Acute Myocardial Infarction. Can we define guidelines for cost-effective care?

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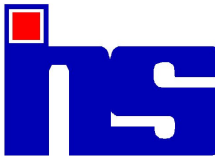

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Acute Myocardial Infarction: Can guidelines be defined for cost-effective care?[1]

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Introduction

Ischaemic heart disease (IHD) is an important source of disease burden in the world and accounts for approximately 4% of the global disease burden. Barring Africa, where the low IHD burden can be explained in terms of delayed demographic transition, it is one of the top ten causes of disease burden in five out of six of the WHO regions with ranks ranging from one (Europe) to seven in the Western Pacific. As demographic and epidemiol-ogic transition progresses, developing country health systems will have to deal with rising disease burden due to various ischaemic heart ailments. Technological alternatives for management of ischaemic heart diseases are many and the cost implications on the overall health system of a country could be very serious. More over, some aspects of IHDs management goes counter to traditional notions of referral systems. Developing countries saddled with the unfinished agenda of controlling infectious disease will find it all the more difficult unless cost-effective strategies are quickly found to manage the large burden of disease due to ischaemic heart diseases. Technology assessment, development and popularization of practice guidelines will be essential for cost-effective management of the ischaemic heart disease burden.

This paper reviews practice guidelines and meta analyses of evidence on efficacy of technological alternatives for medical management of acute myocardial infarction (AMI). A set of evidence - based core technologies is then identified. Potential issues for application

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of these technologies in developing countries are then discussed, using the health system of Mauritius as a case. Effectiveness of adherence to practice guidelines by medical practitioners is finally estimated, using disability adjusted life year (DALY) measure of population health status.

Methods

MEDLINE database for 1984 Oct. 1995 was searched under therapeutic intervention related subheads of four broad MeSH headings relating to ischaemic heart disease. The four MeSH headings are "myocardial ischaemia", "myocardial infarction", "coronary disease", and "angina pectoris". The therapeutic intervention related sub heads are: complications (co), diet therapy (dh), drug therapy (dt), economics (ec), epidemiology (ep), mortality (mo), nursing (nu), prevention and control (pc), radiotherapy (rt), rehabilitation (rh), surgery (su) and therapy (th). The search result was limited to English language articles on human subjects and further limited by publication type to consensus development conferences including NIH, guidelines, meeting reports, meta-analyses, monographs, practice guidelines and technical reports. Title and, where ever necessary, the abstract of the 274 retrievals were browsed for relevancy to medical management of myocardial infarction. A reference was considered irrelevant only if it satisfied any of the 17 non-relevancy codes (Annexe-1). This resulted in 32 references considered to be prima-facie relevant for management of MI. The titles and abstracts of these were reviewed in detail to identify national guidelines and consensus documents (Table 2).

Guidelines (Table-2)

The Canadian consensus *(1)* singled out thrombolytic therapy as the mainstay of medical management of AMI. This is probably a result of the fact that the immediate

motivation for the consensus conference was the role of thrombolytics. For example, the consensus does recommend prescription of aspirin to all AMI patients irrespective of their suitability for thrombolytics. So, in terms of coverage of the suspected AMI patient population, the consensus recommends aspirin in all. Thrombolytics are the mainstay of treatment for a large patient subgroup who are hospitalised within 12 hours of onset of symptoms and have significant ST wave elevation. IV heparin and beta blockers are recommended as good adjuvants. IV nitroglycerine is recommended for specific situations. Routine use of ACE inhibitors, calcium channel blockers, magnesium sulfate and lidocaine is not recommended. The consensus discourages routine revascularisation like PTCA or CABG and advises exercise stress test instead as a means for risk stratification. Aspirin, warfarin and betablockers are recommended for post MI management. Calcium channel blockers are not recommended for routine use and verapamil is recommended as an option for cases with contraindication to betablockers. The 1994 update was mainly about the choice of thrombolytics and the mode of administration of heparin. The original consensus had preferred streptokinase as the drug of choice for thrombolytic therapy. In the update, the panel took note of the latest data in favour of accelerated rtPA for cases reporting within 6 hours of onset of symptoms and also cited the higher cost associated with use of rtPA. The update, based on recent data also preferred subcutaneous route for heparin instead of IV route, except for those receiving rtPA.

The British guidelines developed jointly by the British cardiac society and the Royal college of physicians (*2)* outlined accessibility to cardiac defibrillation and quick ambulation to hospital as first priorities in the pre hospital phase. Oral aspirin, thrombolytics, and, in suitable cases, IV betablockers, are identified as specific treatment for myocardial infarction upon arrival in the hospital. The guideline emphasises the importance of early

administration of thrombolytics and sets a target of at least 50% patients receiving it within 90 minutes. Streptokinase is the preferred thrombolytic. Heparin, in addition to aspirin and thrombolytics, is not recommended in view of evidence from ISIS-3 (*3*). In the post-MI phase aspirin is recommended for all. It is suggested that treatment with betablockers, ACE inhibitors and cholesterol lowering drugs should be given according to clinical judgement and local protocol. Exercise electrocardiography is recommended for all patients post-MI for proper stratification of risks. Coronary angiography is recommended only for those not doing well in the exercise test and with other high risk attributes. Cardiac rehabilitation exercises are recommended.

The Irish guideline (*4)* is about thrombolytics in myocardial infarction. The guideline recommends that all AMI patients receive oral aspirin. Early thromobolytics is recommended for all except for those who have specific contraindication. No heparin is required in case of streptokinase and aspirin combination. Tissue plasminogen activators perforce require heparin to accompany them.

The American College of Cardiology and American Heart Association (ACC/AHA) (*5)* task force report of 1990 offers a fairly detailed guideline for early management of patients with acute myocardial infarction. The guideline discusses each therapeutic issue at various stages of management as they might appear. Thus the sequence of presentation of each therapeutic alternative does not reflect its importance in terms of the magnitude of its effect or the frequency of its use. However, the discussion of evidence for each therapeutic alternative gives enough idea about the task force's emphasis. For example, while things like oxygen, nitroglycerine, analgesia, counter shock, and atropine are all included in the pre-hospital phase, the magnitude of the effect of counter shock (defibrillation) referred to by the task forces alludes to its importance. Thrombolysis is recommended for all patients

who are less than 70 years of age with ST segment elevation (at least 0.1 mv in limb leads) reporting within 6 hours of onset of symptoms. Aspirin is recommended immediately upon admission until discharge and should be continued there after. Subcutaneous or IV heparin is recommended to prevent arterial embolism. IV beta blockers are recommended to all, except in the presence of congestive heart failure or other contraindications like asthma. For calcium channel blockers, the task force notes the absence of clear cut evidence to support routine use. A conservative approach to revascularisation (PTCA/CABG) is advocated. A pre-discharge sub maximal exercise test is advised only if the patient can not return for follow up exercise testing after three weeks, or for all patients receiving thrombolytic treatment. For secondary prevention of myocardial infarction, post-infarction treatment with aspirin and oral anticoagulants like warfarin are recommended.

The national guidelines above were studied to identify technological contents of the current state of the art in medical management of MI. Most guidelines classify their recommendations on the basis of some appreciation of the strength of evidence. Interventions based on class-I or grade-A evidence were flagged for further study for our purposes.

Meta analyses

Meta-analyses are another convenient source of summary information about specific technologies. Eight meta-analyses identified from the 32 relevant retrievals were studied to supplement the review of guidelines. There is some difference, though, between guidelines and meta-analyses as sources of knowledge about "state of the art". Meta-analyses usually cover technology which continues to generate research reports. Issues of patient management, well settled on the basis of trials and studies in an earlier period, might not show up in current meta-analyses. If any such meta-analyses were done in an earlier period,

say before 1984, they would not show up in the current search. Extending the search to earlier periods might have resulted in a large number of outdated guidelines and review articles, making the search less efficient. As our objective was to use the recent meta-analyses to supplement guidelines as a quick source to identify core technologies, the limitation of the time period to last 10 years would be optimal.

De Vreede et al (*6)* did a meta-analysis of mortality after acute myocardial infarction in unselected patients during the period 1960-1987. They identified, from MEDLINE, all studies on myocardial infarction which reported mortality results and met their selection criteria. The median age of myocardial infarction patients, for studies which provided this information, was 60.05, 61.35, 63.3 years for studies in the 1960s, 1970s and 1980s respectively. The median age of patients from all studies from the 1960s to the 1980s was 61.4 years. They found that short term mortality, i.e. inhospital mortality, and one month mortality results for myocardial infarction patients had improved monotonically during the three decades.

Table 4 shows changes in overall mortality after myocardial infarction based on the results of this meta-analysis. The authors reported short term mortality in terms of cumulative probability and the 5 year mortality as probability of death conditional on discharge from hospital. All probabilities have been converted to conditional probabilities for the sake of comparability. It is evident from this table that mortality reduction achieved during these three decades were mainly contributed by the hospital phase of management.

The meta-analysis by Basinski and Naylor (*7)* focused on interaction of aspirin and thrombolytics (streptokinase, tPA etc). They stratified mortality data according to the time of treatment, i.e. within than 5 hours of onset and later. The effect of aspirin and streptokinase on mortality reduction in myocardial infarction has been known to be

additive. This meta-analysis suggests that aspirin and thromobolytics have synergistic interaction effect for patients treated early i.e. within 5-6 hours of onset of symptoms (odds reduction of 24% for fibriniolysis vs placebo and 40% for fibrinolysis and aspirin vs aspirin alone). The effect is additive for those treated later.

On the other hand Roux et al (*8)* pooled data from therapeutic trials for myocardial infarction in the thrombolytic era (1980-1990) to analyse the effect of aspirin on reocclusion rates. Studies of myocardial infarction patients treated with thrombolytics within 6 hours of onset were included. Additional inclusion criteria consisted of performance of early, as well as predischarge (after 8-14 days of stay), coronary angiography and or documentation of recurrent ischaemia during the hospital stay. Altogether, 32 studies consisting of 19 RCTs and 13 others provided data on reocclusion in 932 patients (aspirin group=413 and non-aspirin group=513). The outcome of reocclusion was defined to mean that an infarct related artery was found occluded in the predischarge angiogram but was open in the early angiogram. According to their analysis, the reocclusion rate in the aspirin group was about 12% in comparison to 25% in the non-aspirin group. The results were similar after excluding the non-randomised studies. This points to the emerging evidence in favour of the beneficial effects of aspirin on other outcomes, in addition to the already noted benefit in mortality reduction.

Similarly, the meta-analysis by Granger et al (*9*) focused on intermediate end points representing the mechanism of action of thrombolytics in myocardial infarction. They pooled data from studies reporting effect of different thrombolysis regimen on infarct related arterial patency, reocclusion or left ventricular ejection fraction. The main interest was the difference between alternate thromobolytic agents like streptokinase, tPA and APSAC. Although tPA and APSAC had slightly higher patency rates within the first 90

minutes, the effect of streptokinase caught up in 2-3 hours. Patency rates in all forms of thrombolysis treatment remained similar thereafter. Reocclusion rates were higher with tPA and APSAC. This offsets the marginal benefit in early patency from tPA and APSAC either in part or full. The higher reocclusion rates in tPA/APSAC patients is not inconsistent with the findings from the GUSTO trial. In the later trial, the authors of this meta-analysis argue, a more aggressive anticoagulation regime with heparin was followed. This might have fully corrected the vulnerability to reocclusion following tPA / APSAC administration. All thrombolytics increased left ventricular function, although the magnitude of the improvement was small, i.e. about 3%.

Midgette et al (*10)* pooled data based on anatomical site of infarction i.e. anterior infarction and inferior infarction. Since infarct location clearly influences use of streptokinase by physicians, the authors argue, subgroup analysis on the basis of anatomic site of infarction is important. Although they pooled data from six trials satisfying their selection criteria, most of it was from the ISIS-2 (*11)* and GISSI *(12).* This meta-analysis found that the observed difference in short term (21-35 days) mortality attributable to streptokinase was about a 5 percentage point reduction in the anterior infarction group and about a 1 point reduction in the inferior infarction group. Of the total number of 31940 patients from the six studies, pre randomisation electrocardiograms were not available for 2945 patients. Of the rest (28995), 9155 (32%) had anterior infarction and 9650 (33%) had inferior infarction and the rest had infarction at other sites. This gives some idea about the relative size of these patient sub groups.

Naylor and Jaglal (*13*) pooled data from seven trials to study impact of IV thrombolysis on short term coronary revascularisation (PTCA, CABG) rates. Patients

treated with thrombolytics are significantly more likely to cross the decision threshold and undergo PTCA or CABG by about 80%.

Horner (*14*) did a meta-analysis of randomised control trials on the effect of IV magnesium in myocardial infarction. Data for 930 patients from eight trials was analysed. It was found that IV administration of magnesium was associated with 49% reduction in incidence of ventricular tachy cardia and fibrillation. There was also a significant reduction in mortality in the magnesium group. This analysis was done before findings from ISIS-4 (*15)* were published. The later study based on a sample size of 50000 patients reported a negative effect of magnesium. Note that this later study forms the basis of the Canadian consensus against routine use of IV magnesium referred to earlier.

Hansen (*16*) pooled data primarily from the Danish Verapamil Infarction trials (DAVIT-I and II). DAVIT-I did not demonstrate any significant difference in early mortality in verapamil and control groups. Rather the treatment group (verapamil) had higher incidence of heart failure. The DAVIT-II trial examined the effect of verapamil given to stable post MI patients on long-term survival or reinfarction (upto 6 months) and recorded a 20% reduction in the event rate (death or reinfarction). This meta-analysis essentially repeated the DAVIT-II analysis by combining data from DAVIT-I and II. The result was similar to the DAVIT-II. The author concludes that verapamil may be of use in post-MI patients with preserved left ventricular function. For example, the author cites the findings of Yusuf et al *(17)* following update of their meta-analysis of beta blocker trials after DAVIT-II results. The later authors recommend use of aspirin and beta blockers in preference to any calcium antagonists for secondary prevention in patients with myocardial infarction. Verapamil would be appropriate if beta blockers are contraindicated. Similarly Hilton et al *(18)* opine that beta blockers are more beneficial if judiciously used in

myocardial infarction patients with left ventricular dysfunction. Calcium channel blockers have an adverse survival effect in patients with left ventricular dysfunction. They may be of use in patients who do not have left ventricular dysfunction. We need to recall that the Canadian consensus do discourage use of calcium channel blockers including verapamil

The meta-analysis by Lau and Antman (*19*) provides a grand view of the efficacy of a large number of interventions for myocardial infarction (Table - 5). Most recommendations of various guidelines and findings of other meta-analyses referred to earlier are consistent with the results of this meta-analysis. Aspirin (anti platelet agent), heparin (anticoagulants), thrombolysis (streptokinase, rtPA or APSAC), beta blockers, nitroglycerine and IV magnesium have established favourable outcomes in the patient subgroups for whom they are indicated. Note that the national guidelines generally emphasise that aspirin, thrombolytics, heparin and beta blockers are indicated for the majority of patients. IV nitroglycerine and magnesium are usually recommended in specific patient subgroups that may need them.

Each of these drugs have specific indications and contraindications. Not all MI patients would receive all of these drugs. Nor is it the case that any individual patient would receive only one of these. Each drug, when used in situations for which its usefulness is known, will contribute to the composite efficacy of the intervention. Considering the fact that each patient presents a unique set of clinical signs and symptoms, accounting for the contribution of every therapeutic action is well nigh impossible. However, it is possible to identify the core technology which contributes to most of the mortality / morbidity reduction and is most commonly applied to patients. For example, of all the drugs now available for management of MI, aspirin appears to be the most frequently indicated and with least contraindications. In Table - 6 I have listed, based on a review of the current state of research, core technologies for management of myocardial

infarction. Dissemination of knowledge about the clinical efficacy and cost implications of these technologies among physicians and public health officials will help them contribute to a general health policy regime of cost-effectiveness in medical care.

Note that mere inclusion in this table does not imply that these technologies are all cost-effective for all countries. Our purpose is to list the core technologies first and then examine the relevance of each for the Mauritian situation. The following sections provide more details about each of the above technologies and how they relate to the Mauritian situation.

Core technologies for management of Myocardial infarction and how they relate to the needs of developing country health systems

Pre hospital phase

Two things are very important for prognosis. Considering the differential impact of thrombolysis according to the elapsed time between onset of symptoms and its administration, the speed of transfer to hospital with facilities for management of AMI is important. Secondly, it is observed that some patients develop ventricular fibrillation followed by sudden cardiac arrest. Quick and ready defibrillation in such cases has the potentiality to revive some cases. Here I examine alternate interventions directed at these two aspects.

Rapid Transfer To Hospital

It is well known that quick transfer to a hospital equipped with facilities to take care of persons with myocardial infarction is a key to success of thrombolytic therapy. Since thromobolytics are an important component of current technology for management of myocardial infarction, and protocols for their administration outside of hospital setting are yet to be developed, rapid transfer to hospital becomes a critical link. It would then appear

that an ambulance service would be useful. However, many factors are at work to influence the need and efficacy of an ambulance service. Consequently specific circumstances of each health system need to be examined. Let us take for example the case of Mauritius where dedicated ambulance services are not well developed. Distances in Mauritius are not great compared to many other countries. Secondly, except for the defibrillation equipment that the paramedics in an ambulance may carry, there is no evidence to suggest that the survival experience of ambulance transfer of myocardial infarction patients is any better than that of transportation by ordinary car. A chart review of myocardial infarction patients (Murray, et al, *(20))* revealed that a good number of patients are able to reach the hospital quickly enough for thrombolytic therapy, without any ambulance service (Table - 7). This is because private cars are easily available in most Mauritian villages and towns, and neighbours, friends or family members having such facilities are willing to transport patients in need.

Time to admission data compiled from the ISIS-2 (*11)* study are shown in Table - 8. The time to admission situation in Mauritius is similar or a little better than the general picture in the ISIS-2 hospitals. For example, 40% of cases in Mauritius reach hospital within the first two hours, in comparison to about 10% in the hospitals from 16 industrialised countries participating in the ISIS-2 study. By about 5-6 hours, the cumulative proportion of cases reaching hospital in the ISIS-2 hospitals and Mauritius is about the same (41% by 5 hours in ISIS-2 hospitals and 56% by 6 hours in Mauritius).

Median "time to admission" data from the Cincinnati Heart study (Kereiakes DJ et al, *(21))* for different transportation modes is shown in (Table - 9). Findings from the Cincinnati study suggest that substantial reduction in time to admission is possible only by a

highly specialised and intensely managed system like the emergency medical system with pre-hospital ECG. The gain in median time to admission by local ambulance services and emergency medical systems without pre hospital ECG was not great in comparison to private automobiles.

Health education messages emphasising the importance of quick transportation of myocardial infarction patients directly to hospitals with cardiology services may help better the time to admission further. For example, a study from Sweden (Bloom M et al, *(22))* reports that media campaigns (an initial 3 week intense campaign followed by a maintenance phase for one year) urging people to reduce delay in transportation of persons with possible myocardial infarction reduced the median delay from 3 hours to 2 hours and 20 minutes, without affecting the level of ambulance use. The reduced time to admission was sustained for three years after the campaign. There is overwhelming evidence to suggest that efforts to consult general practitioners is usually associated with a higher time to admission (Heriot AG et al, Bleeker JK et al, Walbridge DR et al, Ahmad RA et al, Rowley JM et al, (*23)*). Hence the health education message should enable people to recognise symptoms suggestive of AMI, encourage them to seek help directly at hospitals with facilities for appropriate care, and clearly identify the hospitals in the locality which are equipped to provide appropriate care.

The flip side of quick transportation is the spread of hospitals with cardiology services. The average time to admission is likely to come down further if expansion of cardiology services is accompanied by a further spread of regional hospitals, where these services are generally organised.

Access to Quick Defibrillation

For an estimate of the incidence of VF in AMI patients an "on the fly" search of MEDLINE 1991-Dec. 1995 was done by intersecting suitable strings (Table - 10). Analysis of activities of an ambulance service in Poland by Witczak W et al *(24)* gives some idea about the frequency of ventricular fibrillation among those developing AMI. They report that 21.9% of the MI patients developed sudden cardiac death due to ventricular fibrillation. 28.5% of these were successfully resuscitated. Chiroboga et al *(25)* have reported incidence of ventricular fibrillation after admission to hospitals based on data from 16 hospitals in Massachussets, USA between 1975. They found that about 5.1% of uncomplicated myocardial infarction patients developed ventricular fibrillation. This rate remained stable during the 15 year period studied by them. So the incidence of ventricular fibrillation immediately after onset of AMI symptoms in the pre hospital phase must be higher. Based on Witczak et al's (*24)* report from Poland we assume a 20% incidence of ventricular defibrillation immediately after attack (i.e. 20% of those who develop myocardial infarction). From the same Polish experience we assume that the potentiality of an ambulance service with paramedics skilled in defibrillation is about 25% avertion of mortality immediately after ventricular fibrillation. In other words 85% of those who develop myocardial infarction would survive to reach a hospital for further care, if quick defibrillation facilities are available, as against 80% in the absence of quick defibrillation.

Hospital Phase

Aspirin

Beneficial effects of long term, low dose oral aspirin on reducing serious vascular events, by about 25%, in patients with unstable angina has been well documented (Anti Platelet Trialists, 1988). The second international study of infarct survival (ISIS-2 *(11))*

provides bench marks about the effect of quickly started oral aspirin in myocardial infarction. The study established, with reasonable degree of certainty, the beneficial effects of aspirin alone in reducing mortality due to myocardial infarction. This finding has important public health implications. Considering the fact that aspirin is cheap, readily available, has minimal adverse effects in myocardial infarction patients and is simple to administer (oral), it naturally would be a cost effective treatment. In addition to having a mortality reduction level similar to the thrombolytics (eg.streptokinase), aspirin reduces reinfarction rates, reduces reocclusions following thrombolytic therapy, and is additive in its mortality reduction effect. The simple lesson from all this evidence is that, except for the very few cases with absolute contraindication (bleeding gastric ulcer, etc) aspirin is a first drug of choice for myocardial infarction. Its administration should start at home, on the way to hospital, or upon admission and continued there after. Low dose oral aspirin is adequate. ISIS-2 (*11)* used a dosage of 160 mg per day. Hence, one important step would be to make sure that all physicians and general practitioners prescribe aspirin right away upon suspecting myocardial infarction. This intervention is feasible in all existing hospitals, such as the district hospitals, and does not require the existence of specialised cardiology units.

Thrombolytics

Convincing evidence about efficacy of thrombolytics became available from the Italian study (GISSI, *(12))* and the second international study on infarct survival (ISIS-2 *(11))*. Table 11 shows the efficacy of thrombolytic treatment reported by these two studies. Intravenous streptokinase was the chosen thrombolytic in both the studies. Subsequent studies have tested the efficacy of the more expensive recombinant tissue plasminogen activator (rtPA) (ASSET study, GUSTO , GISSI-2 *(26))* or APSAC (AIMS, 1988, 1990).

Two important issues regarding efficacy of thrombolytic treatment are; (a) time to admission i.e. the delay between the onset of symptoms and the initiation of thrombolytic treatment and (b) choice of thrombolytic agent. The efficacy of thrombolytic treatment is greater for cases reporting soon after onset of symptoms.

The second issue concerning the choice of thrombolytic is also linked to the time to admission factor. The ISIS-3 *(3)* trial revealed that there is no significant difference in the efficacy of IV streptokinase, rTPA and APSAC for cases reporting after six hours of onset of symptoms. Since a streptokinase regimen is comparatively cheaper, it is to be preferred over the other alternatives. The GISSI-2 (*26)* and ISIS-3 (*3)* trials did not reveal any significant advantage of rTPA over streptokinase for cases reporting within six hours of onset of symptoms. The GUSTO trial, characterised by more aggressive anticoagulation (by heparin) demonstrated an additional 0.01 reduction in attributable risk by rTPA over streptokinase for patients with transmural MI, younger than 75 years and reporting within six hours of onset of symptoms. Note however, the need for more aggressive anticoagulation in the case of rTPA therapy. It appears that a general regime of streptokinase and provision for rTPA for patients who would benefit more from rTPA would be appropriate.

Heparin

Heparin is an useful adjunct to thrombolytic therapy. The choices for treatment with heparin are:

1. Low dose subcutaneous heparin at the rate of 5000U every 12 hours
2. High dose subcutaneous heparin at the rate of about 12500U every 12 hours, sufficient to control activated partial pro thrombin time to 1.5 - 2 times the control level

3. Intravenous heparin starting with a 5000U bolus followed by 600-800U/hour to accompany rTPA regimen

High dose IV heparin has its complications due to increased risk of bleeding. This is another reason why low dose heparin plus streptokinase is more attractive compared to rTPA plus IV heparin.

Early Beta-blockade

The beneficial role of β-blockers in management of post-myocardial patients is well recognised. The issue for consideration here is whether they are of any use in management of acute myocardial infarction. The ACC/AHA (*5)* identified the following two roles that β -blockers could play in acute myocardial infarction:

1. Limitation of myocardial damage
2. Reduced risk of reinfarction.

Most of the randomised control trials (including the first international study of infarct survival (ISIS-1 *(27))* and the Metoprolol in acute myocardial infarction (MIAMI) trial) which provide conclusive evidence about the efficacy of early administration of β-blockers were done in the pre thrombolytic era. So the natural cost-efficacy question is whether the beneficial effects of beta blockers are in addition to the risk reduction attributable to aspirin and thrombolytics. Phase-II of the thrombolysis in myocardial infarction (TIMI) trial looked at this issue. Results from this study show that there is no mortality differential between early intravenous beta blocker with thrombolytics, and deferred oral beta blockers. However, a statistically significant difference in nonfatal reinfarction rates was found. So, one is uncertain about the cost-efficacy of early intravenous beta blockers . It may be useful in low risk patients without any specific contraindications.

Potential for reduction of AMI through use of practice guidelines

Availability of technological alternatives and knowledge of their comparative advantages is not enough for a society to realise its benefits. Many factors intervene to translate the underlying efficacy of a technology into actual effectiveness. Gains to a population from an available treatment for a disease will depend on the efficacy of the treatment itself, and the proportion of cases that actually receive the treatment. Let us call this proportion the treatment factor. This factor is a product of coverage, i.e. proportion of persons with the disease who comes in contact with the health care system providing that treatment, medical compliance and patient compliance. Here medical compliance is defined as the proportion of cases using the health care system, who receive the normative treatment. In case of AMI, oral aspirin and early thrombolysis is the normative treatment. If doctors and nurses advise this normative treatment to all cases coming into the health system, then medical compliance will be complete. On the other hand, if a doctors fail to give the normative advice in a certain proportion of cases the medical compliance would be less than 1, to that extent. Patient compliance means the proportion of patients who were given the normative advice by the health care system, but did not substantially comply with it. In the following computations, coverage and compliance data from Mauritius is used to estimate the potential gains by way of reduced disease burden, if practice guidelines were adopted and complied with and if access to medical services for management of AMI were expanded.

Chart review in the regional hospital of Mauritius showed that only about 60% of patients with myocardial infarction were receiving aspirin as a part of the treatment. Thus medical compliance using the oral aspirin criteria stood at 60%. It would be lower, if the early administration of thrombolytic criteria is added. Since Mauritius is at the higher end

of the developing country spectrum, one could assume that medical compliance in other developing countries, where specific programmes of practice guideline development and reinforcement do not exist, would be similar. Coverage, i.e. access to medical management of persons experiencing acute myocardial infraction in Mauritius was estimated at 25% (Murray, et al. *(20)*. Patient compliance can be assumed to be 100% in this case, since AMI patients are to be hospitalised. Effectiveness of medical management of AMI around the core technology of oral aspirin plus early thrombolysis, is computed using the disability adjusted life year (DALY) measure (Murray and Lopez, *(28))*.

Table - 13 gives an estimate of DALY gain for AMI cases by introduction of practice guidelines requiring aspirin and early thrombolytic therapy and a programme to achieve various levels of medical compliance. Coverage, i.e. access to services providing medical management of MI services is held fixed at 25%. Medical compliance is incremented from the base of 60%. The three columns after medical compliance, show DALY gain per person covered by the intervention (PCI) i.e. per single case reaching the health care system. The absolute DALY gain column shows DALY gained by the intervention in comparison to a state of no medical intervention at all. The next column gives the marginal gain in DALY / PCI at different levels of medical compliance. The column after that labelled "incremental" gives the cumulative DALY gained over the base line scenario of 60% medical compliance. The last two columns show incremental DALY gain for the developing regions of the World, by applying the incremental DALY gain / PCI to the total AMI incidence estimate for 1990 given in the GBD - 1996 study (Murray and Lopez, *(27*). The very last column shows the impact in terms of the percentage of DALY loss due to AMI, that can be averted if medical compliance could be increased from 60% to various levels up until full compliance. If we take a more realistic target of 90% medical

compliance, then about 28% of current disease burden due to AMI could be averted. In terms of cost, interventions designed to improve medical compliance, will be minimal.

Table-14 shows similar computations, fixing the level of medical compliance at 90% and incrementing coverage from the base of 25%. Improving access to medical services for management of AMI, namely hospitalisation by a unit trained to manage AMI cases, will naturally contribute significant DALY gains. Full access would avert 62% of the current disease burden due to AMI. Expanding access to hospitalisation services for medical management of AMI , would imply higher hospital capacity, widely dispersed hospital network and rigorous programme of continuing education to train medical service providers with practice guidelines regarding AMI management. Developing countries, saddled with the unfinished agenda of controlling infectious diseases will have to balance the needs of other public health investments with the need for expansion of hospital services. Significant investments for expansion of hospital services may not be forthcoming in most developing countries. Adoption of practice guidelines and a programme to encourage medical compliance will help towards fairly substantial DALY gains from existing infrastructure investments.

Summary and conclusion

Ischaemic heart disease (IHD) is one of the top ten causes of disease burden in five out of six of the WHO regions and accounts for approximately 4% of the global disease burden (GBD) . Technological alternatives for management of ischaemic heart diseases are many and the cost on the overall health system of country could be very serious. More over, some aspects of IHDs management goes counter to traditional notions of referral systems. Developing countries burdened with the task of controlling infectious disease will find it all the more difficult, unless cost-effective strategies are found to manage the large burden of

disease due to ischaemic heart diseases. Technology assessment, development and popularisation of practice guidelines will be essential for cost-effective management of the ischaemic heart disease burden. This study reviews the state of the art for management of myocardial infarction. Practice guidelines developed in various parts of the world are reviewed. Meta analyses of results from various randomised control trials are reviewed. Some practical aspects of health system design issues are gleaned from literature. Through a case study of the situation in Mauritius, the author tries to show the gap in adherence to practice guidelines, the potential for reduction of disease burden due to myocardial infarction by standardising and improving coverage of medical management. Surprisingly, a significant reduction of disease burden from myocardial infarction is feasible with a very simple and cheap technology, namely aspirin. Oral aspirin contributes almost 50% of the cure that is technically feasible with current state of the art. However, some where 40-60% of MI patients do not probably receive aspirin, mainly on account of lack of clear cut practice guidelines and where such guidelines are available due to inadequate compliance by physicians. Among the many thrombolytic therapy available, streptokinase plus subcutaneous heparin appears to be the most cost-effective treatment. Rigorous evaluation using post MI stress tests, to screen cases that will most benefit from invasive procedures like PTCA and CABG can contribute to lower capital investments on expensive surgical facilities. This paper argues for development of practice guidelines and specific programs to popularise these guidelines. In developing countries general medical specialists working in first referral hospitals should be given continuing education on such practice guidelines, coupled with a program of medical audit.

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Annexure-1: Non relevancy codes

Possible reasons why a reference retrieved from MEDLINE search may not be relevant to the study (relevancy codes)

1. Clinical detail i.e. subject matter is on clinical details. For example details of the clinical management process, management of different patient sub groups, contraindications, prevention and treatment of complications, etc.
2. Drug variants i.e. Comparison of two drugs with similar mechanism of action.
3. Evolving technology.
4. Health system detail.
5. Tutorial i.e. a symposium or conference to inform national / local practitioners about recent advances. Chapters in professional annals and chronicles. A paper to inform readers that cites trials and studies but does not do a systematic review or meta analysis. Literature secondary to consensus documents.
6. Management variant. For example pre hospital thrombolysis vs thrombolysis on admission.
7. Methodological i.e. about protocol, design and methodological aspects of trials or studies related to the interventions.

8. Out of focus i.e. about an intervention / risk factor etc which targets the same disease or group of diseases but is out of the focus of the current exercise. For example coffee and MI, Cardiac education etc. w.r.t. Medical management of MI, angina, PTCA and CABG.
9. Outdated i.e. an old tutorial, guideline or consensus document. Out dated consensus is a consensus document by the same body on the same subject at a more recent date is available.
10. Physiopathology.
11. Procedure variants i.e. Comparison of two variants of the same procedure.
12. Publication variant of another paper. For example proceedings of a conference which has published a guideline also. A variant of a paper by the same authors on the same topic.
13. Small sample.
14. Specific formulation i.e. study on efficacy of a specific formulation like a brand name or a particular variant of a class of drugs.
15. Technical details of main interventions for example measurement of cholesterol, cardiothoracic anaesthesia, cardiopulmonary resuscitation, optimal doses of drugs, sub-interventions etc.
16. Too general to yield any efficacy data or leads to efficacy literature. For example health implications of obesity, highlights / executive summary of a consensus document or a national program, editorials or general discussion which may be related to the intervention but not likely to yield any new efficacy information , conference highlights etc.

17. Unrelated i.e, an unrelated condition or intervention is the primary focus of the paper or the perspective of the paper is totally different from efficacy of health interventions. For example stroke prevention w.r.t coronary artery disease.

Table-1 Top ten causes of disease burden [1] in world and WHO regions[2]

Cause	World		Africa		Americas		E Meditrn		Europe		SEAsia		W Pacific	
	Rnk	%	Rnk	%	Rnk	%	Rnk	%	Rnk	%	Rnk	%	Rnk	%
Acute lower respiratory infections	1	6.0	4	7.0	9	2.9	2	8.1	8	2.5	1	8.1	4	3.9
Perinatal conditions	2	5.8	5	6.2	5	4.2	1	8.2	5	2.9	2	7.9	5	3.7
Diarrhoea diseases	3	5.3	3	7.5	8	3.0	3	7.7	17	1.6	3	7.2	13	1.9
HIV / AIDS	4	5.1	1	16.6	13	2.0	7	2.8	46	0.4	12	2.2	36	0.6
Unipolar major depression	5	4.2	11	1.7	1	5.7	6	3.6	3	5.5	4	4.0	2	6.5
Iscahemic heart disease	**6**	**3.8**	**20**	**0.9**	**2**	**4.9**	**5**	**3.7**	**1**	**9.7**	**5**	**3.8**	**7**	**3.5**
Cerebrovascular disease	7	3.0	13	1.5	6	3.5	12	1.8	2	5.6	13	2.1	3	5.1
Malaria	8	2.8	2	10.6	80	0.1	16	1.5	97	0.0	39	0.6	60	0.2
Road traffic accidents	9	2.8	9	1.9	4	4.7	11	2.1	4	3.7	8	2.9	9	2.8
Measles	10	2.2	6	5.3	92	0.0	8	2.7	67	0.2	11	2.2	48	0.3

[1] Disease burden is measured by Disabilty Adjusted Life Years (DALYs)

[2] Source: The World Health Report 1999: Making a difference; World Health Organization, Geneva, 1999.

Table - 2 National consensus documents or practice guidelines for management of myocardial infarction (MI)

Country, year	Reference	Coverage of efficacy literature.
Canada, 1994	Canadian Consensus Conference on Coronary Thrombolysis--1993 (published in 1994). 1994 update published in 1995.	Panel members did extensive literature search, although specific description of search methodology is not known. About 64 references to randomised control trials, land mark reviews and other studies cited. References included almost all of the well known trials like GISSI, ISIS, GUSTO. Another 25 references are in the update.
U.K., 1994	The management of acute myocardial infarction: guidelines and audit standards of the British Cardiac Society and the Royal College of Physicians. (published in 1994)	No specific mention. Appears to be based on personal contribution of members of the audit committee including cardiologists, physicians, epidemiologists and others. 26 references include reports from ISIS-2-3, GUSTO.
Ireland, 1994	Irish Heart Foundation guidelines for the use of thrombolysis in acute myocardial infarction--second consensus report 1994. (1994).	No specific mention. The 21 references include ISIS-2,3, GISSI,GISSI-2, GUSTO trials.
USA, 1990	ACC/AHA Task force report: Guidelines for the early management of patients with acute myocardial infarction, JACC Vol.16.No2, August, 1990.	Literature search method not described. The document cites about 223 references including publications from most of the well known trials like GISSI, TIMI, TAMI, ISIS, MIAMI, ASSET, European Coop group, AIMS etc.

Table - 3 Strength of evidence definitions used by various national consensus processes

Canada	UK	USA (ACC/AHA)
Grade-A Supported by at least one and preferably more level I randomised trials. Randomised trials with low false positive and / or low false negative errors i.e. high power. are classified as Level-I.	A: Potential audit points. (Based on a convention established by the Royal College of Physicians).	Class-I: Usually indicated, always acceptable and considered useful / effective
Grade-B Supported by at least one level-II trial which means randomised trials with high false positive and / or high false negative errors.		Class-IIa: Acceptable, of uncertain efficacy and may be controversial. Weight of evidence in favour of usefulness / efficacy.
Grade-C Supported by only level-III, IV or V evidence. Level-III evidences are based on non-randomised concurrent cohort comparisons between contemporaneous patients. Level-IV Non-randomised historical cohort comparisons between current patients and former patients. Level-V case series without controls.	R: Subject of controversy or requires further research.	Class-IIb: Acceptable, of uncertain efficacy and may be controversial. Not well established by evidence, can be helpful and probably not harmful.
		Class-III: Not indicated, may be harmful.

Table - 4: Change in mortality after myocardial infarction during the 1960s to 1980s[1]

Time	Mortality (Conditional Probability of Death until end of period)		
	1960s	1970s	1980s
In hospital	0.29	0.21	0.16
1 month	0.0282	0.0506	0.0238
5 years	0.33	0.33	NA

[1] Source: Cumulative (In hospital and 1 month) and conditional probability of death (5 year mortality post discharge) data from de Vreede et al (1991) for all studies converted to conditional probabilities.

Table - 5: Efficacy[1] of interventions for treatment of myocardial infarction (MI) based on a metanalysis of RCTs[2]

Intervention	# of trials	N	Cum OR (Treatment vs controls)
Aspirin	5	19,077	0.77
IV thrombolytic agents (streptokinase, rtPA and APSAC).	60	46,916	0.75
IV vasodilators (nitroglycerine)	11	2,170	0.57
IV magnesium (anti arrhythmic)	7	1,304	0.44
Anticoagulants (heparin, warfarine)	7	4,075	0.78
Betablockers	51	31,669	0.88
Ca channel blockers	16	6,420	1.12
Prophylactic lidocaine	15	8,745	1.15
Secondary prevention			
Anticoagulants	12	4,975	0.78
Rehabilitation regimen	23	5,022	0.8
Betablockers	17	20,138	0.81
Cholesterol lowering	8	10,775	0.86
Antiplatelet agents	9	13,917	0.83
Ca channel blockers	6	13,114	1.01
Class-I anti arrhythmic agents	11	4,336	1.28

1 The end points are mortality up to a limit of three months. When a study reported more than one time period, the authors used the one closest to the time of hospitalization.
2 Source: Lau J, Antman Elliot M. et al. Cumulative analysis of therapeutic trials for myocardial infarction; New Eng J. of Med, July 23, 1992, p248-254.

Table - 6: Core technologies for management of myocardial infarction

Stage	Core technology	Bench mark trials / studies	Remarks
Prehosptial phase	Cardiopulmonary resuscitation (cardiac defibrillation)	The Belfast experience (Dalzell et al, 1987)	AHA
Hospital phase	Aspirin	ISIS-2 (1988)	AHA, Can
	Aspirin -Thrombolytics	ISIS-2 (1988)	AHA, Can
	Hparin - Aspirin - Thrombolytics	GISSI-2 (1990), ISIS-3	AHA, Can
	Aspirin-Betablocker Thrombolytics	ISIS-1 (1986), TIMI-2 (1989), MIAMI (1985).	AHA
	Aspirin-Betablcokers	Betablocker Heart Attack Trials (1982).	
	Heparin-Aspirin		
Post MI phase	Aspirin	Antiplatelet trialists collaboration (Acheson et al, 1988), ISIS-2 (1988)	AHA, Can
	Oral anticoagulants	Meta-analysis of RCTs by Chalmers et al (1977) , Lopez and Mehta (1987).	AHA
	Beta blockers	Betablocker Heart Attack Study (1982), Norwegian Multicenter study (Pederson, 1985).	AHA, Can
	Cardiac rehabilitation		

Table - 7: Time from onset of symptoms to admission of MI patients in Mauritius

Time to Admission (Hours)	Frequency	Percentage	Cumulative percentage
2 or less	16	41.6%	41.65%
>2 and < =6	6	15.3%	56.4%
>6 and < =12	8	20.6%	76.9%
>12 and < =24	7	18%	94.9%
> 24	2	5.4%	100%
Median time to admission: 4 hours			

Table - 8: Time from onset of symptoms to admission of MI patients[1] in two major multicentric studies[2]

ISIS-2 (417 hospitals from 16 industrialised countries)				GISSI (176 Coronary care units in Italy)			
Time to admission	Number of cases	%	Cumula-tive %	Time to admission	Number of cases	%	Cumula-tive %
0-2	2,617	10.70%	10.70%	0-1h	1,275	12.35%	12.35%
3-4	4,845	19.82%	30.52%	0-3h	4,810	46.60%	58.95%
5-12	7,272	29.74%	60.26%	>3-6h	3,643	35.29%	94.25%
13-24	9,717	39.74%	100.00%	>9-12h	594	5.75%	100.00%
All	24,451	100.00%		All	24,451	100.00%	

[1] Source: Compiled from fig-3 of the ISIS-2 study cited in references.
[2] Source: Compiled from table-1 of the GISSI study report (1987) cited in references.

Table - 9: Cincinnati Heart Project

Transportation mode	Median time to admission
Private automobile	64 min
Local ambulance	55 min
Emergency medical system without pre-hospital ECG	50 min
Emergency Medical System with pre-hospital ECG.	30 min

Table - 10: MEDLINE Search Strings and number browsed

Intersection of text strings for search	# titles	# Abstracts	# of articles of relevance
MI & sudden cardiac death & VF	36	8	1
Ambulance & myocardial infarction	50	20	0
VF & MI & incidence	81	4	1

Table - 11: Reduction in risk of death due to myocardial infarction attributable to thrombolytic treatment

Studies	Time to admission	Sample size	Risk among controls	Attributable reduction in risk	% reduction in relative risk
GISSI (One year survival)	0-3 hours	6,085	0.173	0.022	12.72%
	0-6 hours	9,728	0.1874	0.0239	12.75%
	9-12 hours	10,322	0.1873	0.0239	11.01%
ISIS-2 (In-hospital survival)	0-4 hours	7,467	0.123	0.041	33.33%
	0-24 hours	17,187	0.12	0.028	23.33%

Table - 12:Reduction in risk of death due to myocardial infarction attributable to early beta blocker treatment without any thrombolytics

Studies & sample size.	Time period	Risk among controls	Attributable reduction in risk	% reduction in relative risk
ISIS-1 (1027)	0-7 days	0.0457	0.0068	14.88%
	7-365 days	0.07	0.006	8.57%
MIAMI (700)	0-15 days	0.049	0.043	12.25%

Table-13: Potential DALY[1] gain for people with AMI [2]from adoption of practice guidelines[3] and medical compliance[4].

Med Compliance	DALY gained per AMI case receiving treatment			Incremental DALY gain in economically developing World	
	Absolute	Marginal	Incremental	DALY	% of IHD Burden
0.6	6.5				
0.65	7.09	0.6	0.6	2,974,407	5.0%
0.7	7.63	0.5	1.1	5,651,373	9.5%
0.75	8.2	0.6	1.7	8,540,797	14.4%
0.8	8.73	0.5	2.2	11,175,271	18.9%
0.85	9.29	0.6	2.8	13,979,712	23.6%
0.9	9.84	0.6	3.3	16,741,661	28.2%
1	10.92	1.1	4.4	22,138,085	37.3%

[1] AMI incidence of 5014 thousand cases in developing countries around 1990 taken from GBD-1996 estimates (Murray and Lopez, 1996). DALY lost by the developing countries due to AMI, according to the same estimate was 59276 thousands.

[2] Medical management of AMI is assumed to reduce disability by 60% compared to untreated.

[3] Effect of aspiring and thrombolytics, which are at the core of medical management reduce mortality by 40% based on ISIS-1, 1988.

[4] Patient compliance is assumed 100% since these are hospitalised cases

Table-14 Potential DALY gain for people with AMI from increased in access to medical care services for IHD patients[1].

Coverage	DALY gained per person affected by AMI			Incremental DALY gain in economically developing World	
	Absolute	Marginal	Incremental	DALY	% of IHD Burden
0.25	2.5				
0.3	3	0.5	0.5	2,464,328	4.2%
0.4	4	1	1.5	7,424,987	12.5%
0.5	4.9	1	2.5	12,364,311	20.9%
0.6	5.9	1	3.5	17,335,638	29.2%
0.7	6.9	1	4.4	22,274,962	37.6%
0.8	7.9	1	5.4	27,224,953	45.9%
0.9	8.9	1	6.4	32,174,945	54.3%
1	9.9	1	7.4	37,135,604	62.6%

[1] Footnotes for table-13 apply here as well.