THE CHANGING MORTALITY OF MYOCARDIAL INFARCTION

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DR. MACKENZIE: Our next speaker is going to talk on the topic of the changing mortality of acute myocardial infarction. All of us have observed the advances that have occurred in many areas of medicine. One of the advances is the striking changes that are occurring in the management of myocardial infarction. A number of the large randomized clinical trials are now starting to demonstrate very marked changes in the acute or short-term mortality of myocardial infarction, which probably will be translated into the long-term mortality of myocardial infarction. Our speaker, Jean Rouleau, is a cardiologist at our most famous cardiology institute in Canada, the Montreal Heart Institute. He is a former professor of medicine and chief of cardiology at the University of Sherbrooke. He has been the principal investigator in a number of randomized clinical trials done in Canada and the U.S., and it is from this experience that he speaks. He recently wrote an article in the New England Journal of Medicine comparing the management practices in the management of myocardial infarction.

DR. ROULEAU: Thank you. Some of the analyses that I'm going to show you were done in the last two weeks and are going to be relating to a large multi-center registry that we have across Canada, looking at acute myocardial infarctions.

In acute myocardial infarction in the last ten to fifteen years there has been a lot of advancement. All the various thrombolytic agents have decreased mortality. Here you have the line of reference, and anything to the left is improvement, anything to the right is worsening, you have the mean and the 95% confidence intervals. You can see for all the thrombolytics there is an improvement in survival. I agree with the editorial in the New England Journal of Medicine, saying that the use of TPA probably should be restricted to high-risk patients. Thrombolytics are probably the most important intervention that we've come up with in the last ten to fifteen years. Intervenous beta blockers, IV nitrate, calcium antagonists are not very good; heparin is beneficial, and aspirin. So there are many various interventions that could change mortality, and how should this be looked at? How did this change what's going on? Well one of the problems with the studies looking at patient populations is that they were all done in the early- to mid-80's, prior to the widespread use of all these various interventions. So what we in Canada did was a study where we looked at consecutive infarcts coming into hospitals who made it through the door of the emergency in various hospitals in eight centers in Canada. We then separated patients into those that were non-transferred and transferred, and concentrated our work on this group, because we felt this was probably the best reflection of the patient population as it really is. We had 280 in-hospital deaths and 2,860 survivors. This study started in June of 1990, and the registry stopped taking patients in some cases in December of 1992, and in some cases in July of 1992. Of those in-hospital deaths, we then separated patients into those less than 75 years old, and this is an important separation, because most of the studies that we have today are concentrated on this group of patients. But in the last year of the registry, we started taking all patients, including those over 75 years old. So there were no exclusion criteria; if a person came through the door breathing, they were included in this analysis.

Post-discharge survivors, again patients under 75 years old and greater then 75, you'll notice the high in-hospital mortality of those patients greater than 75 years of age. Then we had complete follow-up, and those patients agreed to come back for follow-up at six months, one year, and then every year thereafter. In this complete follow-up, we attempted to do pre-discharge risk stratification, including ejection fractions and Holter monitoring, and we're also trying to evaluate signal-averaging ECG in this broad patient population. Then there were those patients who for various reasons, either geographical or other, would not agree to come back for follow-up, but those patients, we have six-month telephone follow-up on all patients. So there is no patient out of the 4,071, including the non-transferred and transferred that we have not followed, and in many cases, it's two years. Of those 4,071 patients, we have none lost to follow-up. So this is probably one of the more complete and up-to-date registries going on today.

UNIDENTIFIED: Doctor, what's a "transferred" patient?
DR. ROULEAU: A patient transferred from another hospital, could have been transferred for cardiac catheter or arrhythmias or some complication. We had in those eight hospitals, we had some that were university and some that were community-based, some with cath labs and some without. So we eliminated anybody that was transferred for further investigation, or whatnot, to the tertiary referral centers.

Now the complete follow-up group, we had ejection fractions in 83%, and 24-hour Holter monitoring in 76%, and the difference in percentages is that we only accepted 18 hours. Pre-discharge exercise testing, which is quite popular in Canada, we had 55%. And I can say that anybody who gets a pre-discharge exercise test has an excellent prognosis.

So, what was in-hospital mortality? If we go back to the 70's, and this is an analysis where I accepted only studies that took all comers; there may have been some exclusion criteria, but, as a general rule, these are studies that took all comers. Prior to 1970, in-hospital mortality was nearly 26%. In the decade of the '70s, we didn't make that much progress; we thought we did much better, with the coronary care units become more widespread, but mortality remained high. In the 1980's it was 16%, a significant drop in mortality. So in the early '80s we saw the impact of widespread of coronary units. In the early '80s, the thrombolytic era, and again in these studies, no more than 20% of patients in the thrombolytic era were getting thrombolyis. Mortality was not decreased that much, because of the small percentage of patients who were getting thrombolysis. There were some articles in the Annals of Internal Medicine stressing that there was a very small percentage of patients, and most of those were very small risk patients.

Now thrombolytic studies that took all ages, but again patients receiving thrombolytics are patients that are lower risk. The mortality was 8%. There are two small studies between 1989 and the present, with small numbers of patients, one from Canada and one from Sweden, showing a 12.2% mortality. So there was definitely a downward trend. Now in the Sage study, when we take patients 75 years of age or less, we had a 7.8% mortality. When we took all ages, we had 8.3%. So all comers, coming to hospital now, in the last year, I guess it would be October or November of 1991 to December of 1992, there was an 8.3% mortality. So since the early '70s or the '60s, we've reduced mortality to one-third of what it was, in-hospital mortality. And even from the early '80s, we've reduced in-hospital mortality by 50%, and that's if we take all comers. I think it's a tremendous credit to all the work that's going today.

You'll notice that in my previous slide, I showed that patients greater than 75 years of age had a higher mortality and that there's not that much difference between patients of all ages and less than 75. That's because in the last year, overall mortality has continued to decrease. So between 1990 and 1992, there's been a significant further drop in mortality.

Now, if you do a multi-varied of those patients, all coming through the door, what are the things that will identify high-risk patients. In this analysis we took all the demographic risk factors known, all the risk factors of an acute myocardial infarction, such as infarct size, Q, non-Q, and we took all therapies and we put them together to try to find out what appeared to modify mortality. Unfortunately, in this multi-varied analysis, some of the therapeutic interventions were not included. Now, there is a lot of controversy going on whether gender is a major risk factor. Certainly, in multi-varied analyses it is. In this study, male gender gave an insignificant improvement; probably if we'd had more patients, we would have had a significant decrease. So as many people have shown, male gender reduces.

In this type of study, we broke age down in 5-year segments, for patients 75 and younger. We compared them to patients less than 45 years. You can see there is an increased in risk if you go from 45 to 50 up to 70 to 75, but because when you get beyond 55 years of age, there appears to be very little risk in a multi-varied analysis, this was not significant. But clearly, if you're below 45, you have a better risk than if you're 70-75. Diabetes is a very bad independent risk factor. A history of angina was positive, probably because it reflects more widespread coronary artery disease. Previous myocardial infarction was not significant if you considered other clinical factors. Now maximum CPK rise, compared to the upper limit of normal, we compared these less than 2.75 time the upper limit of normal to this greater than 11 times the upper limit of normal, and there was no significant difference here, not that the smaller infarcts didn't seem to do better, but there wasn't much difference between small and medium infarctions. It's when you get to the larger ones that you tend to get a little bit more, but not really, if you considered other important factors such as killep class. Killep class in the Save study, and also in this study, came out as probably the most effective way of assessing somebody's risk. We compared patients killep 3 and 4, so this is a combination of left ventricular systolic and diastolic dysfunction. If you were killep 1, you had .04 the risk of killep 3 or 4, and if you were killep 2, you had .14. There was no difference between killep 3 and 4 in this particular study.
Now this slide will be no surprise to you. This is the univaried analysis, but I show you this slide just to show you the incidence of the various risk factors in patients coming through the door with acute myocardial infarction. In this analysis, if you walk through the door, what is your risk of dying in hospital? This is what we’re showing in our odds ratio on the right, but this is the “n” out of these numbers, 2,800. How many of them have hypertension defined as hypertension requiring therapy and diabetes requiring therapy? You can see that nearly 40% of patients with an acute myocardial infarction coming through the door had some kind of therapy for hypertension or had been treated in the last few years for hypertension. And the diabetes is significantly elevated as well, again, the tremendous risk of the diabetic patient. Interestingly, in a univaried analysis, current smoking is beneficial; of course it’s not, it’s because these patients had lower risks. They were younger, and when you put it in the multi-varied analysis, of course, smoking was of no benefit. A lot of patients had a history of angina. Nearly 60% of patients had angina prior to their acute myocardial infarction. PTCA and bypass surgery are not all that common. Again, I’ll show you some data between Canada and the U.S. We appear to use these a little bit less in Canada than the U.S.

I just want to point out the use of some of these therapies, PTCA, bypass surgery, in hospital, about 8% of the population had bypass and 21% had PTCA, and this is prior to hospital discharge, from the infarction to discharge. So, less than 30% of patients had revascularization procedure. I think this is something that is ongoing in Canada today.

Recurrent myocardial infarction was about 3% in most of the studies; in the late ’70s and early ’80s, it was around 5-6%, so we have had a significant decrease in recurrent myocardial infarction. I understand that in the ’70s the definition was somewhat lax, but the ’80s studies suggest that we have had a decrease in recurrent infarctions. We are picking up the high risk patients a little better.

Forty-six percent of patients had thrombolysis. If you looked at Q-wave myocardial infarctions, it’s over 60%. So, nearly two-thirds of patients with acute myocardial infarctions now with Q-waves are receiving thrombolytic agents. Intravenous nitroglycerin is very common in Canada and a little bit less in the U.S.

Now, what can we look for in the future to try to get this a little better. Well, we know nitrates are useful, but unfortunately, the isis-4 studies looking at beta blockers, and you’ll remember isis-1 is a study that showed beta blockers beneficial in acute myocardial infarction, in isis-4 only 2% of the patients are receiving beta blockers, intravenously.

So, I think that when you look at new studies coming out you have to put it into perspective. People are getting three interventions in isis-4 to decrease blood pressure, people are hesitant to use beta blockers, which are beneficial in improving survival. Magnesium, we don’t know; it’s starting to be used more and more, because all the data are pointing in that direction, but we’re waiting for isis-4 that should come out this fall. Anticoagulants, again, we’re getting better anticoagulants, antithromnants, and the early data suggest that we may be able to do better than we are now.

Free-radical scavengers in the future are going to be very important, I believe, and ace inhibitors used early, we’re waiting for some new studies that’ll be coming out to tell us that.

But, perhaps what we can do better than anything else is to start using thrombolytic agents early, and this is the Jissey-1 study showing that patients coming in under one hour had improvement in survival. It’s tremendous, and you lose your benefit with ongoing time.

Now, in Canada, as well as the U.S., we have a terrible record for giving thrombolytics, patients can wait 60 minutes on an average in an emergency room before getting thrombolytic agents, which is, I would say, 45 minutes too long. But, as this is getting more understood, perhaps we’ll do better. And of course, the results of late, and other studies using thrombolytic agents late, would suggest we can improve survival even more, and increase the use of thrombolytic agents. Here you have the improvement; the placebo group and the TPA group, a decrease in mortality with ongoing thrombolytic agents at 6-12 hours. There are other studies that suggest that perhaps you can do better after that, as well, but certainly 6-12 hours, you can prolong the use of thrombolytic agents.

Now this is the post-hospital discharge mortality, and it’s a similar type of study as I showed you before. Now in reviewing this literature, over the last couple of years, I noticed that there are very few studies available that look at post-discharge survival in the first year. This is one-year mortality, that doesn’t have a lot of exclusion criteria. Nearly all studies you can see here exclude patients 75 years old. Notice that we have analysis 75 and all ages in the Sage to be able to tie in with some of these serious illnesses are killep 1. I’ve just shown you
that Killip greater than 2 is a terrible risk factor. So a lot of these, for example, in the 70's and even in the thrombolytic area, and in select thrombolytic studies were excluded. So whatever numbers you're getting on the right are really underestimating one-year mortality. Contra-indications of thrombolytic therapy, obviously for all thrombolytic studies, this was a contra-indication.

Now, if you look at prior to 1970, you have 11% one-year mortality post-discharge, but in this study these were only patients less than 75 years old. If you compare the Sage 1990-92, we're down to 5.3%, so we've cut that down to 1/2. If you look at 70-79, we had some kind of benefit here; I guess they'd started to use some beta blockers, or at least identifying high-risk patients and doing some revascularization procedures prior to discharge, helped decrease mortality. But again, patients older than 75 were excluded, and these patients or high-risk patients were also excluded. So, 8.8% is an underestimation of one-year mortality. So, again, if you compare it to all ages, at 7.3%, it's significant improvement.

In the non-thrombolytic era of the 80's, you had a decrease, well, maybe beta blockers here. But again, we excluded patients 75, so it's significant improvement in the 90's. In the thrombolytic era, you didn't get a tremendous increase in mortality with thrombolytic agents once you get post-hospital discharge. And I'll show you a slide showing that probably thrombolytic agents are beneficial but don't have a tremendous effect on mortality, post-hospital discharge, mostly in that first month.

Here are select thrombolytic studies, those are the thrombolytic studies where you had to make intervention. And I'm showing this because you get a lot of people from Timme and Tamme and all those various studies as telling us, "look at what one-year mortality is; it's 3.5%." Well, hooey, because in fact, these patients have been shown quite clearly to be a very select group of patients. There are maybe one out of five infarctions coming in; and the mortality of those patients excluded in those studies had a five-fold mortality as compared to those included. So these do not really reflect reality. In spite of that, if you take patients 75 years and younger, you have 5.3 one-year mortality, and this is taking all comers. If you take all ages, mortality is at 7.3%, which I think is tremendous. So both in-hospital and post-discharge mortality have decreased dramatically in the last ten years.

And this is just a slide of isis showing, that really went to get away from those first few days, whether you take streptokinase, aspirin, or the combination of aspirin and streptokinase, those two lines are reasonably parallel. And most of your benefit of thrombolytic agents is in that first couple of weeks.

Now, what were the causes of death in Sage. Again, we're seeing a little bit of a difference as compared to the literature. Now, if you look at in-hospital mortality, cardiovascular, we have here the cardiovascular and non-cardiovascular, and these are patients on whom we're getting more information. Now remember, we have a complete follow-up on all patients. Cardiovascular in-hospital, it's nearly all cardiovascular, incidence of death from low out-put is increasing; it's over 50%. Studies in France and the U.S. have shown the same trend. We're able to take care of recurring infarctions; we're able to take care of arrhythmias better, but we are not able to salvage a patient with low output with a class 3 and 4 Killip.

Now, in post-discharge mortality there are some major differences compared to the past, and I'll illustrate them in graphs later on. As to cardiovascular, it's about 76% one-year mortality is due to cardiovascular causes. Recurrent myocardial infarction is only 19%, so we're really identifying patients at high risk. Low output is only 17%. Now presumed arrhythmic death is 31%; this just means overall at one year, less than 2% of patients have presumed arrhythmic deaths. And you know as well as I do that these patients are nearly exclusively patients with low output; these are patients often with inoperable coronary artery disease, and how much of these are really just terminal arrhythmias or ischemia? Procedural and others, non-cardiovascular deaths, were 14%, cancer in our group, as you would expect as we included all patients.

Now, there are three large categories where we probably dented post hospital discharge mortality; one is the decrease in re-infarction rate; another one is a decrease of incidence of heart failure; and the other one is decreasing sudden death. I'll discuss each one briefly.

Now, this is post-infarction, post-discharge recurrent myocardial infarction, so if you leave hospital what chance do you have of having a recurrent myocardial infarction. And here I separated studies in '71 to '80 by decades, and this is the decade of the '80's, this is the thrombolytic era, and this is selected thrombolytic studies. Again, these are the Tamme and Timme studies. And you can see that there was a tremendous amount of rapid infarction here, up to 8 or 9% in the first year in the '70's. We became much better in the '80's; we were down around 6 or 7%. And in this particular study, we're now down around 3 to 4%, very close to the
Timme studies. One of the reasons we're having improvement in survival is that we are being able to identify patients that are at high risk of recurrent myocardial ischemia and have cut the incidence of recurrent myocardial infarction to about 3 or 4% one year. How have we done that? Well, aspirin has obviously decreased the reinfarction rate about 25%. The use of ace inhibitors in Save and Sage reduces the incidence of recurrent myocardial infarction by about 25%. Cholesterol lowering agents, obviously not in the first year, and it's a long-term proposal. Revascurization I think is the major way that we've improved patients, and beta blockers also reduces the incidence of reinfarction.

Now, of all of these various factors, I'm just going to talk about revascurization, because we did publish the study from Save in the New England in March, looking at this particular subject. You have to understand that Save is a multi-centered trial where we were looking at ace inhibitors in patients with ejection fractions under 40%. Now if there was anybody that the consensus said should have coronary arteriography prior to hospital discharge it is certainly the patients with left ventricular dysfunction that were at higher risk. And as recently as '90, '91, and '92 there are nomograms suggesting that all patients with LV dysfunction should have a cath prior to discharge. And if you look at U.S. and Canada here and the ratio, these are the revascurization and arteriography prior to hospital discharge in the American and Canadian groups, and there over 2,000 patients in this study. Coronary arteriography was 68% in the U.S., 35% in Canada, so nearly double the coronary arteriography in the U.S. PTCA was more than double, bypass double, revascurization procedures 2-1/2 times in the U.S. vs. Canada, and revascurizations per coronary arteriography were more common in the U.S. Now, that suggests that not only do you do more arteriography, but that your tolerance to lesions is lower so you tend to revascurize, even if you do a cath you tend to revascurize more frequently. I would have predicted that we would have had a higher incidence of revascurization per arteriography; this is not the case, suggesting that the threshold for doing these procedures is lower in the U.S.

The threshold for using these procedures is also lower. So the use of invasive diagnostic and therapeutic intervention is much higher in the U.S. for a similar high-risk group.

Now one might say that that's so that we give less drugs, but in fact, in the U.S., American physicians tended to give more drugs whether they were beneficial or detrimental to the patient. These are nitrates that generally are beneficial. You give more nitrates in the U.S., beta blockers are given more frequently, both beneficial drugs on survival, but they do have calcium antagonists which are detrimental probably in this patient population. And you have anti-arrhythmics which are detrimental, and they were given more frequently, as well. So Americans tend to treat patients more with invasive diagnostic therapeutic interventions. And despite using these interventions more frequently, give them more drugs, as well. Now, what kind of result did this have in the same population? Well, this is mortality, Canada in orange and the United States in red. You can see it's very difficult to get a more super-imposable line. Mortality was exactly the same, and all these interventions had no effect on mortality.

Recurrent myocardial infarction was also unchanged between the two countries, suggesting at least in this important morbidity and mortality, there was absolutely no difference between countries. However, what we did find is that a few more patients had angina at one time in Canada; I think it was 33% vs. 28%. Well, these findings suggest that perhaps we're overusing some of these invasive therapeutic and diagnostic interventions, and perhaps more conventional ways of assessing risk prior to reinfarction are useful in this patient population, and we don't necessarily have to do a cath.

Now, the second decrease in mortality is probably due to the decrease in congestive heart failure. And that's due to the use of aspirin and warfarin in those patients. Beta blockers, the Behab study and some analysis in Miami and other multi-center trials suggest that beta blockers are particularly useful with LV dysfunction and that low risk patients get little or no benefit from beta blockers. So, patients with LV dysfunction are those that appear to have ongoing ischemia, are those that have the best effect from beta blockers. Ace inhibitors, again, also, are beneficial in that group. Whether we should use ace inhibitors earlier is under investigation.

Well, this shows a comparison of the MPRG and Sage studies. The MPRG is a study that was done in the early '80's looking at mortality, and this is what identified left ventricular ejection fraction as a major predictor of ongoing mortality, and we just compared our population
to this group. Here you have the ends for each of the various groups, and you have percent mortality at one year. You'll notice that over most ejection fractions we have an improvement in mortality. The overwhelming majority of patients have ejection fractions over 40%, but in fact, in most categories there is an improvement in ejection fraction. Now why do we believe that this is occurring? This is the MPRG and this is the Sage study, well, this is actually reperfusion and late mortality, but it could be the Sage study as well, as the curve is shifted over to the left. Now, here we have mortality and we have ejection fraction, and we believe we get some myocardial salvage improving ejection fractions. And what I did is show that in our study a larger proportion of patients were at high ejection fraction groups than in the MPRG, just slightly better. So we do get some myocardial salvage, and with the open arteries, we get better healing and perhaps improvement in the ischemia, long-term. And we get benefit from probably both of these factors. So, the MPRG curve is now shifted to the left with improved mortality in that patient population.

Now, what about sudden death? Sudden death was the major cause of mortality, post infarction. Here, again, we have by decade the thrombolytic era in red here and that round dot, you can see that at 18 months, there is still a high percentage of sudden deaths in the thrombolytic studies, just the isis, those studies. In the '80's we had pretty high sudden death and in the '70's, as well. So, we really haven't made any great dent, and this is probably because these studies were all done prior to the most recent studies showing that we kill patients with anti-arrhythmic drugs. So, what have we done to improve sudden death? Well, we've improved the substrate, and there is some evidence that suggests that the open artery, and by preventing ventricular dilatation, we reduce the risk of sudden death. We clearly decrease the sub-strate; late potentials are decreased in this population group.

We're now better at preventing ischemia and sudden death; a lot of people believe, and I'm one of these, that a lot of sudden death is due to recurrent ischemia. And we are not pressing the trigger with drugs that improve or that increase mortality. We are now using drugs that perhaps are beneficial. There are ongoing studies that should improve this even more. And this the famous study looking at enkanide and flekanide and you can see that the placebo did much better than the treatment group. And I believe that a large portion of the improved mortality that we have in sudden death, which is now down around 2% vs. 4% as recently as 5 to 8 years ago, is due to the fact that we're not killing patients as efficiently as we were before. And this is the amnioterone study which was where we individualized; it's a Swiss study by Berkhart where they gave randomized amnioterone, individualized therapy or placebo in patients that were at high risk, and they had improved survival in those with amnioterone. There are ongoing multi-center trials looking at this. I would predict that amnioterone will be beneficial in high-risk sub-groups. The problem is identifying the high-risk sub-groups. And most of the studies ongoing today are looking at the PVC's greater than 10 per hour. And here we have the MPRG which identified the high-risk patients by Holter, and this is still used for inclusion criterion in studies ongoing today. And in green you see the MPRG, a nice progression, but the increase in PVC's. You'll notice in the Sage studies there is very little increase until you get to patients with greater than 30 PVC's per hour. In some of the ongoing studies today, 10 is the cut-off. So we are going to be treating low-risk patients with anti-arrhythmic drugs, and negative trials will have to look at sub-group analysis to pick out those high-risk patients here and forget these low-risk patients here. So, clearly the profile of survival by Holter monitoring has change dramatically in the last ten years.

And in the last few slides, I'd just like to show you the multi-varied analysis we had. If you take a patient prior to discharge, and look at various risk factors, which ones will predict survival and which will not? Now this is a multi-varied analysis, and you remember that all clinically important demographic variables, all the variables of acute infarction and all therapy, were considered in this multi-varied analysis. You'll notice the gender is not here, because gender has absolutely no effect on survival. In fact, in a univaried analysis, the risk ratio for male vs. female was 1.02; the female appears to increase risk for in-hospital mortality, but we had no increase in risk in post-hospital discharge. Age is also a little bit less of a risk factor when you get discharged; this is a multi-varied analysis, but it was also true in the univaried analysis. Although patients that are less than 55 have a better survival, we're comparing to patients equal to less than 45 years, and there really is no big difference when you look at other important factors regardless of age. So, age becomes less of a risk factor when you get discharged from hospital. In-hospital it appears to be more of a risk. Diabetes, again a very important risk factor, remembering then our patient population, 20% of patients were treated for diabetes at one time or another, a relative risk of 2.1. Previous myocardial infarction is important probably due to the extent of coronary artery disease as well as the damage you incur, but this is a multivariate analysis, so ejection fraction was considered with an odds ratio of 1.7. So, previous myocardial infarction was a big risk factor. History of bypass was also a risk factor, probably
because you have such extensive coronary artery disease.

What was interesting in this analysis was that if you did not do a multi-varied analysis and just looked at Q-waves and non-Q's, the non-Q-wave myocardial infarction patients had a one-year mortality twice as high as patients with Q-wave myocardial infarctions, but when you do a multi-varied analysis, Q-wave vs. non-Q-wave is not important. Because non-Q-wave patients all had previous angina, nearly all of them had bypasses before, they had more extensive coronary artery disease, and this betrays the change in pattern in patients that we have with acute myocardial infarction.

Killep class again comes out as a major predictor of survival. I can also tell you that in Save, which is another multi-center trial, killep class was more important than LV ejection fraction. And perhaps looking at the systolic and diastolic disfunction and neurohumor response to the infarction, which is seen with killep class is very important. PTCA in hospital also appeared to be an independent predictor of long-term survival.

So, these are now the independent predictors that we have today in our study looking at all therapies and looking at all demographic and acute myocardial infarction risk factors. Now what do the PVC's look like, which was considered in the MPRG. They considered killep class, they considered New York Heart Association class, they looked at PVC's and ejection fraction. This is a univaried analysis here, and you can see that even in the univaried analysis your previous chart's PVC's are not predictive. Of course, this is a little under power, we had only about 1,500-2,000 patients in this study. So, if you have no PVC's, you appear to do better, but when you get to higher PVC's the risk is not that much, as high as one would have predicted from the MPRG study. So, PVC's are of some use, but if there is such a cross-over here it becomes difficult to really know what's useful, except perhaps for patients with greater than 30 PVC's.

Now here is left ventricular ejection for this univaried analysis, so obviously in multi-varied analysis this was even weaker and totally nonsignificant right across the board, which is contrary to previous studies that suggested a multivaried analysis useful for PVC count. Ejection fraction was important in multivaried analysis, as well as univaried analysis, and you can see the high risk of patients with ejection fractions under 40% even in our substudy. So, ejection fraction remains a powerful predictor of long-term mortality.

So, today I went over a little bit of the literature over the last 30 years of acute myocardial infarctions, and I've shown you that in-hospital mortality has decreased to about 1/3. Post-hospital discharge mortality has decreased to about 1/2. That decrease has occurred mostly in the last ten years. I've also tried to show you that the risk factor profile of patients for in-hospital mortality and post-discharge mortality has somewhat changed. So that some of the traditional ways of assessing high risk remain true, but some of the traditional of ways of assessing risk are probably less true in some cases as well, and we'll have to readjust the way we're looking at post-infarction patients and assessing in the oncoming years. Thank you.

DR. MACKENZIE: Thank you very much, Jean. This is going to be very valuable. You've done a lot of work for us. We're open for a few questions.

DR. SALVADOR WHITE, Caracas: In insurance medicine it is very important to know the overall mortality of infarction; but practically, nearly 50% of patients with myocardial infarction die before going into the hospital, that means pre-hospital mortality. Do you think there has been improvement in that area?

DR. ROULEAU: That would be purely speculative on my part. I'm not aware of any large well-done evaluations of this today. I would suspect there is a change. Clearly aspirin and beta blockers prevent sudden death. It's speculative.

LARRY JONES, Underwriting Consultants: Heart enlargement seems to be a predictor of increased mortality, also. Did you do any calculations as to the relationship with enlarged heart and mortality?

DR. ROULEAU: We have a reasonably small sub-group of patients where we did volumes, as well. There were about 700 or 800 patients only in that cohort. There was some risk, but in a multivaried analysis, we couldn't bring it out. Having said that, we did this by radionucleide, and one could criticize the techniques used by radionucleide to try and figure volume. I can tell you that in Save where we did echocardiograms in 600 patients, it was the most potent predictor of survival even more than ejection fraction. In my clinical experience, I would agree 100% with that. There is also good data from Harvey White from New Zealand who published in New England and then again in the Circulation showing that volumes were important independent predictors of survival. But, at this point, we haven't been able to see that, but we haven't analyzed that data in detail. But it's a good point, and my own personal opinion is that it's a terrible risk factor.