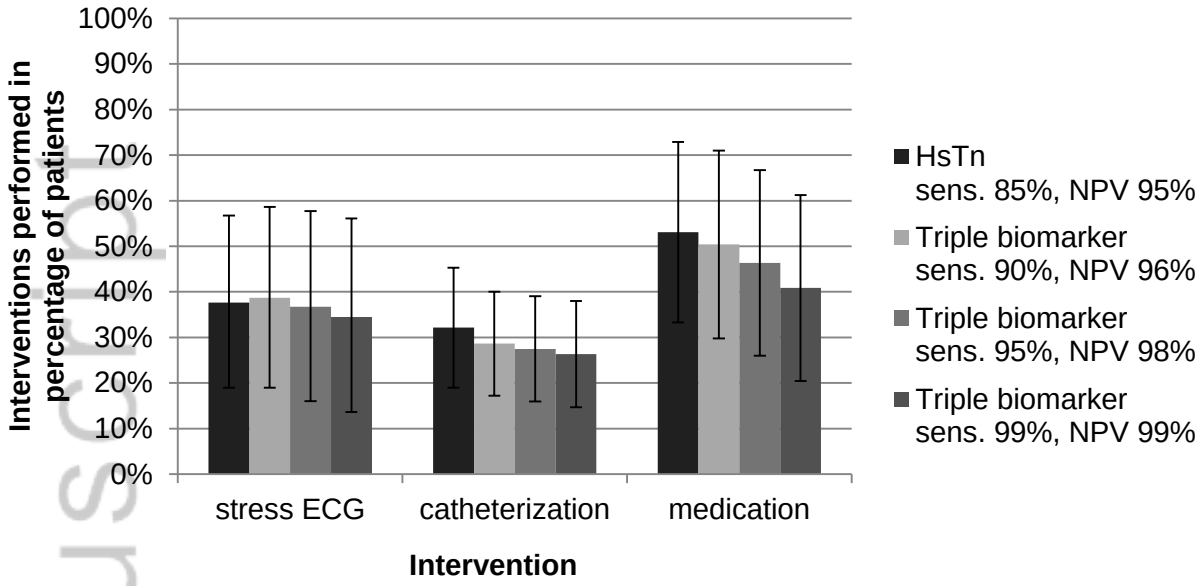
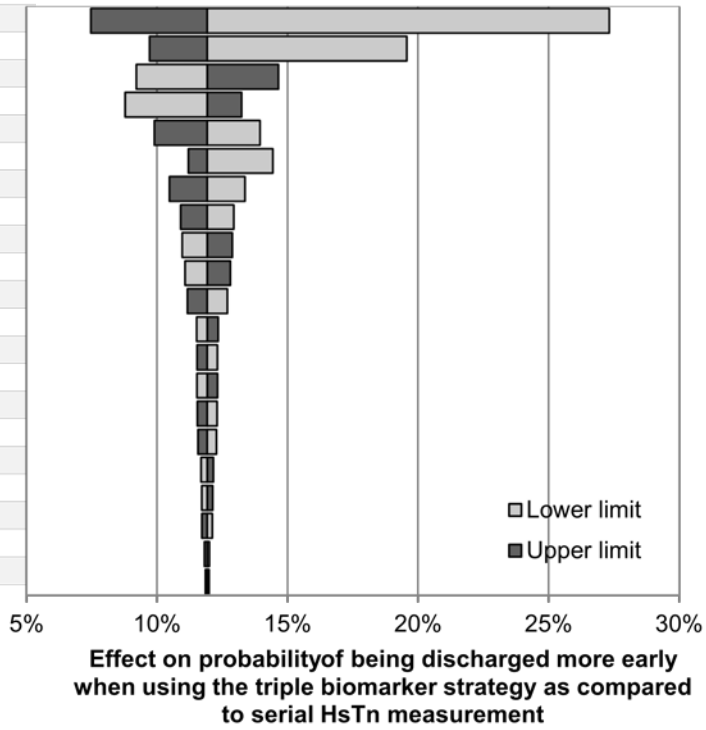


Figure 3 – Interventions performed

Applies to:	Specification:
Both	Specificity HsTn t0
Both	Specificity HsTn t6
Triple biomarker	Discharge at t0 | no stress ECG | triple biomarker –
Triple biomarker	Specificity H-FABP t0
Serial HsTn	Stress ECG | HsTn –
Both	Specificity HsTn t2
Both	Discharge at t2 | no stress ECG | HsTn –
Serial HsTn	Discharge at t0 | stress ECG – | HsTn –
Triple biomarker	Discharge at t0 | no stress ECG | HsTn +
Triple biomarker	Stress ECG | triple biomarker –
Serial HsTn	Discharge at t0 | no stress ECG | HsTn –
Triple biomarker	Discharge at t0 | stress ECG – | HsTn +
Both	Discharge at t2 | stress ECG – | HsTn –
Triple biomarker	Discharge at t0 | stress ECG – | triple biomarker –
Both	Discharge at t6 | no stress ECG | HsTn –
Serial HsTn	Discharge at t0 | no stress ECG | HsTn +
Triple biomarker	Specificity copeptin t0
Triple biomarker	Stress ECG | HsTn +
Serial HsTn	Discharge at t0 | stress ECG – | HsTn +
Serial HsTn	Stress ECG | HsTn +
Both	Discharge at t6 | stress ECG – | HsTn –



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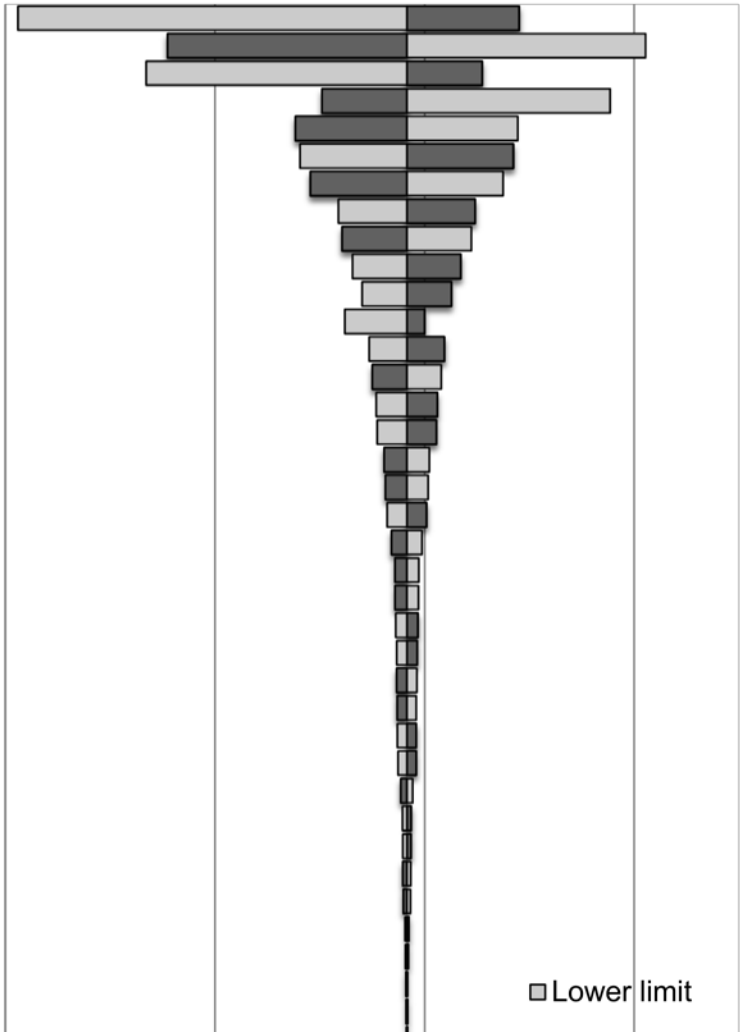
Type:	**Applies to**:	**Specification**:
Probability	Both	Specificity HsTn t2
Costs	Both	Hospital stay | overnight
Probability	Both	Specificity HsTn t0
Probability	Triple biomarker	Specificity H-FABP t0
Probability	Triple biomarker	Discharge at t0 | no stress ECG | triple biomarker –
Costs	Triple biomarker	Laboratory tests at t0 (incl. triple biomarker)
Probability	Serial HsTn	Catheterization | HsTn –
Probability	Triple biomarker	Cathetherization | triple biomarker –
Costs	Serial HsTn	Laboratory tests at t0 (incl. HsTn)
Probability	Serial HsTn	Discharge at t0 | stress ECG – | HsTn –
Probability	Serial HsTn	Stress ECG | HsTn –
Probability	Both	Specificity HsTn t6
Costs	Both	Hospital stay | 1 hour
Costs	Both	Catheterization
Probability	Serial HsTn	Discharge at t0 | no stress ECG | HsTn –
Probability	Both	Discharge at t2 | no stress ECG | HsTn –
Probability	Triple biomarker	Discharge at t0 | no stress ECG | HsTn +
Probability	Triple biomarker	Discharge at t0 | stress ECG – | triple biomarker –
Probability	Triple biomarker	Catheterization | HsTn +
Probability	Triple biomarker	Specificity copeptin t0
Probability	Serial HsTn	Medication | HsTn –
Costs	Both	Hospital stay | 7 hours
Probability	Triple biomarker	Medication | triple biomarker –
Probability	Serial HsTn	Discharge at t0 | no stress ECG | HsTn +
Probability	Triple biomarker	Discharge at t0 | stress ECG – | HsTn +
Probability	Serial HsTn	Catheterization | HsTn +
Probability	Both	Discharge at t2 | stress ECG – | HsTn –
Probability	Serial HsTn	Discharge at t0 | stress ECG – | HsTn +
Costs	Both	Dose of medication
Probability	Both	Discharge at t6 | no stress ECG | HsTn –
Costs	Both	Hospital stay | 3 hours
Costs	Both	Stress ECG
Costs	Both	Follow-up lab at t2 and t6
Probability	Both	NSTEMI
Probability	Triple biomarker	Medication | HsTn +
Probability	Triple biomarker	Stress ECG | HsTn +
Probability	Both	Discharge at t6 | stress ECG + | HsTn –



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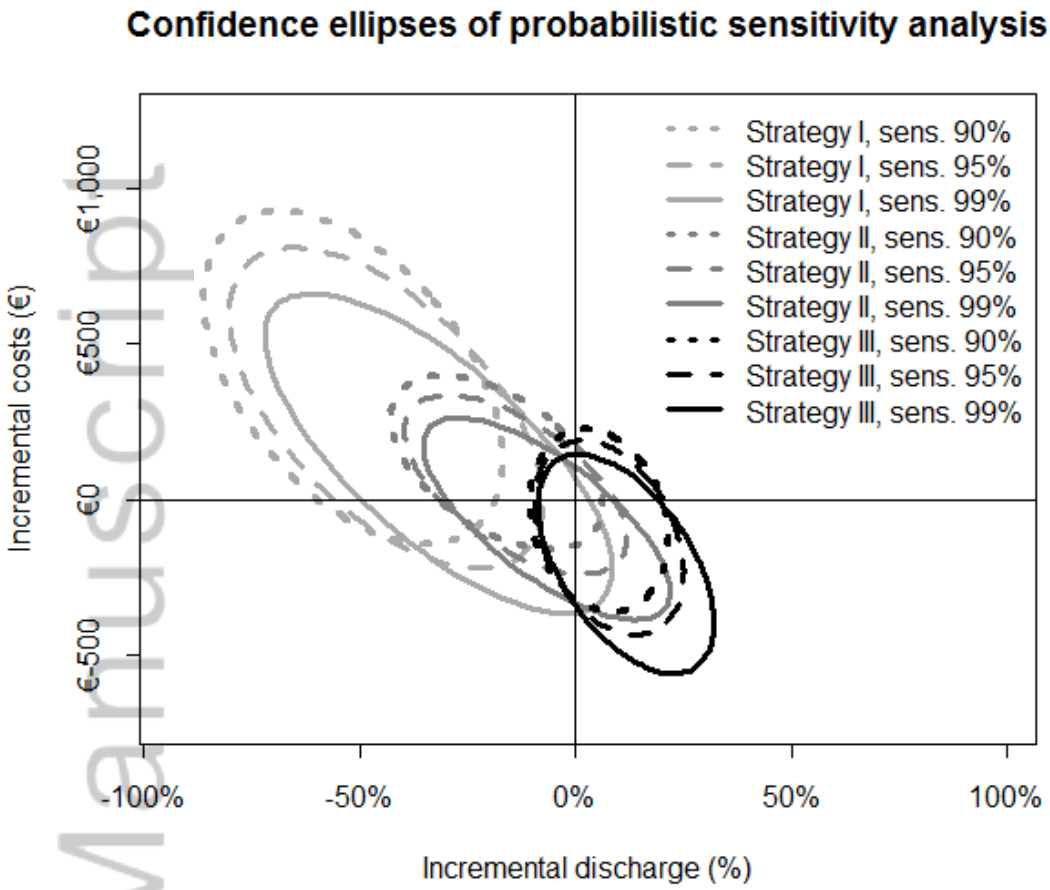

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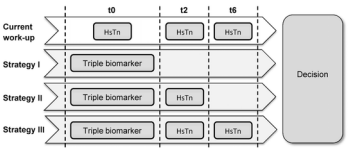

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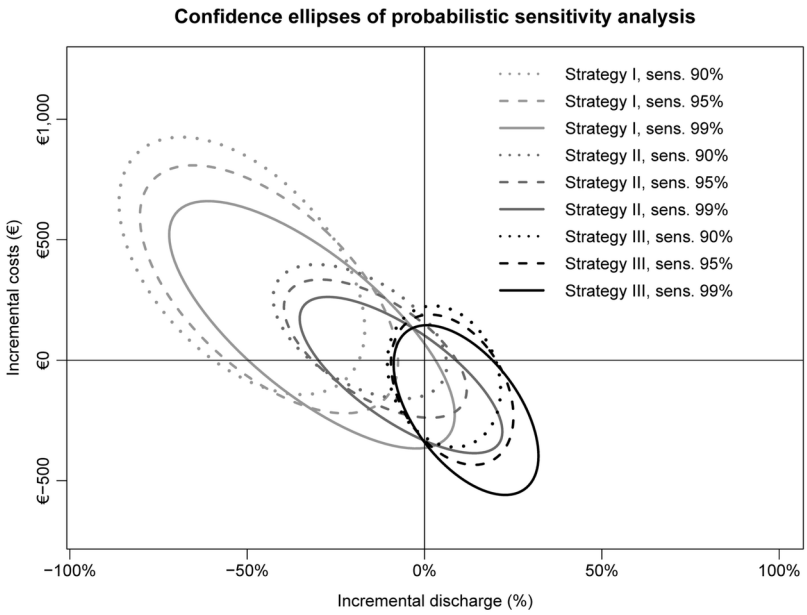

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Triple biomarker	49.8%	Calculated [53]

Table 3: costs and effects of the alternative strategies compared to the current serial HsTn analysis.

			Effectiveness (number of patients discharged)	Incremental effectiveness	Costs (per patient)	Incremental costs	ICER
All patients, n = 1000 (NSTEMI: n = 84)							
Serial HsTn analysis			616	-	€ 1,825	-	-
Triple biomarker	Strategy I	Sens. 90%	101	-512	€ 2,217	€ 393	- 768
		Sens. 95%	177	-435	€ 2,119	€ 296	- 679
		Sens. 99%	298	-314	€ 1,972	€ 148	- 473
	Strategy II	Sens. 90%	433	-179	€ 1,944	€ 120	- 672
		Sens. 95%	477	-135	€ 1,873	€ 49	- 365
		Sens. 99%	549	-63	€ 1,764	- € 60	957
	Strategy III	Sens. 90%	671	58	€ 1,758	- € 66	- 1,132
		Sens. 95%	694	81	€ 1,703	- € 121	- 1,488
		Sens. 99%	733	120	€ 1,618	- € 205	- 1,706
All patients with negative HsTn result at t0, n = 815							
Serial HsTn analysis			604	-	€ 1,036	-	-
Triple biomarker	Strategy I	Sens. 90%	97	-507	€ 1,520	€ 484	- 955
		Sens. 95%	166	-438	€ 1,416	€ 380	- 868
		Sens. 99%	275	-328	€ 1,257	€ 221	- 674
	Strategy II	Sens. 90%	421	-183	€ 1,209	€ 173	- 943
		Sens. 95%	458	-146	€ 1,137	€ 101	- 690
		Sens. 99%	520	-84	€ 1,024	- € 12	149
	Strategy III	Sens. 90%	632	28	€ 994	- € 42	- 1,475
		Sens. 95%	651	48	€ 941	- € 95	- 1,990
		Sens. 99%	684	80	€ 859	- € 177	- 2,215
All patients with a slightly elevated HsTn result at t0 without NSTEMI, n = 101							
Serial HsTn analysis			12	-	€ 1,850	-	-
Triple biomarker	Strategy I	Sens. 90%	3	-8	€ 1,776	- € 74	9,042
		Sens. 95%	11	-1	€ 1,651	- € 200	220,990
		Sens. 99%	23	11	€ 1,471	- € 379	- 34,251
	Strategy II	Sens. 90%	12	1	€ 1,589	- € 262	- 321,508
		Sens. 95%	19	7	€ 1,468	- € 383	- 55,597
		Sens. 99%	29	17	€ 1,291	- € 559	- 32,211
	Strategy III	Sens. 90%	38	27	€ 1,477	- € 373	- 13,999
		Sens. 95%	42	30	€ 1,356	- € 494	- 16,207
		Sens. 99%	49	37	€ 1,180	- € 671	- 17,981

Sens. = sensitivity, ICER = incremental cost-effectiveness ratio. A sensitivity of 90, 95, and 99% corresponds with an NPV of 96, 98 and 99% respectively.