IMPROVING THE OUTCOMES FROM ACUTE CORONARY SYNDROMES: IMPORTANCE OF THE PATIENT AND THE SYSTEM

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MAY 4, 2007

*This is to acknowledge that Dr. Atkins (**has**/has not) disclosed (any) financial interests or other relationships with commercial concerns related directly to this program. Dr. Atkins (**will**/will not) be discussing off-label uses in his/her presentation.*

Over the last five decades, there has been a significant change in the management of patients with acute myocardial infarction and the other acute coronary syndromes. With these changes the apparent mortality and morbidity has been reduced. In the 1950's mortality from an acute myocardial infarction was said to be about 25% in patients who did not have shock or pulmonary edema. By the mid 1960's the mortality was about 18% for these patients. By the late 1960's it had fallen to 12%. Today the mortality is between 4.5 and 6% for this group of patients. Though it is easy to contribute all of this to improved care, some of it is due to patient selection. In the 1950's acute myocardial infarction was diagnosed by the presence of Q waves and ST elevation in a patient with chest pain. Left bundle branch block was also considered diagnostic. Later people began using white blood counts, sed rates, and temperature curves. Analysis of the enzyme AST was added by 1960. Clearly this was a different subset of patients than what we call infarction today when we use sensitive and specific markers. Thus it is difficult to state how much of the reduction in mortality and morbidity is due to changes in definition and how much is due to improvements in care. My belief is that improvements in care accounts for at least half of the reduction in mortality. It should be noted that President Eisenhower was treated with state of the art care when he had an infarction during his presidency. That care included walking him a mile to a car, transporting him to the hospital and then keeping him at strict bed rest for three weeks. There were no monitors or any other significant therapy at this time. Even blood pressure control was not usually achieved.

The various syndromes produced by acute cardiac ischemia present many challenges to primary care physicians and emergency physicians. Acute cardiac ischemia can present with any of three major syndromes - sudden cardiac death, acute myocardial infarction, and angina pectoris (stable or unstable). In patients with asymptomatic coronary atherosclerosis, the first symptom of acute cardiac ischemia is sudden death in about 25% of patients, acute myocardial infarction in about 45% of patients, and angina pectoris in the remainder of the patients.[1-3] A small percentage also present with heart failure. The importance of time, accuracy, and costs must permeate decision making when dealing with a patient with chest discomfort. Time also becomes a critical determinate in the outcome of cardiac arrest victims.

The critical nature of time is obvious when the patient suffers a cardiac arrest. When out-of-the-hospital cardiac arrest is examined, 93% of the long term survivors had witnessed cardiac arrests and ventricular fibrillation.[4-6] Time to defibrillation and CPR seem to be the most important determinants of survival. Several different studies have shown that time to defibrillation, time to CPR, as well as time to ACLS (epinephrine) are very critical. The shorter each of these key times intervals, the greater is the survival. This is important as the initial clinical presentation of coronary artery disease is sudden death in 25% of patients.

Time is also a critical factor when dealing with a patient with an acute myocardial infarction. Obviously a patient with an acute myocardial infarction can have a cardiac arrest at any time. With the advent of thrombolytic therapy and more recently with acute PCI (percutaneous coronary intervention) of the occluded artery in infarcted patients, time to

treatment has also become very important. Tiefenbrunn and Sobel[8-10] have shown the critical nature of time in both animal and human data after thrombolytic therapy. The animal and human thrombolytic data are very consistent, showing a very time dependent benefit curve with the major benefit is in the first two hours. The benefit of thrombolytic therapy appears to be both increased survival as well as salvage of myocardial performance. By pooling many studies Granger, Califf, and Topol[11] have shown a significant increase in ejection fraction; however, the increase in ejection fraction was small. When very early thrombolytic therapy is examined there is a marked improvement in survival and a large salvage of myocardium. The MITI trial[12] has shown that thrombolytic therapy given within 70 minutes of onset of pain can reduce mortality with acute myocardial infarction to less than 1% and can reduce the amount of tissue lost to 0-1% of muscle mass in 40% of patients and to 2-10% loss of muscle mass in another 40% of patients. Thus, very early, muscle mass can be salvaged. At 30 days mortality was 1.2% in those treated within 70 minutes versus 8.7% in those treated after 70 minutes with thrombolytic therapy; infarct sizes were 4.9 and 11.2 respectively. At two years follow-up, the group treated with 70 minutes had a 2% mortality and 65% event free survival while the group treated after 70 minutes had a two year mortality of 12% with a 59% event free survival.[12a] It appears that in the first 1-2 hours the major benefit of thrombolytic therapy is through myocardial salvage. After the first two hours, other mechanisms play a role, possibly through open artery and collateral development or remodeling.[8-10]

Therefore, it is obvious that time to treatment is very critical when looking at many of these patients. When we closely examine the time to treatment issue, there are three major sets of interactions that determine the amount of delay to treatment. The patient must make a decision to obtain medical care. As the patient frequently asks a lay person for advice, this has been called the patient/bystander portion of the delay. Once the patient decides to obtain medical care, there is the transportation phase or emergency medical service phase if that is used. Once the patient has arrived at the hospital, there are further delays; these delays are usually in the emergency department.

There have been a number of studies that look at the time from onset of symptoms until patient arrival at the hospital. The mean arrival time in a number of studies has varied from 4.6 hours to 24 hours (Table 1).[13-19] However, it is inappropriate to use mean times. For example, if nine patients arrive at the hospital within 15 minutes and the tenth patient arrives 48 hours after onset, the mean time is five hours. Therefore, median times are more important. The median times have generally been between two and four hours with a couple of exceptions.[13,15-24] The two exceptions are the studies by Cooper,[16] which was a study of inner-city African-Americans, and the study by Hofgren,[19] which studied delays in 47 selected patients in a Swedish Hospital. When the data was analyzed to identify the number of patients who delayed more than a given time, 26% to 44% of the patients with an acute myocardial infarction delayed more than four hours.[18,24-25] Hence, the majority of patients arrive at the hospital within four hours of onset of symptoms. However, this time is still very long to achieve the maximum effectiveness of thrombolytic therapy. Also, many patients develop a cardiac arrest within this delay time.

Table 1. Delay Time from Onset of Symptoms until Hospital Arrival

Reference	N	Mean (hours)	Median (hours)
Hackett, 1969[13]	100	10.6	4
Moss, 1969[14]	64	4.6	-
Moss, 1970[20]	160	-	3.5
Simon, 1972[21]	160	-	2.75
Schroeder, 1978[15]	211	7.6	3.5
Alonzo, 1986[22]	1102	-	2.2
Cooper, 1986[16]	111	21-24	6.4
Turi, 1986[23]	778	-	2
Rawles, 1988[17]	450	10	2
Wielgosz, 1988[18]	201	7.5	3.2
Hofgren, 1988[19]	47	19.6	4.8
Leitch, 1989[24]	100	-	2

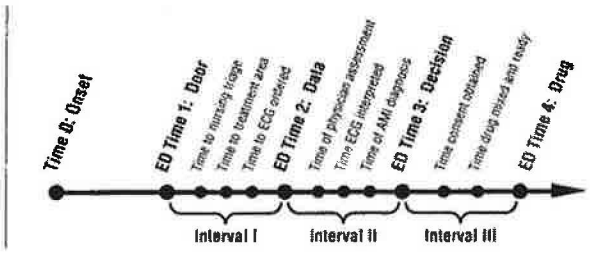
Unstable angina pectoris and recent onset angina pectoris may also be time dependent emergency situations; however, there is little information to clearly identify the importance of time. A few patients with unstable angina pectoris go on to have an acute myocardial infarction or sudden death. A few remain unstable. Most patients with unstable angina quickly quiet down. Though it is our general feeling that time is critical in patients with unstable angina pectoris, this can not be documented.

When you are dealing with chest pain syndromes, two other factors become very important - accuracy and costs. For every 12-15 patients who present to the emergency department or the emergency system with chest pain, only one has an acute myocardial infarction and another one has acute cardiac ischemia without myocardial infarction.[12,26] Because only two patients out of 12-15 have significant disease, it is too costly to do a complete workup on each of the patients. However, if you miss significant disease, sudden death may occur. "Missed myocardial infarction" is one of the most common reasons for a malpractice suit against an emergency physician and one of the most common reasons for losing a malpractice suit. The internist is also frequently sued for "missed myocardial infarction." Thus, the accuracy of the diagnosis is critical. The patient coming to the Emergency Department for chest pain but not having significant disease is a very large expense area for the insurance provider. The insurance provider therefore wishes to limit testing on these patients. The following is a discussion of some of the problems and pitfalls in dealing with acute cardiac ischemic syndromes.

EMERGENCY DEPARTMENT

The Emergency Department has many potential and real problems that can cause delays in the time to thrombolytic or other therapies. This delay time in the Emergency Department is due to many factors. The method of organization of the Emergency Department has been responsible for some of the delays. Patients with chest pain generally go through the registration system and are evaluated by a nurse who may order Fig 1. Emergency Department

delay times[9-10] an ECG. They are then evaluated by a physician who is caring for other patients. In many studies the average time after entry into the system has been two hours. In the Seattle studies, the time before pre-hospital information was provided was 144 minutes. When information was obtained in the pre-hospital environment, the delay time was reduced to 72 minutes.[27] Seattle has shown that obtaining the ECG in the field and transmitting the ECG to the hospital allows the decision for thrombolytic therapy to be made by those physicians present in the Emergency Department and can reduce the time to thrombolytic therapy by 73 minutes in a comparative evaluation. In a large series from multiple hospitals, Kline et al[28] showed that in 1,423 patients the median time was 70 minutes from the time the patient came to the Emergency Department to the time the patient had thrombolytic therapy started. The National Heart Attack Alert Program (NHAAP)[9-10] of the National Heart Lung and Blood Institute of the NIH has published guidelines suggesting that the median door-to-needle time should be 30 minutes or less. When these guidelines for door-to-needle time were published, there was a lot of discussion as to whether they were achievable, with some very strong descent. Gonzalez et al[29] showed that the median time could be reduced to 46 minutes in a multi center study. Several hospitals have achieved major reductions in this time. By taking a very aggressive approach to thrombolytic therapy, median times of 21 to 23 minutes have been achieved in a variety of community and public hospitals (personal communication Maine Medical Center, HCFA CCP project).



It is obvious that if PCI/thrombolytic therapy is going to have its best effect, the patient must be handled in an expeditious manner. The present organization and overload in many of the Emergency Departments of our hospitals have to be examined. The NHAAP has stated that there are four deadly "D's" that have to be evaluated.[9-10] The four "D's" are the four key times that can easily be measured that relate to the speed of administration of thrombolytic therapy. The times are the Door time (time of arrival at the Emergency Department), the Data time (time that the ECG is obtained along with a brief history and vital signs), the Decision time (time the physician decided to give thrombolytic therapy) and the Drug time (the time the thrombolytic therapy was actually given to the patient). Figure 4 shows some of the things that are happening in each of these time intervals. For the times to be minimized, hospitals must develop adequate quality improvement systems that analyze the delays and to try and develop methods of decreasing the delays. Known delays in an institution must be alleviated. Patients with acute cardiac ischemia should bypass many aspects of the registration system. They should immediately be taken to the appropriate patient care area and have immediate vital signs, limited history, and an electrocardiogram. The electrocardiogram should be done expeditiously. The electrocardiogram should be shown immediately to the physician in charge of the patient, and the physician should immediately make a decision on whether the patient is having an acute myocardial infarction. If the patient is having an acute myocardial infarction, the

patient should be immediately evaluated to see if the patient is a candidate for thrombolytic therapy or for acute angioplasty. If the patient is a candidate for therapy, an immediate decision should be made by whoever is present to proceed with the therapy. Do not wait for a consultant to come and see the patient. If the physician is unsure about the ECG, then fax a copy to the cardiologist and make a decision over the telephone. Too much time is wasted repeating key information. The thrombolytic drug must be available in the Emergency Department and should be begun as fast as possible as an emergency procedure.

Another consideration is transmission of a 12-lead ECG from the ambulance to the Emergency Department. Seattle has reported that when the physician at the hospital knows the history of chest pain and has an electrocardiogram showing the infarction, the time until the administration of thrombolytic therapy is greatly decreased. These might also give some time for notification of the admitting physician, so that the admitting physician in some cases could be available when the patient arrives in the Emergency Department. These changes should be considered.[9-10,27,30-31]

EMERGENCY MEDICAL SERVICES

The development of modern emergency medical services in the United States was sparked in the late 1960's and early 1970's by the occurrence of several different factors. The year 1966 was a pivotal year in the development of emergency medical services. The National Academy of Sciences, National Research Council issued two major policy statements. The first dealt with trauma, the neglected disease.[32] The second contained the recommendation that health professionals learn cardiopulmonary resuscitation.[33] The development of CPR followed Dr. Kouwenhoven's description of closed-chest cardiac massage in 1960.[34] Also in 1966, the first battery powered defibrillator that was portable (74 lbs) became available. Over the next five years, many governmental agencies developed standards for training, ambulances, and every aspect of pre-hospital care. The American Heart Association developed training programs in resuscitation. The American College of Surgeons developed standards for trauma facilities. The American College of Orthopedic Surgeons developed training courses for a new breed of personnel: the Emergency Medical Technician - Ambulance. These factors pushed the development of emergency medical services from many angles. On the other side, the old system of multiple ambulance companies usually owned by funeral homes was starting to collapse for many different reasons. People began to expect that an ambulance would come to their aid within 10 minutes, not 30 minutes. There was an increased recognition by the public that there was a better system for treating patients.

Between 1969 and 1973, the pioneers in this field - Pantridge from Belfast, Cobb from Seattle, Nagel from Florida and Baltimore, Grace from New York, as well as many others - showed that patients could be resuscitated in the field and could later return to a useful, functional life. Successful resuscitations were demonstrated at large gatherings of people, such as at football games.[35-39] Pantridge and others in Ireland and Britain published data that physicians and nurses on board the ambulances could salvage a number of patients in the field.[40-47] In the United States, Grace also showed that patients could be resuscitated in

the field.[48-49] A number of studies, particularly in the United States, demonstrated the effectiveness of telemetry of electrocardiograms, which brought about the establishment of paramedics and nurses providing pre-hospital care without a physician being present.[50-56] Finally, the success of these systems was demonstrated by Crampton, Nagel, Pantridge, Cobb, and others.[37,57-67]

In order for there to be rapid delivery of emergency medical services, there must be rapid access, effective dispatch, and rapid transport to an appropriate facility.

Access -- Time is a critical factor for the cardiac patient, both from the standpoint of cardiac arrest and from the potential administration of thrombolytic therapy. It is essential that access to emergency medical services be uniform and quick. A single, nationwide emergency number for emergency services - fire, police, and medical is essential; and the number should be the same - 911. Today 75-80% of the population are covered by 911. There are two types of 911 systems available. One version is the phone number 911 that connects the caller with an operator or dispatcher. A more sophisticated version is the enhanced 911 system that has automatic identification of the caller's telephone number and address. This latter variety has great advantages when dealing with an emergency situation in which people may not be able to communicate calmly the information required to obtain an emergency response. An enhanced 911 system should be a goal.[68-69]

Dispatch -- Centralized dispatch is required to provide fast and efficient emergency medical services. With a centralized dispatch, a quick and efficient response can be obtained by insuring that the closest available unit or units would respond. This is particularly important in areas where there are multiple agencies providing similar or the same service. The dispatcher should be trained to determine what services are needed. The need for centralized dispatch can also be illustrated by the requirements for a cardiac arrest victim. A cardiac arrest victim needs quick and efficient CPR as well as defibrillation. Two individuals on an ambulance cannot quickly and efficiently handle a cardiac arrest victim; but with centralized dispatch of an integrated system, a fire engine or other First Responder could be sent to provide CPR and early defibrillation with an automated defibrillator, while the paramedic crew can provide the drug and other advanced therapy required in a rapid, efficient manner. For dispatch to be effective, dispatchers need to be trained. There is a need for EMD's, Emergency Medical Dispatchers. These dispatchers can determine the types of equipment and personnel required for the problem and can even provide first aid via the telephone. It has been shown that untrained telephone callers can be told how to do CPR until the system can respond. Thus, trained personnel can greatly improve the quality of dispatch.[70 -79] Efficient, centralized dispatch with trained dispatchers should be a national goal.

Pre-hospital 12-lead electrocardiograms for cardiac patients -- One recent advance in technology that may well change a number of factors is the use of 12-lead electrocardiograms in the pre-hospital arena. Paramedics can be taught to quickly perform ECGs both accurately and quickly. High quality 12-lead electrocardiograms with computerized interpretation can be transmitted by cellular phone or radio. This will be useful to the receiving hospital. If the receiving hospital has a 12-lead ECG that reveals an

acute myocardial infarction along with appropriate history, the personnel in the hospital can be ready to give thrombolytic agents, beta blocking agents, nitroglycerin, or other agents as soon as the patient arrives - rather than being delayed while the hospital obtains that data after arrival. This will be of benefit. Seattle has shown that this is of marked benefit to the patient, greatly reducing the time to thrombolytic therapy and decreasing the morbidity and mortality.[12,80-81] We have obtained the equipment needed to perform 12-lead electrocardiograms in the Dallas paramedic program. To date we have done over 300 ECGs that have been reviewed. The quality of the ECGs is very good. Eighteen of the 300 ECGs have shown a definite acute myocardial infarction. Talking to the hospitals involved with several of these patients, the 12-lead ECG made a major difference in the care of the patient. In three cases, the pre-hospital ECG changed either the therapy that was given to the patient or greatly reduced the time to thrombolytic therapy. The Dallas area fire departments have a computerized ECG transmission system at the present time and we are trying to develop the technology to email it to the Emergency Department and possibly to the cell phone or PDA of the cardiologist on call.

PATIENT/BYSTANDER ACTIONS

Case (Presented with permission of the patient)

This is a faculty member in the Department of Surgery who presented more than 20 years ago with an acute inferior myocardial infarction. He noticed a brief tightness or lump in his throat the evening before admission. The next morning he came to the hospital and was beginning to scrub when the tightness returned, he decided not to scrub, he went to his office, and he called another surgeon who took him to the student health service (our only UT clinic at the time) obtained an ECG and paged me. The ECG showed an inferior myocardial infarction and he was taken to the ED and admitted to the CCU. The amount of time between his call to his surgical colleague and arrival in the ED was less than 30 minutes. About 10 years later, he had the onset of the same symptoms while attending a Christmas party in the faculty club. As he did not want to upset his wife, he drove her home and called me. I had him call 9-1-1 and he was transferred to Parkland. Even though he realized what was happening the second time, he delayed obtaining care for a longer period of time than with his first event. He is still active and assures me that if he ever has another event he will act more rapidly.

No matter how great a system is organized, the patient must access the system. It is obvious that until the patient or bystanders decide to access the system, nothing can be accomplished. With cardiac patients, the patient may not realize that there is a problem. There is a major problem with access; the patient and the bystander must make up their minds that access is needed. Certain factors have been shown to vary the time the patient delays before obtaining health care. These factors are summarized in Table 2.

Table 2. Factors That can Vary the Delay Time

Factors that may increase the delay time

- Older age
- Female gender
- African-American race
- Poor socioeconomic condition
- Lay consultation with spouse/friend
- Medical consultation
- Daytime onset of symptoms
- Being at home
- Stable angina
- Diabetes mellitus
- Self-treatment

Factors that may decrease the delay time

- Recognition of cardiac origin
- Severe pain
- Hemodynamically unstable
- Large infarct size
- Education?

Factors that do not change the delay time or are variable

- Day of the week
- Previous myocardial infarction
- Congestive heart failure
- Hypertension
- Known coronary artery disease

Though many studies have not found an effect of gender on the delay time, most of these studies have very few women.[13,15,20,82-87] Two studies have enough women to make a judgement of the effect of gender on the delay. Turi[23] found that the mean arrival time of women was 3.2 hours, while the arrival time for men was 3.0 hours. However, mean times can be very misleading. Alonzo,[22] in the largest study, revealed that the median time for arrival of women was 47 minutes longer than for men. This was due to a markedly prolonged self-evaluation time in women. One fascinating effect of gender on the delay was when men informed their wives of the symptoms - informing a wife greatly increased delay time.

The effect of race has not been well studied. Most of the studies have been in middle and upper income white males. One study has been quoted as showing that African-Americans have a decreased delay time; however, there were only four African-American patients out of 47 patients.[84] The largest number of African-American patients was in a study by

Cooper,[16] in a poor and working class neighborhood in Chicago. These patients had a markedly prolonged delay time, with a median of six hours and mean times of 21-24 hours. However, Turi[23] found no difference between whites and non-whites. The breakdown of the non-whites was not given. Alonzo,[22] in the largest study, found that African-Americans had a longer delay, which was mainly due to younger African-American males trying to find a physician. The studies looking at race as a factor have looked at selected populations; there is insufficient information to draw proper conclusions. There is a need for research into the effects of different cultural groups in obtaining care.

Socioeconomic status has not been a factor in a number of studies.[13,18,21,83-84] However, these studies compared middle and upper income groups and did not contain truly disadvantaged groups. Cooper[16] found that the time was very long in a poor African-American population; but whether this was an African-American cultural effect or an effect of low socioeconomic status can not be determined. The one study that had proper balance between groups showed that low income greatly increased delay time as an independent predictor.[88-89]

Higher education does not have any effect on the delay time in a number of studies.[14,18,21,23,88,90] Lower education levels, less than high school graduation, caused a decrease in delay time in one small series.[84] Education about the signs or symptoms has not influenced delay time in some studies.[25,89] However, these studies have been short-term studies. The longest study in Gothenberg, Sweden did show that a mass education campaign could reduce delay times.[91] It should be noted that anti-smoking campaigns, cholesterol campaigns, and hypertension campaigns did not show any changes in behavior in the three to six months of the early studies. It was usually only after repeated campaigns over years that a change in behavior was seen. Short campaigns can change awareness of a problem, but it takes constant repetition over the years to modify behavior. For this reason, we have little information to understand how behavioral modification occurs in cardiac patients or any understanding of what would be required to modify behavior.

One study of personality traits showed that Type A personalities were slow in labeling their symptoms as cardiac in origin. Once Type A's did recognize that the symptoms were cardiac in nature, they rapidly obtained medical care. Type B personalities more quickly identified their symptoms as cardiac, but they were slow in obtaining medical care. Thus, overall, there was no difference in different personality types.[84]

The clinical status of the patient had an effect on delay time in some patients. Patients who were hemodynamically unstable had significantly decreased delay times.[23,85] Patients with large myocardial infarctions also had shorter delay times.[19] Overall severity of chest pain did not effect the delay.[19,85] However, for those with sudden onset of chest pain, increased severity did decrease the delay time.[13,22,88] Those patients who recognized that their symptoms were cardiac had a shorter delay, while those who thought their symptoms were gastrointestinal or pulmonary had a longer delay.[19]

The majority of studies has shown that a past medical history of cardiac disease either had little affect on delay times[13-14,18,21,23,85] or increased the delay times.[20-21,23] A history of

previous myocardial infarction had no affect on delay times.[12-15,19,23,] History of coronary artery disease without infarction or congestive heart failure also did not have an effect on delay times.[15,21] Stable angina and angina with increasing severity prolonged the delay time.[15,21] Diabetes mellitus also increased the delay time.[20,23] Hypertension has had contradictory results, showing both an increase and a decrease in delay time.[13,23-24]

Most studies have looked at the patient's characteristics and ignored the role of third parties associated with the patient. Alonzo[22] has shown in a study of 1102 patients that 93.2% of the patients received lay consultation from a witness. Patients who make the decision by themselves[14,19] have a markedly shorter delay time than those who ask a family member about the symptoms.[13,22] As the most common lay consultants are family members, this causes the median times to increase from two hours to 12 hours in one study. The shortest delay occurs when an unrelated person assists in making the decision. The motivations for these delays by family members, friends, and co-workers are not clear. A common wish to deny the symptoms may play a role. Also, there may be an unwillingness of family, friends, or co-workers to confront the patient and push for early intervention. This may explain why family members and friends allow more delay than co-workers, while strangers allow very little delay.

Consulting a physician can also greatly increase the delay time.[15,18,21-22,24] The reasons for this delay are varied. Sometimes the physician orders therapy or denies that the patient could be having trouble. Sometimes the call is returned hours later or the office staff fails to have the patient go to the hospital.

Self-treatment by the patient significantly increased the delay time.[19,21-23] The patient frequently took over-the-counter medications or prescriptions and waited for the desired response. Delay time was particularly prolonged if the patient felt the symptoms were gastrointestinal and self-treated the symptoms. Americans tended to wait longer if the symptoms occurred during the day,[15,20,22] while British waited longer at night, and it made no difference to Canadians. The weekend has been shown to both increase and decrease the delay time.[14,18] Heavy exertion at the onset of pain has been shown to decrease the delay.[22] Place had some effect on delay times.[22-23,88] Those who had onset away from home and then went home had the longest delay. Most studies did not have many patients who had onset at work, though it appears that patients at the work site had shorter delays unless the patient went home.

Realizing that there are many complex reasons for these delays, then it makes sense to try and develop educational programs for the patients and most importantly the patients' families as the family often gives advice on whether to obtain medical assistance. The method of educating the family is not known. One major problem is that more patients may come to the Emergency Department with education and further overload the Emergency Department and increase health care costs. Dr. Goldman (personal communication) estimated five years ago that this would greatly increase cost; however that was based on three day hospitalizations. Now that patients usually are ruled out for acute cardiac ischemia with 23 hour observation status or less, the costs are less but significant. The other major problem is in the area of diagnosis. Diagnosing acute cardiac ischemia is

difficult at best. The remainder of this discussion will deal with problems in diagnosing acute cardiac ischemia when first seen in the Emergency Department or the physician's office.

Patient Presentation

From the Framingham study and necropsy studies, clinically unrecognized, or silent myocardial infarctions, comprise between 30 and 40% of all myocardial infarctions (Table 3).[82,92-94] In the Framingham study, serial electrocardiograms revealed a 30% incidence of unrecognized transmural myocardial infarction. Half of these unrecognized myocardial infarctions had absolutely no symptoms when retrospectively questioned, while the other half had symptoms that would be very difficult for the patient to recognize so that the system could be accessed.[92-94] Similarly, it is not possible for a cardiac arrest victim to recognize and access the system himself; so only the one-half of the victims who have a third party witness can receive rapid access. Though it might be possible to develop portable monitors to recognize cardiac arrest or ST segment changes and sound a warning to the patient or alert EMS, this approach is very impractical. Thus, one-third of myocardial infarction and one-half of cardiac arrest victims will not receive rapid entry into the health care system, even if all other factors could be controlled. Efforts must be expended to try to improve the system for the remaining patients.

Table 3. Ten-Year Incidence (Rate per 1000) of Myocardial Infarctions Among 2272 Men and 2845 Women at Risk, According to Age and Sex*

	Men		Women	
Age	Unrecognized Infarcts	All Infarcts	Unrecognized Infarcts	All Infarcts
30-34	2.6 (28.6)	12.9	0.0 (0.0)	2.2
35-44	6.5 (17.9)	38.2	2.6 (41.2)	5.2
45-54	16.6 (25.4)	71.2	2.9 (30.5)	13.0
55-64	28.2 (29.1)	107.9	17.9 (34.7)	47.1
65-74	53.8 (41.9)	141.0	21.3 (35.7)	55.7
75-84	60.2 (33.3)	12.8	34.0 (45.5)	128.3
TOTAL	(27.7)		(34.7)	

*Figures in Parentheses Indicate Per Cent of all infarctions that are unrecognized
Kannel. N Engl J Med 1984;311:1144.

Hence, the sensitivity of our most important determinant for starting a workup of acute cardiac ischemia, chest pain, is only in the 65%-73% range. It must be recognized that a significant number of patients are missed and will continue to be missed with any present technology as they do not have a symptom that will even prompt them to obtain help.

Cardiac pain or discomfort is visceral in nature. Visceral pain or discomfort have several

problems
that are well known. The symptoms are very difficult for the patient to interpret, causing delays and misjudgments and poor descriptions. Further visceral pain or discomfort is commonly seen in patients with all types of gastrointestinal ailments. The ability of the patient to differentiate between these different types of visceral pain is poor. Patients with known disease in both systems often have difficulty telling which type of pain they are having. Patients with angina pectoris frequently have hiatal hernia, another very common disorder. Many patient have difficulty telling the difference between the symptoms of reflux and the symptoms of angina pectoris. This points out a major problem with visceral pain.

Patients presenting to the emergency department Dr. Harry Selker and co-investigators evaluated various aspects of the presentation in a large number of patients presenting with acute coronary syndromes. They defined acute cardiac ischemia as either acute myocardial infarction (AMI) or angina, either new onset or unstable angina. The data was compiled by the Center for Cardiovascular Health Services Research (CCHSR). Data was obtained from two major urban teaching centers, two teaching-affiliate hospitals in smaller cities, and two rural non-teaching hospitals. The inclusion criteria were men 30 years of age or older and women 40 years of age or older. All patients had presented to the hospital Emergency Department with chest pain, arm pain, stomach pain, shortness of breath, or dizziness. The diagnosis of acute cardiac ischemia or not was the discharge diagnosis after workup. The study was comprised of 5,768 patients of whom 56% were men.

Chest pain was the primary symptom in only 45% of patients. Chest pain was a secondary symptom in 34% of patients. Hence, the sensitivity of chest pain appears to be 79% in this study. However, remember one-third of patients with an acute myocardial infarction never come to the hospital with an acute event; hence, the true sensitivity is 79% times 73%(the percentage not having silent myocardial infarction) or 58% in men, and 79% times 66% or 52% in women. This might be an overestimate of the sensitivity, as there is some bias of the physician who is working up these patients, and they may have excluded some as atypical chest pain; as the figures are calculated from final diagnoses. Arm pain was seen in 38% of patients with acute cardiac ischemia. Stomach pain and the primary symptom of shortness of breath or dizziness were not as important as chest or arm pain.

Then you start examining other portions of the history other than the quality of the present complaint, one must be very careful not to fall into a number of traps. There is not a substantive difference between men or women in their presenting complaints. Biases for or against the presenting complaints in women are not justified in this data. It should be understood, however, there may have been bias in making the original diagnosis that the data can not examine. Past history was not a strong predictor of who had disease. When you look at prior myocardial infarction or nitroglycerin usage in patients presenting with chest pain, the highest incidence of acute cardiac ischemia was in those patients with both a prior myocardial infarction and nitroglycerin usage (63%); while in patients with chest pain but neither prior infarction or nitroglycerin usage the incidence of acute cardiac ischemia with chest pain was 34%. When you look at the electrocardiogram, ST segment changes and peaking or inversion of the T waves did correlate with acute events.[26] The presence

of Q waves picked out patients more likely to have acute cardiac ischemia when combined with chest pain. Patients with chest pain and Q waves had a 69% incidence, while those with chest pain without Q waves had a 36% incidence. Patients with chest pain and LVH and RBBB did not have a higher incidence than the normal patients; patients with LBBB had a somewhat higher incidence as compared to normal. When you try combining many of these factors, you can identify some groups with higher versus lower risk; but the risk is substantial in both groups. If you look for a history of infarction or nitroglycerine use or Q waves or any combination of these three, 59% of the patients with chest pain had acute cardiac ischemia while patients with none of these had a 27% incidence. Diabetes also was a discriminating factor. Diabetics with chest pain had a 44% incidence, while non-diabetics had a 26% incidence. Combining diabetes with all of the other best factors does not help. Age, though it correlates with a higher incidence, is not a good discriminator.

Table 4 shows the odds ratios of a number of different factors in men and women for predicting who has acute cardiac ischemia. As can be see in this table, chest pain is the best discriminator of an event. ST segment elevation or flattening is the second best discriminator followed closely by T wave peaking or inversion. Risk factors and prior history were very poor discriminators. The reason for this is probably that patients who have had a prior event or are at high risk come in more frequently as they have just as difficult a time determining the nature of their symptoms as those with no history or risk factors. Patients with prior myocardial infarctions delay as long the second time as the first and they come in as often for symptoms that are non-cardiac in nature as patients with no prior history. The sensations that are visceral are difficult for the patient to interpret. People who have had prior events are more frightened of any visceral symptom.

It is apparent that people who come to the Emergency Department for acute myocardial infarction have problems making decisions about the significance of the event. This causes delays in obtaining care and greatly reduces the likelihood of achieving maximal benefit from the therapies that we are providing.

Table 4 Relative risks for acute ischemia of coronary risk factor reports and other presenting features

	Relative risk (95% CI)	
	Men (n=1008)	Women (n=735)
Risk factor reports		
Hypercholesterolemia	1.3(0.6-2.5)	1.1(0.4-2.8)
Diabetes	2.4(1.2-4.8)	2.0(0.9-4.2)
Cigarette smoking	1.5(1.0-2.4)	1.0(0.6-1.9)
Hypertension	1.0(0.7-1.7)	1.6(0.9-2.8)
Family hx MI	2.1(1.4-3.3)	1.2(0.7-2.2)
Family hx MI<age 50	1.5(0.7-2.8)	0.9(0.4-2.0)
Clinical variables		
Chest pain or pressure	12.1(5.3-27.6)	25.0(5.8-109.6)
ST Elevation or flat	8.7(5.0-14.8)	3.9(2.2-6.9)
T peaked or inversion	5.3(3.1-8.8)	4.0(2.2-7.4)

Jayes. J Clin Epidemiol 1992;45:621[26]

Patients presenting to the clinic A recent study evaluated patients in a large health care delivery system who had and acute myocardial infarction. The system cares for about 250,000 adult patients in 14 ambulatory centers run by the Harvard Vanguard Medical Associates. Between January 1, 2000 and December 31, 2004 there were 1523 admissions for acute myocardial infarction.[100] Nineteen patients had incomplete data and were excluded. Another 538 patient had known coronary heart disease with prior events, PCI, surgery, or positive studies and were not evaluated further. Thus 966 patients with an acute myocardial infarction were naïve to the diagnosis. It would be anticipated that this group of patients would have more problems identifying making decisions about their care. Of these patients, 705 went directly to the hospital and 155 went to their physician and were sent to the hospital. Thus, the majority of these naïve patients went to the hospital directly when they had a health care system available. They may have had problems identifying the need to obtain care causing delay but made the correct choice in determining where to go. There were an additional 106 patients that were seen and evaluated and were not admitted only to have an infarction within 30 days.[100] When the 106 patients who went to the clinic and were not admitted were compared to control patients who had the same outpatient discharge diagnoses; the cases with subsequent admissions for acute myocardial infarction were older (63.6 vs 49 years), male (63% vs 31%), diabetic (33% vs 9%), smokers (27% vs 16%), had a family history (30% vs 16%), had a higher systolic blood pressure (137 vs 127), a higher diastolic pressure (82 vs 79), a lower HDL cholesterol (45 vs 55), and a higher cholesterol (216 vs 206).[100] Thus, risk factors are important in evaluation patients who present to the clinic while they are not important in those present to the Emergency Department.

Patient utilization of EMS There is evidence of benefit of ambulance utilization in patients with acute myocardial infarction. Canto presented data from the NRMI date base in 2002 which included 772,586 patients treated from 1994 to 1998. He stated that patients arriving

by ambulance had a door to lytic therapy time that was 12.1 minutes faster. He also stated that the door to angioplasty time was 31.2 minutes faster. Many smaller studies have had similar results showing that patients entering by ambulance received faster therapy. There is a wide variation in EMS utilization from one area of the country to another. Of patients arriving at the hospital with AMI, use of EMS between 1989 and 2000 varied from 10-59% with the Pacific Northwest having the highest use of EMS. In Dallas it appears to be about 45%.

The REACT trial was an attempt to reduce the delay time through a public education campaign. Though the times declined in the cities where the public education campaign was run, the times also decreased in the matched cities where there was no public education campaign. Though there was no benefit of the public education campaign in reducing the delay time overall, a specific targeted campaign did increase usage of EMS. As a part of this study, Brown et al surveyed by telephone a large number of community members and asked them what they would do if the witnessed a cardiac event such as a heart attack. The interviewees responded that they would call 9-1-1 89% of the time. In reality when the usage rate was analyzed in these communities, only 23% used EMS. Someone else drove 60% of the patients and 16% of the AMI patients drove themselves to the hospital.[101]

When factors were analyzed to look at who used EMS when they had an acute myocardial infarction, there were a number of demographic factors that favored EMS usage.[101-103] Older age was a factor which greatly increased EMS usage; this might be because of lack of alternative transportation. This is supported by the fact that patients living alone were more likely to use EMS. In most areas of the country white ethnicity is more likely to result in EMS usage. In Dallas, there is an interesting variation. White and African American usage is about the same unlike most areas of the country; Hispanic and Asians are much less likely to use EMS when they have an event. Educational level and being in the presence of others increases the probability of using EMS.

Past medical history also affected EMS usage. Previous MI, congestive heart failure, angina, hypertension, and diabetes all increased EMS usage; this differs from older studies where these factors appeared to decrease EMS usage.[102-104] According to REACT surveys, reasons why patients do not use EMS include embarrassment and privacy issues, fear of upsetting other family members, patient s don't recognize symptoms or do not feel bad enough to call. Another significant factor is that patients may not be taken to the hospital of their choice. That is certainly a factor in the Dallas area.

Though an 18 month education program did not reduce patient delay, it was able to increase EMS usage by 20%. One method that has been shown to reduce time and increase EMS usage is the program in King County, Washington. They distributed "A Heart Attack Survival Kit" to 24,000 seniors with a doorknob kit. They compared this to 24,000 controls. There was a significant increase in EMS usage with the kit in the first year after the kits were distributed. During the second year there was a non-significant trend to greater usage.

IMMEDIATE Trial

PURPOSE: The purpose of this study is to test the impact of pharmacological myocardial metabolic support, in the form of intravenous (IV) glucose, insulin and potassium (GIK), for the treatment of patients with threatened or established acute myocardial infarction (AMI).

BACKGROUND: The era of reperfusion therapy for acute myocardial infarction (AMI) has yielded substantial progress in lowering short- and long-term mortality and morbidity from AMI. The key has been the understanding that the time to achieving reperfusion is a critical determinant of the magnitude of benefit; patients in whom complete reperfusion is achieved earlier have a significantly greater survival benefit.

The tight link between time to reperfusion and mortality has led to many national efforts, including National Institute of Health's (NIH) National Heart Attack Alert Program (NHAAP), aimed at minimizing "door-to-needle time" for reperfusion therapy. Moreover, efforts are also underway to educate the at-risk community to help achieve earlier arrival at the Emergency Department (ED) after the onset of symptoms. At some point, however, the maximum benefit to be accrued from such efforts will plateau.

A complimentary strategy, that has not been widely used, is to shift the time course of myocardial necrosis in the post-coronary occlusion setting, such that for any given time to reperfusion, smaller infarct size results. There is a substantial and compelling body of literature that suggests that metabolic modulation with a Glucose-Insulin-Potassium (GIK) solution can attenuate the unfavorable effects associated with hypoxemia and ischemia and may be a key to opening a wider time window for potential myocardial salvage from reperfusion therapy. Data from numerous animal experiments suggest that such metabolic modulation will diminish infarct size and attenuate the pathophysiologic insult from coronary occlusion. Small studies in humans, beginning over 20 years ago, suggest the possibility of similar effects. A recent multicenter trial of the use of GIK conducted outside the United States suggested favorable morbidity and mortality effects for AMI. Unfortunately, the number of outcome events was relatively small, making it under-powered to demonstrate mortality effects, and the study design did not take advantage of the full potential of GIK infusion, as GIK therapy was initiated up to 24 hours after AMI presentation. The results of the clinical trial however were in keeping with those predicted from a previously published meta-analysis reviewing the published smaller series. The full potential of GIK infusion as soon as possible prior to reperfusion therapy, based on data from models of coronary occlusion and reperfusion.

Moreover, compared to many treatments for Acute Coronary Syndrome (ACS), GIK is very inexpensive; a 1-liter IV bag of GIK costs about $20. Thus, if as effective as suggested by preliminary data, and if applicable to all ACS, it will be extremely cost-effective relative to other treatments.

CONCISE SUMMARY OF PROJECT: This is a multi-center, prospective, randomized, double-blind, placebo-controlled trial of administration of a 12-hour intravenous infusion

of GIK started in the emergency medical system (EMS) ambulance setting to subjects who are suspected of having symptoms consistent with ACS. Approximately 7,339 patients will be enrolled locally with a total enrollment of 15,450 expected over all study sites. Those patients considered to be having a threatened or established AMI will be identified by EMS paramedics in the field prior to transport to the receiving hospital. And, then, those within that group who meet the study entry criteria will be asked to participate in the IMMEDIATE Trial.

Prior to the first patient's enrollment, all paramedics in the system will receive training in Human Subjects Protection as well as extensive training on the study itself. They will be tested on their knowledge. This will be followed by a three month ramp-up process, where paramedics will complete the subject screening forms but not enroll patients or start study drugs, thus allowing study personnel to run Quality Control measures.

It was determined that exemption of informed consent in the prehospital setting, followed by written consent as soon as practical after hospital arrival, would best balance the needs for informed consent and unimpeded EMS care. The IMMEDIATE Trial qualifies for an exception of informed consent requirements for emergency research per 21CFR 50.24. Therefore, the Study Drug infusion may be initiated prior to obtaining full informed consent. However, the paramedic will inform the patient (and/or family member if available) of the study and the patient may inform the paramedic that he or she does not want to participate (opt out) prior to the initiation of the Study Drug infusion. Patients must be conscious to meet the eligibility criteria. Spanish-speaking individuals will only be asked to participate if the paramedic is able to communicate with the patient Spanish.

In the prehospital setting, the paramedic will read an Information Card to the patient. Patients may be aware of the Trial as a result of the public disclosure process. However, there will be some patients who will not have heard of the Trial. This notification will act as reminder to patients who had awareness of the Trial and as information and notification of the trial to those patients who are unaware of the trial. Patients will be able to exclude themselves from participation. The script will be provided to the paramedics on a laminated card and on the backside of the Screening Form to ensure availability and ease of use.

The paramedic will document on the prehospital patient care record and the Study Screening Form if the patient opts out of participation (declines) or not. The on-call IMMEDIATE Trial Research Staff member will be notified via page when a patient is enrolled and if Spanish-speaking, a Spanish-speaking researcher will be dispatched.

At the time of enrollment, patients will be randomized to receive a 12-hour IV infusion of either GIK or placebo. The GIK solution will contain 30% Dextrose, 50 units regular insulin and 80 mEq of potassium per liter. The placebo solution will contain 5% Dextrose. The study medication will be infused at 1.5 ml/kg/hour for 12 hours. The study medication will be contained in a "subject packet" that will contain three 1 liter bags. The first 1 liter bag will be administered using a pump in the prehospital setting. The two

remaining liter bags will be given to the receiving hospital's ER nursing staff and will also be administered using a pump in the hospital setting.

Follow-up full written informed consent will be obtained as soon as possible after arrival at the receiving hospital ED by the on-call IMMEDIATE Trial research staff.

The study staff (including paramedics and research assistants) will obtain written informed consent from the patient or the patient's legally authorized representative (LAR) at the earliest opportunity during the infusion, after arrival at the receiving hospital. If the LAR cannot be contacted, attempts will be made by the research staff to contact a family member and ask whether he or she objects to the patient's participation in the IMMEDIATE Trial. In addition, if at anytime the patient's condition improves and he or she is able to give informed consent, it will be obtained. If informed consent has not been obtained during the infusion period, attempts will continue until informed consent is obtained or the patient, LAR or family member declines to provide informed consent. Furthermore, in the event of a patient's death prior to obtaining informed consent, the Trial's research staff will provide information on the Trial to the subjects LAR or family member, when feasible. All attempts to contact the patient's LAR and family members will be documented and available to the site IRB at time of continuing review.

Data will be collected for 30 day, 6 month and 1-year post-treatment follow-up. **No patient visits will be required for study follow-up!** Data will be collected via telephone interview and chart review. A cohort of 550 patients from specified sites will be enrolled in the Biological Mechanism Cohort, and additional physiologic indicators, including left ventricular (LV) function, markers for ventricular arrhythmias, and biochemical tests will be assessed. We are NOT including the Biological Mechanism Cohort in this IRB application, but will make that application at a later time.

INVESTIGATIONAL DRUG INFORMATION

TRACKING SYSTEM

A secure web-based Study Drug accountability tracking system will be used for the IMMEDIATE Trial. The admixture pharmacy, CAPS, will login and enter the following information into the system for each Study Drug packet manufactured and shipped:

- Study Drug Packet number (enrollment ID)
- Location the Study Drug is shipped to, date shipped, and shipment tracking number
- Study Drug Packet manufacture date and expiration date
- Study Drug lot number

Our site (The Dallas Regional Coordinating Center) will:

- Register and confirm the receipt and condition of each Study Drug Packet received

- Specify the firehouse that each Study Drug Packet is distributed to and the date of distribution
- Record when Study Drug is destroyed and the reason (expiration)

Additionally, a Paramedic Research Coordinator, employed to work full-time on the IMMEDIATE Trial, will be responsible for the Study Drug Packet distribution, as well as for documenting and monitoring it in the electronic tracking system.

The electronic tracking system will have the following features:

- An interface with the electronic data capture system allowing for the Study Drug use information that is entered into the EDC system to on a daily basis be reconciled within the Study Drug Accountability system
- An audit trail that will record all changes and corrections.
- Reporting functionality: The Dallas Regional Coordinating Center, CAPS and the Coordinating Center will be able to generate reports that provide the following:
  - Status of Study Drug available at the Regional Coordinating Center, and at the firehouses. These reports will contain sorting features that will allow ordering by expiration date, enrollment ID numbers as well as a number of other key fields.
  - Follow the life cycle of a Study Drug Packet from CAPS, to the Regional Coordination Center, to the firehouse and use in patient, or disposal.

STORAGE

At the Dallas Regional Coordinating Center, Study Drug Packets will be stored at the Emergency Medicine Education offices in a secure, locked closet, developed specifically for that purpose. A supply will be distributed from the Regional Coordinating Center to the firehouses on a regular basis. Each EMS vehicle should have one Study Drug Packet on the vehicle for use, kept in the study drug case. A back-up Study Drug Packet will also be available on each vehicle with a supply maintained at the individual firehouses. These will be stored according to firehouse policies for storing drugs and controlled substances.

CAPS (the admixture pharmacy)

CAPS pharmacy in Atlanta, Georgia will manufacture and distribute all of the study drug. A Project manager at CAPS will oversee compliance with the manufacturing and distribution of the Study Drug. The Study Drug will be shipped priority overnight from Atlanta to the Dallas Regional Coordinating Center so that the supply can be easily maintained and replenished. CAPS is compliant with USP Chapter 797. CAPS' business focus and core competency are compounding sterile preparations. Their

quality system is designed specifically to meet the FDA and USP requirements.

STERILITY AND STABILITY DATA

All IV bags will be labeled with the date of manufacture and the expiration date. The stability and sterility data will be included in the Investigators Brochure. GIK is stable at room temperature for 30 days from date of manufacture.

STORAGE IN AMBULANCES AND INSURANCE OF PROPER STORAGE

The Study Drug Packets will be stored at room temperature in a padded, sturdy case on the ambulance and in accordance with regulations and standard procedures of drug storage on ambulances. The case will be used only for the IMMEDIATE Trial, and is labeled with the Trial logo for easy recognition. This case will also contain the IV pump and IV tubing to be used when infusing the Study Drug.

PATIENT INFORMATION TO GO ON DRUG LABEL

The paramedic will record the patient's name, date and time the insulin (or placebo) solution was added to the bag, and his/her initials onto each Study Drug IV bag.

CRITERIA FOR INCLUSION OF SUBJECTS:

1. Age ≥ 30 years

2. Symptoms of threatened or established AMI including, but not limited to:
   - Chest pain / discomfort / tightness
   - Arm, shoulder pain
   - Jaw pain
   - Epigastric discomfort
   - Shortness of breath

3. 12-lead ECG with 2 or more contiguous leads with ST elevation >1 mm, left bundle branch block (not known to be old), ST depression >0.5 mm, or T wave inversion or other T wave abnormalities (hyperacute T waves)

Why diabetics are not being excluded

Patients with diabetes are not being excluded from the IMMEDIATE Trial since glucose 30% is being infused with regular insulin. In addition, if a patient has an elevated blood glucose level, supplemental regular insulin may be given. Serum glucose levels will be drawn upon arrival to the ED, and at 6 and at 12 hours after initiation of the Study Drug.

The ECLA pilot trial enrolled 407 patients, including patients with diabetes mellitus. Patients were randomized to two different GIK dosing regimes high dose GIK (25% Glucose, 50 units insulin, and 80 mmol KCl per liter infused at 1.5 ml./kg/hr for 24

hours), and low dose GIK (10% Glucose, 20 units insulin, and 40 mmol KCl per liter infused at 1.0 ml./kg/hr for 24 hours) or control therapy. Of the 407 patients enrolled 64 had diabetes (type not specified). Serum glucose levels measured before, at 6, 12 and 48 hours after randomization were not statistically significant between patients receiving GIK or control therapy.[105]

Furthermore the DIGAMI Trial (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction), tested, in diabetic patients with AMI, whether prognosis was improved by intensive metabolic treatment with an insulin-glucose infusion, followed by multidose insulin treatment. The trial randomized 620 patients at an average of 13 hours after symptom onset. Treatment consisted of an insulin-glucose infusion for 24 hours according to a protocol; since an elevated blood glucose level was required for entry, insulin was often the sole intervention. This was followed by subcutaneous insulin 4 times daily for at least 3 months. Over a mean follow-up of 3.4 years, the control group mortality of 44% was reduced to 33% in the treatment group (relative reduction, 25%) (p=0.011). About half of patients received TT, and the treatment and control groups had similar rates of revascularization; these were thought not to influence the results of the insulin-glucose treatment.

In-hospital mortality was reduced more in patients with no previous insulin treatment and at "low cardiovascular risk" (44% of patients), for whom the in-hospital mortality rate was 12% among control patients and 5% for those receiving glucose insulin (relative reduction 58% [p<0.05]). The only adverse effects to the study treatment consisted of hypoglycemic episodes, resulting in 10% of patients discontinuing the insulin therapy over time. Thus, the DIGAMI Trial results suggest that insulin-glucose infusion can significantly reduce AMI mortality in patients with diabetes. It is noteworthy that the average time from symptom onset to start of insulin and glucose treatment was 13 hours in the DIGAMI Trial, late relative to the time-course of ischemic injury. By providing GIK much sooner after the start of ischemia, the IMMEDIATE Trial is expected to amplify such benefits as demonstrated in the DIGAMI Trial.'[106-107]

CRITERIA FOR EXCLUSION OF SUBJECTS:

1. End-stage renal failure requiring dialysis
2. Hemodynamically unstable (systolic blood pressure <100 mm Hg)
3. Rales present more than halfway up the back.
4. Patient is unable to comply with the requirements of study participation.
5. Subject is incarcerated (prisoner)
6. Patient is known to be pregnant or thinks she is pregnant

SOURCES OF RESEARCH MATERIAL: The data will be obtained from ambulance and hospital chart records, EKGs and laboratory specimens both taken en route to the hospital and during hospitalization, as well as follow-up interviews by telephone.

RECRUITMENT OF SUBJECTS: The trial focuses on providing GIK as early as possible in the treatment of AMI and threatened AMI. All patients seen in the EMS setting who present with symptoms suggestive of ACS and have a 12-lead ECG performed will be screened for eligibility. The paramedic, per standard of care, will do a brief clinical assessment of the patient, including assessment of the patient's renal, hemodynamic, respiratory, mental, and cardiac status. The paramedics will use a screening form to determine a patient's eligibility. For those patients identified by the paramedic as meeting the eligibility for inclusion, the paramedic will begin the process

POTENTIAL RISKS: It is recognized that even a carefully conducted trial of GIK used for threatened or established AMI will likely include some patients who do not truly have AMI or unstable angina pectoris (UAP). For such patients, it is important that they not have been put at discernible increased risk due to the infusion. Therefore, the GIK (or placebo) infusion will be terminated if an alternate diagnosis is made upon arrival to the ED. The paramedics operate under medical control, and can review any treatment issue with the overseeing physician and the ED physician upon hospital arrival.

The 12-hour study drug infusion is easily administered by a peripheral IV and is associated with few side effects. There is a risk of inflammation at the IV site that may cause some discomfort, and reports of significant phlebitis range from 2 -4%.

Because the infusion time period for which a patient is under the care and supervision of the paramedic is relatively short, the development of phlebitis will likely not occur in this period of time. The prehospital infusion will often last less than one hour and most often less than 30 minutes. Furthermore, precautions related to the infusion of the GIK solution in the EMS setting are being taken. The paramedics will use one of the 1-liter bags of Study Drug and infuse it via an infusion pump. The remainder of the infusion will occur in the hospital under the care of a nurse in a controlled setting. Per the protocol (section 4.6.7.1), the IV site will be monitored per standard procedures for a patient receiving a glucose and potassium solution. If a paramedic finds evidence of a developing phlebitis during the transport to the receiving hospital the IV site maybe changed. If an IV site change is required and cannot be done during transport. The study drug can be stopped temporarily and restarted when a new IV site is established. If a new IV site is not established the study drug will be permanently discontinued. However, the patient will have remaining tests and procedures performed per the protocol.

It is possible that the patient's potassium level may become elevated or lowered as a result of the infusion, which could result in palpitations, dizziness, or a change in heart rate or rhythm. It is also possible that the patient's glucose level may become elevated or lowered which could result in weakness or confusion if low, or weakness, dizziness, or thirstiness, if high. The rates of hypoglycemia range from 0.04-0.07%. The incidence

of hyperglycemia has not been reported but it is considered a potential adverse effect. In the CREATE ECLA trial hyperkalemia occurred in 4.3% of subjects receiving GIK.

The 12-hour infusion can lead to an accumulation of extra fluid that may require a diuretic, however, these patients are already being monitored for increased fluid levels in the face of having a possible AMI and those patients with significant extant heart failure (HF) will not be included. Approximately 0.1% of subjects with AMI treated with GIK needed treatment with a diuretic. Fortunately, such adverse effects are relatively uncommon.

All patients may consider it an inconvenience to be contacted by phone or mail at 30 days, 6 months and at 1 year.

Women who are known to be pregnant or think they are pregnant will be excluded from enrollment in this study. The incidence of ACS occurring during pregnancy is very low. Approximately 150 cases of myocardial infarction during pregnancy have been documented in the literature worldwide - predominantly anterior wall. Therefore, very few if any, pregnant women will meet the inclusion criteria for the IMMEDIATE Trial. However, it is possible that a pregnant woman could be enrolled in this study. This would only occur if the woman did not have any visible signs of pregnancy and did not know or think she was pregnant at the time of enrollment. As patients are being enrolled in the emergency prehospital setting a test to confirm a woman is not pregnant cannot be performed prior to enrollment in the study. The components of GIK (glucose, insulin, and potassium) are well known and are anticipated to be at physiological levels in the bloodstream. Therefore for the mother and for the fetus, no different risks of GIK than in the non-pregnant state are expected.

SPECIAL PRECAUTIONS: Study drug must be administered via IV pump. All physician and nursing staff (ED, cardiac catheterization lab, CCU, telemetry) taking care of patients during the 12-hour study drug infusion period will undergo an orientation and training session about the IMMEDIATE Trial. They will attend an information lecture, receive an informational sheet (specific to their hospital), and will be oriented to the study drug packet and study patient booklet that will provide information on the study protocol, procedures, and contact information. Study staff will be informed of the nature of the study and that enrollment in the trial does not preclude any other standard treatments for ACS. The study patients' routine caregivers will monitor the effects of the study IV solution and assess the patient's need for treatment of an irritated IV site, abnormal potassium or glucose levels, or fluid overload, and will provide standard care, which may include for example: discontinuing the study drug, giving insulin, or giving diuretics. All standard of care procedures and treatments will continue.

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