4 December 2009

Anastasios Koutsos, PhD.
Scientific Editor BMC-series journals

Dear Dr. Koutsos,

We are please to write a response to the comments provided for manuscript 1937728727277839. Please find comments and responses in italics below.

Reviewer 1:

Minor Essential Revisions
More detail is needed in the Limitations section on the limitations of not stratifying the analysis by age and sex categories. The authors need to mention male/female differences in ACS. Average age of presentation and case-fatality are higher in female compared with male ACS patients. While the authors state the limitation of not modeling a wider age range, they maintain that they mirrored some of the effect of age by varying the prevalence of MI/ACS among chest pain patients. There are effects of age on risk from thrombolysis, case-fatality, non-ischemic ECG abnormalities, hospitalization costs, survival, and life-expectancy that are not considered. The main results of this analysis are robust enough that it is appropriate that these issues can be addressed within the limitations section.

We appreciate the suggestions and have added text in the discussion section pointing out the impact of both age and gender on the results and further cite an earlier analysis showing the effect of age (increases) on the ICER.

The difference in QALY gained between the two strategies is small despite the presumed mortality benefit of increasing thrombolysis in the ECG strategy. The source of the difference and lack of difference in QALY needs more exploration—specifically, is the small QALY benefit of the ECG strategy due to more STEMI patients in the ECG arm receiving thrombolysis, improved overall case-fatality in the ECG arm because more ACS patients are hospitalized, or improved survival due to more longer term secondary prevention in the ECG arm? Comparison of the incremental QALY accrued from each of the components mentioned would better clarify the source of benefit and lack of benefit from ECG along a complex set of outcome pathways.
Again a helpful set of comments and questions. The overall effect is relatively small. However, the QALY gained between the two strategies is reported for the whole population of those presenting with chest pain. We have a baseline prevalence of 10% of those with chest pain who go on to have true ACS. Therefore the gain for those with ACS is roughly 0.1 QALY which is compatible with other screening interventions.

Regarding the separate components of the benefit we recognize that the pathway is complex and while we can estimate the benefits of the individual components we do feel that they are conditional. That is, the gains from reduced case fatality and increased secondary prevention are conditioned on the increased sensitivity and proper referral due to the ECG. Nonetheless, the contribution from increased use of appropriate lytics was responsible for about 57% of the benefit with an additional 12% of the benefit from case fatality in hospital and the remainder from secondary prevention. We have added this to our results section.

Discretionary Revisions

1. The size of the cohort (N) modeled should be mentioned

   We modeled the adult population with mean age of 60 and presenting with chest pain. The population of approximately one billion with a 1.8% incidence rate yields about 18 million about 8 million of which live in urban settings where this intervention might be feasible.

2. The “cycles” of the model—I assume annual cycles—should be specified

   It is annual and we have added this in the methods.

3. QALY “gained” reported for both main strategies (with/without ECG). What is the comparator for the gain for each strategy? Is it no GP visit?

   This was a wrong use of the terms. The table and text for each strategy should have referred to the total years “obtained” for each strategy. Only the ICER comparing the two should refer to years “gained”. We have made the corrections.

Reviewer 2

There are two principal limitations to this analysis. Firstly, the derivation of estimates of sensitivity and specificity are somewhat opaque and the possibility that use of an ECG could paradoxically worsen one parameter or the other has not been explored. Although counter-intuitive, it is not beyond the bounds of possibility that using an ECG could reduce diagnostic performance. For example, the initial ECG is often normal in non-ST elevation ACS. If GPs erroneously decided not to refer such cases to hospital then use of an ECG could reduce sensitivity. The estimates of sensitivity and specificity appear to be based upon observational data rather than a randomized comparison of GP diagnostic accuracy with and without ECG, so there must be considerable uncertainty. The effect of diagnostic testing upon decision-making is often unpredictable, so it would be worthwhile exploring a wider range of conceivable values for sensitivity and specificity including the possibility that one or the other is superior when ECG is not used.

The second limitation is that uncertainty has only been explored through one-way sensitivity analysis. Best current practice in economic analysis would involve undertaking probabilistic
sensitivity analysis based upon distributions around each of the parameters in the model. This would allow calculation of confidence intervals around ICERs and estimation of the probability of pre-hospital ECG being cost-effective at varying thresholds of willingness to pay for health gain. This is a sophisticated technique and would require analysis by someone with expertise in mathematical modeling, but if the authors can undertake such an analysis then it would be a valuable addition to the study. If not then the failure to explore stochastic uncertainty should be acknowledged as a limitation.

Major Compulsory Revisions

The one way sensitivity analysis should be repeated to include the possibility that sensitivity or specificity with the ECG could be worse than without the ECG.

If probabilistic sensitivity analysis is not undertaken then failure to explore stochastic uncertainty should be acknowledged as a limitation.

The limitations in the data used to estimate sensitivity and specificity should also be acknowledged. The ideal data source would be a randomized trial comparing decision-making in GPs with and without ECGs.

We appreciate the reviewer’s comments regarding the sensitivity and specificity for the study. The reviewer is also correct that there is no RCT of GP with ECG vs GP without ECG to guide us and this would be ideal and we have added this to the text. While the possibility exists that the use of the ECG can lead to false negatives (those with AMI but negative ECG) we are not testing just the ECG but the ECG plus clinical decision making. Our sensitivity is not based on the ECG alone but the ECG as interpreted by a clinician with the history and physical. Nonetheless we recognize that the possibility still could exist for a small minority. One study showed that 4% of MIs were sent home from emergency departments but this represented 0.6% of the whole population presenting with chest pain. The analysis when the sensitivity of GP with ECG is lower than GP without ECG shows no ECG is better which is obvious because there cases are missed and costs are incurred. We have reported this result.

However, we also agree that the analysis would be improved with a probabilistic sensitivity analysis (PSA) to address the first limitation as well as the second. This allowed the sensitivity to vary as well as the specificity in addition to other variables. We therefore undertook a probabilistic sensitivity analysis using the sensitivity and specificity ranges outlined in Table 3. The results show a mean ICER for GP plus ECG of $154/QALY (95% CI, Cost-saving - $1830/QALY) and with 99% below a willingness to pay threshold of $3000/QALY.

Minor Essential Revisions

Background: Is primary angioplasty feasible in the Indian health care system? If so, what percentage of Indian STEMI receive primary angioplasty?
About 6% of the Indian population undergoes primary angioplasty.

Background, 2nd paragraph: Is the average cited here a mean or median?

*Mean. We have inserted the correction.*

Background: What sort of emergency ambulance service is available in urban India? Is there any equivalent of the 999 or 911 emergency call system?

*There is no public based EMS system in place in most urban areas.*

Background and methods: It would be helpful to have more details of the data from reference 8 that are used to justify this study and are a source for sensitivity and specificity estimates. I assume they are observational data. Could the association between use of the ECG and reduced delay be confounded other factors? For example, is it possible that patients with characteristic clinical features of MI and a short time from symptom onset to presentation could have been more likely to have an ECG and a more rapid referral? Would the decision to use an ECG be determined by patient characteristics or availability of ECG equipment?

*The data is observational. Unfortunately the investigators not able to determine from the data whether there were other confounders. Certainly the scenario that is suggested is possible. Due to the chance that there is error from confounding we used the broad range of estimates for the sensitivity and specificity in our “sensitivity” analyses. We would recommend that all adult patients with chest pain undergo ECG as this was the protocol for the observation data that the sensitivities and specificities were used for the analysis.*

Methods: It is not entirely clear where the Markov modeling comes in. The model appears to be a simple decision tree. My understanding is that Markov modeling involves assuming that patients move repeatedly between states in cycles of modeling.

*Markov modeling is used for all the patients who present with chest pain to determine costs and QALYs. Markov models are used for both those with ACS and without ACS. The event cycle is 1 year. Patients without ACS face annual probabilities of death for non ACS patients and costs if misdiagnosed and sent to hospital (false positives) in the first year. Patients in the ACS Markov model have great first year and 10-year survivals if STEMI and thrombolytics are applied (using the thrombolytic data). Also, patients admitted with ACS to hospital increase likelihood of receiving secondary prevention. Both of these events are improved with the increased sensitivity of the ECG. False negatives do not get these benefits.*

Methods: Was sensitivity modeled separately for STEMI and NST-ACS or was it assumed that sensitivity was the same the two conditions?

*We used data on the sensitivity for ACS (both STEMI and NSTEMI) combined. The proportion of which was STEMI was used to determine those who would benefit from thrombolytics.*
Discretionary Revisions
If possible, probabilistic sensitivity analysis should be undertaken as outlined above.

We have done so and appreciate this suggestion.

Reviewer 3

I have no particular comment regarding the design and the assumptions of the model; the unit costs are exceptionally low compared to cost in western countries so perhaps a brief reminder of the per capita GDP in India, placed in the methods section instead of the discussion would help. The baseline values and the assumptions in the sensitivity analysis seem correct. The authors have chosen a deterministic instead of probabilistic sensitivity analysis and should justify this choice.

We have added per capita GNI in the methods section. We have also added a probabilistic sensitivity analysis.

My major comments concerns policy implications. I think it would be of great interest for readers outside India to understand the stakes and the barriers to having GPs perform ECGs and refer patients to the hospital.

1) What would be the additional cost incurred (and by whom) to provide additional equipment and training?
2) What is the position of the association of cardiologists?
3) The tornado diagram shows that it would be cost saving to have GPs perform ECGs in areas or populations where the prevalence is high. While this makes a lot of sense medically, what is the feasibility of such a policy

In short, the discussion should focus on the politics of having pre-hospital ECG performed by GPs and i should convince the reader that the results of this study can indeed result in changes in referral practice.

We appreciate the comments and have adjusted the discussion to take into account the questions raised above. We are however unable to answer the position of the association of cardiologists.

Sincerely,

[Signature]

Thomas A. Gaziano, MD, MSc